The Development of Catalytic, Asymmetric Decarboxylative Coupling Reactions

by

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Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Abstract

Erin C. Burger
Department of Chemistry, April 2007
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The generation, and subsequent allylation, of ketone enolates from β-keto allylic esters *via* the transition metal-catalyzed decarboxylative allylation reaction has been thoroughly investigated in regard to the scope, regioselectivity, and enantioselectivity of the reaction. The Pd(0) / Trost ligand-catalyzed transformation with symmetrically substituted acyclic and cyclic allyl groups has been shown to afford high yields of γ,δ-unsaturated ketone products with ee's typically greater than 90% under very mild reaction conditions. In addition, the reaction has been shown to be highly regiospecific; products arise exclusively from the allylation of kinetic enolates. A catalytic system comprised of Pd(0) and either the PHOX ligand or Quinap has also been developed for the enantioselective decarboxylative allylation of fluorinated ketone enolates to yield α-fluoro ketones with ee's typically between 80% and 90%. The enantioselectivity of the reaction with α substituents other than fluorine has also been explored. While iridium, rhodium, and molybdenum catalysts were found to display only moderate reactivity in the decarboxylative allylation reaction, the ruthenium complex Cp*RuCl(bpy) is capable of transforming β-keto esters possessing aryl-substituted allyl groups to γ,δ-unsaturated ketones with yields generally greater than 90%. In addition, the reaction in highly regioselective; products arising from attack of the enolate at the substituted terminus of mono-substituted Ru π-allyls are favored by as much as 101:1 over the other regioisomer.

The reaction is also stereospecific, and it has been demonstrated that the extent of stereospecificity is dependent upon the electronic and steric nature of substituents on the β-keto ester starting material. Elucidation of the mechanism of racemization allowed for the isolation of products with high enantiopurity. Lastly, the scope of nucleophiles generated following the transition metal-catalyzed loss of CO_2 has been broadened to include anions other than ketone enolates. The decarboxylation of allyl esters of α-amino acids protected as diphenyl ketimines has been shown to proceed with palladium catalysts. Nucleophilic α-imino anions react with electrophilic Pd π-allyls to yield protected homoallylic amines, although for certain substrates aziridines are the predominate products. The addition of chiral ligands has been shown to induce modest levels of selectivity in the transformation.

Acknowledgements

I think it's safe to say that how one looks back on their time in graduate school largely depends on the experiences they had in the lab, whether they be good or bad. I have been supremely blessed to have worked in a lab in which almost every memory that I have is pleasant, which I believe is a direct reflection of the way Jon has run our research group. From the very earliest days learning the in's and out's of the lab with Jon, he has always been extremely approachable and consistently full of good advice (although it turns out that you really don't have to try *that* hard to start sodium hydride on fire). His patience with the group is perhaps only matched by the volume of ideas he generates on a daily basis and is something that I strive to achieve in my own career. I will definitely miss laughing with (and at) Jon in lab and can't express how fortunate I feel to have had him as an advisor.

Speaking of laughing with (and at) someone, I could write another dissertation on all of the laughter Shelli and I have shared over the last five years. I think one of the most important qualities of a good friend is the ability to empathize with and truly understand the highs and lows that the other is going through, and I know that no one knows better what life has been like during graduate school than Shelli, because she has been there with me every step of the way. I can't imagine a topic that we haven't covered while standing in front of our hoods, no matter how insignificant or embarrassing, all the while rocking out to Prince or Neil Diamond. I'll miss all the time we have spent together inside of lab and out (rhythmic dancing included), but I know that two people who have been through so much together will never lose touch, no matter what directions our lives take us.

I also need to give credit to all the other group members who have patiently put up with all of the Prince I kept trying to sneak into lab, especially Chao Wang. I've never seen Chao without a smile on his face. His consistently friendly and happy

demeanor was always something I admired and appreciated. Thanks to him and the rest of the Tunge group, the days I spent in the lab were a lot more enjoyable.

I am also incredibly grateful to the other professors at KU who have always been more than willing to provide help and encouragement. Helena, Paul, Dr. Givens, and Dr. Carlson did an amazing job as teachers. With the foundation of knowledge they provided I was well equipped for all of the challenges I faced in graduate school. I will also never forget the words of encouragement provided by Jeff Aubé and Andy Borovik. They really helped me see what I was capable of when I couldn't see it in myself and I can't thank them enough for that.

I also need to thank all of the friends that I have made in graduate school, especially those who started this journey with me. I don't think I would have made it through quantum without the long evenings Heidi and I spent in the library. (I should also probably "thank" Andy for convincing me to take that class in the first place!) I'll definitely miss our girl's nights. Eric has also been a great friend, convincing me to be a Puffin when I had doubts about my softball skills. Who would have known that a bunch of chemists could play softball so well?

Finally, no matter how research was going, I always had the invaluable support of my family to fall back on. Some of the best times I can remember were spent with my parents and the rest of my extended family. Not only are my Mom and Dad way more fun to be around than parents are supposed to be, but they are also two of the hardest working people I know and I think that is one of the most important things they have passed on to me. My sister Jessie and cousin Pam are not only my partners in crime but also my best friends and can always be counted on for a good time, whether that be out at the lake, at a Nebraska football game, or drinking beer in Grandma Burger's basement with the rest of the family. My aunt Amy has always been someone I have looked up to as an example of how to be a successful

professional without taking yourself too seriously. Any amount of time spent with Amy is guaranteed to be a fabulous time and I couldn't ask for a better role model (even though we might spend more time together in bars than most families!) The bond that holds my family together is truly unique and my most cherished possession. I love you all, your support means more to me than I can express.

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Abbreviations

Ac	acetate
acac	acetylacetone
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BIPHEP	2,2'-Bis(diphenylphosphino)-1,1'- biphenyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	*bis*oxazoline
bpy	bipyridyl
BSA	*N,O-bis*(trimethylsilyl)acetamide
Bu	butyl
^{t}Bu	*tert*-butyl
cee	conservation of enantiomeric ratio
Chiraphos	2,3-*Bis*(diphenylphosphino)butane
COD	cyclooctadiene
COT	1,3,5-cyclooctatriene
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIOP	4,5-*Bis*(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMAP	*N,N*-dimethylaminopyridine

DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
dpm	dipivaloylmethanato
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,2-*bis*(diphenylphosphino)ethane
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl
ee	enantiomeric ratio
er	enantomeric ratio
Et	ethyl
GC	gas chromatography
JosiPhos	1-[2-(Diphenylphosphino)ferrocenyl] ethyl dicyclohexylphosphine
L	ligand
L*	chiral, non-racemic ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LG	leaving group
M	molar
Me	methyl
MeDuPhos	1,1'-(1,2-phenylene)bis[2,5-dimethyl]-phospholane

MonoPhos	(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine
MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
Nuc	nucleophile
Ph	phenyl
PhanePhos	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
PHOX	(2-diphenylphosphino)-4,5-dihydrooxazole
PINAP	4-[2-(diphenylphosphino)-1-naphthalenyl]-N-[(1S)-1-phenylethyl]
PLP	pyridoxyl-5-phosphate
^{i}Pr	isopropyl
^{n}Pr	*n*-propyl
Quinap	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
RT	room temperature
SynPhos	6,6'-Bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMSI	trimethylsilyl iodide
Tol	toluene
TsDPEN	*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine

Chapter 1

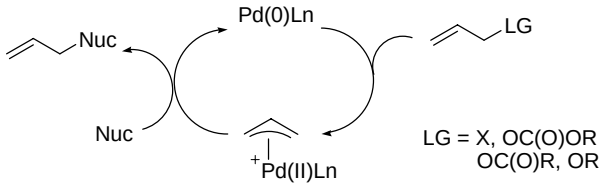
The Palladium-Catalyzed Enantioselective Decarboxylative Allylation of Ketone Enolates

1.1 Introduction: Palladium-Catalyzed Allylation Reactions

1.1.1 The Pd-Catalyzed Allylation of Stabilized Enolates

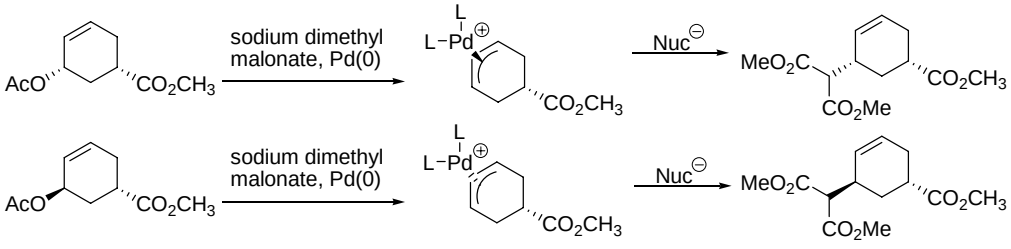
Preliminary communications on the palladium-catalyzed allylic alkylation reaction (Scheme 1.1), also known as the Tsuji-Trost reaction, began to appear over 30 years ago[1] and the transformation continues to receive much attention in the literature.[2] In its most simplistic form, the catalytic cycle is understood to begin with the oxidative addition of the allylic substrate to Pd(0) and concomitant ionization of an allylic leaving group to form a Pd(II) π-allyl complex. Addition of a nucleophile displaces Pd(0) and releases product.[3] In the early reports, as well as in many later studies, the sodium salt of dimethyl malonate is a commonly employed nucleophile. With a pK_a of 13 in water, dimethyl malonate is an advantageous pronucleophile due to the ease with which it can be deprotonated. The enolate of dimethyl malonate is often referred to as a "soft" nucleophile; this term has been used to describe those nucleophiles whose conjugate acids have a pK_a of < 25.[4] In addition, those substrates that contain functional groups that result in a significant decrease in pK_a, such as β-diketones and β-keto esters, may also be referred to as stabilized nucleophiles. In contrast, non-stabilized nucleophiles with pK_a values > 25 are termed "hard" nucleophiles.

Scheme 1.1 *Catalytic cycle for the palladium-catalyzed allylic alkylation reaction*



Several aspects of the regio- and stereochemical course of the palladium-catalyzed allylation reaction have been well explored. The reaction has been shown to occur with net retention of stereochemistry, as illustrated in Scheme 1.2.[5] Furthermore, it has been reported that, rather than first coordinating to palladium, soft nucleophiles directly attack carbon to displace palladium, implicating a double inversion mechanism.[6] It has also been observed that, in most cases, the regiochemistry of the product results from attack of the nucleophile at the less hindered end of the π-allyl terminus. However, if the palladium atom is coordinated to bulky phosphine ligands the regiochemical outcome can be reversed in order to favor attack at the more hindered end of the π-allyl terminus.[7]

Scheme 1.2 *Net Retention of Stereochemistry*

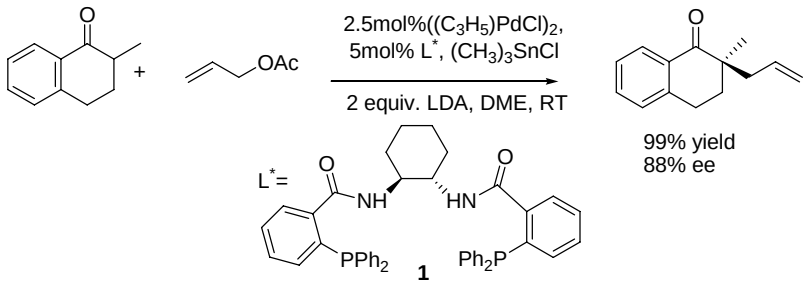


1.1.2 The Pd-Catalyzed Allylation of Non-Stabilized Enolates

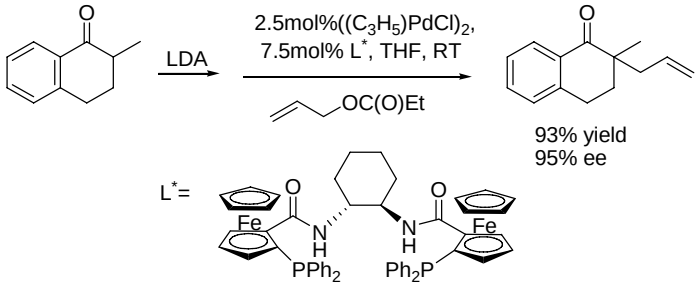
When compared to the significant number of reports on the allylation of stabilized nucleophiles, it is clear that the use of palladium catalysts to allylate *non-*

stabilized nucleophiles has proven to be a significantly more challenging goal. Trost has reported that the enantioselective allylation of ketone enolates proceeds in the presence of a trimethyltin chloride additive, as well as with two equivalents of LDA (Scheme 1.3).[8] Hou published another protocol for the Pd-catalyzed enantioselective allylation of ketone enolates in 2001 in which the use of trimethyltin chloride was avoided, however a stoichiometric amount of LDA was still necessary for the reaction to proceed (Scheme 1.4).[9] This reaction utilized a ferrocence derivative of Trost's ligand **1** to give products of high enantiopurity. A palladium-(*R*)-BINAP catalyst has also been shown to effectively promote the alkylation of cyclohexanone enolates with 1,3-diphenyl allyl acetate in high yields with good enantioselectivity and diastereoselectively.[10] Magnesium enolates of cyclohexanone have also been enantioselectively allylated with the Pd/BINAP catalytic system.[11] A unifying feature of all of these allylation reactions is the need for a stoichiometric amount of strong base in order to form the enolate, which limits the scope of substrates. An alternative route for the allylation of non-stabilized enolates that proceeds under milder reaction conditions would clearly be advantageous as it could encompass a broader scope of substrates that may be base-sensitive.

Scheme 1.3 *Trost's allylation of ketone enolates*



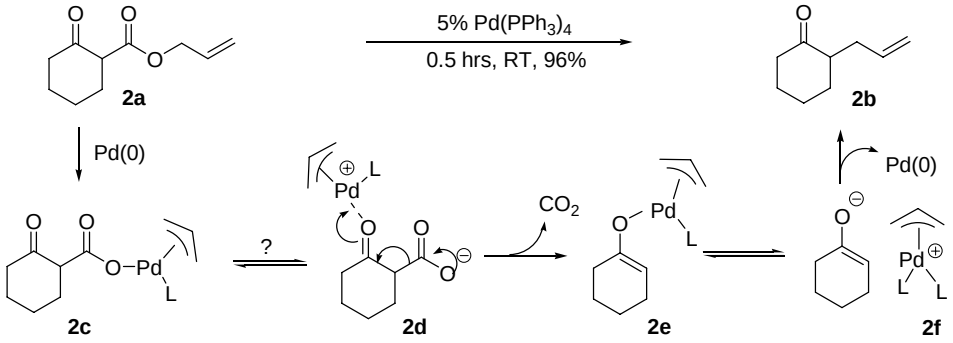
Scheme 1.4 *Hou's allylation of ketone enolates*



1.1.3 The Palladium-Catalyzed Carroll Rearrangement

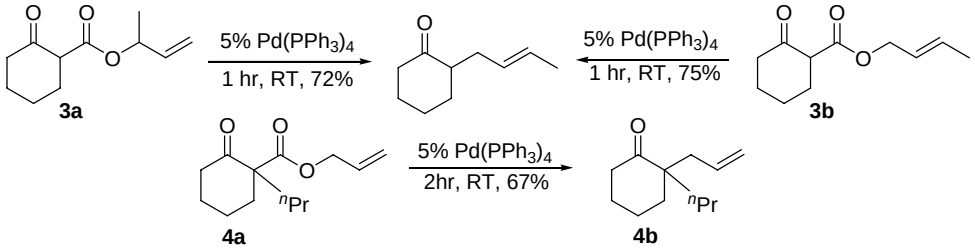
Alternative methodology for the allylation of non-stabilized ketone enolates was reported independently by Saegusa and Tsuji in 1980.[12] It was disclosed that in the presence of $Pd(PPh_3)_4$ various allylic β-keto esters reacted smoothly to provide γ,δ-unsaturated ketone products (Scheme 1.5). The reaction is analogous to the Carroll rearrangement, wherein β-keto esters undergo a [3,3] sigmatropic rearrangement under forcing temperatures, followed by decarboxylation, to provide γ,δ-unsaturated ketones.[13] It was proposed that the catalytic reaction proceeds by the oxidative addition of **2a** to Pd(0) to provide a Pd(II) intermediate which readily undergoes decarboxylation. The precise mechanism of decarboxylation from Pd(II) remains unknown, although the copper-catalyzed decarboxylation of malonic acid has been shown to proceed through an intermediate analogous to **2d**, which can be proposed for this system.[14] The net result of decarboxylation is the *in situ* generation of a non-stabilized enolate, which may or may not be bound to palladium (**2e** and **2f**). Nucleophillic attack of this enolate on the electrophilic Pd π-allyl complex regenerates the Pd(0) catalyst and provides the allylated ketone product without the use of a strong base.

Scheme 1.5 *Decarboxylative allylation*



The details of this mechanism have been probed quite extensively. It was observed that β-keto esters **3a** and **3b** undergo catalysis to provide the same product, strongly suggesting the formation of a common Pd π-allyl intermediate (Scheme 1.6).[a] This set of experiments also illustrates the tendency for nucleophillic attack of the enolate to occur at the less hindered allyl terminus as was first observed for the allylation of stabilized enolates. It was also noted that the kinetic enolate does not undergo equilibration; allylation occurs exclusively at the carbon once bearing the carboxylate group of **4a** to yield **4b**, even though this results in allylation at a more sterically congested carbon.

Scheme 1.6

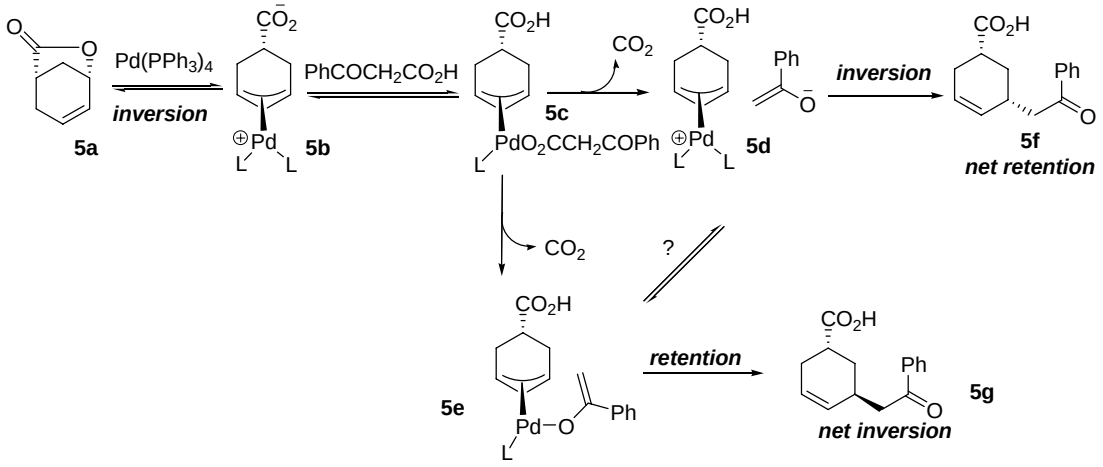


Subsequent mechanistic work also probed the stereochemical course of the reaction, thereby further exploring the true nature of the non-stabilized enolate (**2e** and **2f**).[15] The allylation of stabilized enolates has been shown to occur through a

double inversion mechanism (*vide supra*), and therefore it was of interest to examine if this was also the case for non-stabilized enolates. It would be expected that intermediate **2e** would result in allylation of the Pd-bound enolate from the same face as Pd *via* reductive elimination, leading to retention of configuration for this step. However, if complex **2f** predominates S_N2 attack from the opposite face of palladium would result in an inversion step (leading to the net retention of stereochemistry), as in the case of stabilized nucleophiles.

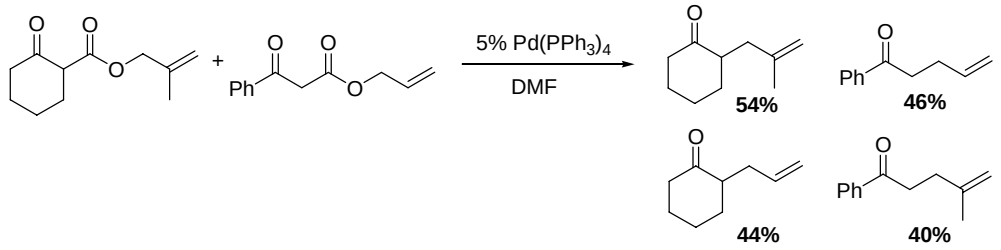
These two possible pathways were explored in the reaction of **5a** with benzoyl acetic acid in THF (Scheme 1.7). Insertion of Pd(0) into lactone **5a** followed by proton exchange and coordination of benzoyl acetate produces intermediate **5c** with *trans* stereochemistry. It is assumed that Pd displaces the carboxylate leaving group in **5a** by a S_N2 type inversion, as has been noted in earlier studies. Decarboxylation of benzoyl acetate results in enolate formation which could conceivably exist in either the Pd bound form **5e** or as the free enolate **5d**. Allylation of **5d** would be expected to occur with inversion of stereochemistry, as in the case of stabilized nucleophiles, to give product **5f** with net retention of stereochemistry. Allylation of **5e** would be expected to occur with retention of stereochemistry to give product **5g** with net inversion.

Scheme 1.7 *Stereochemistry of Allylation*



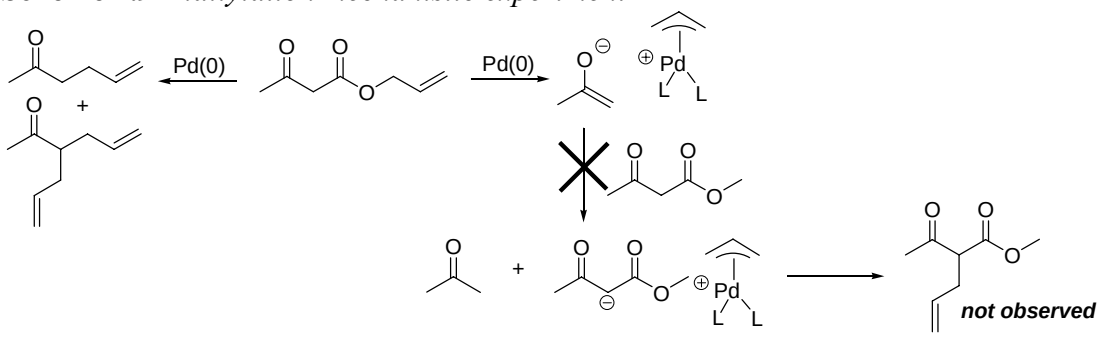
It was found that over the course of the experiment **5f** and **5g** were formed as a 68:32 mixture favoring **5f**, the product with net retention of configuration. This result suggests the formation of non-palladium bound enolates which are free to initiate a back-side attack on the Pd π-allyl. This is in agreement with the outcome of an experiment reported earlier in which complete crossover was observed between the enolate and allyl fragments of two different β-keto esters (Scheme 1.8), although it was noted that crossover was almost completely suppressed when benzene was utilized as the reaction solvent.[12] The moderate selectivity obtained, however, fails to discredit other possible mechanisms for nucleophillic attack. It is also mechanistically interesting, although not entirely understood, that the enolate formed *in situ* does not appear to be protonated by the abundance of benzoyl acetic acid in solution.

Scheme 1.8 *Crossover experiment*



Saegusa also reported that the reaction is not limited only to β-keto esters, but also is viable for β-cyano esters and alkynyl esters. In his report on the catalytic Carroll rearrangement, Tsuji expands the scope of substrates to include β-nitro esters.[16] Further mechanistic work was also reported concerning the isolation of products that had been allylated twice. In order to probe the possibility of diallylated products arising from an intermolecular proton transfer from unreacted β-keto ester to a Pd enolate, followed by allylation of the resulting β-keto ester anion and subsequent decarboxylative allylation, the reaction was run in the presence of methyl acetoacetate (Scheme 1.9).

Scheme 1.9 *Diallylation mechanistic experiment*

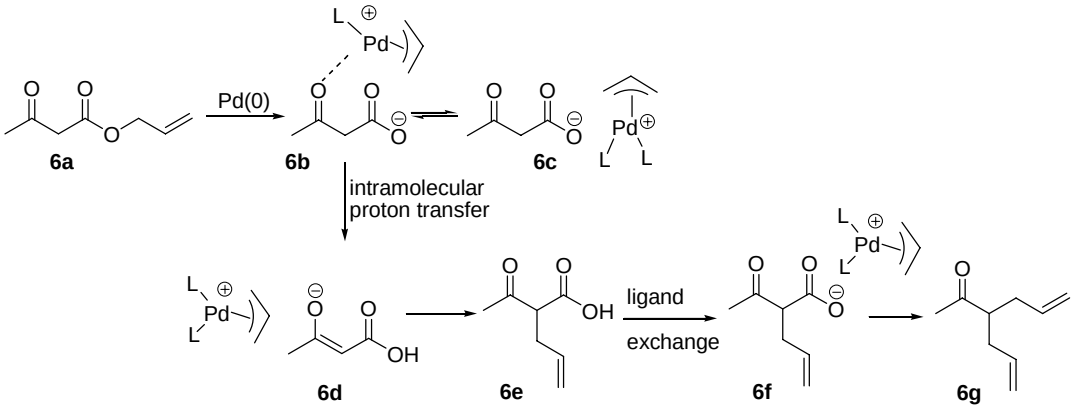


It was found that in the presence of methyl acetoacetate, allyl acetoacetate reacted to give allyl acetone, as well as diallylacetone, however allylated methyl acetoacetate was not observed. This seems to rule out the possibility of

intermolecular proton transfer as a viable route that leads to the formation of diallylated products, therefore an alternative pathway was postulated that involves intramolecular proton transfer.

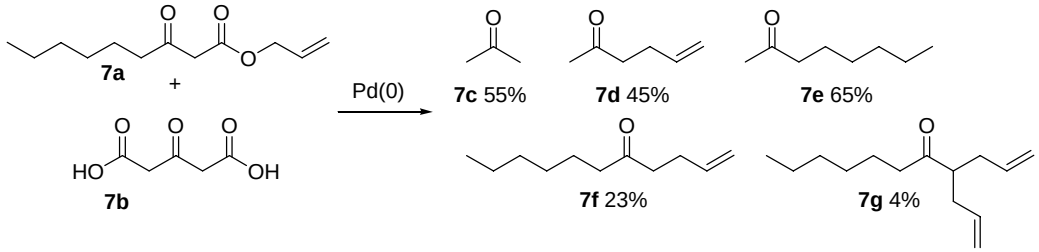
The proposed mechanism (Scheme 1.10) begins with the oxidative addition of allyl acetoacetate to Pd(0). However, rather than decarboxylation occurring, an intramolecular proton transfer occurs following activation of the carbonyl group by coordination to palladium. Intermediate enolate **6d** then undergoes allylation to produce **6e**. It is then proposed that ligand exchange from either intermediate **6d** or a Pd π-allyl non-stabilized enolate intermediate leads to **6f**. Decarboxylation, followed by allylation, forms diallylated products.

Scheme 1.10 *Proposed mechanism for diallylation*



In order to more closely examine the feasibility of acid **6e** undergoing ligand exchange followed by decarboxylation and allylation, the reaction of substrate **7a** was allowed to proceed with an equivalent of acetonedicarboxylic acid. It was found that allylated acid **7d** could be isolated in 45% yield. This lends support to the hypothesis that β-keto acids such as **6e** can re-enter the catalytic cycle and undergo further allylation.

Scheme 1.11 *Allylation in the presence of acetonedicarboxylic acid*



All of the studies which strove to provide a deeper understanding of the scope and mechanism of palladium-catalyzed allylic alkylation reactions have led these reactions to be embraced by synthetic chemists as valuable tools for the construction of new carbon-carbon bonds. The development of an asymmetric variant of the allylic alkylation reaction has significantly increased the utility of the transformation;[17] however, at the early stages of our research, there were very few reports on the enantioselective allylation of unstabilized ketone enolates (*vida supra*). As previously discussed, the reported methods relied on strong bases such as LDA for the generation of ketone enolates, limiting the scope of substrates to those that are not base-sensitive. Additionally, substrates are limited to those that circumvent regioselectivity problems arising from multiple acidic protons. Saegusa and Tsuji's development of the catalytic Carroll rearrangement had demonstrated the utility of palladium catalysts for the *in situ* generation of ketone enolates arising from the decarboxylation of β-keto esters. We sought to capitalize on this decarboxylative method of generating of ketone enolates in order to develop an enantioselective synthesis of γ,δ-unsaturated ketones that would proceed under much milder conditions. γ,δ-Unsaturated ketones are useful products due to the fact that they

contain both an electrophilic carbonyl and nucleophilic double bond that could conceivably participate in subsequent diastereoselective transformations.

1.2 Development of Methodology for the Decarboxylative Synthesis of γ,δ Unsaturated Ketones with the Enantioselective Formation of β Stereocenters

1.2.1Racemic Reactions

Our initial goal was to develop methodology for the enantioselective decarboxylative allylation of β-keto esters possessing the general structure shown in Scheme 1.12. We initially focused on the reaction of substrates containing symmetrically substituted allyl moieties in order to ensure the formation of a new chiral center β to the ketone. To begin, the ability of $Pd(PPh_3)_4$ to catalyze the racemic reaction was explored. It was found that the reaction cleanly, although somewhat slowly, coupled a variety of ketone enolates with cyclic and acyclic allyl fragments at room temperature in benzene (Table 1.1).[18]

Scheme 1.12 *Formation of β stereocenters*

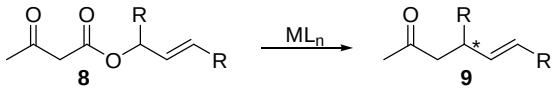
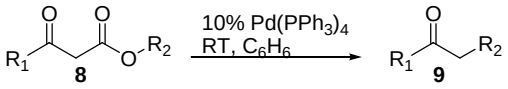
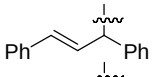
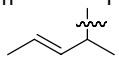
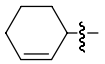
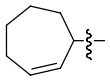
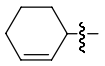
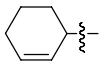
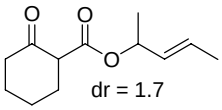


Table 1.1 *Decarboxylative allylation with $Pd(PPh_3)_4$*

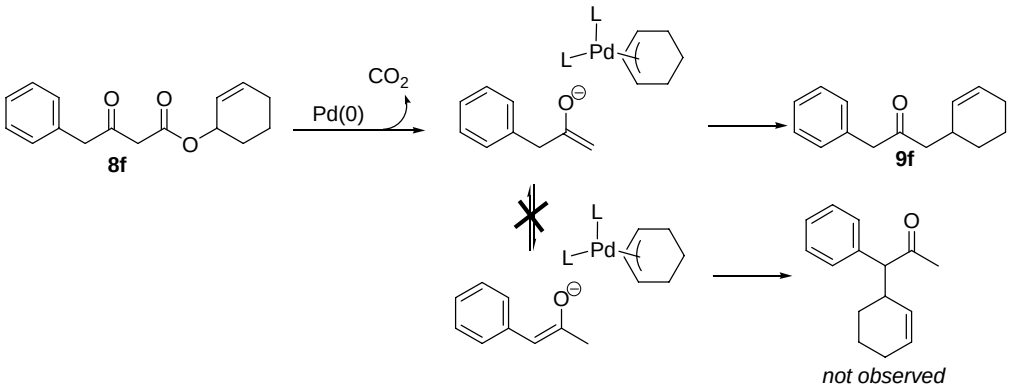


8 **9**

Substrate	R_1	R_2	Time (h)	% Yield
8a	CH_3		1	94
8b	CH_3		15	85
8c	CH_3		15	69
8d	CH_3		24	87
8e	CH_3		45	83
8f	$PhCH_2$		72	63
8g	Ph		16	66
8h	 dr = 1.7		48	69

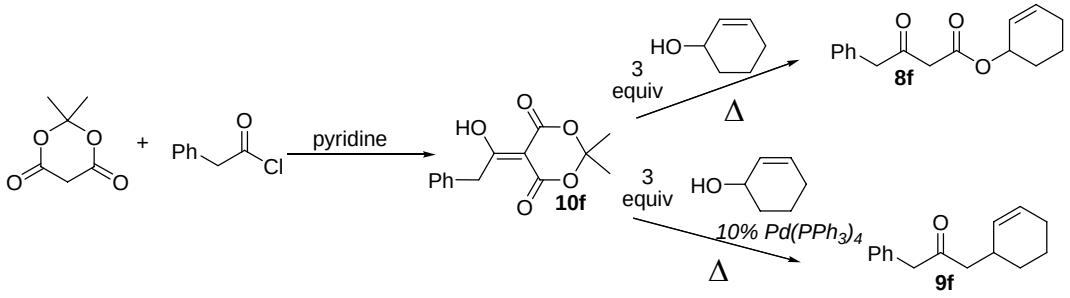
The successful isolation of **9f** illustrates an important characteristic of the decarboxylative allylation reaction; the enolates generated *in situ* are allylated regiospecifically at the carbon originally bearing the carboxylate group. No products arising from thermodynamic equilibration of the enolate followed by allylation of the benzylic carbon were isolated (Scheme 1.13). The enolate generated after decarboxylation would be difficult to generate and subsequently alkylate using conventional methods due to the large pK_a difference between the methyl and methylene protons of phenylacetone. This difference has been reported to be as high as 7.2 pK_a units.[19]

Scheme 1.13 *Allylation of the kinetic enolate*



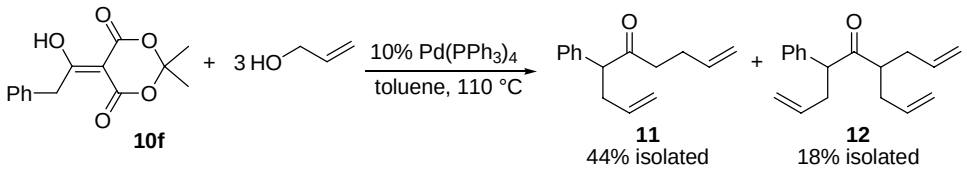
Our synthesis of β-keto esters such as **8f** in which R_1 is not a methyl group typically begins with the deprotonation of Meldrum's acid, followed by the slow addition of the necessary acid chloride to yield **10** (Scheme 1.14).[20] Intermediate **10f** affords β-keto ester when subjected to three equivalents of the desired allylic alcohol in refluxing toluene. Given the successful conversion of **8f** to **9f**, we attempted to develop a protocol in which the β-keto ester starting material is synthesized and undergoes decarboxylative allylation in one pot. We envisioned a more expedient route to the desired γ,δ unsaturated ketone products in which a catalytic amount of palladium, along with **10f** and allylic alcohol, would be allowed to react. This would presumably bypass the isolation of β-keto ester by converting it to the γ,δ unsaturated ketone product immediately upon formation of the ester due to the presence of palladium in the reaction mixture.

Scheme 1.14 *One pot synthesis of* ***9f***



In our initial experiment one equivalent of **10f** and three equivalents of allyl alcohol were refluxed in toluene with 10 mol% $Pd(PPh_3)_4$. The crude reaction mixture was subjected to flash column chromatography to afford products **11** and **12** in 44% and 18% yields, respectively (based on **10f**, Scheme 1.15). Examination of the reaction products indicates that diallylation, which was reported to lead to the formation of side products in the initial communication on the decarboxylative allylation reaction (see Scheme 1.10), is also problematic in this system. Additionally, it can be observed from both **11** and **12** that, unlike in the reaction of **8f**, allylation also occurs at the more acidic benzylic position. Both of these problems may be a consequence of the smaller, unsubstituted Pd π-allyl formed in the reaction. We have shown that diallylation is more prevalent with small, unsubstituted allyls.

Scheme 1.15

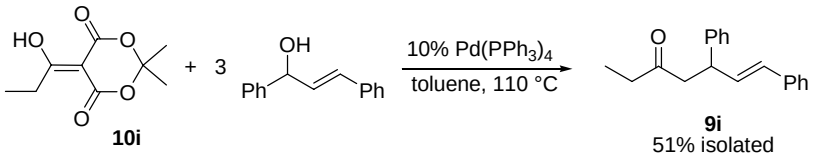


One way to address the problem of over-allylation in this system is by simply decreasing the amount of allyl alcohol present in the reaction mixture. To examine

this hypothesis the reaction was re-run in the presence of only 1.1 equivalents of allyl alcohol, rather than three. Unfortunately the ^{1}H NMR spectrum of the crude reaction mixture indicated that **11** was still the major product of the reaction.

In order to examine the conjecture that the small size of unsubstituted allyl alcohol was leading to over-allylation, the reaction was attempted with 1,3-diphenylprop-2-en-1-ol. In addition, the Meldrum's acid adduct derived from propionyl chloride (**10i**) was chosen to reduce the acidity of the methylene protons in an attempt to improve the regioselectivity of allylation. These adjustments led to some amount of success; the desired product, **9i**, was isolated in a 51% yield.

Scheme 1.16

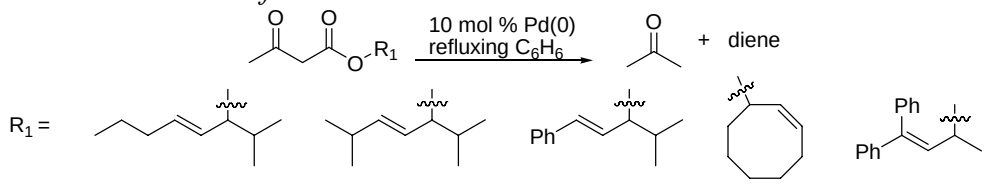


10i

9i
51% isolated

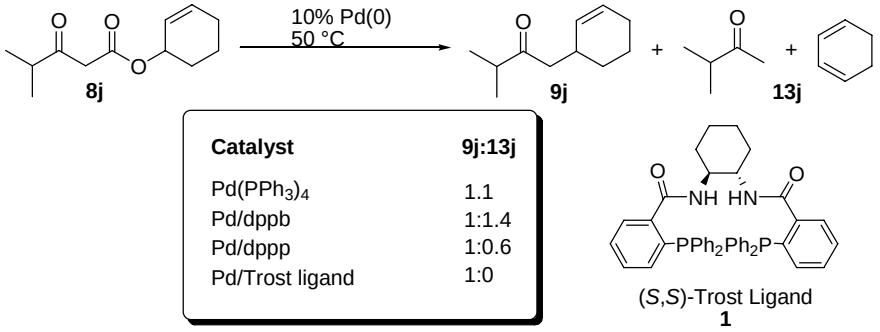
In an attempt to further expand the scope of the decarboxylative allylation reaction a variety of other allyl β-keto esters were synthesized (Scheme 1.17). Unfortunately, it became clear that increasing the steric bulk of the allylic substituents shut down the reaction at room temperature and led to a large amount of β-hydride elimination at elevated temperatures, resulting in the formation of acetone and conjugated diene. Tsuji had reported in one of the preliminary communications on the catalytic rearrangement of allylic esters of acetoacetic acid that running the reactions in the presence of sodium hydride and *tert*-butanol suppressed β-hydride elimination,[12b] however in the case of the cylooctene β-ketoester derivative no reaction occurred under similar reaction conditions.

Scheme 1.17 *Unsuccessful substrates*



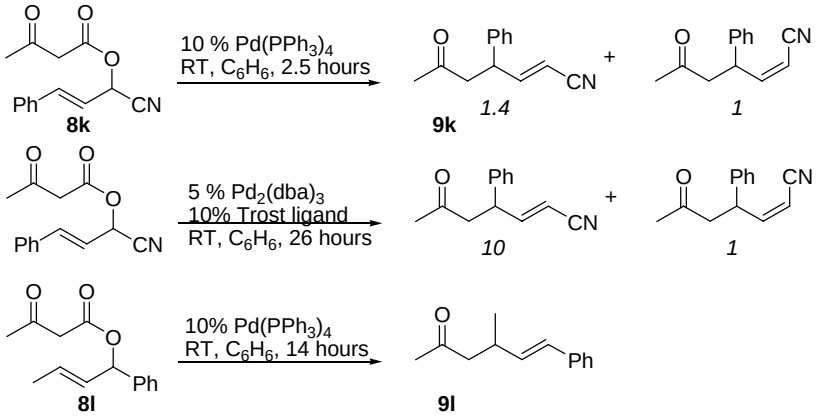
The nature of the catalyst was also found to influence the amount of β-hydride elimination that occurred during the reaction. As illustrated in Scheme 1.18, $Pd(PPh_3)_4$ results in a substantial increase in the amount of elimination when compared to reactions catalyzed by the combination of $Pd_2(dba)_3$ and Trost's ligand (**1**). Substrate **8j** yields a 1:1 mixture of cyclohexadiene and **9j** when subjected to $Pd(PPh_3)_4$ in refluxing benzene, whereas subjection of the substrate to $Pd_2(dba)_3$ and the Trost ligand yields allylation product exclusively. The increased amount of β-hydride elimination arising from catalytic systems utilizing $Pd(PPh_3)_4$ when compared to bidentate phosphine ligands such as the Trost ligand has been noted in other systems and is attributed to the more facile dissociation of triphenylphosphine from the Pd center. This results in an open coordination site that has been long thought to be needed in order for elimination to occur,[21] although some experimental evidence suggests that elimination to form cyclohexadiene from Pd π-allyls proceeds by external deprotonation.[22]

Scheme 1.18 *Formation of diene side products*



Despite the failure of the asymmetrically substituted β-keto esters in Scheme 1.17 to yield allylated products, we were able to probe the regioselectivity of enolate addition to unsymmetrically substituted Pd π-allyls to a limited extent. Ester **8k** underwent decarboxylative allylation to yield **9k** exclusively upon addition of either $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ and Trost's ligand, however Trost's ligand resulted in a higher *E:Z* ratio (10:1) (Scheme 1.19). The observed preference for the formation of α,β-unsaturated nitrile products has been reported for other palladium-catalyzed allylic alkylation reactions of 4-phenyl-3-butenenitrile derivatives.[23] Deardorff has attributed the high regioselectivity of the reaction to favorable orbital overlap of the alkene with the cyano π orbitals.[b] Regrettably, an enantioselective separation method for **9k** was not found, therefore the enantioselectivity of the reaction remains unknown.

Scheme 1.19 *Asymmetrically disubstituted allyl groups*



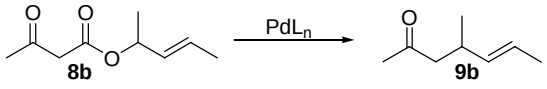
Substrate **8l** also participated in a very regioselective reaction to yield **9l**. In this case nucleophilic attack at the methyl-substituted terminus of the Pd π-allyl is attributed to the decreased steric hindrance at that position compared to the benzylic carbon, as well as to the energetically favored formation of the conjugated benzylidene species.

1.2.2 Enantioselective Reactions

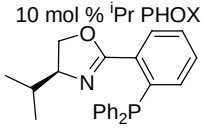
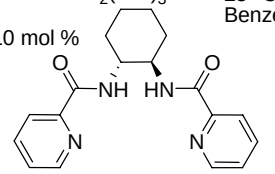
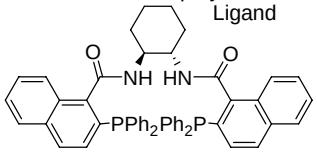
Having demonstrated that the decarboxylative allylation of symmetrically substituted allyl β-keto esters was viable with a Pd(0) catalyst, we turned our attention to the development of the asymmetric reaction. A brief screen of chiral ligands was conducted for the conversion of **8b** to **9b**. These experiments revealed that the combination of 10 mol% of (*S*,*S*)-Trost ligand (**1**)[24] with 5 mol% $Pd_2(dba)_3$ produced an active catalyst capable of yielding **(*R*)-9b** with a high enantiomeric ratio (er) (Table 1.2, entry 5). Increasing the ligand to palladium ratio to 1.5:1 led to a decrease in enantioselectivity (entry 7), which has been observed in other palladium-catalyzed allylic alkylation reactions and is attributed to the formation of Pd/ligand

oligomers.[25] Benzene was again chosen as the optimal solvent as polar solvents such as THF resulted in lower er's (entry 6). Initially reactions were run at room temperature overnight, but it was found that heating the reaction mixture to 75 °C shortened the reaction time to 30 minutes with only a minor decrease in enantioselectivity (entry 8).

Table 1.2 *Optimization of enantioselectivity*



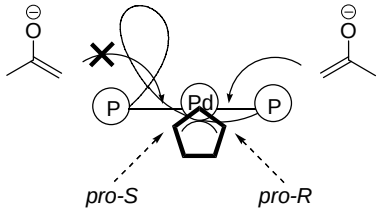
8b **9b**

Entry	Catalyst	Conditions	er
1	10 mol % $Pd(PPh_3)_4$ 10 mol % Trost Ligand	25 °C Benzene, 24 hr	57:43
2	10 mol % $Pd(PPh_3)_4$ 10 mol % ^{i}Pr PHOX 	25 °C Benzene, 15 hr	54:46
3	5 mol % $Pd_2(dba)_3$ 10 mol % 	25 °C Benzene, 36 hr	no reaction
4	10 mol % Pd_2dba_3 10 mol % Napthyl Trost Ligand 	85 °C Benzene, 6 hr	64:36
5	5 mol % $Pd_2(dba)_3$ 10 mol % Trost's Ligand	25 °C Benzene, 15 hr	93:7
6	5 mol % $Pd_2(dba)_3$ 10 mol % Trost's Ligand	25 °C THF, 26 hr	89:11
7	5 mol % $Pd_2(dba)_3$ 15 mol % Trost's Ligand	25 °C Benzene, 17 hr	89:11
8	5 mol % $Pd_2(dba)_3$ 10 mol % Trost's Ligand	75 °C Benzene, 0.5 hr	92:8

The ability of the Trost ligand (**1**) to catalyze the enantioselective allylation of nucleophiles with symmetrically substituted allyl moieties, which requires discrimination between two enantiotopic termini, has been well documented, and the origin of enantiotopic discrimination has recently been proposed.[26] NMR spectroscopy indicated that at low catalyst concentrations the palladium / Trost ligand catalyst exists as a 1:1 complex which, rather than existing in a planer 13-membered ring, forms a complex lacking C_2 symmetry. The complex has been figuratively

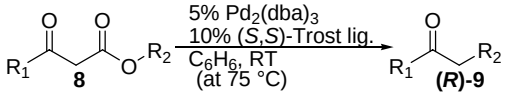
depicted as illustrated in Scheme 1.20. In this representation the model cyclopentyl allyl fragment is positioned in a way which directs the methylene substituents of the enantiotopic carbon atoms away from the bulkier portion of the ligand, represented by the lobe on the left-hand side of the scheme. Nucleophilic attack occurs preferentially at the allyl terminus that is less hindered by the coordination of the Trost ligand to palladium. We have obtained a crystal structure of the Trost ligand coordinated to Pd(II) through both phosphorus atoms and amide nitrogens from a sample prepared by exposing the crude reaction mixture from the decarboxylative allylation reaction to air. This structure can be found in the supporting information.

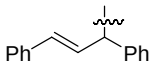
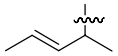
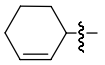
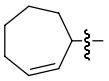
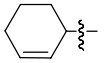
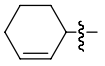
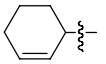
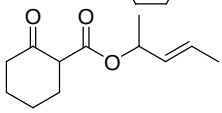
Scheme 1.20 *Source of enantiodiscrimination with the Trost ligand*



After establishing that the Trost ligand provided the highest levels of enantioselectivity when the reaction was run in benzene at room temperature, we were able to examine the scope of the enantioselective reaction (Table 1.3). While the reaction of methyl substituted **8b** proceeded with high levels of enantioselectivity, the analogous reaction of phenyl substituted substrate **8a** yielded **(*R*)-9a** with only a modest er (84:16). While this decrease in selectivity is not fully understood, it is an improvement on the reported 78:22 ratio of enantiomers obtained in the Pd/Trost ligand catalyzed allylic alkylation of dimethyl malonate with 1,3-diphenylallyl acetate.[27]

Table 1.3 *Substrate scope of the enantioselective reaction*



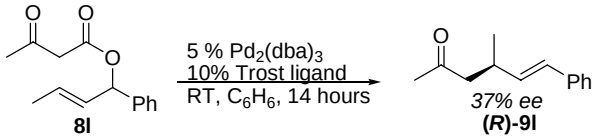
Substrate	R_1	R_2	Time (h)	% Yield	er
8a	CH_3		1	79	84:16
8b	CH_3		15 (0.5)	82	93:7 (92:8)
8c	CH_3		15	85	93:7
8m	Et		18 (@50 °C)	84 (@50 °C)	97:3
8d	CH_3		24 (0.5)	75	97:3 (95:5)
8e	CH_3		45 (0.5)	81	99:1 (99:1)
8f	$PhCH_2$		27	71	95:5
8g	Ph		18	69	96:4
8j	^{i}Pr		18 (@50 °C)	94	90:10
8h			187 (1)	81	77:23 (*S*) (73:27) dr = 1:1.5

Cycloalkene-derived substrates reacted to yield products with high levels of enantiopurity; it was observed that as the cycloalkene ring size increased the enantioselectivity of the reaction also increased. The reaction time also increased with ring size, however it was confirmed for substrates **8d** and **8e** that running the reactions at 75 °C leads to complete conversion to product in under one hour while maintaining high levels of enantioselectivity in the reaction. It was also found that increased reaction temperatures could be used to decrease the catalyst loading without decreasing the enantiomeric ratio; substrate **8c** reacted in 18 hours in refluxing

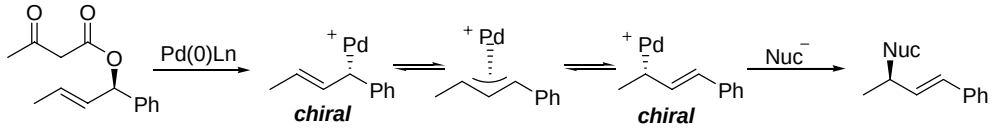
benzene to give a 71% yield of **9c** with a 94:6 er upon addition of only 0.2 mol% of $Pd_2(dba)_3$ and 0.4 mol% of Trost's ligand. This corresponds to a turnover number of greater than 175.

The unsymmetrically substituted β-keto ester **8l** also participated in the decarboxylative allylation reaction upon addition of Trost's ligand and $Pd_2(dba)_3$ (Scheme 1.21). It is interesting to note that **(*R*)-9l** was produced with a 37% ee when Trost's ligand was included in the reaction mixture. Similarly, the chiral, non-racemic, isopropyl PHOX (see Table 1.2) and (*R*)-BINAP ligands were also used in the transformation of **8l** to **9l,** resulting in enantiomeric excesses of 34% (*S)* and 37% (*R*), respectively. Any amount of stereoinduction in this system is unexpected since the asymmetrical Pd π-allyl is unable to racemize through a π-σ-π mechanism[28] due to the presumed stereospecific reaction pathway resulting from an assumed double inversion mechanism (Scheme 1.22).

Scheme 1.21



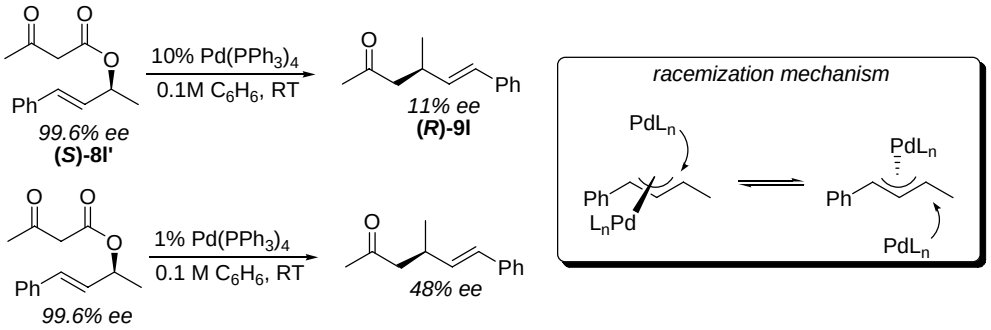
Scheme 1.22 *Predicted retention of configuration in the reaction of **8l***



This result seems to indicate that racemization of the intermediate Pd π-allyl is occurring to some extent during the catalytic cycle, allowing for the enantioselective reaction to occur. This possibility was probed *via* the synthesis of highly enantiopure

(*S*)-8l' (Scheme 1.23). Almost complete racemization of the Pd π-allyl was confirmed; the product was obtained with only an 11% ee after addition of 10 mol% $Pd(PPh_3)_4$. However, when the concentration of the catalyst was reduced by decreasing the catalyst loading to only 1 mol% while maintaining the substrate concentration at 0.1M, the stereospecificity of the reaction increased to yield **(*R*)-9l** with a 48% ee. The dependence of the stereospecificity of the reaction on the concentration of palladium in the reaction mixture is consistent with a racemization mechanism in which the Pd π-allyl undergoes displacement by a Pd(0) species in solution, inverting the stereogenic center.[29] This mechanism has been shown to lead to racemization in the allylation of stabilized nucleophiles with cyclic allylic acetates[30] and is most consistent with the experimental results.

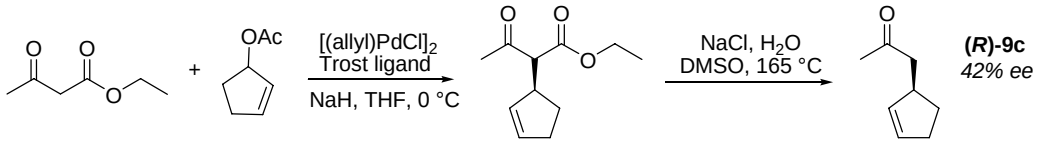
Scheme 1.23 *Stereospecific reactions*



The products isolated from the decarboxylative allylation of allyl β-keto esters can also be synthesized *via* the asymmetric allylic alkylation of stabilized acetoacetate nucleophiles, followed by hydrolysis and decarboxylation of the ester moiety. In order to directly compare the two methods we subjected 2-cyclopentenyl acetate to ethylacetoacetate in the presence of sodium hydride, palladium allyl

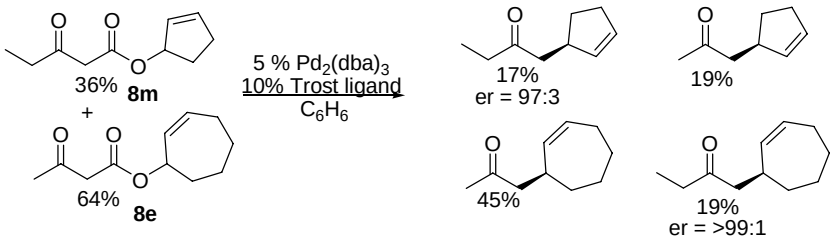
chloride, and the (*S*,*S*)-Trost ligand, as originally described by Trost (Scheme 1.24).[31] The ester was then hydrolyzed and decarboxylated in the presence of DMSO, water and sodium chloride to yield the same major enantiomer as that obtained from the decarboxylative allylation of **8c**, assigned to be the *R* enantiomer. Compound **(*R*)-9c** was produced with only a 42% ee using the method described by Trost, compared to the 86% ee of the product synthesized by our method.

Scheme 1.24



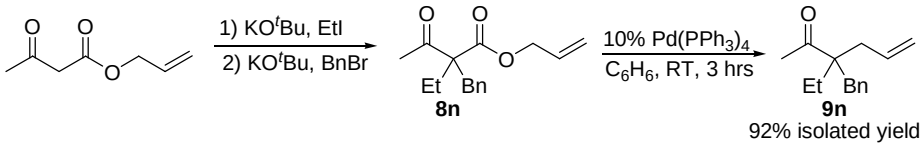
As discussed previously, it has been shown that stabilized nucleophiles such as ethylacetoacetate attack the allyl electrophile on the opposite face of palladium in a S_N2-type mechanism. The observation that the same major enantiomer is obtained from both the allylation of the stabilized ethylacetoacetate nucleophile and in our system implies that the nucleophiles generated *in situ* from β-keto esters also attack from the opposite face of palladium. The assertion that the enolate nucleophiles do not remain bound to palladium, which is contrary to what has been suggested for nonstabilized enolates, is consistent with a crossover experiment conducted (Scheme 1.25). As shown, a mixture of two different β-keto esters was subjected to the standard reaction conditions, yielding a mixture of products arising from nucleophilic attack of the acetone and butanone enolates on both cyclopenenyl and cycloheptenyl Pd π-allyls.

Scheme 1.25 *Crossover experiment*



To further demonstrate the utility of the decarboxylative allylation reaction compared to the traditional Tsuji-Trost allylation reaction substrate **8m** was prepared by successive alkylations of the acidic methylene position of allyl acetoacetate (Scheme 1.26). Treatment of **8n** with $Pd(PPh_3)_4$ for three hours at room temperature afforded **9n** in a 92% isolated yield. This experiment not only illustrates the ability of our reaction to synthesize products not accessible *via* the Tsuji-Trost reaction, but also validates the assertion that decarboxylation occurs prior to allylation, which is necessary in order to form the quaternary center in **9n**.

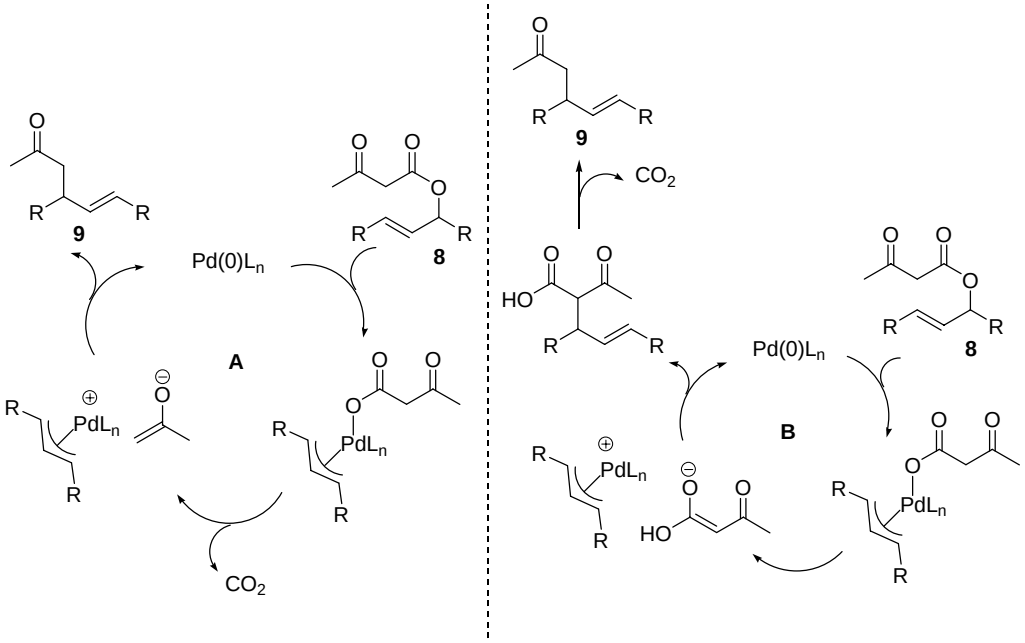
Scheme 1.26 *Formation of quaternary carbon centers*



Based on these experiments, the following mechanisms have been proposed for the catalytic transformation. Oxidative addition of **8** to Pd(0) yields the allyl Pd(II) carboxylate, which, upon loss of CO_2, affords an unstabilized ketone enolate (cycle **A**). We have shown that allylation occurs to yield the same enantiomer of product as obtained in the allylation of stabilized enolates (Scheme 1.24), implying

that allylation of the enolate generated *in situ* occurs from the opposite face of palladium to yield **9**. Alternatively, we have not conclusively ruled out the possibility that, for substrates possessing an acidic α-proton, an intramolecular proton transfer occurs in the Pd(II) carboxylate complex (cycle **B**), as proposed for the mechanism leading to diallylated products in the decarboxylative allylation reaction (Scheme 1.10) and supported by subsequent mechanistic studies (*vida supra*). Allylation of this intermediate would yield a β-keto carboxylate, which, upon Pd(II) assisted loss of CO_2, affords **9**.

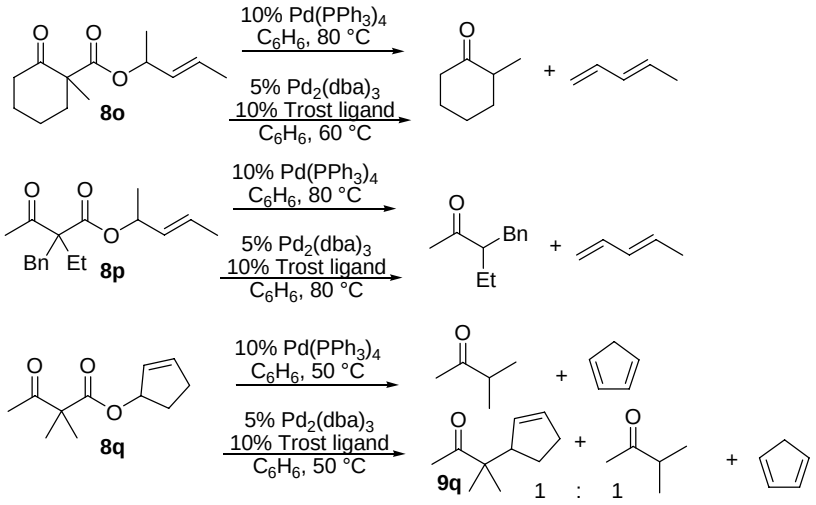
Scheme 1.27 *Proposed catalytic cycles*



The successful conversion of **8n** to **9n** prompted a closer examination of the effect of α substituents on the course and enantioselectivity of the decarboxylative allylation reaction. Unfortunately, it became clear that our racemic and enantioselective systems fail to catalyze the formation of quaternary centers when substituted Pd π-allyls are involved in the reaction (Scheme 1.28). For instance,

reaction of **8o-q** resulted almost exclusively in products arising from β-hydride elimination when both $Pd(PPh_3)_4$ and the Pd/Trost ligand catalyst systems were employed.

Scheme 1.28 *β-Hydride elimination products*



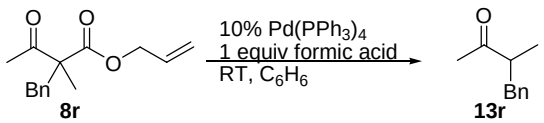
1.3 Research on Enantioselective Protonation

Despite the failure of substrates **8o-q** to undergo the decarboxylative allylation reaction, the synthesis of substrates **8n-q** illustrated one nice feature of our β-keto ester starting materials; they are extremely easy to functionalize at the acidic methylene carbon. We initially sought to capitalize on the ease with which derivatives could be made by attempting to develop an enantioselective protonation reaction that could be used to convert β-keto esters into α chiral ketones. Prior to our work Shimizu had developed methodology for the decarboxylative protonation of α-fluoro-β-keto allyl esters to yield racemic α-fluoroketones.[32] Chiral α-fluoroketones have also been synthesized from α-fluoro-β-keto benzyl esters using a cascade

reaction that commences with deprotection of the benzyl ester with palladium on carbon.[33]

Substrate **8r** was synthesized as the model substrate for the protonation studies. Formic acid and dimethylmalonate were tested as proton sources. The addition of formic acid successfully shut down the allylation reaction and resulted in almost exclusive protonation. The addition of dimethylmalonate had no effect on the reaction; allylated ketone was formed exclusively.

Scheme 1.29 *Decarboxylative protonation*



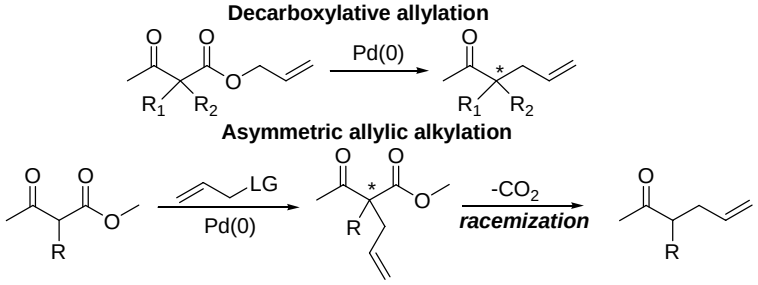
The enantioselective protonation of **8r** to yield **13r** was attempted in the presence of 5 mol% $Pd_2(dba)_3$ and 10 mol% of the Trost ligand. Unfortunately racemic **13r** was isolated from reaction mixture. Similar results were obtained when the napthyl Trost ligand was used. The isopropyl PHOX ligand was also tested but the Pd/PHOX complex failed to catalyze the reaction of **8r**. Next, enantioenriched **8r** was synthesized with a 78% ee in an attempt to probe the stereospecificity of the reaction. Addition of 10 mol% $Pd(PPh_3)_4$ in the presence of formic acid yielded racemic **13r**. It is noteworthy that when this reaction was run in the absence of formic acid allylated product was recovered with an 18% ee. While we were unable to obtain any synthetically useful results, some time later the Stoltz group disclosed an enantioselective, decarboxylative protonation of allylic β-keto esters which utilized formic acid in the presence of $Pd_2(dba)_3$ and the *tert*-butyl PHOX ligand. Notably,

they found that the complete absence of water was necessary for the reaction to proceed selectively. The ee's were found to increase greatly upon the addition of molecular sieves.[34]

1.4 Development of Methodology for the Decarboxylative Synthesis of γ,δ Unsaturated Ketones with the Enantioselective Formation of α Stereocenters

Given our success in the development of methodology for the enantioselective construction of β stereocenters *via* a decarboxylative allylation strategy and the ease with which α substituents can be incorporated into β-keto esters, we turned our attention to the development of a complimentary method for the enantioselective construction of γ,δ unsaturated ketones with α stereocenters. We recognized that successful completion of this project would be a significant contribution to the development of palladium-catalyzed allylic alkylation reactions. Non-racemic products with an α-stereocenter cannot be made using the traditional asymmetric allylic alkylation methodology due to the inevitable racemization of the chiral center during decarboxylation (Scheme 1.30).

Scheme 1.30

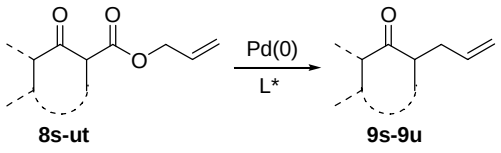


To begin, the linear substrate **8n** (R_1 = Et, R_2 = Bn) was subjected to a catalytic amount of $Pd_2(dba)_3$ and a variety of chiral ligands. Surprisingly, multiple attempts at converting **8n** to **9n** using our standard Trost ligand reaction conditions

failed to catalyze the reaction past 20% conversion, at which time palladium black would precipitate out of solution. Substituting BINAP, ^{i}Pr PHOX, and the napthyl Trost ligand for the Trost ligand led to product formation, but **9n** was only produced with a 2%, 10%, and 0% ee, respectively.

Encouraged by results reported by Stoltz[35a] and Trost[b] on the enantioselective decarboxylative allylation of cyclic allylic enol carbonates we shifted our focus to the enantioselective allylation of cyclic enolates and began to screen a variety of chiral ligands in the transformation of **8s-u** to **9s-u**.

Table 1.4 *Survey of chiral ligands*



8s-ut **9s-9u**

Entry	Substrate	Conditions	er
1	**8s**	2.5% Pd_2dba_3 6% ^{i}Pr PHOX 50 °C, C_6H_6	88:12
2	**8s**	2.5% Pd_2dba_3 5.5% ^{t}Bu PHOX 40 °C, C_6H_6	87:13
3	**8s**	2.5% Pd_2dba_3 5.5% **1'** RT, C_6H_6	53:47
4	**8s**	2.5% Pd_2dba_3 5.5% QUINAP RT, C_6H_6	66:34
5	**8s**	5% Pd_2dba_3 10% Trost Lig. RT, C_6H_6	50:50
6	**8t**	2.5% Pd_2dba_3 5.5% ^{t}Bu PHOX 40 °C, C_6H_6	57:43
7	**8u**	2.5% Pd_2dba_3 5.5% ^{t}Bu PHOX RT, C_6H_6	56:44

1'

The outcome of these reactions revealed conflicting results. As was expected based on the Stoltz report, the PHOX based ligands provided the highest selectivities

in the conversion of **8s** to **9s** (entries 1 & 2). The complete lack of selectivity obtained from the Trost ligand and its bicylic derivative **1'** was unexpected as the communication from Trost reported the synthesis of **9s** with a 78% ee from the corresponding allylic enol carbonate upon the addition of 5.5 mol% of **1'** and 2.5 mol% $Pd_2(dba)_3$. The origin of this discrepancy is not known for certain, but it may reflect a change in reaction mechanism between enol carbonates and β-keto esters. Equally as surprising was the diminished selectivity obtained for the tetralone and indanone derivatives **8t** and **8u** when subjected to the ^{t}Bu PHOX ligand and Pd(0).

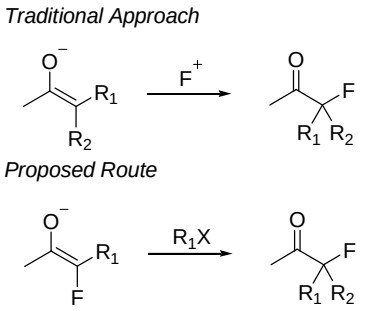
1.4.1 The Enantioselective Synthesis of α-Fluoro Ketones

Faced with these conflicting results, we decided to shift our focus to a different substrate class and examine the enantioselective decarboxylative allylation of α-fluoro substituted β-keto esters as a method of synthesizing enantioenriched α-fluoro ketones. The incorporation of fluorine into organic compounds has generated a significant amount of interest due to the application of these materials in pharmaceuticals, material science, and in agricultural chemistry.[36] The development of electrophilic fluorinating agents such as Selectfluor has revolutionized methods for the addition of fluorine to organic compounds by providing a safe and convenient alternative to toxic molecular fluorine.[37] This in turn has spurned more interest in enantioselective fluorination reactions.[38] The most promising results have arisen from studies on the enantioselective fluorination of enolizable β-keto compounds; chiral, non-racemic zinc,[39a] nickel,[b] copper,[c] and palladium[d] catalysts have been successfully developed.

In contrast, enantioselective methods for the synthesis of α-fluoro ketones were far less developed when we began our studies. Preliminary systems relied on the stoichiometric addition of *N*-fluorosultams[40] or cinchona alkaloids[41] to preformed silyl enol ethers or to the desired ketone along with a strong base such as LDA or butyllithium and produced only modest enantioenrichments in the products. Most recently, catalytic amounts of proline derivatives have been used in the presence of Selectfluor to fluorinate aldehydes and ketones, however, only moderate enantioselectivities were obtained; α-fluorocyclohexanone was produced with only a 36% ee.[42]

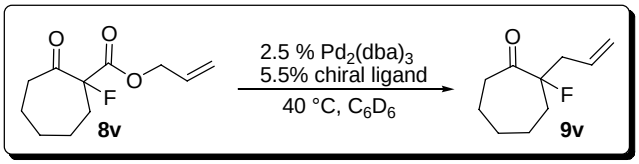
It is important to note that our approach for enantioselectively forming a fluorinated chiral center is fundamentally different from those previously described in the literature. Rather than the enantioselective addition of fluorine to a ketone enolate, we strove to accomplish the enantioselective addition of an alkyl group to a fluorinated enolate (Scheme 1.31). When we began this project we knew of no reported enantioselective methods based on this strategy, although the racemic synthesis of allylated α-fluoroketones from β-keto esters had been reported over ten years prior to our work.[b]

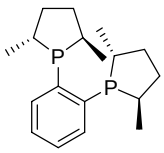
Scheme 1.31 *Strategies for the enantioselective synthesis of α-fluoro ketones*



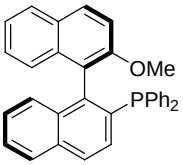
Substrate **8v** was conveniently synthesized upon the addition of Selectfluor to the unfluorinated allyl β-keto ester and was subjected to an array of chiral ligands in the presence of $Pd_2(dba)_3$ at 40 °C in benzene. As illustrated in Table 1.5, diamine ligands such as diaminoBINAP and TsDPEN led to the formation of an inactive catalyst for the decarboxylation reaction. Surprisingly, the Trost ligand, which formed an active catalyst for the reaction of non-fluorinated substrates, also failed to catalyze the reaction. The other diphosphine ligands also gave disappointing results as they failed to induce high levels of enantioselectivity in the reaction.

Table 1.5 *Survey of chiral ligands*

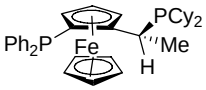




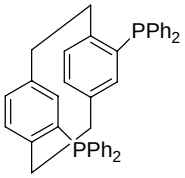
(*R*,*R*)-MeDuPhos
13% ee (*S*)



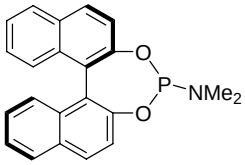
(*R*)-MOP
30% ee (*S*)



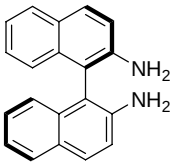
(*R*,*S*)-JosiPhos
2% ee (*S*)



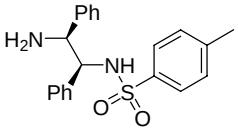
(*S*)-PhanePhos
8% ee (*R*)



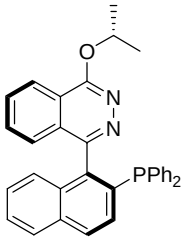
(*R*)-MonoPhos
7% ee (*S*)



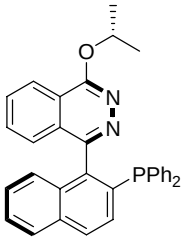
(*R*)-DiaminoBINAP
no reaction



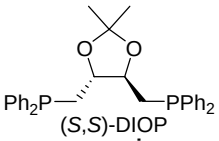
(*S*,*S*)-TsDPEN
no reaction



(*R*,*M*)-PINAP
38% ee (*S*)



(*R*,*P*)-PINAP
11% ee (*R*)



(*S*,*S*)-DIOP
racemic

(*S*)-QUINAP
85.5% ee (*S*)

(*R*,*R*)-Pyridyl Trost
no reaction

(*S*,*S*)-Trost
no reaction

(*R*)-^{i}Pr PHOX
76% ee (*S*)

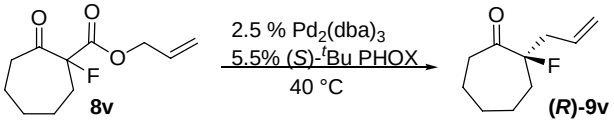
(*S*)-^{t}Bu PHOX
88% ee (*R*)

In contrast, the addition of P,N ligands such as QUINAP and the PHOX ligands led to the synthesis of **9v** with very good enantiopurity. The ^{t}Bu PHOX ligand yielded **9v** with the highest ee (88%) and was used in all subsequent studies. It was noted, however, that QUINAP also performed well in the reaction and often produced results that were equal to or sometimes slightly better than that of the ^{t}Bu

PHOX ligand. For instance, the cyclohexanone derivative of **8v**, **8w**, was synthesized and subjected to catalysis with the ^{i}Pr PHOX, ^{t}Bu PHOX, and Ph PHOX ligands, as well as with QUINAP. When the reaction was run with the Ph PHOX ligand **9w** was produced with only a 25% ee. The other ligands afforded **9w** with higher enantiopurity; the addition of ^{i}Pr PHOX yielded product with a 73% ee, while the addition of ^{t}Bu PHOX yielded product with an 83% ee, and QUINAP yielded product with an 84% ee.

A variety of solvents were screened in the Pd(0)/^{t}Bu PHOX catalyzed conversion of **8v** to **(*R*)-9v** in hopes of improving the enantioselectivity of the reaction (Table 1.6). These experiments revealed that strongly coordinating solvents such as DMF and acetonitrile inhibit the reaction, as do polar protic solvents such as *tert*-butanol. Unlike the enantioselective decarboxylative allylation reaction with the Trost ligand, changing the solvent to THF does not lead to any significant decreases in enantioselectivity. Ethereal solvents such as MTBE (methyl *tert*-butyl ether) also do not alter the selectivity of the reaction. The halogenated aromatic solvent chlorobenzene results in only a slightly lower enantiomeric excess. This is in contrast to methylene chloride, which was shown to lower the ee of **9w** from 84% to 29% when QUINAP was used as the chiral ligand.

Table 1.6 *Survey of solvents*



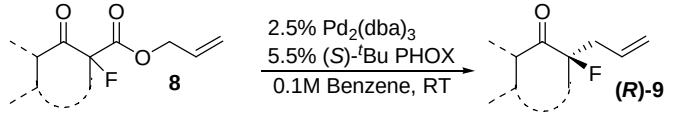
Solvent	%ee	Solvent	%ee
Benzene	88%	THF	88%
MTBE	89%	DMF	no reaction
ClPh	82%	Toluene	89%
Acetonitrile	no reaction	^{t}BuOH	no reaction

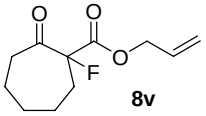
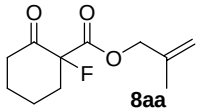
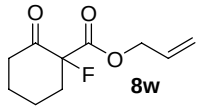
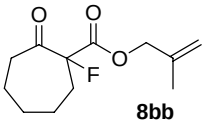
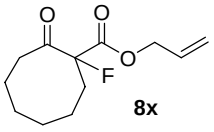
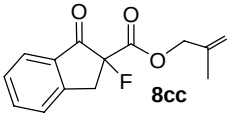
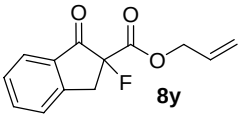
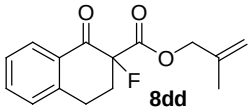
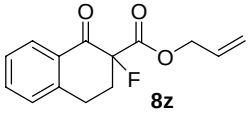
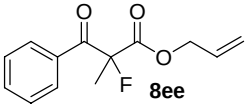
Further optimization studies on the ^{t}Bu PHOX/$Pd_2(dba)_3$ catalytic system revealed that the concentration of the reaction had a very minor impact on the enantioselectivity; when reactions were run in 0.02 M benzene **(*R*)-9v** was obtained in an 85% ee. This is compared to the 88% ee obtained in 0.1 M benzene. Also, in contrast to the enantioselective reaction with Trost's ligand, increasing the ligand to palladium ratio from 1:1 to 2:1 did not alter the enantioselectivity of the reaction. Increasing the reaction temperature from 40 °C to 70 °C decreased the ee of **(*R*)-9v** from 88% to 84%.

With these results in hand, the scope of the reaction was explored using a variety of cyclic ketone substrates and the ^{t}Bu PHOX ligand in benzene. The results are included in Table 1.7. The Pd-catalyzed addition of allyl or methallyl groups to a variety of fluorinated, cyclic enolates occurred smoothly and selectively to give very good yields of products with high enantiomeric ratios. The exception to this is **(*R*)-9bb**, which was produced with a lower enantiomeric ratio than was expected. Typically substitution of a methallyl group for the allyl group afforded products with a higher enantiomeric ratio (see **8w** and **8aa**, **8y** and **8cc,** and **8z** and **8dd**). Unfortunately, the reaction of the cyclopentanone analog of **8v** failed to proceed past

50% conversion and produced a 1:1 mixture of allylated 2-fluorocyclopentanone and protonated 2-fluorocyclopentanone. It was found that the acyclic substrate **8ee** reacted cleanly, although less selectively, to form **(*R*)-9ee**.

Table 1.7 *Scope of enantioselective reaction*



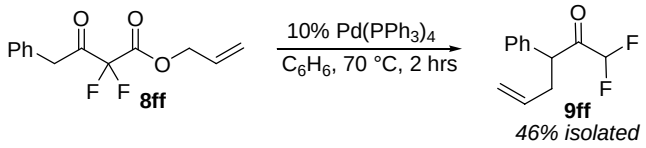
Substrate	Time(hr)	%Yield	er	Substrate	Time(hr)	%Yield	er
 **8v**	12[a]	91	94:6	 **8aa**	12[a]	85[b]	93:7
 **8w**	14	73	91.5:8.5	 **8bb**	12[a]	64	73:27
 **8x**	1[a]	94	90.5:9.5	 **8cc**	5	81	94:6
 **8y**	3	94	92.5:7.5	 **8dd**	5[a]	94	96.5:3.5
 **8z**	3[a]	96	92:8	 **8ee**	1[a]	74	66.5:33.5

[a] Reactions run at 40 °C. [b] Product isolated with 87% purity.

It is also worth noting that, as was the case for reactions studied in the decarboxylative allylation with Pd(0) and the Trost ligand, the allylation of fluorinated β-keto esters also proceeds regioselectively at the carbon once bearing the carboxylate group when both $Pd(PPh_3)_4$ and $Pd_2(dba)_3$/^{t}Bu PHOX were used as catalysts. An interesting exception to this was noted in the decarboxylative allylation of **8ff** (Scheme 1.32). This difluorinated substrate undergoes allylation at the

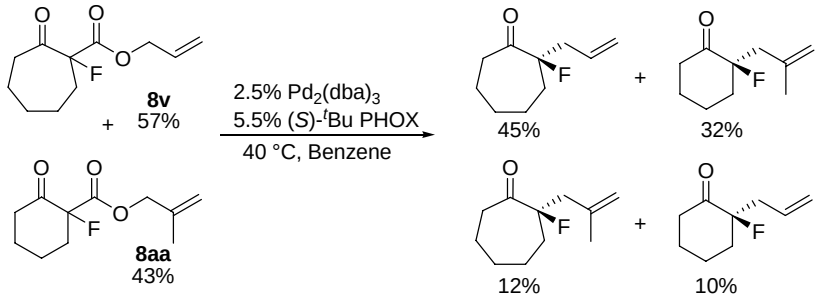
benzylic carbon. Unfortunately the monofluorinated analog of **8ff** was not available for comparison.

Scheme 1.32 *Reversal of regiochemistry of allylation*



A crossover experiment was employed in order to further probe the nature of the fluorinated enolate. The results highlight yet another difference between our Trost ligand-based catalytic system and that of the fluorinated enolates with the PHOX ligand. As illustrated in Scheme 1.33, only partial crossover was observed when **8v** and **8aa** were allowed to react in the same flask. This seems to indicate tighter coordination between the fluorinated enolate and the palladium(II) allyl intermediate.

Scheme 1.33 *Crossover experiment*

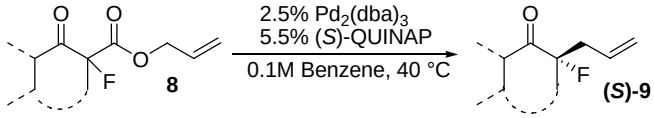


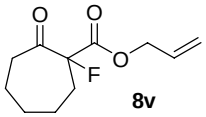
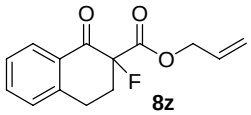
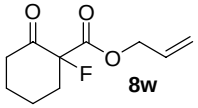
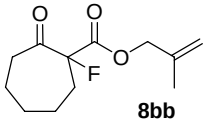
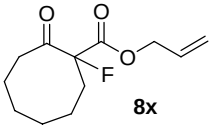
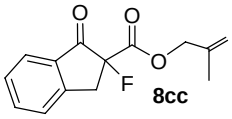
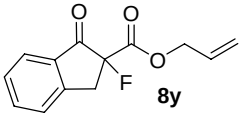
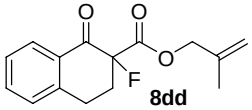
A few days prior to the submission of this data for publication the Nakamura group published their research on the enantioselective decarboxylative allylation of fluorinated β-keto esters with a Pd(0)/^{t}Bu PHOX catalyst system.[43] We were then

forced to turn our attention to the Pd(0)/QUINAP catalytic system and assess how it compared to the PHOX ligand.[44]

As shown in Table 1.8, replacing the (*S*)-^{t}Bu PHOX ligand with (*S*)-QUINAP gave mixed results that were complicated by discrepancies in the experimentally determined enantiomeric ratio which seemed to depend on the source of the product (i.e. from a 10 mg NMR experiment or a 100 mg benchtop experiment). By comparing the results in Tables 1.7 and 1.8 it can be seen that for substrates **8v**, **8y-z**, and **8cc-dd** the ^{t}Bu PHOX ligand outperforms QUINAP. In contrast, the moderate enantiomeric ratio obtained for **8bb** in the presence of the ^{t}Bu PHOX ligand is greatly improved when QUINAP is used. Substrates **8w-x** were isolated with higher er's when the ^{t}Bu PHOX ligand was used, but QUINAP performed better when comparing the results of samples obtained from NMR experiments.

Table 1.8 *Scope of the enantioselective reaction with the QUINAP ligand*



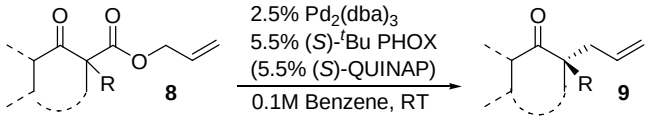
Substrate	Time(hr)	%Yield	isolated er (NMR expt)	Substrate	Time(hr)	%Yield	isolated er
 **8v**	8	92	82:12 (93:7[a])	 **8z**	3	83	89:11
 **8w**	3.5	84	84:16 (92:8[a])	 **8bb**	12	82[a]	94:6[a]
 **8x**	8	83	88:12 (92.5:7.5[a])	 **8cc**	5	87	88:12
 **8y**	5	97	86:14 (89.5:10.5[a])	 **8dd**	6	58	94:6

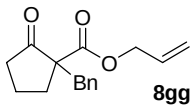
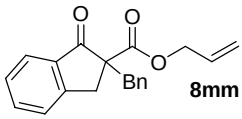
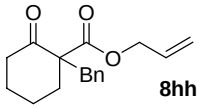
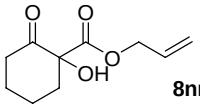
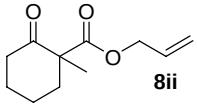
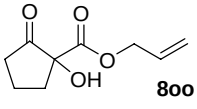
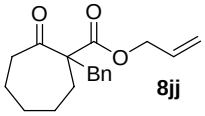
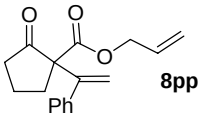
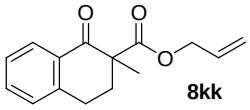
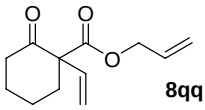
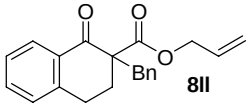
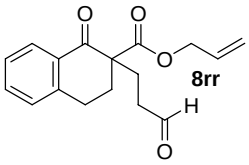
[a] Experiments performed by author. All other results obtained by Briana Barron.

1.4.2 The Effect of Other α Substituents

The successful development of methodology for the enantioselective synthesis of α-fluoro stereocenters prompted us to examine the effect of substituents other than fluorine on the enantioselective reaction. The scope of substrates examined can be found in Table 1.9.

Table 1.9 *Enantioselective formation of non-fluorinated α stereocenters*



Substrate	Time (h)	%Yield	er	Substrate	Time (h)	%Yield	er
 **8gg**	4	79	81:19	 **8mm**	1	---	82:18 (76:24)
 **8hh**	2	95	89.5:10.5	 **8nn**	5	---	76:24 (65:35)
 **8ii**	12[a]	80	89:11	 **8oo**	2[b]	---	56:44
 **8jj**	3	91	93:7 (86:14)	 **8pp**	20	---	67:33 (50:50)
 **8kk**	12[a]	87	92.5:7.5	 **8qq**	1	---	58:42
 **8ll**	12[a]	98	93:7	 **8rr**	6[a]	---	52:48

[a] Reactions run at 40 °C. [b] Reaction run at 90 °C.

Several conclusions can be drawn from this study. First, in reactions where both QUINAP and the ^{t}Bu PHOX ligand were screened, the ^{t}Bu PHOX ligand provides superior results. In addition, it can be seen that β-keto esters substituted with methyl or benzyl groups reacted with the highest levels of selectivity. The one exception to this is substrate **8mm** which yielded **(*S*)-9mm** with a disappointing 64% ee. Somewhat surprisingly, hydroxy substituted **8nn** and **8oo** were viable substrates

for the reaction. Although the products were produced with moderate to low enantiomeric ratios, to the best of our knowledge this is the first example of a decarboxylative allylation reaction occurring with this class of substrate. We attempted to improve the enantiomeric ratio of **9nn** by switching to both the Trost ligand and the Trost ligand derivative **1'** (see Table 1.4), however the reaction was still not very enantioselective; the Trost ligand based catalytic system yielded **9nn** in only a 27% ee and **1'** in a 47% ee. Substrates **8pp-rr** also demonstrate the wide variety of substituents that can be introduced without shutting down the reaction, although the products were formed with low enantiomeric ratios.

At the conclusion of these studies it was clear that the palladium-catalyzed decarboxylative generation of ketone enolates is a valuable synthetic tool whose full potential had not been recognized when we began our research in the area. The field is continuing to receive more attention as publications detailing its synthetic usefulness, as well as those focused on new reaction development based on decarboxylative strategies, become more prevalent.[45] The unique way that Pd-catalyzed decarboxylations can generate unstabilized enolate nucleophiles under very mild reaction conditions ensures that this methodology will continue to be of interest in our research group, as well as in many others.

1.5 Supporting Information

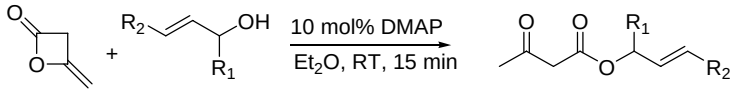
Materials

Benzene was dried over sodium metal and distilled under vacuum. THF, toluene, methylene chloride and diethyl ether were dried over activated alumina on a

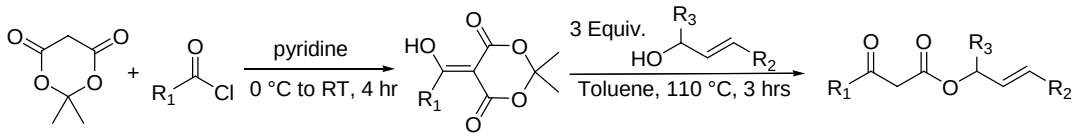
solvent system purchased from Innovative Technology, Inc. Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Products were purified on silica gel from Sorbent Technologies (40-63 μm particle size, 60 Å porosity, pH 6.5-7.5). The *tert*-butyl PHOX[46] and PINAP[47] ligands were synthesized according to published procedures. The bicyclic Trost ligand derivative **1'** was synthesized according to a procedure obtained through personal communication.[48] All other chiral ligands and palladium compounds were obtained from Strem. NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on ^{1}H, ^{13}C, DEPT-135, COSY, and HMQC spectroscopies. ^{19}F NMR spectra shift assignments were referenced to trifluoroacetic acid (δ -76.55). High resolution mass spectrometry of non-fluorinated compounds was performed on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). High resolution mass spectrometry of fluorinated compounds was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument. Gas chromatography was performed with a Shimadzu GC-17A instrument with an attached AOC-20i auto injector.

Preparation of Starting Materials

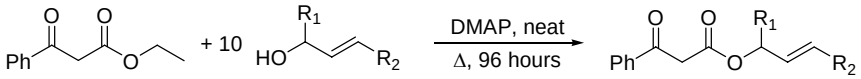
β-Keto esters **8** in which R_1 = CH_3 were synthesized by the DMAP-catalyzed addition of the appropriate allylic alcohol to diketene and purified by flash column chromatography (SiO_2, 5-10% ethyl acetate in hexane).[49]



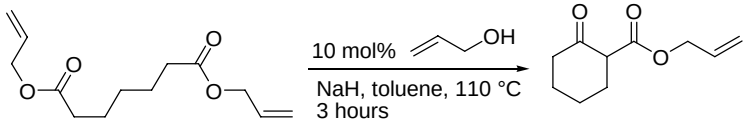
Many allylic alcohols are commercially available, although 2-cyclohexene-1-ol, 2-cyclopentene-2-ol, and 2-cycloheptene-1-ol were prepared by reduction of the corresponding α,β-unsaturated ketone with LAH.[50] 2-Hydroxy-4-phenylbut-3-ene-nitrile was synthesized by the addition of trimethylsilyl cyanide to cinnamyl aldehyde.[51] Other disubstituted allylic alcohols were prepared by the addition of Grignard reagents to β-substituted α,β-unsaturated aldehydes.[52] Compound **(S)-8l'** (99.6% ee) was prepared from the corresponding allylic alcohol that had been enzymatically resolved by lipase AK Amano 20.[53] β-Keto esters **8** in which R_1 = Bn, ^{i}Pr, or Et were synthesized by the addition of the appropriate allylic alcohol to the desired Meldrum's acid adduct,[54] prepared by the addition of either phenylacetyl chloride, isobutyryl chloride, or propionyl chloride to Meldrum's acid in the presence of pyridine.[55]



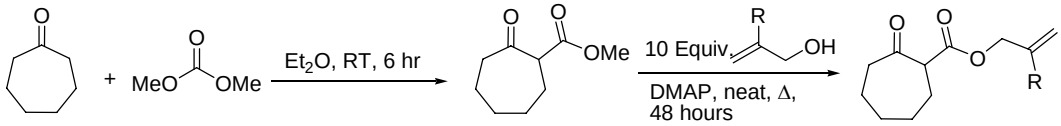
This method failed when R_1 = Ph; in this case it was necessary to reflux ethyl benzoylacetate in 10 equivalents of allylic alcohol along with 1 equivalent of DMAP for 96 hours.[56]



2-Allyloxycarbonylcylohexanone (**8s**) and 2-allyloxycarbonylcyclopentanone were synthesized *via* a Dieckmann condensation of diallyl pimelate or diallyl adipate.[57] The diesters were prepared by a Fischer esterification of pimelic or adipic acid with allyl alcohol.[58]

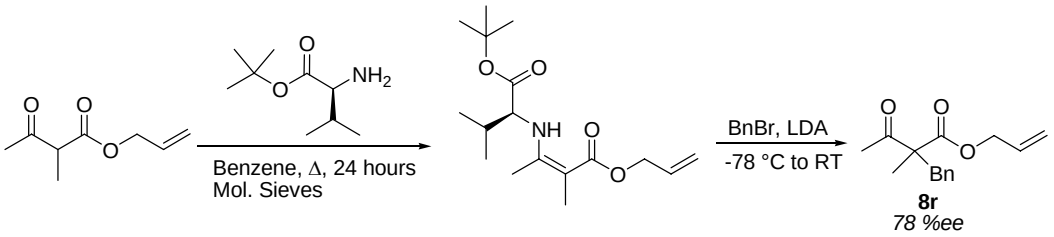


It was necessary to prepare the methallyl analogs of these compounds by first preparing the methyl ester *via* a Dieckmann condensation of dimethyl pimelate or adipate. This was followed by transesterification of the methyl ester with methallyl alcohol. Cycloheptanone and cyclooctanone derivatives were prepared by condensation of the cyclic ketone with dimethylcarbonate,[59] followed by transesterification of the methyl ester with the desired allylic alcohol.



Installation of α- methyl, ethyl, or benzyl groups was accomplished by deprotonation of the β-keto ester with potassium *tert*-butoxide, followed by addition of methyl iodide, ethyl iodide, or benzyl bromide.[60] The enantioselective α-benzylation to yield enantioenriched **8r** was accomplished by the addition of benzyl

bromide to the enamine[61] formed from the condensation of α-methyl allyl acetoacetate with valine.[62]

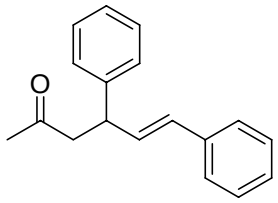


The addition of Selectfluor and a catalytic amount of $TiCl_4$ successfully fluorinated β-keto esters.[63] A cerium-catalyzed oxidation with O_2 was used to hydroxylate β-keto esters.[64] Vinylation was accomplished by the indium-catalyzed addition of acetylene.[65] **8rr** was synthesized by the addition of acrolein to the sodium salt of the β-keto ester.[66]

General procedure for the catalytic decarboxylative allylation reaction with $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ and the Trost ligand:

In a Schlenk tube under Ar, allyl-β-ketoester (1.2 mmol) and either $Pd(PPh_3)_4$ (10 mol %) or the combination of $Pd_2(dba)_3$ (5 mol %) and (*S*,*S*)-Trost ligand (10 mol %) were dissolved in benzene (4 mL). The solution was allowed to stir under Ar for the reported time (Tables 1.1 and 1.3). Following solvent evaporation the crude product was purified via flash chromatography (SiO_2, 10% Et_2O: Hex). The absolute configuration was assigned *via* comparison of **9c** synthesized by decarboxylative allylation to a sample prepared as described by Trost[67] (see Scheme 1.24).

Spectroscopic Data



(*E*)-4,6-diphenylhex-5-en-2-one
9a[68] (eb2295)
yellow oil
$Pd(PPh_3)_4$: 94% yield
Pd/Trost ligand : 79% yield, 68% ee (*R*)

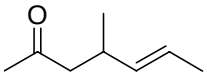
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 10H: aromatic H), 6.38 (m, 2H: C*H*=), 4.12 (app. q, *J* = 7 Hz, 1H: CH), 3.01 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.95 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2), 2.14 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.36 (C=O), 143.35 (aromatic C), 137.49 (aromatic C), 132.76 (*C*H=), 130.39 (*C*H=), 129.13 (aromatic CH), 128.91 (aromatic CH), 128.06 (aromatic CH), 127.75 (aromatic CH), 127.12 (aromatic CH), 126.65 (aromatic CH), 49.82 (CH_2), 44.36 (CH), 31.20 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1710, 1490, 1255.

HRMS calcd for $C_{18}H_{18}O$ [M+] 250.1358, found 250.1352.

HPLC (Daicel Chiralpak AD : 99:1 hexane/isopropanol, 0.5 mL/min) t_r = 27.1 (major), 28.6 (minor) minutes



(*E*)-4-methylhept-5-en-2-one

9b[69] (eb2172)

colorless oil

$Pd(PPh_3)_4$: 85% yield

Pd/Trost ligand : 82% yield, 86% ee (*R*)

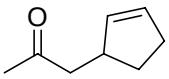
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (m, 1H: =C*H*-CH_3), 5.34 (dd, *J* = 7 Hz, 15 Hz, 1H: =C*H*-CH), 2.66 (app. sep, *J* = 7 Hz, 1H: =CH-C*H*), 2.44 (dd, *J* = 7 Hz, 15.6 Hz, 1H: diastereotopic CH_2), 2.34 (dd, *J* = 7 Hz, 15.6 Hz, 1H: diastereotopic CH_2), 2.13 (s, 3H: (C=O)CH_3), 1.64 (d, *J* = 6 Hz, 3H: =CH-C*H*$_3$), 1.00 (d, *J* = 7 Hz, 3H: CH-C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.92 (C=O), 135.90 (=*C*H-CH), 124.14 (=*C*H-CH_3), 51.40 (CH_2), 33.11 (=CH-*C*H), 30.90 ((C=O)*C*H_3), 20.93 (CH-*C*H_3), 18.28 (=CH-*C*H_3).

FTIR ($CDCl_3$): ν_{max} 1705, 1454, 1357.

HRMS calcd for $C_8H_{15}O$ [M+H] 127.1123, found 127.1105.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 1 ^oC /min to 75 ^oC) t_r = 27.6 (major), 29.3 (minor) minutes



1-(cyclopent-2-enyl)propan-2-one

9c[70] (eb2145)

colorless oil

$Pd(PPh_3)_4$: 69% yield

Pd/Trost ligand : 85% yield, 86% ee (*R*)

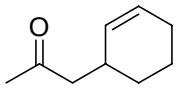
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H: =CH), 5.76 (m, 1H: =CH), 3.11 (m, 1H: CH), 2.54 (dd, *J* = 7 Hz, 16.5 Hz, 1H: diastereotopic (C=O)CH_2), 2.44 (dd, *J* = 7 Hz, 16.5 Hz, 1H: diastereotopic (C=O)CH_2), 2.32 (m, 2H: cyclopentyl CH_2), 2.16 (s, 3H: CH_3), 2.14 (m, 1H: diastereotopic cyclopentenyl CH_2), 1.38 (m, 1H: diastereotopic cyclopentenyl CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 209.01 (C=O), 134.30 (5.76) (=CH), 131.67 (5.83) (=CH), 50.32 ((C=O)*C*H_2), 41.36 (CH), 32.21 (cyclopentenyl CH_2), 30.70 (CH_3), 30.20 (cyclopentenyl CH_2).

FTIR ($CDCl_3$): ν_{max} 1700, 1403, 1362.

HRMS calcd for $C_8H_{12}O$ [M+H] 125.0966, found 125.0970.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 0.5 ^oC/min to 75 ^oC) t_r = 47.3 (major), 48.5 (minor) minutes



1-(cyclohex-2-enyl)propan-2-one

9d[71] (eb2155)

colorless oil

$Pd(PPh_3)_4$: 87% yield

Pd/Trost ligand : 75% yield, 94% ee (*R*)

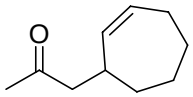
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (m, 1H: =CH), 5.51 (m, 1H: =CH), 2.65 (m, 1H: =CH-C*H*), 2.46 (dd, *J* = 7 Hz, 16.3 Hz, 1H: diastereotopic (C=O)CH_2), 2.40 (dd, *J* = 7 Hz, 16.3 Hz, 1H: diastereotopic (C=O)CH_2), 2.16 (s, 3H: CH_3), 1.98 (m, 2H: cyclohexenyl CH_2), 1.81 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.69 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.56 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.23 (m, 1H: diastereotopic cyclohexenyl CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.81 (C=O), 130.85 (5.51) (=CH), 128.38 (5.71) (=CH), 50.46 ((C=O)*C*H_2), 31.55 (CH), 30.92 (CH_3), 29.29 (1.81, 1.23) (cyclohexenyl CH_2), 25.43 (1.98) (cyclohexenyl CH_2), 21.43 (1.69, 1.56) (cyclohexenyl CH_2).

FTIR ($CDCl_3$): ν_{max} 1700, 1450, 1357.

HRMS calcd for $C_9H_{15}O$ [M+H] 139.1123, found 139.1129.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 0.5 ^oC/min to 85 ^oC) t_r = 71.9 (major), 72.8 (minor) minutes



(*Z*)-1-(cyclohept-2-enyl)propan-2-one

9e (eb2140)

$Pd(PPh_3)_4$: 83% yield

Pd/Trost ligand : 81% yield, 98% ee (*R*)

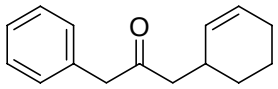
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H: =C*H*-CH_2), 5.45 (dd, *J* = 4 Hz, 11 Hz, 1H: =C*H*-CH), 2.81 (m, 1H: CH), 2.55 (dd, *J* = 7 Hz, 16.4 Hz, 1H: diastereotopic (C=O)CH_2), 2.47 (dd, *J* = 7 Hz, 16.4 Hz, 1H: diastereotopic (C=O)CH_2), 2.15 (s, 3H: CH_3), 2.15 (m, 2H: cyloheptenyl CH_2), 1.92 (m, 1H: diastereotopic cycloheptenyl CH_2), 1.64 (broad m, 3H), 1.29 (m, 2H: cycloheptenyl CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.86 (C=O), 136.60 (=*C*H-CH), 132.43 (=*C*H-CH_2), 51.20 ((C=O)*C*H_2), 35.93 (CH), 33.88 (1.59, 1.29) (cycloheptenyl CH_2), 30.79 (CH_3), 30.65 (cycloheptenyl CH_2), 29.10 (cycloheptenyl CH_2), 27.20 (cycloheptenyl CH_2).

FTIR ($CDCl_3$): ν_{max} 1710, 1450, 1357.

HRMS calcd for $C_{10}H_{17}O$ [M+H] 153.1279, found 153.1286.

GC (Chiraldex B-TA : Hold 80 ^oC) t_r = 76.2 (minor), 77.1 (major) minutes



1-(cyclohex-2-enyl)-3-phenylpropan-2-one

9f[72] (eb3090)

colorless oil

$Pd(PPh_3)_4$: 63% yield

Pd/Trost ligand : 71% yield, 90% ee (*R*)

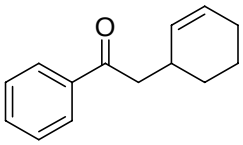
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H: aromatic H), 7.30 (m, 1H: aromatic H), 7.23 (m, 2H: aromatic H), 5.69 (m, 1H: =CH), 5.48 (m, 1H: =CH), 3.70 (s, 2H: C*H*$_2$-Ph), 2.66 (m, 1H: C*H*-CH=), 2.45 (d, *J* = 7 Hz, 2H: (C=O)C*H*$_2$-CH), 1.97 (m, 2H: cyclohexenyl CH_2), 1.77 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.64 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.54 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.14 (m, 1H: diastereotopic cyclohexenyl CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.03 (C=O), 134.58 (aromatic C), 130.89 (5.47) (=CH), 129.84 (aromatic CH), 129.13 (aromatic CH), 128.36 (5.68) (=CH), 127.41 (aromatic CH), 51.14 (*C*H_2-Ph), 48.60 ((C=O)*C*H_2-CH), 31.42 (*C*H-CH=), 29.20 (1.77, 1.14) (cyclohexenyl CH_2), 25.43 (1.97) (cyclohexenyl CH_2), 21.39 (1.54, 1.64) (cyclohexenyl CH_2).

FTIR ($CDCl_3$): ν_{max} 1710, 1497, 1454.

HRMS calcd for $C_{15}H_{19}O$ [M+H] 215.1436, found 215.1461.

HPLC (Daicel Chiralpak AD : 99:1 hexane/isopropanol, 0.5 mL/min) t_r = 17.0 (minor), 19.2 (major) minutes



2-(cyclohex-2-enyl)-1-phenylethanone

9g[73] (eb3095)

colorless oil

$Pd(PPh_3)_4$: 66% yield

Pd/Trost ligand : 69% yield, 92% ee (*R*)

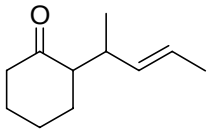
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2H: aromatic H), 7.59 (m, 1H: aromatic H), 7.49 (app. t, J = 7 Hz, 2H: aromatic H), 5.75 (m, 1H: =CH), 5.61 (m, 1H: =CH), 2.98 (d, *J* = 7 Hz, 1H: diastereotopic (C=O)CH_2), 2.97 (d, *J* = 7 Hz, 1H: diastereotopic (C=O)CH_2), 2.85 (m, 1H: =CH-C*H*), 2.02 (m, 2H: cyclohexenyl CH_2), 1.89 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.73 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.61 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.34 (m, 1H: diastereotopic cyclohexenyl CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.08 (C=O), 137.72 (aromatic C), 133.37 (aromatic CH), 131.17 (5.61) (=CH), 128.98 (aromatic CH), 128.52 (aromatic CH), 128.37 (5.75) (=CH), 45.23 ((C=O)*C*H_2), 32.02 (*C*H-CH=), 29.49 (1.89, 1.34) (cyclohexenyl CH_2), 25.53 (2.02) (cyclohexenyl CH_2), 21.50 (1.61, 1.73) (cyclohexenyl CH_2).

FTIR ($CDCl_3$): ν_{max} 1684, 1448, 1261.

HRMS calcd for $C_{14}H_{17}O$ [M+H] 201.1279, found 201.1278.

HPLC (Daicel Chiralpak AD : 99:1 hexane/isopropanol, 0.5 mL/min) t_r = 15.3 (major), 16.0 (minor) minutes



(*E*)-2-(pent-3-en-2-yl)cyclohexanone

9h (eb2214)

colorless oil

$Pd(PPh_3)_4$: 69% yield, dr = 1.7

Pd/Trost ligand : 81% yield, 54% ee (*S*), dr = 1.5

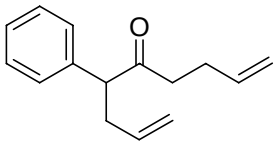
^{1}H NMR (400 MHz, $CDCl_3$) Major diastereomer: δ 5.37 (overlapping multiplet, 1H: =C*H*-CH_3), 5.19 (ddd, *J* = 2 Hz, 8 Hz, 15 Hz, 1H: =C*H*-CH), 2.57 (app. hex, *J* = 7 Hz, 1H: C*H*-CH_3), 2.27 (overlapping multiplet, cyclohexyl CH_2), 2.12 (m, 1H: (C=O)CH), 1.93 (overlapping multiplet, cyclohexyl CH_2), 1.92 (overlapping multiplet, cyclohexyl CH_2), 1.65 (overlapping multiplet, =CH-C*H*$_3$), 1.59 (overlapping multiplet, cyclohexyl CH_2), 0.97 (d, *J* = 6.6 Hz, 3H: CH-C*H*$_3$). Minor diastereomer: δ 5.39 (overlapping multiplet, =C*H*-CH), 5.37 (overlapping multiplet, =C*H*-CH_3), 2.65 (m, 1H: C*H*-CH_3), 2.37 (overlapping multiplet, cyclohexyl CH_2), 2.23 (m, 1H: (C=O)CH), 1.84 (overlapping multiplet, cyclohexyl CH_2), 1.74 (overlapping multiplet, cyclohexyl CH_2), 1.65 (overlapping multiplet, =CH-C*H*$_3$), 1.59 (overlapping multiplet, cyclohexyl CH_2), 0.99 (d, *J* = 6.6 Hz, 3H: CH-C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer: δ 214.03 (C=O), 134.72 (=*C*H-CH), 125.39 (=*C*H-CH_3), 56.71 ((C=O)*C*H), 42.32 (2.27) (cyclohexyl CH_2), 36.26 (*C*H-CH_3), 31.32 (1.93) (cyclohexyl CH_2), 28.54 (1.92) (cyclohexyl CH_2), 24.20 (1.59) (cyclohexyl CH_2), 19.47 (CH-*C*H_3), 18.36 (=CH-*C*H_3). Minor diastereomer: δ 213.12 (C=O), 135.35 (=*C*H-CH), 124.48 (=*C*H-CH_3), 56.16 ((C=O)*C*H), 42.51 (2.37) (cyclohexyl CH_2), 35.47 (*C*H-CH_3), 29.21 (1.59) (cyclohexyl CH_2), 28.08 (1.74) (cyclohexyl CH_2), 24.69 (1.84) (cyclohexyl CH_2), 18.39 (=CH-*C*H_3), 17.00 (CH-*C*H_3).

FTIR ($CDCl_3$): ν_{max} 1700, 1449.

HRMS calcd for $C_{11}H_{19}O$ [M+H] 167.1436, found 167.1431.

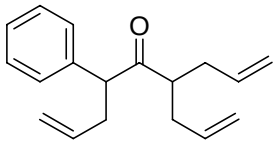
GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 1 ^oC/min to 115 ^oC) Major diastereomer: t_r = 67.3 (major), 69.8 (minor) minutes Minor diastereomer: t_r = 68.5 (major), 68.8 (minor) minutes



4-phenylnona-1,8-dien-5-one

11 (eb4029-3)
colorless oil
44% yield

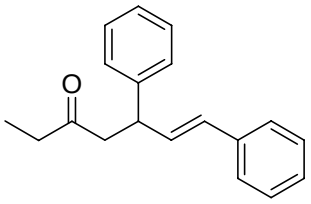
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (m, 1 H: aromatic CH) 7.20 - 7.25 (m, 4H: aromatic CH) 5.67 (m, 2 H: overlapping =CH) 4.98 (m, 4H: overlapping $=CH_2$) 3.72 (t, *J*=7.5 Hz, 1 H: benzylic CH) 2.82 (m, 2 H: diastereotopic CH_2) 2.47 (m, 3 H: overlapping CH_2) 2.26 (ddd, *J*=17.4, 6.8, 1.4 Hz, 2 H: allylic CH_2-*CH_2*)



4-allyl-6-phenylnona-1,8-dien-5-one

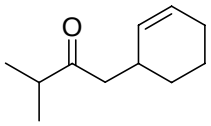
12 (eb4029-2)
colorless oil
18% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (m, 5 H: aromatic CH) 5.56 - 5.80 (m, 4 H: overlapping =CH) 5.21 - 5.34 (m, 1 H: =CH) 4.89 - 5.11 (m, 4 H: overlapping $=CH_2$) 4.79 (m, 2 H: $=CH_2$) 3.76 (t, *J*=7.5 Hz, 1 H: benzylic CH) 2.78 (m, 1 H: diastereotopic CH_2) 2.67 (m, 1 H: diastereotopic CH_2) 2.39 - 2.51 (m, 1 H: diastereotopic CH_2) 2.29 (m, 1 H: diastereotopic CH_2) 2.12 - 2.24 (m, 2 H: CH_2) 1.94 - 2.06 (m, 1 H: diastereotopic CH_2)



(*E*)-5,7-diphenylhept-6-en-3-one
9i[74] (eb4040-2)
colorless oil
51% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (m, 10 H: aromatic CH) 6.38 (m, , 2 H: overlapping =CH) 4.09 - 4.16 (m, 1 H: CH) 2.95 (dd, *J*=7.2, 5.4 Hz, 2 H: CH-*CH_2*) 2.39 (m, 2 H: CH_3-*CH_2*) 1.01 (t, *J*=7.3 Hz, 3 H: CH_3)



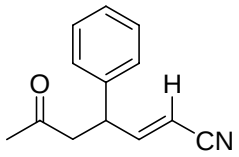
1-(cyclohex-2-enyl)-3-methylbutan-2-one
9j (eb3116)
colorless oil
94% yield, 80% ee (*R*)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (m, 1H: =CH), 5.50 (m, 1H: =CH), 2.68 (m, 1H: =CH-C*H*), 2.61 (app. pen, *J* = 7 Hz, 1H: $(CH_3)_2$-C*H*), 2.45 (d, *J* = 7 Hz, 2H: (C=O)CH_2), 1.99 (m, 2H: cyclohexenyl CH_2), 1.81 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.69 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.58 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.20 (m, 1H: diastereotopic cyclohexenyl CH_2), 1.11 (d, *J* = 7Hz, 6H: $(CH_3)_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 214.49 (C=O), 131.23 (5.50) (=CH), 128.17 (5.71) (=CH), 47.09 ((C=O)*C*H_2), 41.61 ((CH_3)$_2$-*C*H), 31.37 (*C*H-CH=), 29.39 (1.81, 1.20) (cyclohexenyl CH_2), 25.49 (1.99) (cyclohexenyl CH_2), 21.48 (1.69, 1.58) (cyclohexenyl CH_2), 18.52 ((CH_3)$_2$).

FTIR ($CDCl_3$): ν_{max} 1707, 1265, 1467.

HPLC (Daicel Chiralpak AD : 99.5:1 hexane/isopropanol, 0.5 mL/min) t_r = 9.7 (major), 10.5 (minor) minutes



(*E*)-6-oxo-4-phenylhept-2-enenitrile

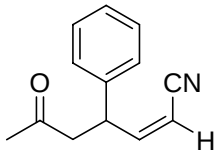
***trans*-9k** (eb2278-2,4,5,6,& 10)

colorless oil

$Pd(PPh_3)_4$: 28% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 - 7.39 (m, 2 H: aromatic CH) 7.27 - 7.32 (m, 1 H: aromatic CH) 7.15 - 7.20 (m, 2 H:aromatic CH) 6.85 (dd, *J*=16.4, 6.8 Hz, 1 H: (CN)C=*CH*) 5.25 (dd, *J*=16.3, 1.6 Hz, 1 H: =(*CH*)(CN)) 4.12 (m, 1 H: CH) 2.95 (d, *J*=7.3 Hz, 2 H: CH_2) 2.15 (s, 3 H: CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 205.71 (C=O) 157.30 (*CH*=C(CN)) 139.90 (aromatic C) 129.54 (aromatic CH) 128.20 (aromatic CH) 128.04 (aromatic CH) 117.68 (CN) 100.80 ((CN)(*CH)*=) 47.98 (CH_2) 44.04 (CH) 30.94 (CH_3)



(*Z*)-6-oxo-4-phenylhept-2-enenitrile

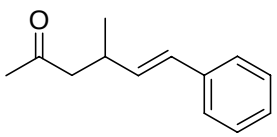
***cis*-9k** (eb2278-3,7,8,&9)

colorless oil

$Pd(PPh_3)_4$: 16% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 - 7.39 (m, 2 H: aromatic CH) 7.25 - 7.32 (m, 3 H: aromatic CH) 6.58 (dd, 1 H: *J*=11.1, 10.2 Hz, 1H: *CH*=C(CN)) 5.36 (d, *J*=11.1 Hz, 1 H: =(*CH*)(CN)) 4.44 (ddd, *J*=10.2, 7.8, 6.4 Hz, 1 H: CH) 3.00 (dd, *J*=18.3, 7.2 Hz, 2 H: CH_2) 2.17 (s, 3 H: CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 205.65 (C=O) 155.78 (*CH*=C(CN)) 140.61 (aromatic C) 129.57 (aromatic CH) 127.94 (aromatic CH) 127.73 (aromatic CH) 116.18 (CN) 99.72 ((CN)(*CH)*=) 48.73 (CH_2) 43.64 (CH) 30.63 (CH_3)



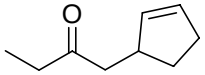
(*E*)-4-methyl-6-phenylhex-5-en-2-one

9l[75] (eb4019-2)
Pd / Trost ligand : 80% NMR yield, 37% ee (*R*)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 (m, 4 H: aromatic CH) 7.22 (m, 1 H: aromatic CH) 6.41 (d, *J*=16.2 Hz, 1 H: =(*CH*)(Ph)) 6.16 (dd, *J*=16.2, 7.3 Hz, 1 H: =(*CH*)(CH)) 2.92 (m, 1 H: CH) 2.60 (dd, 1 H: *J*=9.1, 7.1 Hz, 1H: diastereotopic CH_2) 2.49 (dd, *J*= 7.3, 7.1 Hz, 1 H: diastereotopic CH_2) 2.17 (s, 3 H: CH_3-C=O) 1.15 (d, *J*=6.6 Hz, 3 H: CH-*CH_3*)

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 0.5 ^oC/min to 120 ^oC, hold 30 minutes) t_r = 169.3 (major), 171.1 (minor) minutes (*from Trost ligand reaction)*

HPLC (Daicel Chiralpak OD-H HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 15.2 (minor), 14.8 (major) minutes (*from stereospecific reaction (R))*.



1-(cyclopent-2-enyl)butan-2-one
9m (eb3120)
colorless oil
84% yield, 94% ee (*R*)

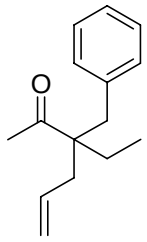
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H: =CH), 5.65 (m, 1H: =CH), 3.12 (m, 1H: C*H*-CH=), 2.52 (dd, *J* = 7 Hz, 16.5 Hz, 1H: diastereotopic CH-CH_2), 2.43 (overlapping multiplet, 1H: diastereotopic CH-CH_2), 2.43 (overlapping multiplet, 2H: CH_2-CH_3), 2.33 (m, 2H: cyclopentenyl CH_2), 2.14 (m, 1H: diastereotopic cyclopenenyl CH_2), 1.38 (m, 1H: diastereotopic cyclopentenyl CH_2), 1.07 (t, *J* = 7.3 Hz, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.63 (C=O), 134.48 (5.65) (=CH), 131.56 (5.76) (=CH), 48.99 (CH-*C*H_2), 41.43 (*C*H-CH=), 36.70 (*C*H_2-CH_3), 32.22 (2.33) (cyclopentenyl CH_2), 30.28 (1.38) (cyclopentenyl CH_2), 8.21 (CH_3).

FTIR ($CDCl_3$): ν_{max} 1710, 1460, 1115.

HRMS calcd for $C_9H_{14}O$ [M+H] 166.1358, found 166.0780.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 0.5 ^oC/min to 75 ^oC) t_r = 60.1 (major), 62.1 (minor) minutes



3-benzyl-3-ethylhex-5-en-2-one

9n (eb3035)
colorless oil
92% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 3H: aromatic H), 7.11 (d, *J* = 8 Hz, 2H: aromatic H), 5.77 (m, 1H: =CH), 5.14 (d, *J* = 12 Hz, 1H: =CH(H)$_{cis}$), 5.14 (d, *J* = 17 Hz, 1H: =CH(H)$_{trans}$), 2.89 (s, 2H: CH_2-Ph), 2.38 (dd, *J* = 7 Hz, 15Hz, 1H:

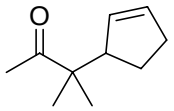
diastereotopic CH_2-CH=), 2.28 (dd, J = 7 Hz, 15Hz, 1H: diastereotopic CH_2-CH=), 2.11 (s, 3H: (C=O)-CH_3), 1.64 (m, 2H: CH_2-CH_3), 0.90 (t, J = 7 Hz, 3H: CH_2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.40 (C=O), 138.01 (aromatic C), 134.10 (=CH), 130.45 (aromatic CH), 128.58 (aromatic CH), 126.82 (aromatic CH), 118.72 (=CH_2), 56.42 (C), 39.67 (CH$_2$-Ph), 37.81 (CH_2=CH-CH$_2$), 27.31 ((C=O)-CH$_3$), 27.26 (CH$_2$-CH_3), 8.96(CH_2-CH$_3$).

FTIR ($CDCl_3$): ν_{max} 1699, 1454, 1261, 1269.

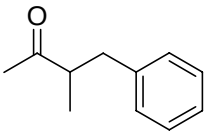
HRMS calcd for $C_{15}H_{21}O$ [M+H] 217.1592, found 217.1602.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 115 ^{o}C) t_r = 67.8, 68.9 minutes



3-(cyclopent-2-enyl)-3-methylbutan-2-one
9q[76] (eb3062-2)
50% NMR yield

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.76 (m,1 H: =CH) 5.58 (m,1 H: =CH) 2.13 - 2.25 (m, 4 H: overlapping cyclopentenyl CH_2) 1.90 (s, 3H: C=O-CH_3), 1.35 (s, 6H: CH_3)



3-methyl-4-phenylbutan-2-one
13r[77] (eb3246)
$Pd(PPh_3)_4$: 75% NMR yield

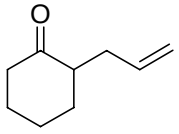
^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.06 - 7.28 (m, 5 H: aromatic CH) 2.98 (dd, J=13.1, 6.6 Hz, 1 H: diastereotopic CH_2) 2.39 - 2.61 (m, 1 H: overlapping diastereotopic CH_2) 2.39 - 2.61 (m, 1 H: overlapping CH) 1.74 (s, 3 H: C=O-CH_3) 0.93 (d, J=6.8 Hz, 3 H: CH-CH_3)

GC (Chiraldex B-TA : Begin 80 ^{o}C, ramp 0.5 ^{o}C/min to 100 ^{o}C, hold 40 minutes) t_r = 39.4, 41.6 minutes

General procedure for catalytic decarboxylative allylation reaction with $Pd_2(dba)_3$ and either ^{t}Bu PHOX or QUINAP:

In a Schlenk tube under Ar, $Pd_2(dba)_3$ (2.5 mol %) and (*S*)-^{t}Bu PHOX or (*S*)-QUINAP (5.5 mol %) were dissolved in benzene (2 mL) and stirred at the appropriate temperature (Tables 1.7, 1.8, and 1.9) until the maroon solution became orange. The solution of catalyst was then cannula transferred to a Schlenk tube under Ar containing allyl-β-ketoester (4 mmol) in benzene (2 mL). Upon addition the solution became green. The reaction was allowed to stir under Ar until the solution returned to orange. Following solvent evaporation the crude product was purified via flash chromatography (SiO_2, 5% Et_2O: Hex). The absolute configuration was determined by comparison to published results. [78,79]

Spectroscopic Data



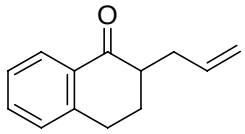
2-allylcyclohexanone

9s[80] (eb5237-3)

Pd / ^{t}Bu PHOX : >90% NMR yield, 74% ee

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.84 (m, 1 H: =CH) 5.04 - 5.15 (m, 2 H: $=CH_2$) 2.27 - 2.38 (m, 2 H: CH_2 or CH & diastereotopic CH_2) 2.22 (m, 1 H: diastereotopic CH_2 or CH) 2.09 (t, *J*=6.8 Hz, 2 H: CH_2) 1.83 (m, 1 H: diastereotopic CH_2) 1.58 (m, 1 H: diastereotopic CH_2) 1.40 - 1.52 (m, 3 H: overlapping CH_2) 1.22 (m,1 H: diastereotopic CH_2)

GC (Chiraldex B-TA : Begin 50 °C, hold 5 minutes, ramp 1 °C/min to 90 °C.) t_r = 40.0 (major), 41.5 (minor) minutes



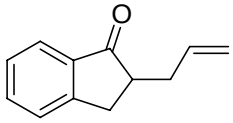
2-allyl-3,4-dihydronaphthalen-1(2*H*)-one

9t (eb5051)

Pd / ^{t}Bu PHOX : >90% NMR yield, 14% ee

^{1}H NMR (400 MHz, C_6D_6) δ ppm 8.43 (dd, *J*=7.7, 1.6 Hz, 1 H: aromatic CH) 6.97 - 7.21 (m, 3 H: aromatic CH) 5.78 - 5.94 (m, 1 H: =CH) 5.10 (d, *J*=11.2 Hz, 1 H: =CH(H)$_{cis}$) 5.10 (d, *J*=15.8Hz, 1 H: =CH(H)$_{trans}$) 2.79 - 2.96 (m, 1 H: CH) 2.53 (dd, *J*=4.3, 3.5 Hz, 2 H: benzylic CH_2) 2.31 (m, 1 H: diastereotopic CH_2) 2.21 (m, 1 H: diastereotopic CH_2) 1.83 (m, 1 H: diastereotopic CH_2) 1.52 (m, 1 H: diastereotopic CH_2)

HPLC (Daicel Chiralpak AD : 99.5:1 hexane/isopropanol, 0.5 mL/min) t_r = 20.2 (major), 21.4 (minor) minutes



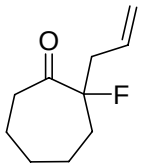
2-allyl-2,3-dihydroinden-1-one

9u (eb5009)

Pd / ^{t}Bu PHOX : >90% NMR yield, 12% ee

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.91 (d, *J*=7.6 Hz, 1 H: aromatic CH) 6.98 - 7.12 (m, 3 H: aromatic CH) 5.64 - 5.79 (m, 1 H: =CH) 5.01 (d, *J*=10.4 Hz, 1 H: =CH(H)$_{cis}$) 5.01 (d, *J*=18.5 Hz, 1 H: =CH(H)$_{trans}$) 2.74 - 2.83 (m, 1 H: CH) 2.64 - 2.75 (m, 1 H: diastereotopic CH_2) 2.51 (m, 1 H: diastereotopic CH_2) 2.46 (m, 1 H: diastereotopic CH_2) 2.10 - 2.21 (m, 1 H: diastereotopic CH_2)

HPLC (Daicel Chiralpak AD : 99.0:1 hexane/isopropanol, 0.5 mL/min) t_r = 18.1 (major), 19.0 (minor) minutes



2-allyl-2-fluorocycloheptanone

9v (eb5097)

colorless oil

Pd / ^{t}Bu PHOX : 91% yield, 88% ee (*R*)

Pd / Quinap : 92% yield, 70% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (ddt, *J* = 7 Hz, 10 Hz, 18 Hz, 1H: C*H*=CH_2), 5.01 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.00 (d, *J* = 18 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.53 (m, 2H: overlapping diastereotopic CH_2), 2.33 (m, 2H: overlapping diastereotopic CH_2), 1.91 (m, 1H: diastereotopic cycloheptyl CH_2), 1.73 (m, 2H: cycloheptyl CH_2), 1.55 (m, 3H: overlapping diastereotopic cycloheptyl CH_2), 1.44 (m, 1H: diastereotopic cycloheptyl CH_2), 1.16 (m, 1H: diastereotopic cycloheptyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.82 (d, *J* = 24.0 Hz: C=O), 130.85 (=CH), 119.40 (=CH_2), 101.70 (d, *J* = 185.22 Hz: CF), 41.11 (d, *J* = 22.6 Hz: allylic CH_2), 39.94 (cycloheptyl CH_2), 35.18 (d, *J* = 23.9 Hz: cycloheptyl CH_2), 27.80 (cycloheptyl

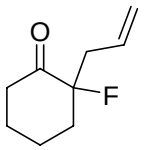
CH_2), 24.29 (d, J = 2.5 Hz: cycloheptyl CH_2), 24.02 (d, J = 2.5 Hz: cycloheptyl CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -161.66 (m).

FTIR (CD_2Cl_2): ν_{max} 1712, 1606, and 1433.

HRMS calcd for $C_{10}H_{15}OF$ [M+H] = 171.1185, found 171.1184.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 1 ^oC/min to 95 ^oC) t_r = 43.4 (major), 44.8 (minor) minutes (*from PHOX ligand reaction)*



2-allyl-2-fluorocyclohexanone

9w[81]**:** (eb5098)

colorless oil

Pd / ^{t}Bu PHOX : 73% yield, 83% ee (*R*)

Pd / Quinap : 84% yield, 68% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddt, J = 7 Hz, 10 Hz, 18 Hz, 1H: C*H*=CH_2), 5.09 (d, J = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.08 (d, J = 18 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.60 (m, 2H: cyclohexyl CH_2), 2.43 (m, 1H: diastereotopic allylic CH_2), 2.30 (m, 1H: diastereotopic allylic CH_2), 2.03 (m, 1H: diastereotopic cyclohexyl CH_2), 1.82 (overlapping m, 4H: overlapping cyclohexyl CH_2), 1.62 (m, 1H: diastereotopic cyclohexyl CH_2).

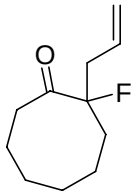
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.28 (d, J = 20.2 Hz: C=O), 130.77 (=CH), 119.26 (=CH_2), 97.71 (d, J = 183.78 Hz: CF), 39.36 (allylic CH_2), 38.76 (d, J = 2.5 Hz: cyclohexyl CH_2), 37.19 (d, J = 2.5 Hz: cyclohexyl CH_2), 27.18 (cyclohexyl CH_2), 21.42 (cyclohexyl CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -156.44 (m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1604, and 1413.

HRMS calcd for $C_9H_{13}OF$ [M+H] = 157.1029, found 157.1034.

GC (Chiraldex B-TA : Hold 50 ^oC for 5 minutes, ramp 1 ^oC/min to 95 ^oC) t_r = 37.9 (major), 43.6 (minor) minutes (*from PHOX ligand reaction)*



2-allyl-2-fluorocyclooctanone

9x (eb5172)
colorless oil
Pd / ^{t}Bu PHOX : 94% yield, 81% ee (*R*)
Pd / Quinap : 83% yield, 76% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.05 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.03 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.63 (m, 1H: diastereotopic cyclooctyl CH_2), 2.55 (ddd, *J* = 7 Hz, 14 Hz, 20 Hz, 1H: diastereotopic allylic CH_2), 2.37 (ddd, *J* = 7 Hz, 14 Hz, 19 Hz, 1H: diastereotopic allylic CH_2), 2.23 (m, 1H: diastereotopic cyclooctyl CH_2), 2.10 (m, 1H: diastereotopic cyclooctyl CH_2), 1.98 (m, 1H: diastereotopic cyclooctyl CH_2), 1.87 (m, 1H: diastereotopic cyclooctyl CH_2), 1.71 (m, 1H: diastereotopic cyclooctyl CH_2), 1.55 (m, 5H: overlapping diastereotopic cycloheptyl CH_2), 1.17 (m, 1H: diastereotopic cyclooctyl CH_2).

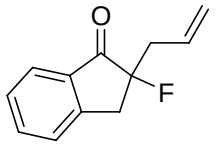
^{13}C NMR (125 MHz, $CDCl_3$) δ 215.97 (d, *J* = 25.0 Hz: C=O), 131.10 (=CH), 119.49 (=CH_2), 101.93 (d, *J* = 188.1 Hz: CF), 42.12 (d, *J* = 22.6 Hz: allylic CH_2), 39.70 (cyclooctyl CH_2), 37.68 (d, *J* = 22.6 Hz: cyclooctyl CH_2), 27.41 (cyclooctyl CH_2), 26.00 (cyclooctyl CH_2), 24.85 (cyclooctyl CH_2), 21.37 (cyclooctyl CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -167.59 (m).

FTIR (CD_2Cl_2: ν_{max} 1712, 1606, 1465.

HRMS calcd for $C_{11}H_{17}OF$ [M+H] = 185.1342, found 185.1353.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 100 ^{o}C) t_r = 52.5 (major), 53.1 (minor) minutes (*from PHOX ligand reaction)*



2-allyl-2-fluoro-2,3-dihydroinden-1-one

9y (eb5096)
colorless oil
Pd / ^{t}Bu PHOX : 94% yield, 85% ee (*R*)
Pd / Quinap : 97% yield, 72% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 1H: aromatic CH), 7.51 (app. t, *J* = 7 Hz, 1H: aromatic CH), 7.28 (overlapping m, 2H: aromatic CH), 5.63 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.06 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 5.02 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 3.27 (dd, *J* = 11 Hz, 17 Hz, 1H: diastereotopic benzylic CH_2), 3.16 (dd, *J* = 17 Hz, 23 Hz, 1H: diastereotopic benzylic CH_2), 2.67 (ddd, *J* = 7 Hz, 14 Hz, 20 Hz, 1H: diastereotopic allylic CH_2), 2.38 (ddd, *J* = 7 Hz, 14 Hz, 22 Hz, 1H: diastereotopic allylic CH_2).

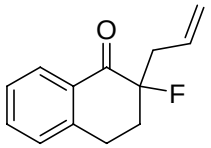
^{13}C NMR (125 MHz, $CDCl_3$) δ 200.59 (d, *J* = 17.75 Hz: C=O), 150.16 (aromatic C), 136.18 (aromatic CH), 133.89 (aromatic C), 130.32 (=CH), 128.11 (aromatic CH), 126.52 (aromatic CH), 124.87 (aromatic CH), 120.14 (=CH_2), 96.81 (d, *J* = 188.10 Hz: CF), 39.25 (d, *J* = 25.2 Hz: allylic CH_2), 37.46 (d, *J* = 23.9 Hz: benzylic CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -155.97 (m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1610, 1429.

HRMS calcd for $C_{12}H_{11}OF$ [M+H] = 191.0872, found 191.0890.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 120 ^{o}C, hold 20 min) t_r = 85.3 (major), 86.8 (minor) minutes (*from PHOX ligand reaction)*



2-allyl-2-fluoro-3,4-dihydronaphthalen-1(2*H*)-one

9z (eb5099)

colorless oil

Pd / ^{t}Bu PHOX : 96% yield, 84% ee (*R*)

Pd / Quinap : 83% yield, 78% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8 Hz, 1H: aromatic CH), 7.55 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.38 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.29 (m, 1H: aromatic CH), 5.92 (ddt, *J* = 8 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.25 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.21 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 3.14 (dt, *J* = 5 Hz, 17 Hz, 1H: diastereotopic benzylic CH_2), 3.04 (m, 1H: diastereotopic benzylic CH_2), 2.74 (ddd, *J* = 8 Hz, 14 Hz, 23 Hz, 1H: diastereotopic allylic CH_2), 2.61 (ddd, *J* = 8 Hz, 14 Hz, 23 Hz, 1H: diastereotopic allylic CH_2), 2.42 (m, 2H: cyclohexyl CH_2).

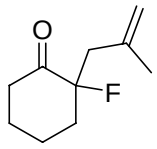
^{13}C NMR (125 MHz, $CDCl_3$) δ 193.99 (d, *J* = 17.75 Hz: C=O), 142.71 (aromatic C), 134.08 (aromatic CH), 130.92 (aromatic C), 130.86 (=CH), 128.75 (aromatic CH), 128.31 (aromatic CH), 127.31 (aromatic CH), 119.89 (=CH_2), 94.98 (d, *J* = 184.26 Hz: CF), 37.99 (d, *J* = 22.6 Hz: allylic CH_2), 31.91 (d, *J* = 22.6 Hz: cyclohexyl CH_2), 25.89 (d, *J* = 10.1 Hz: benzylic CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -158.79 (m).

FTIR (CD_2Cl_2): ν_{max} 1701, 1604, 1238.

HRMS calcd for $C_{13}H_{13}OF$ [M+H] = 205.1029, found 205.1036.

HPLC (Daicel Chiralpak AD HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) - t_r = 15.6 (major), 16.6 (minor) minutes (*from PHOX ligand reaction)*



2-fluoro-2-(2-methylallyl)cyclohexanone

9aa[82] (eb5204)

colorless oil

Pd / ^{t}Bu PHOX : 74% yield, 86% ee (*R*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (s, 1H: diastereotopic $=CH_2$), 4.70 (s, 1H: diastereotopic $=CH_2$), 2.60 (m, 1H: diastereotopic cyclohexyl CH_2), 2.59 (dd, *J* = 15 Hz, 25 Hz, 1H: diastereotopic allylic CH_2), 2.42 (dd, *J* = 15 Hz, 28 Hz, 1H: diastereotopic allylic CH_2), 2.34 (m, 1H: diastereotopic cyclohexyl CH_2), 2.00 (m, 1H: diastereotopic cyclohexyl CH_2), 1.84 (broad m, 4H: cyclohexyl CH_2's), 1.72 (s, 3H: CH_3), 1.63 (m, 1H: diastereotopic cyclohexyl CH_2).

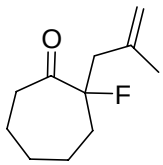
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.50 (d, *J* = 19.2 Hz: C=O), 140.00 (=C), 115.68 ($=CH_2$), 98.78 (d, *J* = 186.9 Hz: CF), 42.11 (d, *J* = 22.6 Hz: allylic CH_2), 39.64 (cyclohexyl CH_2), 37.49 (d, *J* = 22.6 Hz: cyclohexyl CH_2), 27.38 (cyclohexyl CH_2), 23.69 (CH_3), 22.04 (cyclohexyl CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ -153.25 (m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1647, 1363.

HRMS calcd for $C_{10}H_{15}FO$ [M+Na] = 193.1005, found 193.0947.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 95 ^{o}C) t_r = 45.6 (major), 48.9 (minor) minutes



2-fluoro-2-(2-methylallyl)cycloheptanone

9bb (eb5258)

colorless oil

Pd / ^{t}Bu PHOX : 64% yield, 46% ee (*R*)

Pd / Quinap : 82% yield, 88% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H: diastereotopic $=CH_2$), 4.68 (s, 1H: diastereotopic $=CH_2$), 2.68 (m, 1H: diastereotopic cycloheptyl CH_2), 2.55 (dd, *J* = 14 Hz, 26 Hz, 1H: diastereotopic allylic CH_2), 2.40 (overlapping dd, *J* = 14 Hz, 23 Hz, 1H: diastereotopic allylic CH_2), 2.37 (overlapping m, 1H: diastereotopic cycloheptyl CH_2), 1.99 (m, 1H: diastereotopic cycloheptyl CH_2), 1.80 (m, 2H: cycloheptyl CH_2), 1.69 (s, 3H: CH_3), 1.55 (broad m, 4H: cycloheptyl CH_2), 1.22 (m, 1H: diastereotopic cycloheptyl CH_2).

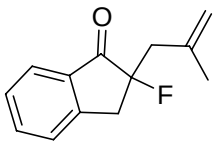
^{13}C NMR (125 MHz, $CDCl_3$) δ 210.93 (d, *J* = 23.8 Hz: C=O), 140.06 (=C), 115.60 ($=CH_2$), 102.65 (d, *J* = 186.9 Hz: CF), 44.46 (d, *J* = 22.6 Hz: allylic CH_2), 39.82 (cycloheptyl CH_2), 35.56 (d, *J* = 23.9 Hz: cycloheptyl CH_2), 27.92 (cycloheptyl CH_2), 24.59 (cycloheptyl CH_2), 24.16 (cycloheptyl CH_2), 23.95 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -160.23 (m).

FTIR (CD_2Cl_2): ν_{max} 1712, 1452, 1269.

HRMS calcd for $C_{11}H_{17}OF$ [M+H] = 185.1342, found 185.1329.

HPLC (Daicel Chiralpak AS-H HPLC column: 99.0% hexane/isopropanol, 1.0 mL/min) - t_r = 5.5 (minor), 6.1 (major) minutes (*from PHOX ligand reaction)*



2-fluoro-2-(2-methylallyl)-2,3-dihydroinden-1-one

9cc (eb5267)

colorless oil

Pd / ^{t}Bu PHOX : 81% yield, 88% ee (*R*)

Pd / Quinap : 87% yield, 76% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H: aromatic CH), 7.59 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.36 (overlapping m, 2H: aromatic CH), 4.86 (s, 1H: diastereotopic $=CH_2$), 4.72 (s, 1H: diastereotopic $=CH_2$), 3.44 (dd, *J* = 12 Hz, 18 Hz, 1H: diastereotopic benzylic CH_2), 3.22 (dd, *J* = 18 Hz, 23 Hz, 1H: diastereotopic benzylic CH_2), 2.74 (app. t, *J* = 14.5 Hz, 1H: diastereotopic allylic CH_2), 2.35 (dd, *J* = 14.5 Hz, 32 Hz, 1H: diastereotopic allylic CH_2), 1.72 (s, 3H: CH_3).

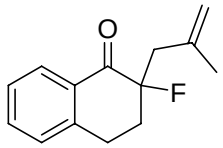
^{13}C NMR (125 MHz, $CDCl_3$) δ 200.64 (d, *J* = 18.2 Hz: C=O), 150.45 (aromatic C), 140.24 (=C), 136.25 (aromatic CH), 133.81 (aromatic C), 128.24 (aromatic CH), 126.71 (aromatic CH), 125.16 (aromatic CH), 115.87 ($=CH_2$), 97.67 (d, *J* = 188.6 Hz: CF), 42.36 (d, *J* = 24.5 Hz: allylic CH_2), 37.34 (d, *J* = 25.0 Hz: benzylic CH_2), 23.72 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -155.25 (m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1608, 1222.

HRMS calcd for $C_{13}H_{13}OF$ [M+H] = 205.1029, found 205.1045.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 120 ^{o}C, hold 35 min) t_r = 99.6 (major), 100.5 (minor) minutes (*from PHOX ligand reaction)*



2-fluoro-2-(2-methylallyl)-3,4-dihydronaphthalen-1(2*H*)-one

9dd (eb5296)
colorless oil
Pd / ^{t}Bu PHOX : 94% yield, 93% ee (*R*)
Pd / Quinap : 58% yield, 88% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8 Hz, 1H: aromatic CH), 7.45 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.28 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.19 (d, *J* = 8 Hz, 1H: aromatic CH), 4.91 (s, diastereotopic $=CH_2$), 4.70 (s, diastereotopic $=CH_2$), 3.00 (m, 2H: benzylic CH_2), 2.59 (dd, *J* = 15 Hz, 19 Hz, 1H: diastereotopic allylic CH_2), 2.47 (dd, *J* = 15 Hz, 32 Hz, 1H: diastereotopic allylic CH_2), 2.33 (m, 2H: cyclohexyl CH_2), 1.79 (s, 3H, CH_3).

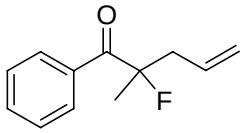
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.21 (d, *J* = 18.2 Hz: C=O), 142.61 (aromatic C), 140.27 (=C), 134.01 (aromatic CH), 130.93 (aromatic C), 128.68 (aromatic CH), 128.32 (aromatic CH), 127.11 (aromatic CH), 116.03 ($=CH_2$), 95.73 (d, *J* = 186.2 Hz: CF), 41.25 (d, *J* = 22.6 Hz: allylic CH_2), 31.71 (d, *J* = 23.0 Hz: cyclohexyl CH_2), 26.30 (d, *J* = 10.2 Hz: benzylic CH_2), 23.80 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -156.77 (m).

FTIR (CD_2Cl_2): ν_{max} 1704, 1602, 1290.

HRMS calcd for $C_{14}H_{15}OF$ [M+H] = 219.1185, found 219.1189.

HPLC (Daicel Chiralpak AD HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 13.2 (major), 14.8 (minor) minutes (*from PHOX ligand reaction)*



2-fluoro-2-methyl-1-phenylpent-4-en-1-one

9ee (eb5252 & eb5256)

colorless oil

Pd / ^{t}Bu PHOX : 74% yield, 33% ee (*R*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8 Hz, 2H: aromatic CH), 7.49 (app. t, *J* = 8 Hz, 1H: aromatic CH), 7.32 (app. t, *J* = 8 Hz, 2H: aromatic CH), 5.74 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.09 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 5.08 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 2.80 (ddd, *J* = 7 Hz, 14 Hz, 21 Hz, 1H: diastereotopic allylic CH_2), 2.57 (ddd, *J* = 7 Hz, 14 Hz, 21 Hz, 1H: diastereotopic allylic CH_2), 1.58 (d, *J* = 22 Hz, 3H: CH_3).

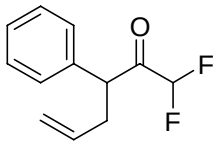
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.19 (d, *J* = 26.6 Hz: C=O), 134.9 (aromatic C), 133.08 (=CH), 131.12 (aromatic CH), 129.86 (aromatic CH), 128.32 (aromatic CH), 119.86 (=CH_2), 101.57 (d, *J* = 186.0 Hz: CF), 43.06 (d, *J* = 22.6 Hz: allylic CH_2), 23.90 (d, *J* = 23.8 Hz, CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -150.56 (app. hex, *J* = 22 Hz).

FTIR (CD_2Cl_2): ν_{max} 1710, 1683, 1242.

HRMS calcd for $C_{12}H_{13}FO$ [M+H] = 189.1029, found 193.1091.

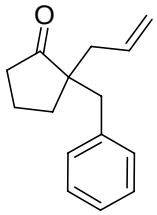
GC (Chiraldex B-DM : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 150 ^{o}C) t_r = 67.6 (major), 67.9 (minor) minutes



1,1-difluoro-3-phenylhex-5-en-2-one

9ff (eb7293)
colorless oil
$Pd(PPh_3)_4$: 46% isolated

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.17 - 7.30 (m, 5 H: aromatic CH) 5.59 (t, *J*=53.3 Hz, 1H: CF_2H) 5.52 - 5.63 (m, 1 H: =CH) 4.98 (d, *J*=17.3 Hz, 1 H: =CH(H)$_{trans}$) 4.93 (d, *J*=10.4 Hz, 1 H: =CH(H)$_{cis}$) 4.09 (td, *J*=7.6, 2.5 Hz, 1 H: benzylic CH) 2.77 (ddd, *J*=14.5, 7.3 Hz, 1 H: diastereotopic CH_2) 2.44 (ddd, *J*=14.3, 7.1, 6.9 Hz, 1 H: diastereotopic CH_2)



2-allyl-2-benzylcyclopentanone

9gg (eb5220)
colorless oil
Pd / ^{t}Bu PHOX : 79% yield, 62% ee (*S*)

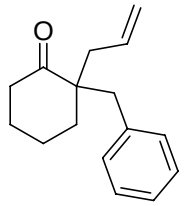
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (m, 3H: aromatic CH), 7.04 (d, *J* = 7 Hz, 2H: aromatic CH), 5.67 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.05 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.02 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.86 (d, *J* = 13 Hz, 1H: diastereotopic benzylic CH_2), 2.54 (d, *J* = 13 Hz, 1H: diastereotopic benzylic CH_2), 2.23 (dd, *J* = 7 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.10 (overlapping m, 1H: diastereotopic cyclopentyl CH_2), 2.09 (overlapping dd, *J* = 7 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 1.86 (overlapping m, 1H: diastereotopic cyclopentyl CH_2), 1.68 (m, 1H: diastereotopic cyclopentyl CH_2), 1.41 (m, 1H: diastereotopic cyclopentyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 222.80 (C=O), 137.78 (aromatic C), 133.67 (=CH), 130.30 (aromatic CH), 128.15 (aromatic CH), 126.47 (aromatic CH), 118.72 (=CH_2), 53.23 (C), 41.73 (benzylic CH_2), 40.93 (allylic CH_2), 38.90 (cyclopentyl CH_2), 31.01 (cyclopentyl CH_2), 18.67 (cyclopentyl CH_2).

IR (CD_2Cl_2): ν_{max} 1731, 1454, 1440.

HRMS calcd for $C_{15}H_{18}O$ [M+Na] = 237.1255, found 237.1227.

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 120 ^{o}C, hold 50 min) t_r = 121.9 (minor), 123.4 (major) minutes



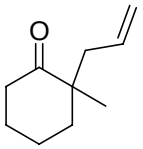
2-allyl-2-benzylcyclohexanone

9hh (eb5235)
colorless oil
Pd / ^{t}Bu PHOX : 95% yield, 79% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.11 - 7.20 (m, 3 H: aromatic CH) 7.04 (d, *J*=6.6 Hz, 2 H: aromatic CH) 5.61 - 5.71 (m, *J*=17.1, 10.1, 7.2, 7.2 Hz, 1 H: =CH) 5.02 (d, *J*=10.1 Hz, 1 H: =CH(H)$_{cis}$) 4.99 (d, *J*=17.1Hz, 1 H: =CH(H)$_{trans}$) 2.83 (s, 2 H: benzylic CH_2) 2.32 - 2.42 (m, 2 H: CH_2) 2.21 (d, *J*=6.9 Hz, 1 H: CH_2) 1.66 - 1.74 (m, *J*=9.9, 9.9, 9.6, 2.2 Hz, 4 H: overlapping CH_2) 1.58 - 1.64 (m, 2 H: CH_2)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 214.19 (C=O) 137.61 (aromatic C) 133.81 (=CH) 130.65 (aromatic CH) 128.00 (aromatic CH) 126.35 (aromatic CH) 118.24 (=CH_2) 52.62 (C) 40.89 (benzylic CH_2) 39.66 (CH_2) 39.27 (CH_2) 35.58 (CH_2) 26.83 (CH_2) 20.87 (CH_2)

HPLC (Daicel Chiralpak AD HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 10.5 (major), 11.7 (minor) minutes



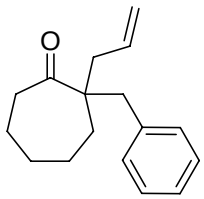
2-allyl-2-methylcyclohexanone

9ii (eb5243)
colorless oil
Pd / ^{t}Bu PHOX : 80% yield, 78% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.58 - 5.67 (m, *J*=16.4, 10.7, 7.4, 7.4 Hz, 1 H: =CH) 4.98 (d, *J*=10.7 Hz, 1 H: =CH(H)$_{cis}$) 4.97 (d, *J*=16.4Hz, 1 H: =CH(H)$_{trans}$) 2.26 - 2.35 (m, 3 H: overlapping CH_2) 2.14 - 2.22 (m, 1 H: diastereotopic CH_2) 1.67 - 1.75 (m, 5 H: overlapping CH_2) 1.48 - 1.57 (m, 1 H: diastereotopic CH_2) 1.00 (s, 3 H: CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 215.44 (C=O) 133.83 (=CH) 117.92 (=CH_2) 48.44 (C) 41.98 (allylic CH_2) 38.84 (cyclohexyl CH_2) 38.62 (cyclohexyl CH_2) 27.42 (cyclohexyl CH_2) 22.69 (CH_3) 21.09 (cyclohexyl CH_2)

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 90 ^{o}C) t_r = 42.7 (major), 43.3 (minor) minutes



2-allyl-2-benzylcycloheptanone

9jj (eb5201)
colorless oil
Pd / ^{t}Bu PHOX : 91% yield, 86% ee (*S*)
Pd / Quinap : 72% ee (*R*)

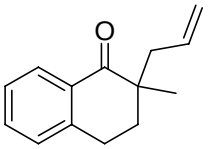
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 3H: aromatic CH), 7.10 (m, 2H: aromatic CH), 5.83 (ddt, *J* = 7 Hz, 10 Hz, 14 Hz, 1H: C*H*=CH_2), 5.44 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.10 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.86 (s, 2H: benzylic CH_2), 2.47 (m, 1H: diastereotopic cycloheptyl CH_2), 2.29 (overlapping m, 1H: diastereotopic cycloheptyl CH_2), 2.29 (overlapping d, *J* = 7 Hz, 2H: allylic CH_2), 1.72 (m, 2H: cycloheptyl CH_2), 1.56 (broad m, 6H: cylcoheptyl CH_2's).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.40 (C=O), 137.74 (aromatic C), 134.14 (=CH), 130.53 (aromatic CH), 128.05 (aromatic CH), 126.36 (aromatic CH), 118.39 (=CH_2), 55.05 (C), 42.46 (benzylic CH_2), 42.11 (allylic CH_2), 40.68 (cycloheptyl CH_2), 32.40 (cycloheptyl CH_2), 30.65 (cycloheptyl CH_2), 26.25 (cycloheptyl CH_2), 24.26 (cycloheptyl CH_2).

FTIR (CD_2Cl_2): ν_{max} 1695, 1494, 1454.

HRMS calcd for $C_{17}H_{22}O$ [M+H] = 243.1749, found 243.1761.

HPLC (Daicel Chiralpak AD HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 11.6 (major), 12.4 (minor) minutes (*from PHOX ligand reaction)*



2-allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one

9kk[83] (eb5251)

colorless oil

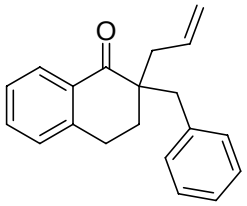
Pd / ^{t}Bu PHOX : 87% yield, 85% ee (*S*)

^{1}H NMR (500 MHz,$CDCl_3$) δ ppm 7.97 (dd, *J*=7.88, 1.58 Hz, 1 H: aromatic CH) 7.39 (td, *J*=7.49, 1.73 Hz, 1 H: aromatic CH) 7.23 (t, *J*=7.09 Hz, 1 H: aromatic CH) 7.15 (d, *J*=7.57 Hz, 1 H: aromatic CH) 5.67 - 5.77 (m, *J*=16.39, 10.72, 7.41, 7.41 Hz, 1 H: =CH) 5.01 (d, *J*=10.72 Hz, 1 H: =CH(H)$_{cis}$) 5.00 (d, *J*=16.39Hz, 1 H: =CH(H)$_{trans}$) 2.91 (td, *J*=6.23, 4.89 Hz, 2 H: benzylic CH_2) 2.39 (dd, *J*=13.87, 7.25 Hz, 1 H: diastereotopic allylic CH_2) 2.21 (dd, *J*=13.87, 7.57 Hz, 1 H: diastereotopic allylic CH_2) 2.01 (ddd, *J*=13.48, 7.65, 5.36 Hz, 1 H: diastereotopic CH_2-CH_2) 1.85 (td, *J*=6.94, 5.36 Hz, 1 H: diastereotopic CH_2-CH_2) 1.12 (s, 3 H: CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 202.10 (C=O) 143.35 (aromatic C) 133.99 (=CH) 133.09 (aromatic CH) 128.69 (aromatic C) 128.04 (aromatic CH) 126.66 (aromatic CH) 118.23 (=CH_2) 44.65 (C) 41.16 (allylic CH_2) 33.38 (CH_2-CH_2) 25.38 (benzylic CH_2) 21.95 (CH_3)

HRMS calcd for $C_{14}H_{17}O$ [M+H] = 201.1279, found 201.1287.

HPLC (Daicel Chiralpak AD HPLC column: 99.5% hexane/isopropanol, 0.5 mL/min) t_r = 14.0 (minor), 14.6 (major) minutes



2-allyl-2-benzyl-3,4-dihydronaphthalen-1(2*H*)-one

9ll[84] (eb5103b)

colorless oil

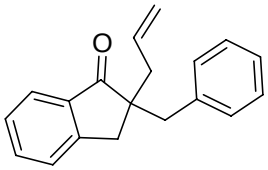
Pd / ^{t}Bu PHOX : 98% yield, 86% ee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J*=7.9, 1.6 Hz, 1 H: aromatic CH) 7.48 (td, *J*=7.4, 1.6 Hz, 1 H: aromatic CH) 7.34 (t, *J*=7.4 Hz, 1 H: aromatic CH) 7.21 - 7.29 (m, 4 H: aromatic CH) 7.16 - 7.19 (m, 2 H: aromatic CH) 5.79 - 5.89 (m, *J*=17.1, 10.0, 7.3, 7.3 Hz, 1 H: =CH) 5.13 (d, *J*=10.0 Hz, 1 H: =CH(H)$_{cis}$) 5.09 (d, *J*=17.1Hz, 1 H: =CH(H)$_{trans}$) 3.28 (d, *J*=13.6 Hz, 1 H: diastereotopic C-CH_2-Ph) 2.99 - 3.07 (m, 2 H: CH_2-CH_2-Ph) 2.79 (d, *J*=13.6 Hz, 1 H: diastereotopic C-CH_2-Ph) 2.54 - 2.59 (m, 1 H: diastereotopic allylic CH_2) 2.22 (dd, *J*=14.0, 7.7 Hz, 1 H: diastereotopic allylic CH_2) 2.04 (dt, *J*=13.9, 6.0 Hz, 1 H: Ph-CH_2-CH_2) 1.91 - 1.99 (m, 1 H: Ph-CH_2-CH_2)

^{13}C NMR (126 MHz, CHLOROFORM-*d*) δ ppm 200.75 (C=O) 143.09 (aromatic C) 137.60 (aromatic C) 133.86 (=CH) 133.17 (aromatic CH) 132.12 (aromatic C) 130.76 (aromatic CH) 128.67 (aromatic CH) 128.10 (aromatic CH) 128.0 (aromatic CH) 126.70 (aromatic CH) 126.32 (aromatic CH) 118.60 (=CH_2) 49.27 (C) 40.61 (C-CH_2-Ph) 39.69 (allylic CH_2) 30.00 (Ph-CH_2-CH_2) 25.23 (Ph-CH_2-CH_2)

HRMS calcd for $C_{20}H_{21}O$ [M+H] = 277.1592, found 277.1612.

HPLC (Daicel Chiralpak AD HPLC column: 99.5% hexane/isopropanol, 0.5 mL/min) t_r = 18.5 (minor), 21.6 (major) minutes



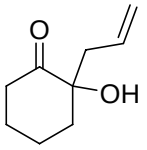
2-allyl-2-benzyl-2,3-dihydroinden-1-one

9mm (eb5015)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 64% ee (*S*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.87 (d, *J*=8.1 Hz, 1 H: aromatic CH) 7.05 - 7.18 (m, 5 H: aromatic CH) 6.93 - 7.03 (m, 3 H: aromatic CH) 5.68 (m, 1 H: =CH) 5.01 (d, *J*=16.9 Hz, 1 H: =CH(H)$_{trans}$) 4.94 (d, *J*=10.5 Hz, 1 H: =CH(H)$_{cis}$) 3.21 (d, *J*=13.1 Hz, 1 H: diastereotopic CH_2) 3.01 (d, *J*=17.4 Hz, 1 H: diastereotopic CH_2) 2.81 (d, *J*=13.8 Hz 1 H: diastereotopic CH_2) 2.76 (d, *J*=17.1 Hz 1 H: diastereotopic CH_2) 2.61 (dd, *J*=13.6, 6.6 Hz, 1 H: diastereotopic allylic CH_2) 2.30 (dd, *J*=13.6, 8.1 Hz, 1 H: diastereotopic allylic CH_2)

HPLC (Daicel Chiralpak OD-H HPLC column: 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 13.9 (major), 14.4 (minor) minutes



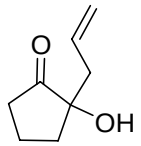
2-allyl-2-hydroxycyclohexanone

9nn[85] (eb5078-2)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 52% ee (*R*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.92 (m, 1 H: =CH) 5.09 (d, *J*=10.1 Hz, 1 H: =CH(H)$_{cis}$) 5.06 (d, *J*=17.2 Hz, 1 H: =CH(H)$_{trans}$) 4.21 (s, 1 H: OH) 2.26 (m, 3 H: diastereotopic CH_2) 2.08 (m, 1 H: diastereotopic CH_2) 1.94 - 2.04 (m, 1 H: diastereotopic CH_2) 1.52 (m, 2 H: CH_2) 1.12 - 1.36 (m, 3 H: overlapping diastereotopic CH_2)

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1.0 ^{o}C/min to 110 ^{o}C) t_r = 54.3 (minor), 56.6 (major) minutes



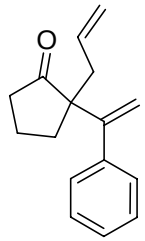
2-allyl-2-hydroxycyclopentanone

9oo (eb5087)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 12% ee (*R*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.86 (dddd, *J*=16.9, 10.4, 8.2, 6.4 Hz, 1 H: =CH) 5.12 (d, *J*=10.3 Hz 1 H: =CH(H)$_{cis}$) 5.06 (d, *J*=16.9, 1 H: =CH(H)$_{trans}$) 2.16 - 2.27 (m, 1 H: diastereotopic CH_2) 2.10 (m, 1 H: diastereotopic CH_2) 1.96 (m, 2 H: CH_2) 1.77 (m, 2 H: CH_2) 1.49 - 1.62 (m, 1 H: diastereotopic CH_2) 1.24 - 1.42 (m, 1 H: diastereotopic CH_2)

GC (Chiraldex B-TA : Hold 50 ^{o}C for 5 minutes, ramp 1.0 ^{o}C/min to 110 ^{o}C) t_r = 50.5 (major), 55.2 (minor) minutes



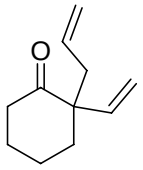
2-allyl-2-(1-phenylvinyl)cyclopentanone

9pp (eb5152)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 34% ee (*S*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.58 (m, 1 H: aromatic CH) 7.17 - 7.26 (m, 2 H: aromatic CH) 7.00 - 7.11 (m, 2 H: aromatic CH) 5.91 (dddd, *J*=17.1, 10.1, 7.3, 7.2 Hz, 1 H: =CH) 5.41 - 5.48 (d, *J*=1 Hz, 1 H: vinyl =CH(H)) 5.20 (d, *J*=1 Hz, 1 H: vinyl =CH(H)) 5.11 (d, *J*=10.2, 1 H: allylic =CH(H)$_{cis}$) 5.08 (d, *J*=16.9 Hz, 1 H: allylic =CH(H)$_{trans}$) 2.55 - 2.70 (m, 2 H: CH_2) 2.09 - 2.19 (m, 3 H: overlapping diastereotopic CH_2) 1.85 - 2.01 (m, 3 H: overlapping diastereotopic CH_2)

HPLC (Daicel Chiralpak AD HPLC column: 99.5% hexane/isopropanol, 0.5 mL/min) t_r = 11.6 (major), 12.4 (minor) minutes



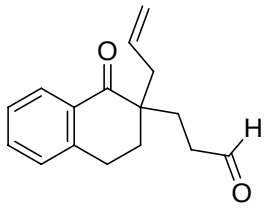
2-allyl-2-vinylcyclohexanone

9qq[86] (eb5238)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 16% ee (*S*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.70 - 5.97 (m, 2 H: overlapping =CH) 5.03 - 5.17 (m, 3 H: overlapping =CH(*H*)) 4.97 (dd, *J*=17.7, 1.0 Hz, =CH(*H*)$_{trans}$) 2.53 (dt, *J*=7.3, 1.3 Hz, 2 H: C=O-CH_2) 2.20 - 2.40 (m, 2 H: CH_2) 1.69 - 1.78 (m, 1 H: diastereotopic CH_2) 1.52 - 1.61 (m, 1 H: diastereotopic CH_2) 1.42 - 1.50 (m, 1 H: diastereotopic CH_2) 1.29 - 1.42 (m, 2 H: CH_2)

GC (Chiraldex B-DM : Begin at 50 ^{o}C, ramp 0.5 ^{o}C/min to 150 ^{o}C) t_r = 85.9 (major), 86.4 (minor) minutes



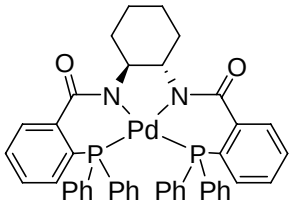
3-(2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanal

9rr (eb5234-2)

Pd / ^{t}Bu PHOX : > 90% NMR yield, 4% ee (*R*)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 9.35 (t, *J*=1.3 Hz, 1 H: HC=O) 8.39 (dd, *J*=7.8, 1.5 Hz, 1 H: aromatic CH) 7.16 (m, 2 H: aromatic CH) 7.09 (t, *J*=7.5 Hz, 1 H: aromatic CH) 5.71 (dddd, *J*=16.9, 7.3, 4.5, 2.8 Hz, 1 H: =CH) 5.06 (dd, *J*=10.1, 2.3 Hz, 1 H: =CH(*H*)$_{cis}$) 5.01 (dd, *J*=16.9, 2.3 Hz, 1 H: =CH(*H*)$_{trans}$) 2.57 (t, *J*=6.4 Hz 2 H: CHO-CH_2-*CH_2*) 2.31 - 2.39 (m, 1 H: diastereotopic CH_2) 2.17 (m, 1 H: diastereotopic CH_2) 2.01 - 2.13 (m, 2 H: CH_2) 1.91 (m, 1 H: diastereotopic CH_2) 1.80 (m,1 H: diastereotopic CH_2) 1.65 (m, 1 H: diastereotopic CH_2) 1.56 (m, 1 H: diastereotopic CH_2)

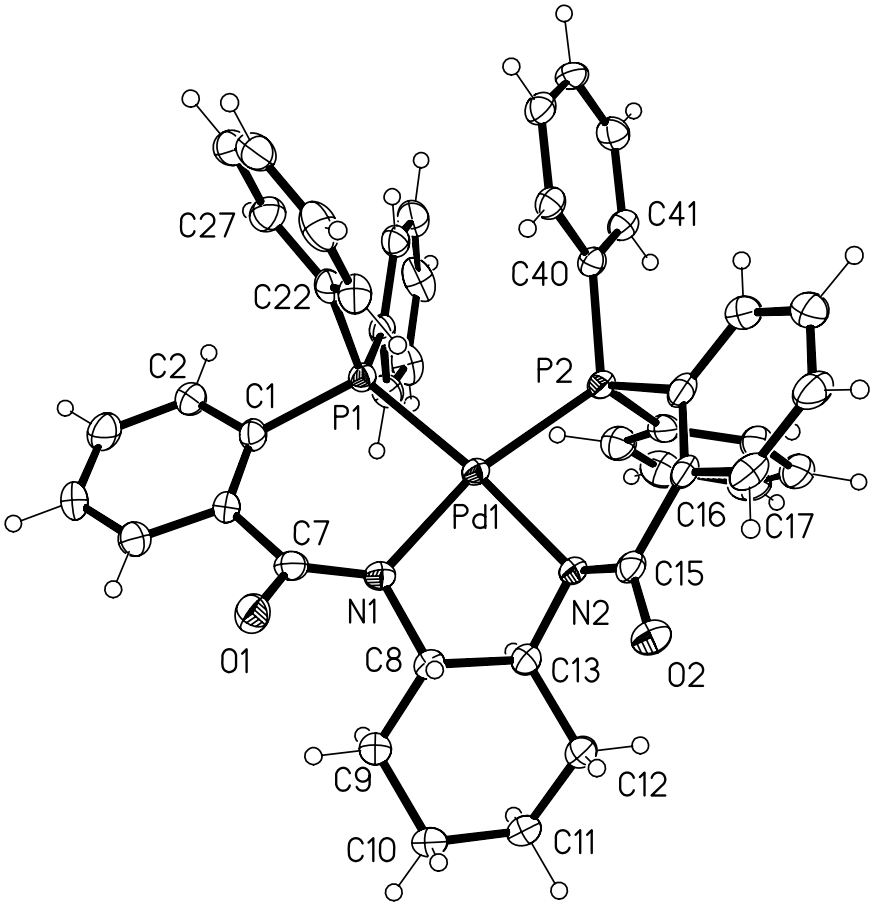
HPLC (Daicel Chiralpak AD HPLC column: 98% hexane/isopropanol, 1.0 mL/min) t_r = 23.7 (minor), 26.7 (major) minutes

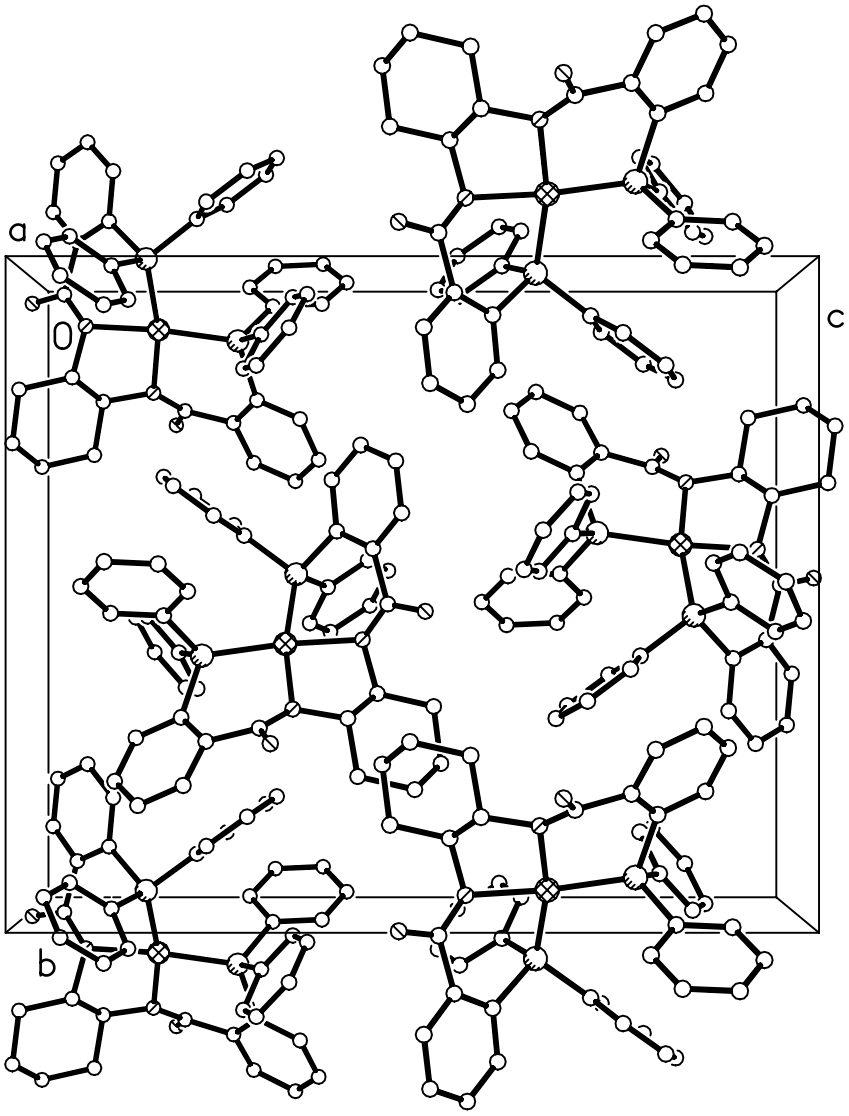


EB-3-104

EB-3-104 was synthesized by the addition of $Pd_2(dba)_3$ (5 mol%, 0.0051 mm, 4.7mg) and (*S*,*S*)-Trost ligand (10 mol%, 0.0101 mm, 7 mg) to cyclohex-2-enyl 3-oxopentanoate (0.102 mm, 20mg) in C_6D_6 (0.6 mL) under argon in an NMR tube. After the reaction had proceeded to 100% conversion the reaction mixture was exposed to air and was left to sit for a period of several days in a screw-capped vial. Yellow crystals with a slight green hue were formed from the green C_6D_6 solution.

Crystal Structure Data:





Comment

The displacement ellipsoids were drawn at the 50% probability level.

Experimental

A yellow block-shaped crystal of dimensions 0.45 x 0.28 x 0.22 mm was selected for structural analysis. Intensity data for this compound were collected using a Bruker APEX ccd area detector[87] using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The sample was cooled to 100(2) K. The intensity data were measured as a series of ω oscillation frames each of 0.3 ° for 5 sec / frame. Coverage of unique data was 100.0 % complete to 26.00 degrees in θ. Cell parameters were determined from a non-linear least squares fit of 8039 peaks in the range $2.26 < \theta < 26.00°$. A total of 31123 data were measured in the range $1.94 < \theta < 26.00°$. The data were corrected for absorption by the semi-empirical method[88] giving minimum and maximum transmission factors of 0.7567 and 0.8691. The data were merged to form a set of 6972 independent data with R(int) = 0.0299.

The orthorhombic space group $P2_12_12_1$ was determined by systematic absences and statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2[89]. Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 (1.5 for methyl) times the displacement parameters of the bonded atoms. A total of 460 parameters were refined against 6972 data to give $wR(F^2) = 0.0754$ and S = 1.009 for weights of $w = 1/[\sigma^2 (F^2) + (0.0560 P)^2 + 1.0000 P]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final R(F)

was 0.0281 for the 6853 observed, [$F > 4\sigma(F)$], data. The largest shift/s.u. was 0.002 in the final refinement cycle. The final difference map had maxima and minima of 0.895 and -0.285 e/Å^3, respectively. The absolute structure was determined by refinement of the Flack parameter[90].

Table 1.10. Crystal data and structure refinement for 04150.

Empirical formula	$C_{44}\ H_{38}\ N_2\ O_2\ P_2\ Pd$	
Formula weight	795.10	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.704(3) Å	α= 90°
	b = 17.429(5) Å	β= 90°
	c = 20.961(6) Å	γ= 90°
Volume	3545.2(18) Å^3	
Z, Z'	4, 1	
Density (calculated)	1.490 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	1632	
Absorption coefficient	0.656 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and minutes transmission	0.8691 and 0.7567	
Theta range for data collection	1.94 to 26.00°	
Reflections collected	31123	
Independent reflections	6972 [R(int) = 0.0299]	
Data / restraints / parameters	6972 / 0 / 460	
$wR(F^2$ all data)	$wR2$ = 0.0754	
$R(F$ obsd data)	$R1$ = 0.0281	
Goodness-of-fit on F^2	1.009	
Observed data [I > 2σ(I)]	6853	

Absolute structure parameter	-0.002(16)
Largest and mean shift / s.u.	0.002and 0.000
Largest diff. peak and hole	0.895 and -0.285 e/Å^3

$wR2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$

Table 1.11. Atomic coordinates and equivalent isotropic displacement parameters for 04150. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Pd(1)	0.736790(19)	0.575350(10)	0.338976(8)	0.01660(6)
P(1)	0.73210(7)	0.59326(3)	0.23306(3)	0.01767(13)
P(2)	0.60913(7)	0.46874(4)	0.35068(3)	0.01794(14)
O(1)	1.0713(2)	0.71862(12)	0.32670(9)	0.0290(4)
O(2)	0.8927(2)	0.52526(12)	0.51607(9)	0.0273(4)
N(1)	0.8562(2)	0.67222(13)	0.35036(10)	0.0209(5)
N(2)	0.7504(2)	0.56872(11)	0.43678(9)	0.0203(4)
C(1)	0.7998(3)	0.68603(15)	0.20897(12)	0.0215(5)
C(2)	0.7589(3)	0.71780(15)	0.15045(12)	0.0265(5)
C(3)	0.8242(4)	0.78175(19)	0.12641(13)	0.0332(7)
C(4)	0.9331(3)	0.81437(17)	0.15963(14)	0.0316(6)
C(5)	0.9742(3)	0.78311(17)	0.21733(14)	0.0275(6)
C(6)	0.9076(3)	0.71951(15)	0.24331(12)	0.0206(5)
C(7)	0.9529(3)	0.69863(15)	0.31076(13)	0.0223(6)
C(8)	0.8825(3)	0.68581(15)	0.41944(12)	0.0208(5)
C(9)	0.8874(3)	0.77264(16)	0.43177(13)	0.0254(6)
C(10)	0.8893(3)	0.79209(17)	0.50287(13)	0.0265(6)
C(11)	0.7652(3)	0.75667(15)	0.53595(12)	0.0257(6)
C(12)	0.7642(3)	0.67001(14)	0.52684(11)	0.0242(5)
C(13)	0.7622(3)	0.65063(14)	0.45565(11)	0.0206(5)
C(15)	0.8171(3)	0.51451(16)	0.46902(12)	0.0203(5)
C(16)	0.7946(3)	0.43075(15)	0.45029(11)	0.0199(5)
C(17)	0.8686(3)	0.37771(18)	0.48660(13)	0.0273(6)
C(18)	0.8489(4)	0.29935(18)	0.47919(13)	0.0323(7)
C(19)	0.7523(4)	0.27293(16)	0.43458(13)	0.0352(7)
C(20)	0.6825(3)	0.32439(17)	0.39728(13)	0.0295(7)

C(21)	0.7020(3)	0.40320(15)	0.40374(11)	0.0223(6)
C(22)	0.8485(3)	0.53188(16)	0.18876(13)	0.0218(6)
C(23)	0.9540(3)	0.49537(16)	0.22213(14)	0.0263(6)
C(24)	1.0548(3)	0.45532(18)	0.18926(17)	0.0350(7)
C(25)	1.0508(4)	0.45186(18)	0.12326(16)	0.0358(8)
C(26)	0.9469(3)	0.48809(18)	0.08981(15)	0.0334(7)
C(27)	0.8465(3)	0.52829(18)	0.12222(14)	0.0279(6)
C(28)	0.5606(3)	0.59041(15)	0.19818(12)	0.0203(5)
C(29)	0.5151(3)	0.53437(16)	0.15600(13)	0.0232(5)
C(30)	0.3791(3)	0.53649(19)	0.13526(14)	0.0311(7)
C(31)	0.2888(3)	0.59255(17)	0.15675(15)	0.0337(7)
C(32)	0.3340(3)	0.64828(18)	0.19945(15)	0.0312(7)
C(33)	0.4706(3)	0.64786(17)	0.21929(14)	0.0262(6)
C(34)	0.4454(3)	0.48863(16)	0.38926(13)	0.0226(6)
C(35)	0.3995(3)	0.44598(17)	0.44127(13)	0.0292(6)
C(36)	0.2718(4)	0.46196(18)	0.46773(14)	0.0366(7)
C(37)	0.1893(3)	0.5182(2)	0.44270(16)	0.0382(8)
C(38)	0.2340(4)	0.56009(18)	0.39009(16)	0.0368(7)
C(39)	0.3625(3)	0.54567(18)	0.36447(14)	0.0292(6)
C(40)	0.5643(3)	0.40855(14)	0.28257(12)	0.0191(5)
C(41)	0.4291(3)	0.39061(16)	0.26608(12)	0.0222(5)
C(42)	0.4037(3)	0.34412(16)	0.21279(13)	0.0253(6)
C(43)	0.5120(3)	0.31638(16)	0.17673(12)	0.0246(6)
C(44)	0.6470(3)	0.33285(16)	0.19365(13)	0.0233(6)
C(45)	0.6721(3)	0.37884(15)	0.24607(12)	0.0207(5)

Table 1.12. Bond lengths [Å] and angles [°] for 04150.

Pd(1)-N(2)	2.058(2)	N(2)-C(15)	1.330(3)
Pd(1)-N(1)	2.062(2)	N(2)-C(13)	1.486(3)
Pd(1)-P(1)	2.2424(9)	C(1)-C(6)	1.398(4)
Pd(1)-P(2)	2.2466(9)	C(1)-C(2)	1.403(4)
P(1)-C(22)	1.812(3)	C(2)-C(3)	1.378(4)
P(1)-C(1)	1.817(3)	C(2)-H(2)	0.9500
P(1)-C(28)	1.819(3)	C(3)-C(4)	1.387(5)
P(2)-C(34)	1.816(3)	C(3)-H(3)	0.9500
P(2)-C(40)	1.824(3)	C(4)-C(5)	1.385(4)
P(2)-C(21)	1.831(3)	C(4)-H(4)	0.9500
O(1)-C(7)	1.246(3)	C(5)-C(6)	1.394(4)
O(2)-C(15)	1.244(3)	C(5)-H(5)	0.9500
N(1)-C(7)	1.335(4)	C(6)-C(7)	1.524(4)
N(1)-C(8)	1.489(3)	C(8)-C(13)	1.521(4)

C(8)-C(9)	1.536(4)	C(23)-C(24)	1.386(4)
C(8)-H(8)	1.0000	C(23)-H(23)	0.9500
C(9)-C(10)	1.529(4)	C(24)-C(25)	1.385(5)
C(9)-H(9A)	0.9900	C(24)-H(24)	0.9500
C(9)-H(9B)	0.9900	C(25)-C(26)	1.381(5)
C(10)-C(11)	1.521(4)	C(25)-H(25)	0.9500
C(10)-H(10A)	0.9900	C(26)-C(27)	1.379(4)
C(10)-H(10B)	0.9900	C(26)-H(26)	0.9500
C(11)-C(12)	1.523(4)	C(27)-H(27)	0.9500
C(11)-H(11A)	0.9900	C(28)-C(29)	1.389(4)
C(11)-H(11B)	0.9900	C(28)-C(33)	1.400(4)
C(12)-C(13)	1.530(3)	C(29)-C(30)	1.391(4)
C(12)-H(12A)	0.9900	C(29)-H(29)	0.9500
C(12)-H(12B)	0.9900	C(30)-C(31)	1.387(5)
C(13)-H(13)	1.0000	C(30)-H(30)	0.9500
C(15)-C(16)	1.527(4)	C(31)-C(32)	1.392(4)
C(16)-C(17)	1.396(4)	C(31)-H(31)	0.9500
C(16)-C(21)	1.411(4)	C(32)-C(33)	1.389(4)
C(17)-C(18)	1.388(4)	C(32)-H(32)	0.9500
C(17)-H(17)	0.9500	C(33)-H(33)	0.9500
C(18)-C(19)	1.402(5)	C(34)-C(39)	1.380(4)
C(18)-H(18)	0.9500	C(34)-C(35)	1.393(4)
C(19)-C(20)	1.369(4)	C(35)-C(36)	1.385(5)
C(19)-H(19)	0.9500	C(35)-H(35)	0.9500
C(20)-C(21)	1.393(4)	C(36)-C(37)	1.371(5)
C(20)-H(20)	0.9500	C(36)-H(36)	0.9500
C(22)-C(23)	1.394(4)	C(37)-C(38)	1.392(5)
C(22)-C(27)	1.396(4)	C(37)-H(37)	0.9500
C(38)-C(39)	1.381(4)	C(42)-C(43)	1.382(4)
C(38)-H(38)	0.9500	C(42)-H(42)	0.9500
C(39)-H(39)	0.9500	C(43)-C(44)	1.388(4)
C(40)-C(41)	1.392(4)	C(43)-H(43)	0.9500
C(40)-C(45)	1.396(4)	C(44)-C(45)	1.381(4)
C(41)-C(42)	1.402(4)	C(44)-H(44)	0.9500
C(41)-H(41)	0.9500	C(45)-H(45)	0.9500

N(2)-Pd(1)-N(1)	83.95(8)	C(1)-P(1)-C(28)	104.09(12)
N(2)-Pd(1)-P(1)	174.61(6)	C(22)-P(1)-Pd(1)	114.37(9)
N(1)-Pd(1)-P(1)	90.69(6)	C(1)-P(1)-Pd(1)	113.07(9)
N(2)-Pd(1)-P(2)	83.11(6)	C(28)-P(1)-Pd(1)	114.38(8)
N(1)-Pd(1)-P(2)	167.06(6)	C(34)-P(2)-C(40)	104.45(12)
P(1)-Pd(1)-P(2)	102.25(2)	C(34)-P(2)-C(21)	106.20(13)
C(22)-P(1)-C(1)	99.07(12)	C(40)-P(2)-C(21)	103.53(12)
C(22)-P(1)-C(28)	110.39(13)	C(34)-P(2)-Pd(1)	111.91(9)

C(40)-P(2)-Pd(1)	121.44(9)	N(1)-C(8)-C(13)	106.8(2)
C(21)-P(2)-Pd(1)	108.12(10)	N(1)-C(8)-C(9)	109.0(2)
C(7)-N(1)-C(8)	115.4(2)	C(13)-C(8)-C(9)	109.7(2)
C(7)-N(1)-Pd(1)	127.28(18)	N(1)-C(8)-H(8)	110.4
C(8)-N(1)-Pd(1)	109.82(16)	C(13)-C(8)-H(8)	110.4
C(15)-N(2)-C(13)	120.7(2)	C(9)-C(8)-H(8)	110.4
C(15)-N(2)-Pd(1)	125.27(17)	C(10)-C(9)-C(8)	112.5(2)
C(13)-N(2)-Pd(1)	102.48(14)	C(10)-C(9)-H(9A)	109.1
C(6)-C(1)-C(2)	119.8(2)	C(8)-C(9)-H(9A)	109.1
C(6)-C(1)-P(1)	119.9(2)	C(10)-C(9)-H(9B)	109.1
C(2)-C(1)-P(1)	119.5(2)	C(8)-C(9)-H(9B)	109.1
C(3)-C(2)-C(1)	120.6(3)	H(9A)-C(9)-H(9B)	107.8
C(3)-C(2)-H(2)	119.7	C(11)-C(10)-C(9)	110.2(2)
C(1)-C(2)-H(2)	119.7	C(11)-C(10)-H(10A)	109.6
C(2)-C(3)-C(4)	119.9(3)	C(9)-C(10)-H(10A)	109.6
C(2)-C(3)-H(3)	120.0	C(11)-C(10)-H(10B)	109.6
C(4)-C(3)-H(3)	120.0	C(9)-C(10)-H(10B)	109.6
C(5)-C(4)-C(3)	119.8(3)	H(10A)-C(10)-H(10B)	108.1
C(5)-C(4)-H(4)	120.1	C(10)-C(11)-C(12)	110.5(2)
C(3)-C(4)-H(4)	120.1	C(10)-C(11)-H(11A)	109.5
C(4)-C(5)-C(6)	121.4(3)	C(12)-C(11)-H(11A)	109.5
C(4)-C(5)-H(5)	119.3	C(10)-C(11)-H(11B)	109.5
C(6)-C(5)-H(5)	119.3	C(12)-C(11)-H(11B)	109.5
C(5)-C(6)-C(1)	118.5(2)	H(11A)-C(11)-H(11B)	108.1
C(5)-C(6)-C(7)	114.8(2)	C(11)-C(12)-C(13)	110.0(2)
C(1)-C(6)-C(7)	126.4(2)	C(11)-C(12)-H(12A)	109.7
O(1)-C(7)-N(1)	125.3(2)	C(13)-C(12)-H(12A)	109.7
O(1)-C(7)-C(6)	116.6(2)	C(11)-C(12)-H(12B)	109.7
N(1)-C(7)-C(6)	117.2(2)	C(13)-C(12)-H(12B)	109.7
H(12A)-C(12)-H(12B)	108.2	C(16)-C(17)-H(17)	119.3
N(2)-C(13)-C(8)	108.3(2)	C(17)-C(18)-C(19)	119.3(3)
N(2)-C(13)-C(12)	118.2(2)	C(17)-C(18)-H(18)	120.3
C(8)-C(13)-C(12)	112.8(2)	C(19)-C(18)-H(18)	120.3
N(2)-C(13)-H(13)	105.5	C(20)-C(19)-C(18)	119.8(3)
C(8)-C(13)-H(13)	105.5	C(20)-C(19)-H(19)	120.1
C(12)-C(13)-H(13)	105.5	C(18)-C(19)-H(19)	120.1
O(2)-C(15)-N(2)	125.7(3)	C(19)-C(20)-C(21)	121.6(3)
O(2)-C(15)-C(16)	115.6(2)	C(19)-C(20)-H(20)	119.2
N(2)-C(15)-C(16)	118.6(2)	C(21)-C(20)-H(20)	119.2
C(17)-C(16)-C(21)	118.6(3)	C(20)-C(21)-C(16)	119.3(3)
C(17)-C(16)-C(15)	114.8(2)	C(20)-C(21)-P(2)	119.3(2)
C(21)-C(16)-C(15)	126.4(2)	C(16)-C(21)-P(2)	121.4(2)
C(18)-C(17)-C(16)	121.3(3)	C(23)-C(22)-C(27)	119.4(3)
C(18)-C(17)-H(17)	119.3	C(23)-C(22)-P(1)	118.1(2)

C(27)-C(22)-P(1)	122.0(2)	C(31)-C(32)-H(32)	120.3
C(24)-C(23)-C(22)	119.9(3)	C(32)-C(33)-C(28)	120.3(3)
C(24)-C(23)-H(23)	120.0	C(32)-C(33)-H(33)	119.9
C(22)-C(23)-H(23)	120.0	C(28)-C(33)-H(33)	119.9
C(25)-C(24)-C(23)	119.9(3)	C(39)-C(34)-C(35)	119.5(3)
C(25)-C(24)-H(24)	120.0	C(39)-C(34)-P(2)	118.7(2)
C(23)-C(24)-H(24)	120.0	C(35)-C(34)-P(2)	121.8(2)
C(26)-C(25)-C(24)	120.5(3)	C(36)-C(35)-C(34)	119.5(3)
C(26)-C(25)-H(25)	119.8	C(36)-C(35)-H(35)	120.3
C(24)-C(25)-H(25)	119.8	C(34)-C(35)-H(35)	120.3
C(27)-C(26)-C(25)	119.9(3)	C(37)-C(36)-C(35)	120.9(3)
C(27)-C(26)-H(26)	120.1	C(37)-C(36)-H(36)	119.6
C(25)-C(26)-H(26)	120.1	C(35)-C(36)-H(36)	119.6
C(26)-C(27)-C(22)	120.3(3)	C(36)-C(37)-C(38)	119.7(3)
C(26)-C(27)-H(27)	119.8	C(36)-C(37)-H(37)	120.1
C(22)-C(27)-H(27)	119.8	C(38)-C(37)-H(37)	120.1
C(29)-C(28)-C(33)	120.4(3)	C(39)-C(38)-C(37)	119.6(3)
C(29)-C(28)-P(1)	124.4(2)	C(39)-C(38)-H(38)	120.2
C(33)-C(28)-P(1)	115.1(2)	C(37)-C(38)-H(38)	120.2
C(28)-C(29)-C(30)	118.8(3)	C(34)-C(39)-C(38)	120.7(3)
C(28)-C(29)-H(29)	120.6	C(34)-C(39)-H(39)	119.6
C(30)-C(29)-H(29)	120.6	C(38)-C(39)-H(39)	119.6
C(31)-C(30)-C(29)	121.1(3)	C(41)-C(40)-C(45)	119.1(2)
C(31)-C(30)-H(30)	119.5	C(41)-C(40)-P(2)	123.2(2)
C(29)-C(30)-H(30)	119.5	C(45)-C(40)-P(2)	117.6(2)
C(30)-C(31)-C(32)	120.1(3)	C(40)-C(41)-C(42)	119.6(3)
C(30)-C(31)-H(31)	120.0	C(40)-C(41)-H(41)	120.2
C(32)-C(31)-H(31)	120.0	C(42)-C(41)-H(41)	120.2
C(33)-C(32)-C(31)	119.3(3)	C(43)-C(42)-C(41)	120.3(3)
C(33)-C(32)-H(32)	120.3	C(43)-C(42)-H(42)	119.9
C(41)-C(42)-H(42)	119.9	C(45)-C(44)-H(44)	120.4
C(42)-C(43)-C(44)	120.4(2)	C(43)-C(44)-H(44)	120.4
C(42)-C(43)-H(43)	119.8	C(44)-C(45)-C(40)	121.3(3)
C(44)-C(43)-H(43)	119.8	C(44)-C(45)-H(45)	119.3
C(45)-C(44)-C(43)	119.3(3)	C(40)-C(45)-H(45)	119.3

Table 1.13. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04150. The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Pd(1)	18(1)	18(1)	14(1)	0(1)	-1(1)	-1(1)
P(1)	18(1)	19(1)	16(1)	1(1)	-1(1)	-1(1)
P(2)	19(1)	20(1)	15(1)	-1(1)	2(1)	0(1)
O(1)	22(1)	40(1)	25(1)	2(1)	-1(1)	-8(1)
O(2)	29(1)	31(1)	22(1)	-2(1)	-3(1)	1(1)
N(1)	23(1)	23(1)	17(1)	-2(1)	-2(1)	-4(1)
N(2)	26(1)	22(1)	13(1)	-1(1)	0(1)	-6(1)
C(1)	26(1)	18(1)	21(1)	3(1)	3(1)	0(1)
C(2)	32(1)	26(1)	21(1)	2(1)	-1(1)	-3(1)
C(3)	47(2)	31(2)	22(1)	7(1)	0(1)	1(1)
C(4)	39(2)	28(2)	27(1)	6(1)	7(1)	-10(1)
C(5)	25(1)	31(2)	27(1)	-3(1)	4(1)	-6(1)
C(6)	24(1)	20(1)	18(1)	2(1)	3(1)	-3(1)
C(7)	26(1)	21(1)	20(1)	-3(1)	-2(1)	-1(1)
C(8)	25(1)	22(1)	16(1)	0(1)	-1(1)	-1(1)
C(9)	29(2)	25(1)	22(1)	0(1)	0(1)	-5(1)
C(10)	34(2)	24(1)	22(1)	-4(1)	-2(1)	-4(1)
C(11)	31(2)	27(1)	19(1)	-3(1)	0(1)	-1(1)
C(12)	31(2)	23(1)	19(1)	-1(1)	3(1)	0(1)
C(13)	22(1)	22(1)	18(1)	1(1)	0(1)	-1(1)
C(15)	20(1)	25(1)	16(1)	-1(1)	5(1)	-2(1)
C(16)	24(1)	23(1)	13(1)	3(1)	4(1)	3(1)
C(17)	30(2)	35(2)	18(1)	-2(1)	2(1)	5(1)
C(18)	49(2)	28(2)	20(1)	1(1)	-1(1)	12(1)
C(19)	55(2)	24(1)	27(1)	-1(1)	1(2)	0(2)
C(20)	40(2)	25(2)	23(1)	-2(1)	1(1)	0(1)
C(21)	27(1)	26(1)	14(1)	3(1)	4(1)	3(1)
C(22)	21(1)	21(1)	24(1)	2(1)	3(1)	-4(1)
C(23)	25(1)	26(2)	28(1)	4(1)	3(1)	1(1)
C(24)	26(2)	26(2)	54(2)	8(1)	4(1)	2(1)
C(25)	31(2)	26(2)	51(2)	-11(1)	18(2)	-6(1)
C(26)	32(2)	35(2)	34(2)	-9(1)	8(1)	-11(1)
C(27)	26(2)	33(2)	25(1)	-3(1)	0(1)	-3(1)
C(28)	22(1)	23(1)	17(1)	5(1)	-3(1)	-3(1)
C(29)	27(1)	23(1)	20(1)	3(1)	-2(1)	-4(1)
C(30)	33(2)	33(2)	27(1)	6(1)	-8(1)	-10(1)

C(31)	23(1)	31(2)	47(2)	15(1)	-14(1)	-5(1)
C(32)	25(2)	30(2)	39(2)	10(1)	-3(1)	3(1)
C(33)	26(2)	24(1)	29(1)	2(1)	-1(1)	0(1)
C(34)	20(1)	24(1)	23(1)	-6(1)	4(1)	-4(1)
C(35)	32(2)	32(2)	24(1)	-3(1)	6(1)	-9(1)
C(36)	40(2)	39(2)	30(1)	-7(1)	13(1)	-11(2)
C(37)	26(2)	47(2)	42(2)	-17(2)	11(1)	-5(1)
C(38)	29(2)	34(2)	48(2)	-7(1)	2(1)	5(1)
C(39)	26(2)	31(2)	31(2)	-3(1)	4(1)	0(1)
C(40)	22(1)	20(1)	15(1)	1(1)	-1(1)	0(1)
C(41)	23(1)	24(1)	20(1)	-1(1)	2(1)	2(1)
C(42)	24(1)	26(1)	26(1)	0(1)	-3(1)	-3(1)
C(43)	35(2)	23(1)	16(1)	-3(1)	-3(1)	-1(1)
C(44)	27(1)	23(1)	20(1)	1(1)	5(1)	4(1)
C(45)	21(1)	22(1)	18(1)	2(1)	0(1)	2(1)

Table 1.14. Hydrogen coordinates and isotropic displacement parameters for 04150.

	x	y	z	U(eq)
H(2)	0.6854	0.6950	0.1272	0.032
H(3)	0.7948	0.8035	0.0871	0.040
H(4)	0.9793	0.8580	0.1429	0.038
H(5)	1.0493	0.8055	0.2397	0.033
H(8)	0.9711	0.6612	0.4327	0.025
H(9A)	0.9709	0.7942	0.4114	0.030
H(9B)	0.8061	0.7970	0.4118	0.030
H(10A)	0.9751	0.7723	0.5224	0.032
H(10B)	0.8877	0.8485	0.5085	0.032
H(11A)	0.6795	0.7788	0.5181	0.031
H(11B)	0.7683	0.7688	0.5821	0.031
H(12A)	0.6819	0.6478	0.5478	0.029
H(12B)	0.8471	0.6474	0.5469	0.029
H(13)	0.6778	0.6761	0.4383	0.025
H(17)	0.9338	0.3956	0.5170	0.033
H(18)	0.9004	0.2640	0.5041	0.039
H(19)	0.7353	0.2195	0.4303	0.042
H(20)	0.6193	0.3059	0.3663	0.035
H(23)	0.9567	0.4979	0.2674	0.032
H(24)	1.1266	0.4303	0.2120	0.042

H(25)	1.1201	0.4244	0.1008	0.043
H(26)	0.9445	0.4853	0.0446	0.040
H(27)	0.7756	0.5537	0.0992	0.033
H(29)	0.5759	0.4953	0.1416	0.028
H(30)	0.3474	0.4989	0.1059	0.037
H(31)	0.1960	0.5929	0.1423	0.040
H(32)	0.2721	0.6862	0.2149	0.037
H(33)	0.5031	0.6867	0.2473	0.031
H(35)	0.4552	0.4062	0.4585	0.035
H(36)	0.2411	0.4335	0.5037	0.044
H(37)	0.1019	0.5286	0.4612	0.046
H(38)	0.1764	0.5984	0.3719	0.044
H(39)	0.3942	0.5753	0.3294	0.035
H(41)	0.3545	0.4097	0.2908	0.027
H(42)	0.3116	0.3316	0.2014	0.030
H(43)	0.4939	0.2858	0.1401	0.030
H(44)	0.7215	0.3127	0.1695	0.028
H(45)	0.7645	0.3905	0.2575	0.025

Table 1.15. Torsion angles [°] for 04150.

N(2)-Pd(1)-P(1)-C(22)	108.3(7)	N(2)-Pd(1)-N(1)-C(8)	-1.77(17)
N(1)-Pd(1)-P(1)-C(22)	101.88(12)	P(1)-Pd(1)-N(1)-C(8)	177.62(16)
P(2)-Pd(1)-P(1)-C(22)	-78.59(10)	P(2)-Pd(1)-N(1)-C(8)	-0.3(4)
N(2)-Pd(1)-P(1)-C(1)	-4.1(7)	N(1)-Pd(1)-N(2)-C(15)	-112.5(2)
N(1)-Pd(1)-P(1)-C(1)	-10.52(12)	P(1)-Pd(1)-N(2)-C(15)	-118.9(7)
P(2)-Pd(1)-P(1)-C(1)	169.01(10)	P(2)-Pd(1)-N(2)-C(15)	67.9(2)
N(2)-Pd(1)-P(1)-C(28)	-123.0(7)	N(1)-Pd(1)-N(2)-C(13)	30.31(17)
N(1)-Pd(1)-P(1)-C(28)	-129.43(12)	P(1)-Pd(1)-N(2)-C(13)	23.9(8)
P(2)-Pd(1)-P(1)-C(28)	50.10(10)	P(2)-Pd(1)-N(2)-C(13)	-149.37(17)
N(2)-Pd(1)-P(2)-C(34)	68.86(12)	C(22)-P(1)-C(1)-C(6)	-87.7(2)
N(1)-Pd(1)-P(2)-C(34)	67.4(3)	C(28)-P(1)-C(1)-C(6)	158.5(2)
P(1)-Pd(1)-P(2)-C(34)	-110.49(10)	Pd(1)-P(1)-C(1)-C(6)	33.8(2)
N(2)-Pd(1)-P(2)-C(40)	-167.00(12)	C(22)-P(1)-C(1)-C(2)	82.2(2)
N(1)-Pd(1)-P(2)-C(40)	-168.4(3)	C(28)-P(1)-C(1)-C(2)	-31.6(3)
P(1)-Pd(1)-P(2)-C(40)	13.65(10)	Pd(1)-P(1)-C(1)-C(2)	-156.3(2)
N(2)-Pd(1)-P(2)-C(21)	-47.76(11)	C(6)-C(1)-C(2)-C(3)	0.1(4)
N(1)-Pd(1)-P(2)-C(21)	-49.2(3)	P(1)-C(1)-C(2)-C(3)	-169.8(2)
P(1)-Pd(1)-P(2)-C(21)	132.89(9)	C(1)-C(2)-C(3)-C(4)	1.2(5)
N(2)-Pd(1)-N(1)-C(7)	146.2(2)	C(2)-C(3)-C(4)-C(5)	-1.0(5)
P(1)-Pd(1)-N(1)-C(7)	-34.4(2)	C(3)-C(4)-C(5)-C(6)	-0.5(5)
P(2)-Pd(1)-N(1)-C(7)	147.7(2)	C(4)-C(5)-C(6)-C(1)	1.7(4)

C(4)-C(5)-C(6)-C(7)	-172.4(3)	C(10)-C(11)-C(12)-C(13)	-58.1(3)
C(2)-C(1)-C(6)-C(5)	-1.5(4)	C(15)-N(2)-C(13)-C(8)	90.5(3)
P(1)-C(1)-C(6)-C(5)	168.3(2)	Pd(1)-N(2)-C(13)-C(8)	-54.5(2)
C(2)-C(1)-C(6)-C(7)	171.9(3)	C(15)-N(2)-C(13)-C(12)	-39.4(4)
P(1)-C(1)-C(6)-C(7)	-18.3(4)	Pd(1)-N(2)-C(13)-C(12)	175.7(2)
C(8)-N(1)-C(7)-O(1)	15.2(4)	N(1)-C(8)-C(13)-N(2)	55.4(3)
Pd(1)-N(1)-C(7)-O(1)	-131.3(3)	C(9)-C(8)-C(13)-N(2)	173.5(2)
C(8)-N(1)-C(7)-C(6)	-153.2(2)	N(1)-C(8)-C(13)-C(12)	-171.8(2)
Pd(1)-N(1)-C(7)-C(6)	60.3(3)	C(9)-C(8)-C(13)-C(12)	-53.8(3)
C(5)-C(6)-C(7)-O(1)	-25.6(4)	C(11)-C(12)-C(13)-N(2)	-175.5(2)
C(1)-C(6)-C(7)-O(1)	160.7(3)	C(11)-C(12)-C(13)-C(8)	56.8(3)
C(5)-C(6)-C(7)-N(1)	143.8(3)	C(13)-N(2)-C(15)-O(2)	0.1(4)
C(1)-C(6)-C(7)-N(1)	-29.8(4)	Pd(1)-N(2)-C(15)-O(2)	136.7(2)
C(7)-N(1)-C(8)-C(13)	-179.2(2)	C(13)-N(2)-C(15)-C(16)	176.3(2)
Pd(1)-N(1)-C(8)-C(13)	-27.1(2)	Pd(1)-N(2)-C(15)-C(16)	-47.0(3)
C(7)-N(1)-C(8)-C(9)	62.3(3)	O(2)-C(15)-C(16)-C(17)	-3.4(3)
Pd(1)-N(1)-C(8)-C(9)	-145.55(19)	N(2)-C(15)-C(16)-C(17)	180.0(2)
N(1)-C(8)-C(9)-C(10)	170.2(2)	O(2)-C(15)-C(16)-C(21)	172.4(2)
C(13)-C(8)-C(9)-C(10)	53.5(3)	N(2)-C(15)-C(16)-C(21)	-4.2(4)
C(8)-C(9)-C(10)-C(11)	-56.4(3)	C(21)-C(16)-C(17)-C(18)	-2.3(4)
C(9)-C(10)-C(11)-C(12)	58.2(3)	C(15)-C(16)-C(17)-C(18)	173.8(3)
C(16)-C(17)-C(18)-C(19)	-0.3(5)	C(22)-C(23)-C(24)-C(25)	0.2(5)
C(17)-C(18)-C(19)-C(20)	2.5(5)	C(23)-C(24)-C(25)-C(26)	0.0(5)
C(18)-C(19)-C(20)-C(21)	-1.9(5)	C(24)-C(25)-C(26)-C(27)	0.3(5)
C(19)-C(20)-C(21)-C(16)	-0.7(5)	C(25)-C(26)-C(27)-C(22)	-0.7(5)
C(19)-C(20)-C(21)-P(2)	178.2(2)	C(23)-C(22)-C(27)-C(26)	0.9(5)
C(17)-C(16)-C(21)-C(20)	2.8(4)	P(1)-C(22)-C(27)-C(26)	172.3(2)
C(15)-C(16)-C(21)-C(20)	-172.8(3)	C(22)-P(1)-C(28)-C(29)	16.7(3)
C(17)-C(16)-C(21)-P(2)	-176.1(2)	C(1)-P(1)-C(28)-C(29)	122.2(2)
C(15)-C(16)-C(21)-P(2)	8.3(4)	Pd(1)-P(1)-C(28)-C(29)	-114.0(2)
C(34)-P(2)-C(21)-C(20)	88.4(2)	C(22)-P(1)-C(28)-C(33)	-166.4(2)
C(40)-P(2)-C(21)-C(20)	-21.3(3)	C(1)-P(1)-C(28)-C(33)	-60.9(2)
Pd(1)-P(2)-C(21)-C(20)	-151.4(2)	Pd(1)-P(1)-C(28)-C(33)	62.9(2)
C(34)-P(2)-C(21)-C(16)	-92.7(2)	C(33)-C(28)-C(29)-C(30)	0.0(4)
C(40)-P(2)-C(21)-C(16)	157.5(2)	P(1)-C(28)-C(29)-C(30)	176.7(2)
Pd(1)-P(2)-C(21)-C(16)	27.5(2)	C(28)-C(29)-C(30)-C(31)	-1.0(4)
C(1)-P(1)-C(22)-C(23)	103.7(2)	C(29)-C(30)-C(31)-C(32)	0.5(4)
C(28)-P(1)-C(22)-C(23)	-147.5(2)	C(30)-C(31)-C(32)-C(33)	1.1(4)
Pd(1)-P(1)-C(22)-C(23)	-16.8(2)	C(31)-C(32)-C(33)-C(28)	-2.1(4)
C(1)-P(1)-C(22)-C(27)	-67.8(3)	C(29)-C(28)-C(33)-C(32)	1.6(4)
C(28)-P(1)-C(22)-C(27)	41.0(3)	P(1)-C(28)-C(33)-C(32)	-175.4(2)
Pd(1)-P(1)-C(22)-C(27)	171.7(2)	C(40)-P(2)-C(34)-C(39)	-80.6(2)
C(27)-C(22)-C(23)-C(24)	-0.7(4)	C(21)-P(2)-C(34)-C(39)	170.4(2)
P(1)-C(22)-C(23)-C(24)	-172.4(2)	Pd(1)-P(2)-C(34)-C(39)	52.6(2)

C(40)-P(2)-C(34)-C(35)	96.8(2)
C(21)-P(2)-C(34)-C(35)	-12.2(3)
Pd(1)-P(2)-C(34)-C(35)	-130.0(2)
C(39)-C(34)-C(35)-C(36)	-0.6(4)
P(2)-C(34)-C(35)-C(36)	-178.0(2)
C(34)-C(35)-C(36)-C(37)	1.2(4)
C(35)-C(36)-C(37)-C(38)	-0.1(5)
C(36)-C(37)-C(38)-C(39)	-1.4(5)
C(35)-C(34)-C(39)-C(38)	-0.9(4)
P(2)-C(34)-C(39)-C(38)	176.5(2)
C(37)-C(38)-C(39)-C(34)	2.0(5)
C(34)-P(2)-C(40)-C(41)	4.2(3)
C(21)-P(2)-C(40)-C(41)	115.2(2)
Pd(1)-P(2)-C(40)-C(41)	-123.3(2)
C(34)-P(2)-C(40)-C(45)	-175.1(2)
C(21)-P(2)-C(40)-C(45)	-64.1(2)
Pd(1)-P(2)-C(40)-C(45)	57.3(2)
C(45)-C(40)-C(41)-C(42)	-0.9(4)
P(2)-C(40)-C(41)-C(42)	179.8(2)
C(40)-C(41)-C(42)-C(43)	-0.1(4)
C(41)-C(42)-C(43)-C(44)	1.4(4)
C(42)-C(43)-C(44)-C(45)	-1.6(4)
C(43)-C(44)-C(45)-C(40)	0.5(4)
C(41)-C(40)-C(45)-C(44)	0.7(4)
P(2)-C(40)-C(45)-C(44)	-179.9(2)

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Chapter 2

The Decarboxylative Allylation of Ketone Enolates with Iridium, Rhodium, Molybdenum, and Ruthenium Catalysts

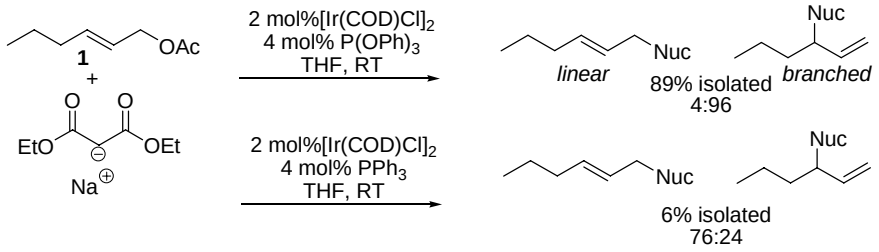
2.1.1 Introduction

While palladium has been the catalyst of choice for many transition metal-catalyzed allylic alkylation reactions, other metals such as iridium, molybdenum, rhodium, and ruthenium are also known to catalyze allylic alkylation reactions. Catalysts incorporating these metals are often complementary to palladium in terms of the scope of substrates they are compatible with, and in the observed regioselectivity of allylation. Many of these metals have also been shown to catalyze the decarboxylative allylation of β-keto esters, and were, therefore, of interest to us.

2.1.1 Iridium-Catalyzed Allylic Alkylation Reactions

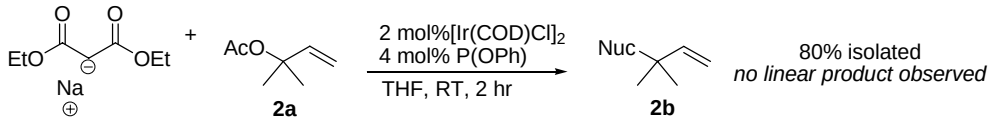
The ability of iridium(I) complexes to catalyze allylic alkylation reactions was first described by the Takeuchi group in 1997.[1] The alkylation of stabilized diester nucleophiles was studied. As illustrated in Scheme 2.1, when $[Ir(COD)Cl]_2$ was employed as the iridium source the effect of added ligand on the yield and regioselectivity of the reaction was dramatic. Whereas **1** participated in a very regioselective reaction in the presence of triphenylphosphite to afford allylated products with an 89% yield favoring formation of branched product, the addition of triphenylphosphine reduced the yield to only 6% and altered the regioselectivity of the reaction to favor the linear product.

Scheme 2.1 *Allylic alkylation with iridium*



The preferential formation of branched products was confirmed by the reaction of **2a** with diethylmalonate in the presence of $[Ir(COD)Cl]_2$ and triphenylphosphite (Scheme 2.2). It was reported that the reaction occurred smoothly at room temperature to yield **2b** with complete selectivity for the product in which a quaternary carbon center was formed rather than for the linear product.

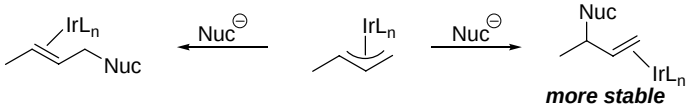
Scheme 2.2 *Formation of quaternary centers*



The finding that catalytic amounts of iridium and triphenylphosphite could selectively form branched products in the allylic alkylation reaction was very significant since it provided a new route for the synthesis of products that could not be made using traditional palladium-catalyzed allylic alkylation (Tsuji-Trost) chemistry. The unique regioselectivity of the iridium system was attributed to two factors. First, the authors recognized that the intermediate formed following nucleophilic attack on the Ir π-allyl, which contains Ir coordinated to the double bond of the newly formed product, is more stable when the double bond is monosubstituted

compared to the disubstituted double bond found in the linear product (Scheme 2.3).[2] It was proposed that this would favor formation of the branched product.

Scheme 2.3 *Relative stability of Ir-alkene complexes*



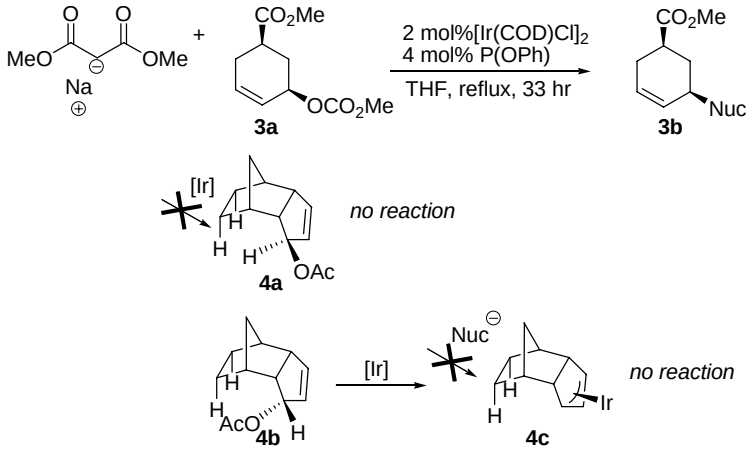
Secondly, and perhaps more importantly, it was reasoned that the strong π acceptor properties of the phosphite ligand promotes more carbocationic character in the π-allyl complex. It would be expected that the majority of this positive charge would reside on the more highly substituted carbon of the π-allyl, leading to nucleophilic attack at the more substituted terminus and formation of branched product. The importance of the π acceptor property of the ligand is evident when comparing the product distributions obtained when triphenylphosphite and triphenylphosphine are added to the reaction mixture (Scheme 2.1). As would be expected based on the above argument, the poorer π acceptor ligand, triphenylphosphine, yields a catalyst that no longer selectively forms branched product.

The proposed mechanism of the iridium-catalyzed allylation reaction is analogous to that of the palladium-catalyzed reaction. Specifically, oxidative addition of Ir(I) into the C-O bond of the allylic acetate yields an Ir(III) allyl intermediate which undergoes nucleophilic attack by the stabilized anion to yield product. The postulated Ir π-allyl intermediate is supported by the conversion of hex-1-en-3-yl acetate, the regioisomer of **1**, to the same mixture of products as those obtained when

1 was subjected to the conditions of catalysis. This implies that a common π-allyl intermediate is formed in the reaction of both substrates.

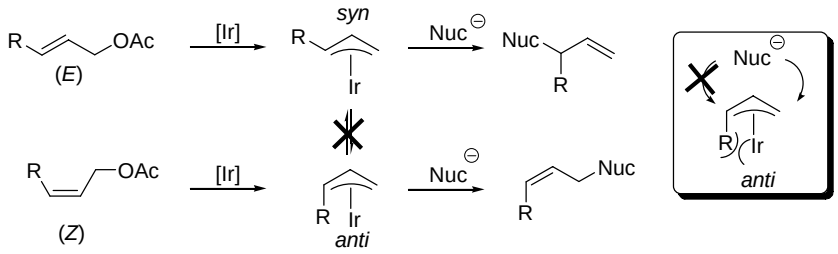
The stereochemical course of the reaction was probed by the conversion of *cis*-**3a** to *cis*-**3b** (Scheme 2.4). Although the reaction was much slower and **3b** was isolated in only 37% yield, it was the only allylation product observed. A double inversion mechanism leading to the net retention of configuration was postulated and was supported by the results of a detailed mechanistic study in 2002.[3] The norbornane derivatives **4a** and **4b** were synthesized with the expectation that, if the reaction truly proceeds *via* a double inversion mechanism, backside attack of iridium on the acetate leaving group in **4a** or of the nucleophile on the iridium π-allyl **4c**, derived from the oxidative addition of **4b**, would be too hindered to proceed and the reaction would fail. However, if a double retention mechanism predominates, **4a** would be expected to react. It was found that subjection of **4a** and **4b** to standard catalytic conditions did not produce any allylated product. Importantly, in the control reaction, cyclopentenyl acetate participated in the reaction under the same conditions, adding support to the hypothesis that the steric hindrance encountered in each of the inversion steps is blocking product formation.

Scheme 2.4 *Evidence of a double inversion mechanism*



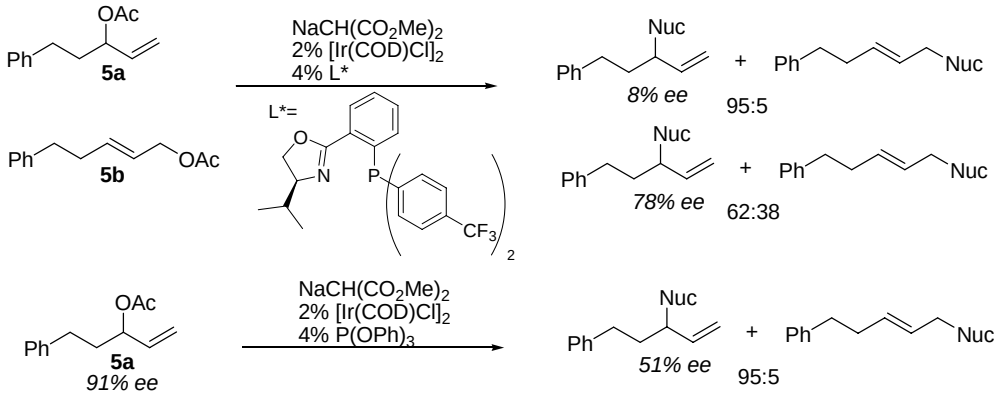
A more in-depth study of the iridium-catalyzed allylic alkylation reaction uncovered an interesting correlation between the regioselectivity of the reaction and the configuration of the double bond in the allylic starting material.[4] Contrary to the high selectivity for formation of the branched isomer obtained in allylation reactions with (*E*)-alkenes, allylations with (*Z*)-alkenes predominately lead to the isolation of linear products with a *cis* double bond. This was attributed to the absence of an equilibrium between the *syn* π-allyl initially formed after oxidative addition of the (*E*)-alkene and the *anti* π-allyl formed after oxidative addition of the (*Z*)-alkene (Scheme 2.5). It was postulated that attack at the substituted terminus of the *anti* π-allyl leads to an increased amount of steric repulsion between the *R* substituent on the allyl group and iridium, and therefore the formation of linear products is favored.

Scheme 2.5 *Formation of syn and anti π-allyl intermediates*



The "memory effect" noted in these studies also influenced the development of enantioselective allylation reactions.[5] The absence of isomerization between the *anti* and *syn* π-allyl intermediates suggests that, along with the geometry of the double bond, the stereochemistry of the starting allylic acetate may also be preserved. Experiments to investigate the stereospecificity of the reaction, along with the enantioselectivity of the reaction with chiral ligands, were conducted with the regioisomeric allylic acetates **5a** and **5b** (Scheme 2.6).

Scheme 2.6

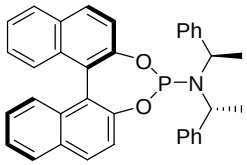


The existence of a memory effect was indeed observed when comparing reactions run with **5a** and **5b**. While **5a** yielded branched product with an 8% ee in a 95:5 ratio with the linear isomer, **5b** afforded only a 62:38 mixture of branched and

linear products, although the branched isomer was isolated with a 78% ee. The low enantioselectivity obtained in the reaction of **5a** suggests that the configuration of the chiral center in the starting material may be conserved; this was confirmed by preparing **5a** with a 91% ee and subjecting it to the allylation reaction in the presence of triphenylphosphite and $[Ir(COD)Cl]_2$. The branched isomer was isolated with a 51% ee, indicating that the reaction is stereospecific, but not highly so.

Hartwig's group has made the most recent advances the field of asymmetric iridium-catalyzed allylation reactions with the development of asymmetric amination and etherification reactions.[6] Linear allylic carbonates were utilized as starting materials, avoiding possible complications arising from stereospecific reactions. It was disclosed that for both etherification reactions and amination reactions, employing the chiral phosphoramidite ligand in Scheme 2.7 led to the formation of products often with ee's greater than 90%.

Scheme 2.7 *Hartwig's chiral phosphoramidite ligand*

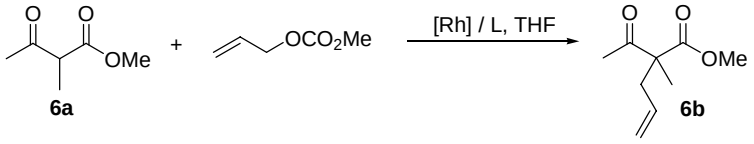


2.1.2 Rhodium-Catalyzed Allylic Alkylation Reactions

In addition to iridium, rhodium complexes have also been explored as an alternative to palladium catalysts for allylic alkylation reactions. Preliminary data suggesting that rhodium is able to catalyze C-C bond forming reactions at the more hindered allylic terminus of Rh π-allyls was disclosed by Tsuji in 1984.[7] The initial communication focused the allylation of stabilized β-keto compounds with allylic

carbonates. A variety of rhodium sources and ligands were screened in the conversion of **6a** to **6b** (Table 2.1). The optimal reaction conditions employed $RhH(PPh_3)_4$ as the catalyst in the presence of $P(n\text{Bu})_3$ to afford **6b** in a 93% yield after only one hour. Wilkinson's catalyst ($RhCl(PPh_3)_3$) was also found to be effective upon addition of tri-*n*-butylphosphine, although the reactions had to be refluxed in THF. Rh(III) catalysts were ineffective.

Table 2.1 *Optimization of the Rh-catalyzed allylic alkylation reaction*

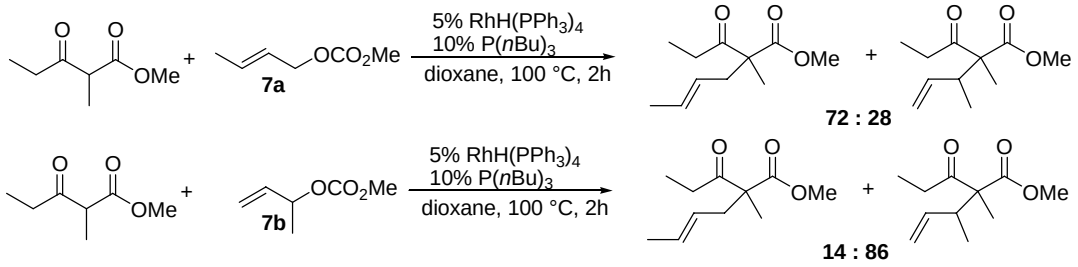


6a **6b**

Catalyst	Ligand	Conditions	Yield	Catalyst	Ligand	Conditions	Yield
$RhCl(PPh_3)_3$	------	20 °C, 3 h	4%	$RhH(PPh_3)_4$	------	20 °C, 25 h	97%
$RhCl(PPh_3)_3$	$P(n\text{Bu})_3$	65 °C, 1 h	95%	$RhH(PPh_3)_4$	$P(n\text{Bu})_3$	20 °C, 1 h	93%
$RhCl(PPh_3)_3$	$P(OEt)_3$	65 °C, 3 h	90%	$RhCl_3$	------	65 °C	no reaction
$RhCl(PPh_3)_3$	dppe	65 °C,31 h	12%				

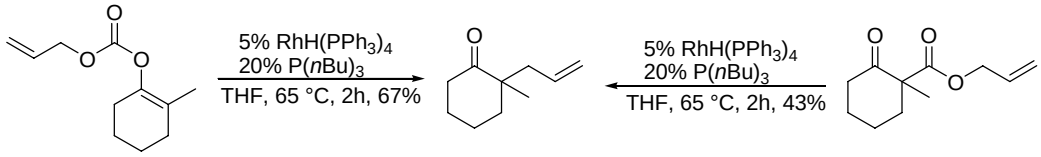
Subjection of the regioisomeric carbonates **7a** and **7b** to identical reaction conditions provided interesting insight into the reaction mechanism (Scheme 2.8). Upon oxidative addition of **7a** or **7b** to Rh(I) it would be expected that an identical Rh π-allyl complex would be formed as an intermediate, and consequently identical product distributions should arise from both reactions. Perhaps unexpectedly, very different product ratios were obtained from the reaction of **7a** and **7b**. While the linear carbonate **7a** primarily yielded linear product, the branched carbonate **7b** primarily yielded branched product. This seems to indicate that conventional π-allyl electrophiles are not intermediates in the reaction; rather it was proposed that σ allyls may be the predominate rhodium intermediates.

Scheme 2.8 *Regioselectivity of reactions*



Shortly after publication of this data, the catalytic system developed for the allylation of stabilized nucleophiles with allylic carbonates was applied to the decarboxylative allylation of allyl carbonates and β-keto esters. Although the reactions were more sluggish than the corresponding allylation of stabilized nucleophiles, they provided an early example of the *in situ* generation and allylation of ketone enolates.[b] Only unsubstituted allyls were employed in the reaction and therefore the regioselectivity of addition to the Rh-allyl intermediate was not apparent. It was noted, however, that the kinetic enolate was allylated exclusively, even if this led to the formation of a more sterically congested quaternary center (Scheme 2.9).

Scheme 2.9 *Rhodium-catalyzed decarboxylative allylation reactions*

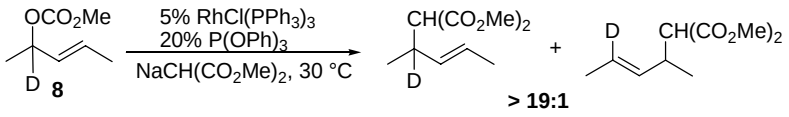


No further progress was reported in the field until 1998 when the Evans group initiated studies designed to more closely examine the mechanistic details of the rhodium-catalyzed allylic alkylation reaction.[8] Initially they disclosed that the

combination of Wilkinson's catalyst and trimethylphosphite catalyzed the very selective formation of branched allylation products. For instance, dimethylmalonate underwent allylation in the presence of **7b**, 5 mol% $RhCl(PPh_3)_3$ and 20 mol% $P(OMe)_3$ to afford a 91% yield of the terminal alkene product. It should also be noted that Takeuchi reported that the combination of $[Rh(COD)Cl]_2$ and triphenylphosphite was catalytically active in the allylic alkylation reaction soon after Evans's publication.[9]

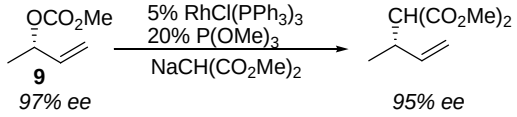
Although the original Tsuji studies suggested that the mechanism of the rhodium-catalyzed allylation reaction may not proceed *via* traditional π-allyl chemistry (*vida supra*), work by the Evans group led to a more thorough understanding of the unique nature of the reaction. Deuterium labeling studies supported Tsuji's proposal of Rh σ-allyl intermediates to explain the different product ratios obtained from regioisomeric allyl carbonate starting materials (i.e. **7a** and **7b**). Allylic carbonate **8** was deuterated at the carbon bearing the carbonate leaving group in order to probe the regioselectivity of alkylation without sterically biasing allylation at one terminus over the other; if a Rh π-allyl is formed in the reaction a methyl group will be located on both termini and nucleophilic attack should occur in equal amounts at both positions. Rather than obtaining an equal distribution of products, however, nucleophilic attack occurred overwhelmingly at the deuterated carbon once bearing the carbonate (Scheme 2.10).

Scheme 2.10 *Deuterium-labeling studies*



The stereochemical course of the reaction was explored by synthesizing highly enantiopure **9** (Scheme 2.11). Almost complete transfer of chirality occurred, which would not be expected from a Rh π-allyl intermediate. Facile σ-π-σ isomerization would lead to complete racemization of such a species.

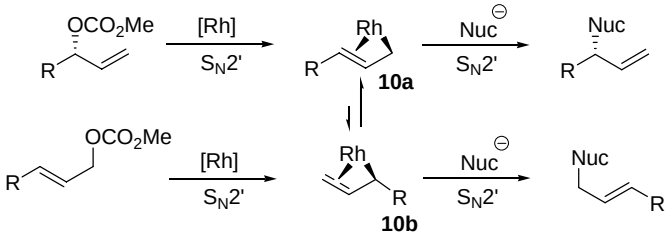
Scheme 2.11 *Stereospecificity of the Rh-catalyzed allylation reaction*



Based on these results a reaction mechanism was proposed in which a Rh-*enyl* complex is formed; that is one which contains distinct σ and π interactions of the ligand with the metal (Scheme 2.12). The Rh-*enyl* complex is proposed to arise from a S_N2' displacement of the carbonate by rhodium, which inverts the original stereocenter without permitting racemization. A S_N2' displacement was proposed rather than a S_N2 displacement in order to account for the decreased reactivity of crotyl carbonate compared to allyl carbonate. It is then proposed that the nucleophile adds *via* another S_N2' displacement, which results in the net retention of stereochemistry and substitution of the nucleophile on the carbon once bearing the leaving group, as observed in the deuterium labeling study. It was also proposed that for certain systems in which it was observed that linear carbonates form significant

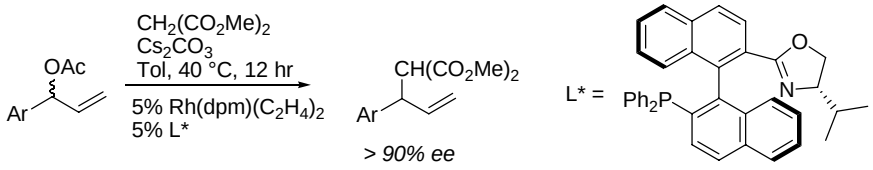
amounts of branched product, isomerization of **10a** to **10b** is slow compared to the reverse reaction as a result of increased steric interactions in **10b**. Such an isomerization pathway would allow for the development of enantioselective reactions.

Scheme 2.12 *Rh-enyl intermediates*



In the ensuing years, allylic amination[10] and etherification[11] reactions were developed using rhodium catalysts. Then, in 2003, the Hayashi group reported the enantioselective allylation of stabilized nucleophiles which capitalizes on the isomerization of *enyl* intermediates **10a** and **10b**.[12] In order to achieve high levels of enantioselectivity in the reaction it was disclosed that the concentration of the nucleophile in solution had to be kept low. This in turn gave the proposed Rh-*enyl* intermediates time to equilibrate prior to nucleophilic attack. A low concentration of nucleophile was achieved by the slow addition of dimethyl malonate, as well as through the use of a weaker base, Cs_2CO_3, which decreased the amount of deprotonation, and therefore nucleophile, in the reaction mixture. The optimized reaction conditions successfully yielded aryl, terminal alkenes in greater than 90% ee (Scheme 2.13).

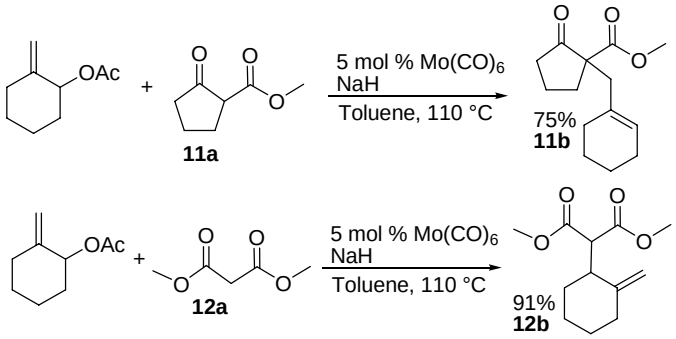
Scheme 2.13 *Enantioselective Rh-catalyzed allylation*



2.1.3 Molybdenum-Catalyzed Allylic Alkylation Reactions

Molybdenum has also been shown to catalyze allylic alkylation reactions. In the initial communication on the decarboxylative allylation reaction, Tsuji reported that molybdenum hexacarbonyl catalyzed the reactions illustrated in Scheme 2.9 to yield the same products as those obtained in the Rh-catalyzed reaction, although more forcing conditions and increased catalyst loadings were necessary.[b] Research primarily conducted by the Trost group has provided interesting insight into the selectivity of these reactions.[13] Initially $Mo(CO)_6$ and $Mo(bpy)(CO)_4$ were used as catalysts, and although they showed lower catalytic activity than palladium, the regioselectivity of nucleophilic attack on the Mo π-allyl was complementary to that observed for palladium in certain cases. As shown in Scheme 2.14, the regioselectivity of addition was strongly influenced by the identity of the nucleophile. While allylation of **11a** yielded primarily product derived from attack at the least hindered terminus of the Mo π-allyl, **12a** reacted to afford a 91% yield of the terminal double bond product **12b**. Further experimentation supported the initial hypothesis that, presumably because of steric reasons, bulkier nucleophiles preferentially attack the less hindered π-allyl terminus.

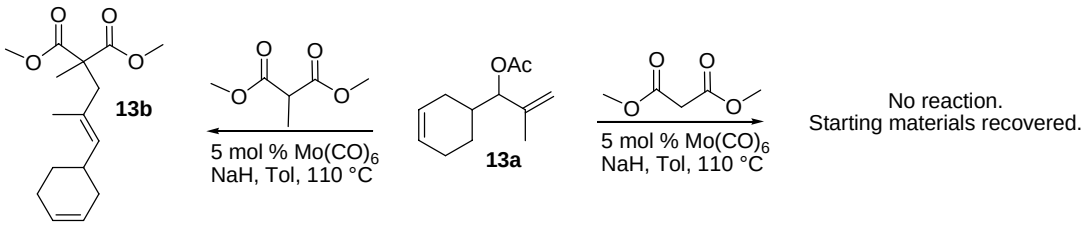
Scheme 2.14 *Regioselectivity of Mo-catalyzed allylation reactions*



This result indicates that there is a delicate balance between the steric requirements imposed by the size of the nucleophile and electronic factors which favor nucleophilic attack at the more substituted carbon bearing a larger portion of carbocation character in the electrophilic Mo π-allyl complex. Further complications arise when highly substituted allylic acetates are used in the coupling reaction. For example, when **13a** is subjected to the conditions of catalysis with dimethyl malonate, no reaction occurs. However, addition of dimethyl methyl malonate affords allylated product in 73% yield (Scheme 2.15). While this result supports the hypothesis that larger nucleophiles attack at the less hindered terminus of the π-allyl, the failure of the less hindered dimethyl malonate to react was unexpected. This result was attributed to the *in situ* formation of a molybdenum-dimethyl malonate complex which is catalytically inactive. It was hypothesized that the increased substitution present in **13a** slowed ionization of the acetate group by molybdenum, which gave the inactive complex time to form. In contrast to dimethyl malonate, the authors proposed that dimethyl methyl malonate was too hindered to effectively coordinate to

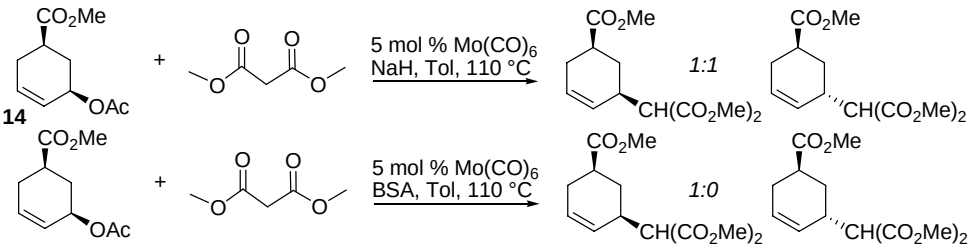
the metal, inhibiting complex formation and allowing for the formation of allylated product.

Scheme 2.15 *Allylation with bulky electrophiles*



The choice of base also influenced the outcome of allylation reactions.[14] While conducting experiments to probe the stereochemical outcome of molybdenum-catalyzed allylation reactions it was found that switching the base from sodium hydride to BSA (*N*,*O*-bis(trimethylsilyl)acetamide) dramatically altered the results (Scheme 2.16). Reactions in which sodium hydride was employed produced a 1:1 mixture of *cis* and *trans* products. Contrary to this, BSA led to the exclusive formation of *cis* product. This result was also explained by the *in situ* formation of a new catalyst complex in which BSA is coordinated to molybdenum. There was insufficient data to speculate on how this new complex is able to alter the selectivity of the reaction as well as if the net retention of stereochemistry results from a double inversion or double retention mechanism.

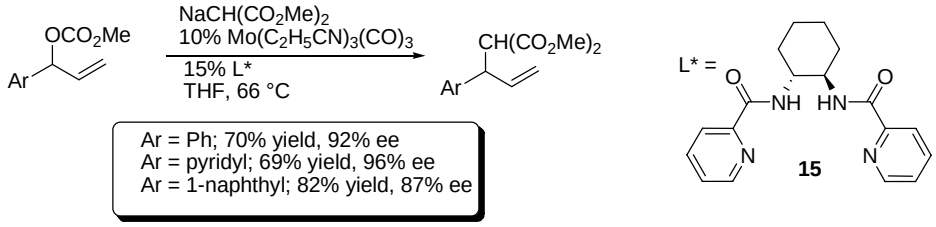
Scheme 2.16 *Base-dependent retention of configuration*



In 1990 Trost disclosed the synthesis of isonitrile analogs of $Mo(CO)_6$ that rendered the catalyst more active and selective.[15] By changing the catalyst to $Mo(CO)_2(^t\text{-BuNC})_4$ the reaction of dimethyl malonate with **13a** proceeded to afford a 48% yield of allylated product. This result also indicates that, in addition to bulky nucleophiles, highly substituted π-allyls can also lead to the preferential formation of linear products. The modified Mo complex also catalyzed the allylation of dimethyl malonate with **14** in the presence of sodium hydride with much higher levels of selectivity; the product was obtained as 99:1 ratio of diastereomers favoring the *cis* product.

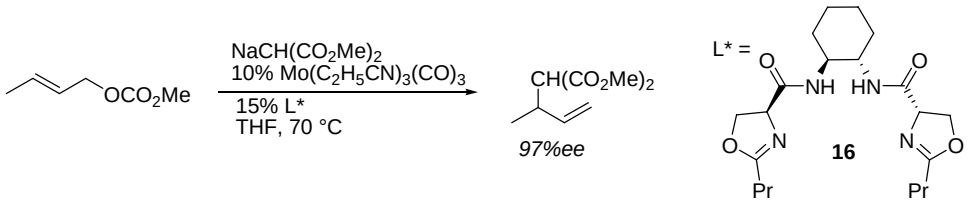
Having explored the details of the racemic Mo-catalyzed allylic alkylation reaction, the Trost group turned their attention toward the development of an enantioselective variant. The addition of ligand **15** to the reaction mixture provided arylated, branched products with high enantiopurity (Scheme 2.17). It was assumed that ligand **15** was bound in a bidentate fashion through interaction of the metal with the pyridyl nitrogens, although it was subsequently shown that this is not the case. Rather, NMR experiments and theoretical calculations indicate that deprotonation of the amide nitrogens in the basic reaction mixture results in tridentate coordination of the ligand with only one of the pyridyl nitrogens and either both amide nitrogens or one amide nitrogen and one amide carbonyl oxygen atom.[16]

Scheme 2.17 *Enantioselective Mo-catalyzed allylations*



The enantioselective molybdenum-catalyzed synthesis of alkyl-substituted branched, terminal alkenes was reported shortly thereafter.[17] A bisoxazoline derivative of **15**, ligand **16**, provides allylated products that are highly enantioenriched (Scheme 2.18).

Scheme 2.18 *Enantioselective Mo-catalyzed allylations*



Most recently, the pathway leading to retention of stereochemistry (Scheme 2.16) in Mo-catalyzed allylic alkylation reactions has been deduced.[18] By utilizing deuterium-labeled, branched allylic carbonates, NMR studies, and X-ray crystal structures, the authors were able to identify a double retention pathway, rather than the more common double inversion mechanism, as the reason for the net retention of configuration of the chiral center in the allylation reaction.

2.1.4 Ruthenium-Catalyzed Allylic Alkylation Reactions

The first example of a ruthenium-catalyzed allylic alkylation reaction was reported by Tsuji in which an analog of methyl acetoacetate was allylated with 1-

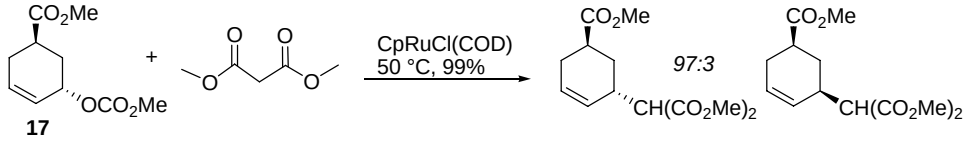
methylallyl carbonate in the presence of $RuH_2(PPh_3)_4$ at room temperature to yield a 32:58 mixture of linear and terminal alkene products.[c] Subsequent studies on ruthenium-catalyzed allylic alkylation reactions were conducted by Watanabe and co-workers. In their preliminary communication, a variety of Ru complexes were screened for their ability to catalyze the allylation of ethyl acetoacetate with cinnamyl carbonate.[19] While $Ru_3(CO)_{12}$, $RuH_2(PPh_3)_4$, $RuCl_2(PPh_3)_4$, and $RuCl_3$ showed little to no catalytic activity, Ru(cod)(cot) successfully catalyzed the allylation reaction at 80 °C in *N*-methylpiperidine to afford a 69% yield of products. The reaction was quite regioselective; a 93:7 ratio of products was obtained favoring the formation of the terminal alkene product that results from allylation at the more substituted terminus of the proposed Ru π-allyl intermediate.

While this result was encouraging and promised to offer yet another alternative to palladium catalysts for the allylation of stabilized nucleophiles, subjection of a variety of 1,3-dicarbonyl compounds to identical reaction conditions gave mixed results. Allylation of dimethyl and diethyl malonate proceed to give a 1:1 mixture of branched and linear products, while only trace amounts of acetylacetone were allylated under the reaction conditions. Allylation with crotyl carbonate resulted in a 90:10 mixture of branched and linear isomers when ethyl acetoacetate was employed as a nucleophile, however only a 1:1 mixture of regioisomers was recovered in the allylation diethyl malonate. This work was followed shortly thereafter by the disclosure of the Ru(II) complex, Cp*RuCl(COD), as an effective

catalyst for the allylic amination of cinnamyl carbonate with piperidine, which provided an 84:16 mixture of branched and linear alkene products.[20]

The non-methylated cyclopentadienyl analog of this complex, CpRuCl(COD), was found to be an effective catalyst for the allylic alkylation of stabilized nucleophiles with cyclic carbonates, and therefore the stereochemical outcome of the reaction was explored using this catalyst.[21] *Trans*-**17** underwent reaction with dimethyl malonate to yield primarily the *trans* product in a 97:3 ratio (Scheme 2.19). Similarly, the allylic amination of *trans*-**17** with piperidine yielded the *trans* product, whereas *cis*-**17** yielded the *cis* amination product. These results indicate that the ruthenium-catalyzed allylic alkylation reaction proceeds with net retention of stereochemistry, although the authors could only speculate that this is the consequence of a double inversion mechanism.

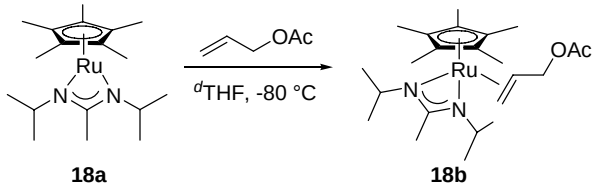
Scheme 2.19 *Retention of configuration*



It has also been reported that $[Cp^*Ru(OMe)]_2$ is an active catalyst for the decarboxylative allylation of allyl acetoacetate.[22] A 70:15:15 mixture of allyl acetone, diallylacetone, and acetone was recovered in a combined yield of 99% after five hours at 0 °C. In the same report it was disclosed that variable temperature NMR experiments conducted with the Ru-amidinate complex **18a** provided evidence that alkene coordination precedes oxidative addition of allyl acetate to Cp*Ru(II) (Scheme

2.20). Complex **18b** was characterized by ^{1}H and ^{13}C NMR at -80 °C; upon warming oxidative addition occurred to yield the η^3-allyl complex.

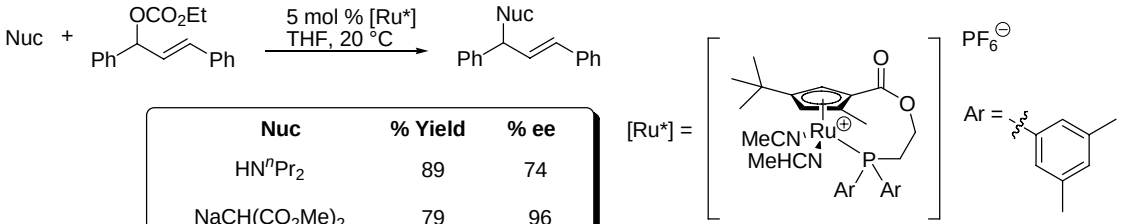
Scheme 2.20 *Pre-coordination of alkene*



18a **18b**

An asymmetric variant of the Ru-catalyzed allylation of stabilized nucleophiles was developed in 2001.[23] The incorporation of a ligand bearing planar-chirality resulted in the enantioselective formation of C-C and C-N bonds (Scheme 2.21). Catalyst modifications indicated that the length of the tether connecting the Cp ligand to phosphorus had a large impact on not only the selectivity of the catalyst, but also on the reactivity.

Scheme 2.21 *Enantioselective Ru-catalyzed allylation*

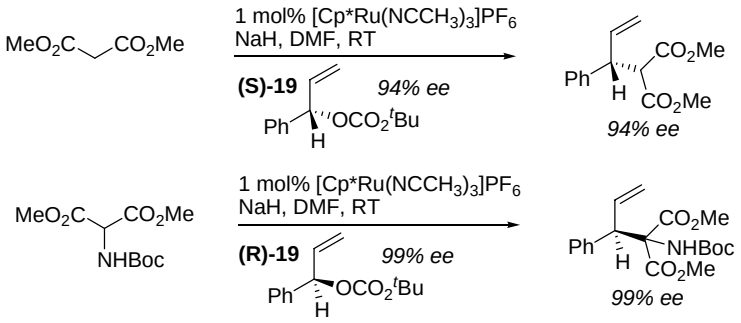


Nuc	% Yield	% ee
HN^nPr_2	89	74
$NaCH(CO_2Me)_2$	79	96
$NaCH(CO_2Et)_2$	77	96
$NaC(CH_3)(CO_2Me)_2$	68	83

Development of the enantioselective reaction was followed by research from the Trost group that demonstrated that the allylic alkylation of stabilized nucleophiles with $[Cp^*Ru(NCCH_3)_3]PF_6$ is highly stereospecific.[24] Complete retention of

configuration was observed when both **(*S*)-19** and **(*R*)-19** participated in the allylation reaction (Scheme 2.22). This result implies that nucleophilic attack is faster than epimerization of the chiral, non-racemic Ru π-allyl formed initially upon oxidative addition of the allylic carbonate.

Scheme 2.22 *Stereospecific reactions*

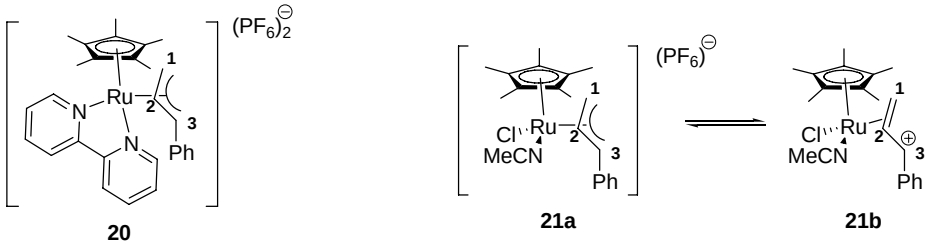


Also included in Trost's report was a brief survey of reaction conditions aimed at optimizing the selectivity of the reaction for the formation of branched, terminal alkenes. Increasing the size of the cyclopentadienyl ligand on Ru resulted in a dramatic increase in selectivity; while $[CpRu(NCCH_3)_3]PF_6$ catalyzed the allylation of dimethyl malonate with cinnamyl carbonate to preferentially form the linear isomer in a 1:2 (branched:linear) ratio, $[Cp^*Ru(NCCH_3)_3]PF_6$ catalyzed the selective formation of branched products in a 9:1 ratio under otherwise identical reaction conditions.

Several crystallographic studies have since been conducted that attempt to explore the origin of the regioselective addition of nucleophiles to the substituted terminus of Ru π-allyls. An X-ray structure of **20** revealed that the Ru-C_3 distance was substantially longer (0.202 Å) than the Ru-C_1 and Ru-C_2 distances (Scheme

2.23).[25] This indicates that slightly more carbocation character is present at the benzylic carbon, which can explain preferential nucleophilic attack at that position. Despite the elongated Ru-C_3 bond, subsequent ^{13}C NMR studies on **21a** were used to show that, although **21b** could be a conceivable resonance structure of **21a** based on the extended Ru-C_3 distance measured in **20**, the ^{13}C shift of the para carbon in the phenyl ring does not indicate any carbocation character.[26] This would be expected if the resonance stabilized benzylic carbocation of **21b** were a significant resonance contributor. Although a Ru-*enyl* intermediate, such as those proposed by Evans to explain the stereospecificity of Rh-catalyzed allylic alkylations (*vida supra*), could also conceivably be invoked in the Ru system to rationalize the retention of stereochemistry reported by Trost, this possibility was also dismissed upon examination of the X-ray structure of **21a**. The bond distances between C_1 and C_2, as well as between C_2 and C_3, were reported to be almost identical (1.415 Å and 1.412 Å), which would not be expected in a structure with a discrete double and single bond. It seems the best way to conceptualize intermediates such as **20** is to regard them as traditional, although asymmetric, π-allyl complexes with an extended Ru-C bond to the benzylic carbon.

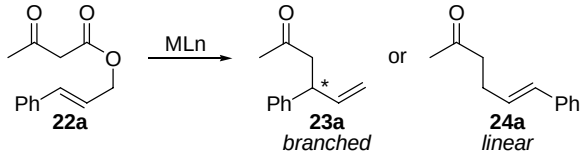
Scheme 2.23 *X-ray structure determination*



2.2 Efforts in the Development of Iridium-Catalyzed Decarboxylative Allylation Reactions

In conjunction with our studies on the palladium-catalyzed decarboxylative allylation of ketone enolates, we sought to identify other transition metal complexes that were viable catalysts for the allylation reaction. Specifically, we wanted to target catalysts that selectively formed branched, terminal alkene products (i.e., **23a**) from β-keto ester starting materials such as **22a** (Scheme 2.24). We viewed the development of such a reaction as an important complement to the palladium-catalyzed system, which favors the synthesis of linear alkenes. In addition, this type of regioselectivity would allow for the development of an enantioselective variant of the decarboxylative allylation reaction for substrates such as **22a** that do not give rise to symmetrically substituted π-allyl intermediates upon oxidative addition of the substrate to the transition metal catalyst.

Scheme 2.24



As discussed previously, iridium complexes are known to effectively catalyze the allylation of stabilized nucleophiles with very high selectivity for formation of branched alkene products. In addition to this, results from the Hartwig group indicated that iridium-phosphoramidite complexes such as that depicted in Scheme 2.7 were capable of inducing high levels of enantioselectivity in allylic etherification and amination reactions. This made iridium complexes an attractive choice for catalyst development as they appeared to not only preferentially yield branched

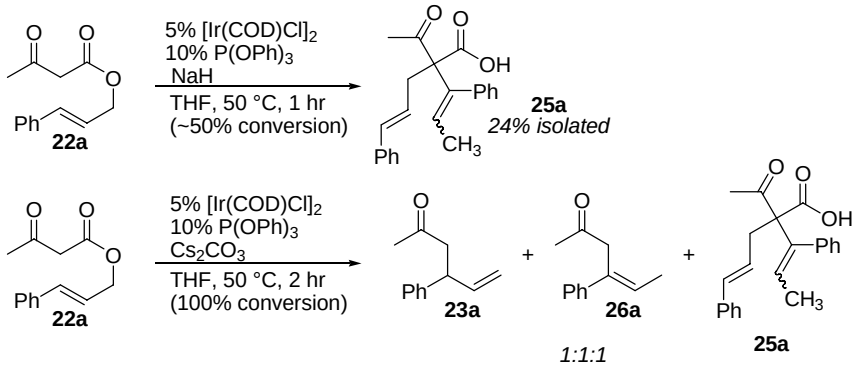
products in the related allylic alkylation of stabilized nucleophiles, but also showed promise to do so with high levels of enantioselectivity.

β-Keto ester **22a** was selected as a model substrate for the development of the proposed iridium-catalyzed decarboxylative allylation reaction. To begin, **22a** was subjected to 10 mol% $[Ir(COD)Cl]_2$ and 40 mol% $P(OPh)_3$ in THF. The reaction temperature was slowly increased to 65 °C over the course of 48 hours. The starting material remained unreacted until the temperature reached 65 °C; at this temperature branched product **23a** formed over the next 24 hours. Although the desired terminal alkene was the predominant product of the reaction by ^1H NMR, attempts to repeat this reaction, even with a stoichiometric amount of iridium, were largely unsuccessful. The reaction was also attempted in acetonitrile and methanol, however acetonitrile caused a large amount of iridium metal to deposit on the reaction flask and methanol only converted **22a** into the dimethoxy ketal.

The effect of base was also explored. While the addition of potassium carbonate produced a very complex mixture of products, the addition of sodium hydride led to the unexpected isolation of **25a** in a 24% yield (Scheme 2.25). Compound **25a** presumably arises from diallylation of the acidic α position of **22a** or an intermediate Ir π-allyl carboxylate. The isolation of carboxylic acid product appears to indicate that decarboxylation of the Ir(III) allyl carboxylate intermediate is not facile under these conditions. Presumably the first allylation event occurs at the more substituted terminus of the Ir π-allyl, and is then followed by isomerization of the terminal double bond to form the tri-substituted alkene. These kinds of

isomerizations are known to be catalyzed by $[Ir(COD)Cl]_2$ under basic conditions.[27] Examination of the product indicates that the second allylation occurs at the unsubstituted terminus of the π-allyl, perhaps due to the increased steric hindrance present at the α position following addition of the first allyl group. Changing the base from sodium hydride to cesium carbonate produced similar results, although the desired branched product **23a**, along with **26a**, derived from a double bond isomerization of **23a**, were also formed in a 1:1:1 ratio by ^{1}H NMR. Replacing triphenylphosphite with tributylphosphite only led to an even more complex mixture of products.

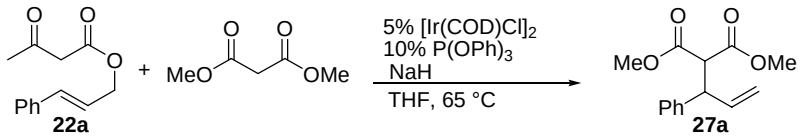
Scheme 2.25 *Formation of carboxylic acid products*



The addition of dimethylmalonate to the Ir-catalyzed reaction of **22a** with sodium hydride revealed that the intermolecular allylation of dimethylmalonate was faster than the intramolecular reaction (Scheme 2.26). This result, along with the isolation of diallylated product **25a**, demonstrates that formation of the Ir π-allyl is readily occurring upon addition of $[Ir(COD)Cl]_2$ to a solution of **22a**. Unfortunately, decarboxylation and nucleophilic attack seem to be much more sluggish. These results led us to turn our attention to other transition metal complexes, although

several notable reports on Ir-catalyzed allylation reactions have been reported since our study. Hartwig's group successfully employed iridium catalysts to enantioselectively allylate ketone nucleophiles *via* the addition of silyl enol ethers to allylic carbonates,[28] while the Han group disclosed the enantioselective decarboxylative allylic amidation of allyl benzyl imidodicarbonates with $[Ir(COD)Cl]_2$ in the presence of DBU and proton sponge.[29] In good agreement with our observations, the researchers reported that decarboxylation was slow and occurred only after the allylation of nitrogen.

Scheme 2.26 *Intermolecular allylation*



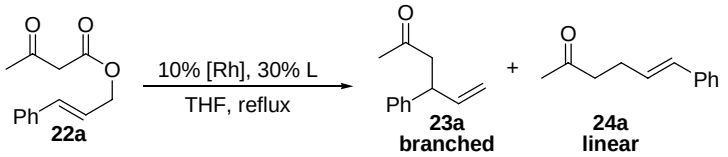
2.3 Efforts in the Development of Rhodium-Catalyzed Decarboxylative Allylation Reactions

Rhodium complexes were viewed as a possible alternative to $[Ir(COD)Cl]_2$ that would possibly undergo more facile decarboxylation. Not only has rhodium been shown to catalyze the allylic alkylation of stabilized nucleophiles, $RhH(PPh_3)_4$ has been used successfully in the decarboxylative allylation reaction (*vida supra*). We initially focused on Wilkinson's catalyst, $RhCl(PPh_3)_3$, in the presence of different phosphite ligands.

Substrate **22a** was again chosen as a model compound for the rhodium studies. Our initial experiment involved subjection of **22a** to 10 mol% $RhCl(PPh_3)_3$ and 30 mol% $P(OPh)_3$ in refluxing THF. Disappointingly, only starting material was

present after two days. We soon discovered that an equivalent of base was necessary for reaction to occur. The addition of sodium hydride led to the formation of the linear product **24a** (Table 2.2, entry 1). While this result was encouraging, **24a** was not the isomer we desired. We found that changing the phosphite ligand from $P(OPh)_3$ to $P(OBu)_3$ led to the formation of the desired terminal alkene, however the linear isomer was formed along with it as a 1:1 mixture (entry 2). Changing the base from sodium hydride to cesium carbonate altered the selectivity to again favor production of **24a**; only a trace amount of **23a** was observed by ^{1}H NMR.

Table 2.2 *Survey of conditions*



Entry	Catalyst	Ligand	Base	b:l (% NMR conv.)
1	$RhCl(PPh_3)_3$	$P(OPh)_3$	NaH	0:1 (100%)
2	$RhCl(PPh_3)_3$	$P(OBu)_3$	NaH	1:1 (100%)
3	$RhCl(PPh_3)_3$	$P(OBu)_3$	Cs_2CO_3	0:1 (100%)
4	$Rh(acac)(CH_2{=}CH_2)_2$	----	NaH	1:2 (75%)
5	$Rh(acac)(CH_2{=}CH_2)_2$	$P(OBu)_3$	Cs_2CO_3	1:2 (100%)
6	$Rh(acac)(CH_2{=}CH_2)_2$	$P(OBu)_3$	NaH	1:2 (70%)
7	$Rh(acac)(CH_2{=}CH_2)_2$	$P(OPh)_3$	NaH	0:1 (40%)

We also explored other rhodium sources in the reaction. While $Rh(acac)(CO)_2$ failed to catalyze the decarboxylation of starting material, $Rh(acac)(CH_2{=}CH_2)_2$ displayed catalytic activity, although the product selectivity remained poor. The reaction of **22a** with $Rh(acac)(CH_2{=}CH_2)_2$, $P(OBu)_3$, and either sodium hydride or cesium carbonate yielded a 1:2 ratio of branched and linear products (entries 6 and 7). As was the case when Wilkinson's catalyst was employed

as the Rh source, the addition of $P(OPh)_3$ led to exclusive formation of the linear product isomer (Entry 7). We also examined the effect of a less polar solvent. Unfortunately, reactions conducted in refluxing toluene did not yield any product.

Dimethylmalonate was also introduced into the reaction of **22a** with 10 mol% $RhCl(PPh_3)_3$, 30 mol% $P(OPh)_3$ and NaH. Unlike the reaction with iridium, only intramolecular allylation occurred. No products arising from the allylation of dimethylmalonate were observed.

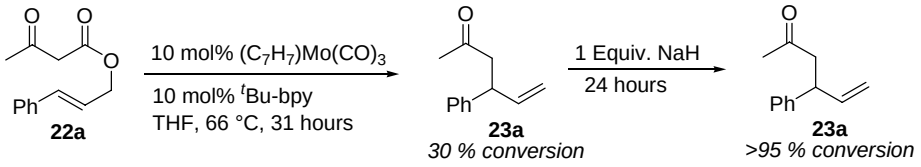
While the formation of a 1:1 mixture of regioisomers from linear starting material indicates that the mechanism of decarboxylative allylation does not proceed by a simple double S_N2' displacement as proposed by Evans for the allylation of stabilized nucleophiles[b] (Scheme 2.12), the product distribution resulting from branched β-keto ester starting material would be an interesting observation given the known impact of the position of the allylic leaving group on the regiochemistry of allylation. Nevertheless, the lack of any appreciable selectivity for the formation of branched, terminal alkene product in the rhodium-catalyzed decarboxylative allylation reaction indicated to us that our time would be better spent exploring the catalytic activity of molybdenum and ruthenium complexes.

2.4 Efforts in the Development of Molybdenum-Catalyzed Decarboxylative Allylation Reactions

The screening of molybdenum complexes for catalytic activity also began with β-keto ester **22a**. In one of the initial experiments **22a** was subjected to 10 mol% $(C_7H_7)Mo(CO)_3$ and 10 mol% *tert*-butyl bipyridine (^{t}Bu-bpy) in refluxing THF. After 31 hours ^{1}H NMR indicated that the reaction had proceeded to only 30%

conversion although, gratifyingly, the branched isomer **23a** appeared to be the major product. In an effort to increase the rate of reaction sodium hydride was added. This had an advantageous effect on the reaction; after an additional 24 hours no starting material was detected by ^{1}H NMR spectroscopy. Instead it appeared that an almost quantitative conversion to the desired terminal alkene had occurred (Scheme 2.27). Other bases such as cesium carbonate and BSA were later shown to be ineffective.

Scheme 2.27 *Effect of adding base to the reaction mixture*

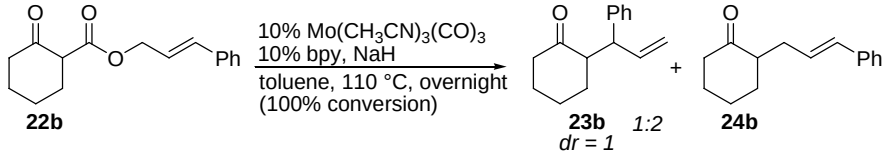


The selectivity of the reaction was slightly altered upon changing the solvent from THF to toluene and increasing the temperature to 110 °C. When **22a** was subjected to 10 mol% $(C_7H_7)Mo(CO)_3$,10 mol% ^{t}Bu-bpy and one equivalent of NaH in refluxing toluene the branched regioisomer was still the major product, although the linear isomer was also formed in a 1.6:1 ratio. Repeating the experiment yielded a slightly improved 2.2:1 ratio of products by ^{1}H NMR. Given the higher reaction temperature in toluene we were curious to see if the reaction would proceed without the addition of base. Our first attempt at converting **22a** to decarboxylation products without adding base was successful. After refluxing overnight in toluene with 10 mol% $(C_7H_7)Mo(CO)_3$ and 10 mol% ^{t}Bu-BPY the reaction proceeded to approximately 60% conversion, preferentially yielding the branched isomer. Unfortunately, multiple attempts at repeating this result were fruitless.

We also explored the catalytic activity of $Mo(CH_3CN)_3(CO)_3$. The reaction of **22a** with 10 mol% $Mo(CH_3CN)_3(CO)_3$, 10 mol% bpy, and sodium hydride afforded a slightly reduced 1.3:1 ratio of allylation products favoring the branched isomer. Running the reaction without base yielded only a trace amount of product. The reaction was also conducted in the presence of dimethylmalonate; it was found that only intramolecular allylation occurred.

Substrate **22b** was synthesized in order to probe the reactivity of substrates with α substituents. As illustrated in Scheme 2.28, **22b** was successfully allylated when sodium hydride was added to the reaction mixture. It was noted that the selectivity of the reaction was reversed after altering the enolate to that of cyclohexanone. The linear product **24b** was favored over the branched product in a 1:2 ratio. The reversal of selectivity is in line with the observation of the Trost group that increasing the size of the nucleophile can lead to an increase in the amount of nucleophilic attack at the unsubstituted terminus of the Mo π-allyl.

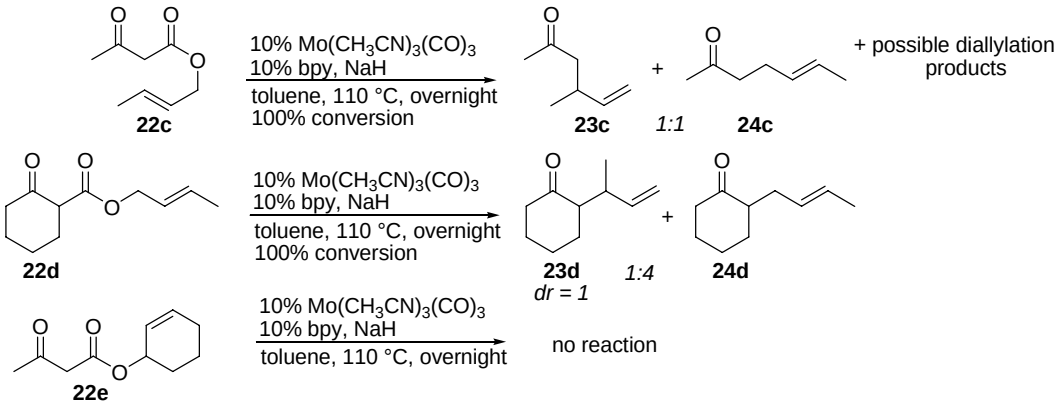
Scheme 2.28 *Regioselectivity of allylation*



The scope of the reaction was further explored by synthesizing the crotyl alcohol derived β-keto ester **22c** (Scheme 2.29). Substrate **22c** participated in the decarboxylative allylation reaction to afford a mixture of products by ^1H NMR. One half of the mixture consisted of the terminal alkene **23c**, and the remaining material

consisted of primarily the linear product, along with what was tentatively identified as diallylated product.

Scheme 2.29 *Regioselectivity of allylation*



As was the case for **22b**, the bulkier cylclohexanone derivative of **22c**, **22d,** reacted to preferentially form the linear alkene in a 1:4 ratio. Unfortunately, the cyclohexenol derived **22e** did not participate in the reaction. The selectivity of these reactions was not considered to be high enough to pursue molybdenum-catalyzed reactions any further, especially given our concurrent development of ruthenium-catalyzed decarboxylative allylation reactions which proceeded under much milder conditions.

2.5 The Development of Ruthenium-catalyzed Decarboxylative Allylation Reactions

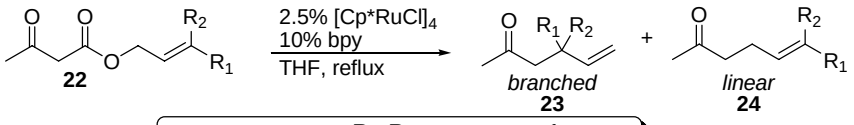
2.5.1 Racemic Reactions

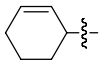
We were interested in pursing ruthenium catalysts for the decarboxylative allylation reaction for the same reasons that we were interested in iridium, rhodium, and molybdenum catalysts; ruthenium-catalyzed allylic alkylations had been shown

to proceed with high levels of regioselectivity favoring formation of branched products. In addition to this, the almost perfect retention of configuration demonstrated by Trost in the allylation of stabilized nucleophiles with chiral, non-racemic allylic carbonates hinted at the possibility of developing a stereospecific decarboxylative allylation reaction. Unlike iridium, rhodium, and molybdenum, ruthenium proved to be capable of catalyzing very regioselective decarboxylative allylation reactions under extremely mild reaction conditions.

Many of the reported Ru complexes that catalyze highly regioselective allylation reactions contain a Cp* ligand (*vida supra*), therefore many of the ruthenium complexes screened for catalytic activity in the decarboxylative allylation reaction contained this ligand. One of these complexes, $[Cp^*RuCl]_4$, along with bipyridine (bpy) ligand, was screened for activity with a variety of β-keto ester substrates.

Table 2.3 *Substrate scope*



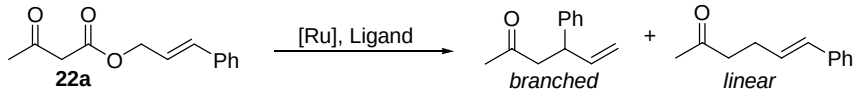
Substrate	R_1, R_2	23:24 (*by ^{1}H NMR*)
22a	Ph, H	3:1
22c	Me, H	2:1
22f	Et, H	complex mixture
22g	Me, Me	no reaction
22e		no reaction

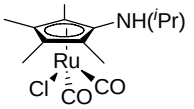
It is apparent when examining the results in Table 2.3 that aryl-substituted β-keto esters undergo reaction much more readily than those with alkyl substituents.

Substrate **22a** reacted with the highest regioselectivity, 3:1, in favor of the branched isomer. While **22c** reacted with moderate selectivity (2:1), the closely related ethyl analog, **22f**, afforded a complex mixture of products under the conditions of catalysis. Substrates **22g** and **22e** failed to yield any decarboxylation products. Due to its more favorable reactivity, **22a** was selected for further optimization studies.[30]

A series of ruthenium complexes were screened for activity in the presence of different ligands. Table 2.4 shows the results obtained when 10 mol% ruthenium and 10 mol% ligand were employed as the catalyst. The ruthenium tetramer, $[Cp^*RuCl]_4$, was the most active and regioselective catalyst, although the addition of bpy was critical for achieving the best results. For instance, catalysis with 2.5 mol% $[Cp^*RuCl]_4$ and no additional ligand in methylene chloride only proceeded to 9% conversion in 1.5 hours and ultimately yielded a 6.2:1 ratio of regioisomers (branched:linear), whereas upon the addition of bpy the reaction was complete in 1.5 hours and linear product was not visible in the ^1H NMR of the crude product. The addition of two equivalents of pyridine failed to generate a catalyst that was comparable to the combination of $[Cp^*RuCl]_4$ and bpy. This is most likely due to the reported formation of a Ru dimer, rather than the desired monomer, upon the addition of pyridine to $[Cp^*RuCl]_4$.[31] This complex produced the branched product in a 2.5:1 ratio with linear product. The addition of the bidentate ligand TMEDA (tetramethylenediamine) improved the selectivity somewhat (9.1:1), but bpy is still clearly the optimal ligand for the reaction.

Table 2.4 *Catalyst optimization*



[Ru]	Ligand	Time (h)	Solvent	Temp	Conversion	b:l
$[Cp^*RuCl]_4$	---	1.5	CH_2Cl_2	25 °C	9%	6.2:1
$[Cp^*RuCl]_4$	2 equiv pyridine	1.5	CH_2Cl_2	25 °C	19%	2.5:1
$[Cp^*RuCl]_4$	*bpy*	*1.5*	*CH_2Cl_2*	*25 °C*	*100%*	*>19:1*
$[Cp^*RuCl]_4$	TMEDA	4	CH_2Cl_2	25 °C	100%	9.1:1
$[Cp^*RuCl]_4$	bpy	4	THF	25 °C	100%	10.7:1
$[Cp^*RuCl]_4$	---	1.5	CH_3CN	50 °C	66%	3:1
$[Cp^*RuOMe]_2$	bpy	0.25	CH_2Cl_2	25 °C	25%	10:1
$(methallyl)_2Ru(COD)$	bpy	16	THF	65 °C	100%	2:1
$(methallyl)_2Ru(COD)$	---	16	CH_2Cl_2	40 °C	no reaction	
$(methallyl)_2Ru(COD)$	bpy	16	CH_2Cl_2	40 °C	no reaction	
$CpRu(NCCH_3)_3PF_6$	bpy	16	CH_2Cl_2	25 °C	49%	10:1
$[RuCl_2(cymene)]_2$	bpy	16	CH_2Cl_2	25 °C	no reaction	
$[RuCl_2(BINAP)]_x$	bpy	16	CH_2Cl_2	25 °C	no reaction	
$RuCl_2(COD)$	bpy	16	CH_2Cl_2	25 °C	no reaction	
	---	16	THF	65 °C	no reaction	

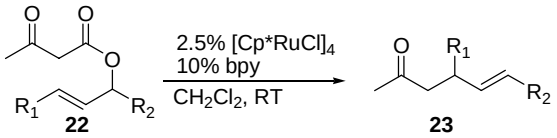
Solvent and reaction temperature also influenced the outcome of the reaction. For example, when THF was used as the solvent in the presence of $[Cp^*RuCl]_4$ and bpy a 10.7:1 mixture of regioisomers was obtained after four hours, compared to the >19:1 mixture obtained after 1.5 hours when the solvent was methylene chloride. Even more significantly, when the substrate was allowed to react in refluxing THF the regioselectivity plummeted to 3:1 (see Table 2.3).

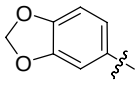
Having identified the optimal catalytic system for the Ru-catalyzed decarboxylative allylation reaction as 2.5 mol% $[Cp^*RuCl]_4$ and 10 mol% bpy in methylene chloride at room temperature, we sought to expand the substrate scope. A

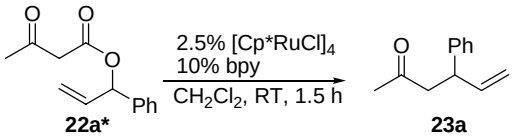
brief re-examination of alkyl substituted β-keto esters such as **22e** and **22f** indicated that these substrates did not react under the optimized conditions. Instead we chose to focus on the rearrangement of aryl-substituted β-keto esters.

As Table 2.5 shows, a variety of cinnamyl β-keto esters possessing electron-withdrawing and electron-donating groups reacted cleanly to give very high yields of branched products. While substrates possessing electron-donating groups such as **22j** underwent complete conversion to product very rapidly, substrates bearing electron-withdrawing groups reacted much more slowly. The presence of an *ortho* substituent also slowed the reaction considerably; **22i** took five days to reach complete conversion. We attribute the decreased reactivity of **22i** to the increased steric hindrance present in close proximity to the alkene. This may inhibit the pre-coordination of Ru, which has been proposed to initiate ionization of the leaving group in Ru-catalyzed allylic alkylation reactions (see Scheme 2.20). Substrate **22o**, possessing an acidic proton, reacted to yield a complex mixture of products including **23o**, which was isolated in only an 18% yield.

Table 2.5 *Substrate scope*

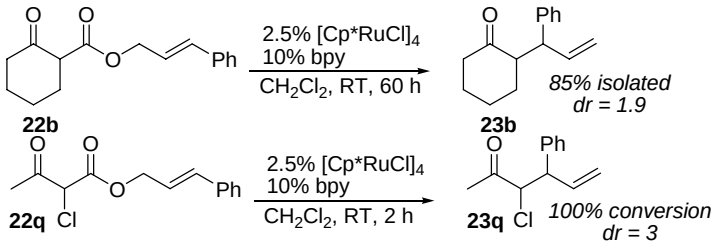


Substrate	R_1	R_2	Time	% Yield	Substrate	R_1	R_2	Time	% Yield
22a	Ph	H	1.5 h	94	**22m**	*p*-$C_6H_4CF_3$	H	40 h	90
22h	*p*-tolyl	H	2 h	96	**22n**	Ph	Ph	1 h	67
22i	*o*-tolyl	H	5 d	81	**22o**	*p*-C_6H_4OH	H	1 hr	18
22j	*p*-C_6H_4OMe	H	15 min	91	**22p**		H	30 min	91
22k	*o*-C_6H_4OMe	H	15 min	93					
22l	*p*-C_6H_4Cl	H	4 h	96					



Substrates that decarboxylate to yield enolates other than that derived from acetone were also subjected to catalysis with $[Cp^*RuCl]_4$ and bpy. Cyclohexanone derived **22b** reacted slowly at room temperature, but provided a very good yield of **23b** (Scheme 2.30). Unfortunately the diastereoselectivity was only 1.9. The rearrangement of α-chloro ester **22q** was quite facile and occurred with a slightly improved dr of 3.

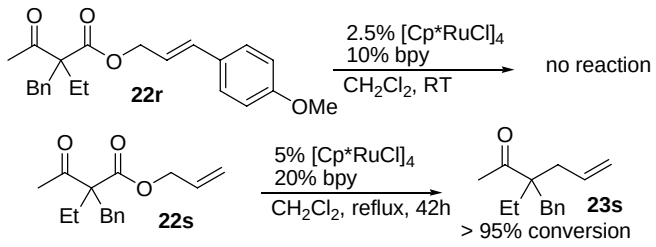
Scheme 2.30 *Diastereoselectivity of allylation*



The presence of two α substituents slowed the reaction considerably (Scheme 2.31). Substrate **22r** failed to react under standard conditions, despite the presence of

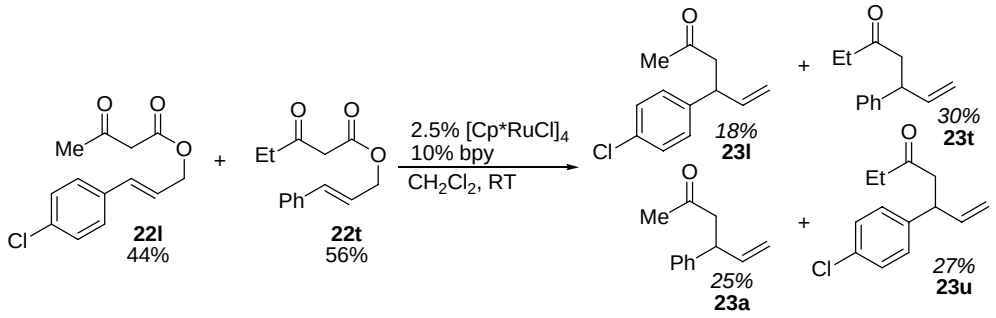
a *p*-methoxy group on the aryl ring, which had been shown to significantly accelerate the reaction (Table 2.5). Allyl acetoacetate derivative **22s** also failed to react at room temperature. It was necessary to increase both the catalyst loading and reaction temperature in order to achieve high levels of conversion to **23s**.

Scheme 2.31 *Formation of quaternary centers*



A crossover experiment was performed with substrates **22l** and **22t** in an effort to gain a more thorough understanding of the nature of the Ru enolate complex. Following subjection of a mixture of the two substrates to the optimized reaction conditions, an almost equimolar mixture of four products was observed by GC and mass spectrometry. These products were identified as those shown in Scheme 2.32, indicating possible intermolecular crossover of enolates formed following decarboxylation. It was also shown in a related study that during the course of the reaction recombination of Ru-carboxylates with π-allyls occurs to regenerate β-keto esters, which could scramble the starting material (*vida infra*). It is feasible that crossover products could form through this pathway as well.

Scheme 2.32 *Crossover experiment*

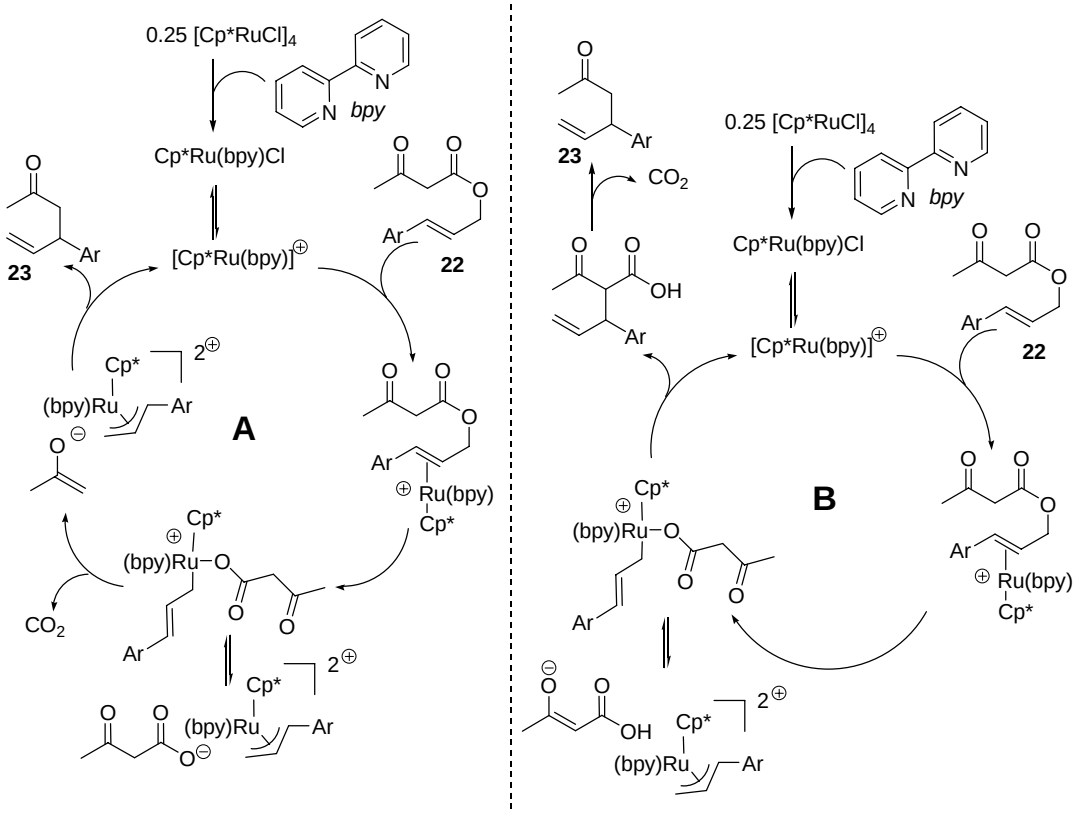


The successful conversion of **22t** to **23t** and **23u** demonstrates another important feature of the Ru-catalyzed decarboxylative allylation reaction. As was the case in the palladium-catalyzed reaction, the kinetic enolate generated immediately following decarboxylation is allylated exclusively. No products were observed that arise from allylation of the methylene carbon of the ethyl group. In fact, exposure of **22t** to the optimal conditions of catalysis afforded an 80% yield of **23t** after 7 hours.

More information about the enolate generated *in situ* was gained by adding one equivalent of dimethylmalonate to **22a** under standard reaction conditions. Rather than proton transfer from the acidic methylene carbon of dimethylmalonate to the unstabilized enolate, the reaction proceeded as before to yield **23a**. Dimethymalonate was not allylated, indicating that nucleophilic attack of the enolate on the Ru π-allyl is faster than deprotonation of dimethylmalonate.

Two possible catalytic cycles for this transformation are illustrated in Scheme 2.33. ^{1}H NMR experiments suggest that the role of bpy in the reaction is to aid in the dissociation of the ruthenium tetramer to the bpy ligated ruthenium monomer Cp*Ru(bpy)Cl. This conjecture is supported by the dramatic increase in reaction rate when bpy is added to the reaction mixture (see Table 2.4).

Scheme 2.33 *Proposed catalytic cycles*

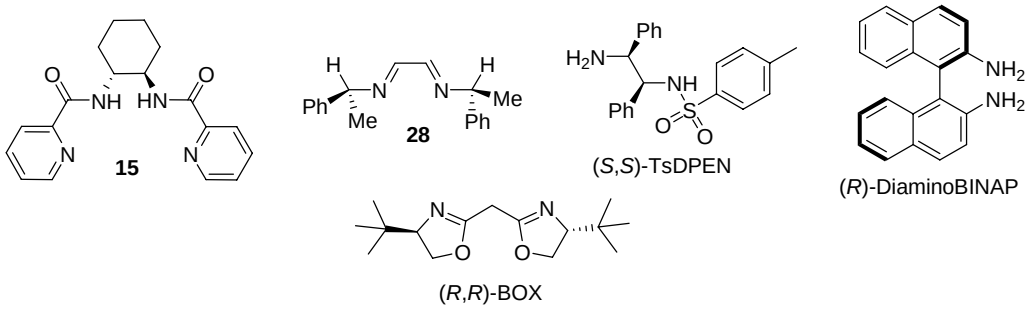


The resulting 18-electron Ru(II) complex is then proposed to undergo ionization of chloride in order to form a catalytically active 16-electron complex. The facile ionization of a related Cp*Ru(TMEDA)Cl complex has been reported.[32] We then propose that the β-keto ester undergoes oxidative addition to $[Cp^*Ru(bpy)]^+$, yielding a 18-electron ruthenium carboxylate. Pre-coordination of the alkene prior to oxidative addition is likely based on previous studies and the depressed reactivity of ortho-substituted **22i**. As shown in Cycle **A**, the decarboxylation of this intermediate produces an unstabilized enolate and a Ru π-allyl complex. The existence of a Ru π-allyl intermediate is supported by the successful conversion of the regiosiomeric β-keto esters **22a** and **22a*** to identical products (Table 2.5). Nucleophilic attack of the

enolate on the Ru π-allyl at the more substituted terminus liberates ketone product and regenerates the active 16-electron Ru(II) complex. Alternatively, we have not conclusively dismissed the possibility that intramolecular proton transfer and allylation precedes decarboxylation, as shown in Cycle **B**, although the reaction of disubstituted **22s** indicates that for certain substrates decarboxylation must precede allylation, as shown in Cycle **A.**

Having realized our initial goal of developing a catalytic system for the conversion of linear β-keto esters into branched ketone products, we turned our attention to the development of an enantioselective variant of the reaction. We originally chose to examine the effect of chiral, non-racemic, bidentate nitrogen based ligands, which we believed would be appropriate replacements for bpy. Unfortunately the pyridyl Trost ligand **15** and *t*-BuBOX failed to yield products with any enantioenrichment in the reaction of **22a**. Diimine ligand **28**, as well as diaminoBINAP and TsDPEN failed to induce any selectivity in the conversion of **22n** to **23n**.

Scheme 2.34

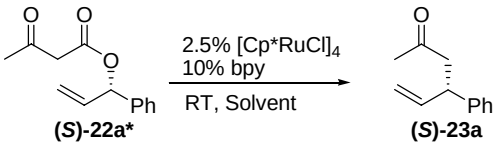


2.5.2 Stereospecific Reactions

Encouraged by Trost's disclosure that $[Cp^*Ru(NCCH_3)_3]PF_6$ catalyzed the stereospecific allylation of stabilized nucleophiles with enantioentriched allylic carbonates, we sought to examine the possibility that the Ru-catalyzed decarboxylative allylation reaction was also stereospecific.[33] The preparation of highly enantiopure β-keto esters began with the enzymatic kinetic resolution of allylic alcohols.[34] Upon addition of vinyl acetate, the lipase AK Amano 20 was able to resolve a variety of allylic alcohols to attain ee's greater than 90%. The highly enantioenriched alcohols were then converted to β-keto esters in one step following esterification with diketene[35] or Meldrum's acid[36] adducts.

Substrate **(*S*)-22a*** was synthesized with a 95% ee and subjected to 2.5 mol% $[Cp^*RuCl]_4$ and 10 mol% bpy in methylene chloride at room temperature. We were pleased to find that **(*S*)-23a** was synthesized with retention of configuration in a 79% ee. This translates to an 83% conservation of enantiomeric excess (cee = [product ee/reactant ee]).

Table 2.6 *Solvent effects on % cee*



(*S*)-22a* **(*S*)-23a**

Solvent	% cee
CH_2Cl_2	83
C_6H_6	86
THF	79
CH_3CN	89
Et_2O	89
MTBE	89
Acetone	84

In an effort to maximize the stereospecificity of the reaction a variety of solvents were screened in the transformation of **(*S*)-22a*** to **(*S*)-23a**. The highest

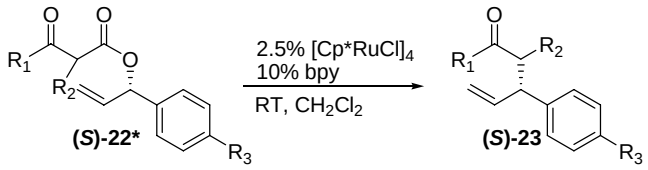
cee's were obtained in ethereal solvents. Utilization of diethyl ether or MTBE (methyl *tert*-butyl ether) increased the %cee to 89% (Table 2.6). Unfortunately, the reaction was very slow in these solvents; **(*S*)-22a*** proceeded to only 60% conversion after 6 hours at room temperature. When acetonitrile was employed as the solvent **(*S*)-23a** was also produced with an 89% cee, however sluggish reaction rates and poor regioselectivity had been noted in earlier catalyst optimization studies (Table 2.4), limiting its practicality as a solvent for the reaction. The superior reaction regioselectivity obtained in methylene chloride led to its selection for further studies.

A variety of other reaction conditions were explored in an attempt to maximize the conservation of ee in the transformation of **(*S*)-22a*** to **(*S*)-23a**. Lowering the reaction temperature had a negative impact on the stereospecificity of the reaction; the % cee of the reaction dropped to 77% when the reaction was run at 0 °C. Increasing the reaction temperature to 120 °C by heating the reaction mixture in a microwave had no effect on the stereochemical outcome of the reaction. Changing the Ru source to $[Cp^*RuOMe]_2$ with bpy functioning as the ligand also failed to alter the cee. These results led us to conclude that the reaction conditions identified as optimal for the racemic synthesis of allylated ketone enolates were also best for the stereospecific Ru-catalyzed reaction.

Having identified the optimal reaction conditions, the scope of the reaction was explored with the substrates illustrated in Table 2.7. Substrates possessing electron withdrawing and donating groups reacted to yield products with very good conservation of ee. Introduction of a *para* nitro group lowers the yield of the reaction

but provides products with a 98% cee. It is somewhat noteworthy that **(*S*)-22v*** reacts at all given that substitution of an electron withdrawing group on linear, aryl β-keto esters was previously shown to have a deleterious effect on the rate. It was found that the reaction of the achiral, straight chain analog **22v** was approximately 20 times slower than that of the unsubstituted phenyl analog **22a** (Scheme 2.35). The introduction of an α methyl group in **(*S*)-22w*** also increased the % cee relative to **(*S*)-22a***. Although the diastereoselectivity was low (1.5), the major diastereomer was isolated with a 93% cee. Lastly, variation of the enolate in substrates **(*S*)-22x*** and **(*S*)-22y*** decreased the cee of the reaction, although the successful isolation of products again demonstrates the unique kinetic selectivity of the reaction. Allylation only occurred at the methylene carbon once bearing the carboxylate and not, in the case of **(*S*)-22x***, at the more acidic benzylic position.

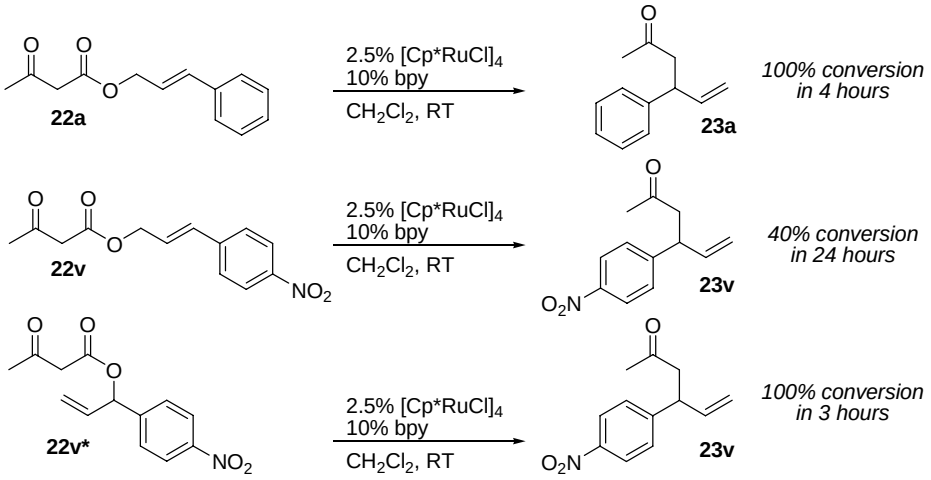
Table 2.7 *Substrate scope*



Substrate (.1M)	R_1	R_2	R_3	Time	%cee	%Yield
(*S*)-22a*	Me	H	H	1.5 hr	83	86
(*S*)-22h*	Me	H	Me	4 hr	87	81
(*S*)-22j*	Me	H	OMe	15 min	93	83
(*S*)-22l*	Me	H	Cl	4 hr	86	70
(*S*)-22v*	Me	H	NO_2	3 hr	98	49
(*S*)-22w*	Me	Me	H	2 hr	93[+]	76
(*S*)-22x*	Bn	H	H	3 hr	72	71
(*S*)-22y*	^{i}Pr	H	H	3 hr	58	68

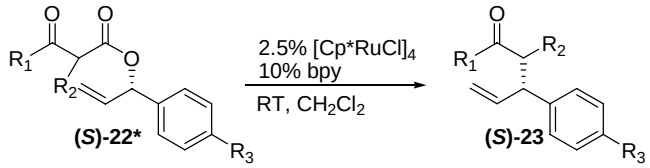
[+] of major diastereomer; dr = 1.5

Scheme 2.35 *Effect of a nitro group on the reaction rate of linear β-keto esters*

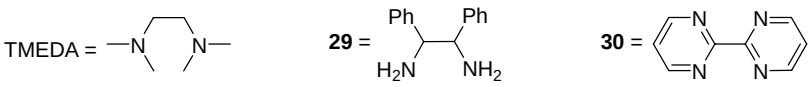


With a variety of substrates in hand we examined the effect of bidentate, nitrogenous ligands other than bpy on the stereospecificity of the reaction (Table 2.8). Mixed results were obtained with TMEDA serving as the ligand. While the % cee of **(*S*)-23a** increased from 83% to 87%, substitution of bpy with TMEDA led to a decline in % cee for all other substrates. The primary diamine ligand diphenylethylenediamine (**29**), led to a decrease in cee for **(*S*)-23a**, while bipyramidine (**30**) increased the cee to 92%. Unfortunately the reaction with this ligand was very slow, taking two days to reach 100% conversion. No clear trends were seen in this data, making it difficult to draw any meaningful conclusions regarding the effect of ligand on the stereospecificity of the reaction.

Table 2.8 *Ligand effects*

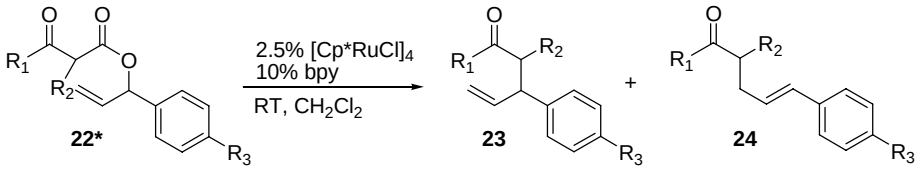


Substrate	R_1	R_2	R_3	Ligand	% cee (with bpy)
(*S*)-22a*	Me	H	H	TMEDA	87 (83)
(*S*)-22h*	Me	H	Me	TMEDA	73 (87)
(*S*)-22j*	Me	H	OMe	TMEDA	52 (93)
(*S*)-22v*	Me	H	NO_2	TMEDA	45 (98)
(*S*)-22a*	Me	H	H	**29**	70 (83)
(*S*)-22a*	Me	H	H	**30**	92 (83)



Contrary to the results reported by Trost, the Ru-catalyzed allylation of unstabilized enolates occurs with less than perfect retention of configuration. In an attempt to provide a thorough comparison of the two methods we initiated studies to determine the regioselectivity of the reaction. While the best branched:linear ratio reported by Trost was 19:1, we were pleased to find that the decarboxylative allylation reaction proceeded with much higher regioselectivity in many cases. Samples of the linear products, **24**, were synthesized *via* the palladium-catalyzed decarboxylative allylation of **22*** (Table 2.9). Gas chromatography and ^{1}H NMR analysis of the crude reaction mixture obtained from the Ru-catalyzed reaction indicated that the reaction was extremely selective for the formation of branched products. For instance, **22h*** reacted to yield a 101:1 ratio of regioisomers. The Ru phenyl substituted π-allyl was alkylated to yield a 75:1 mixture of products, whereas the same Ru π-allyl was alkylated to yield a 19:1 mixture of regioisomers under the optimized Trost reaction conditions.

Table 2.9 *Regioselectivity of allylation*



Substrate	R_1	R_2	R_3	Time	23:24
22a*	Me	H	H	1.5 hr	75:1
22h*	Me	H	Me	4 hr	101:1
22j*	Me	H	OMe	15 min	19:1
22l*	Me	H	Cl	4 hr	89:1
22v*	Me	H	NO_2	3 hr	>19:1
22w*	Me	Me	H	2 hr	59:1
22x*	Bn	H	H	3 hr	20:1
22y*	^{i}Pr	H	H	3 hr	38:1

We also sought to determine the mechanism by which partial racemization of the chiral Ru π-allyl intermediates was occurring, leading to imperfect retention of configuration. Perhaps the simplest explanation that could be invoked is racemization of the Ru π-allyl through a π-σ-π interconversion. We do not believe that this can account for the degree of racemization seen in our system as the Ru π-allyl intermediates formed in the decarboxylative allylation reaction are expected to be identical to those formed in the Ru-catalyzed allylation of stabilized nucleophiles, which occurs without racemization.

Another possibility is that a Ru(II) complex in solution displaces the Ru atom in a Ru π-allyl *via* a S_N2 type of process, inverting the chiral center. This mechanism has been shown to account for the racemization of Pd π-allyl intermediates[37] and was implicated in Chapter 1 as the source of lost stereospecificity in the Pd-catalyzed decarboxylative allylation reaction. This type of a racemization mechanism should

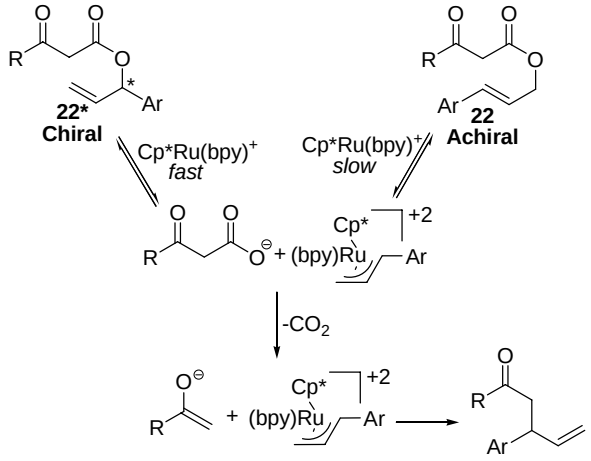
exhibit a strong dependence on the concentration of the catalyst in solution, therefore we examined the stereospecificity of the conversion of **(*S*)-22j*** to **(*S*)-23j** at different concentrations. While maintaining the catalyst loading at 10 mol% Ru, it was found that when the concentration of **(*S*)-22j*** was reduced from 0.32 M to 0.04 M the %cee increased from 86% to 94%. While this is the trend that would be expected if racemization was occurring through a bimetallic mechanism, an 8-fold increase in concentration would be expected to increase the rate of isomerization by a factor of 64. Since changes of this magnitude were not observed we had reason to believe that some another unidentified racemization mechanism was leading to the degradation of the enantiospecificity of the reaction.

Two important pieces of information were obtained when the ee of the product and starting material was monitored as a function of time during the course of the reaction. The conservation of enantiomeric excess in the conversion of **(*S*)-22a*** to **(*S*)-23a** decreased steadily over time (2 min = 99%, 10 min = 97%, 20 min = 83%), as did the ee of starting material during the course of the reaction. After only five minutes under the conditions of catalysis (~50% conversion), the ee of **(*S*)-22j*** decreased from 94% to 78%. In order to account for these observations any racemization mechanism proposed must explain the time-dependent decrease in enantiomeric purity of the product as well as of the starting material.

Further investigation of the course of the reaction by ^{1}H NMR spectroscopy proved to be particularly revealing. After five minutes of catalysis (ca. 50% conversion) under standard reaction conditions we observed partial isomerization of

the branched, chiral β-keto ester **(*S*)-22j*** to linear, achiral β-keto ester **22j** (4:1 ratio of **(*S*)-22j***:**22j**). The isomerization of branched, chiral starting material to achiral, linear β-keto ester was subsequently observed for all substrates (Scheme 2.36). This isomerization can lead to a loss of stereochemistry *via* two related routes: A) the racemization of branched starting material *via* equilibration between chiral, branched and achiral, linear β-keto ester and B) the production of racemic product from the decarboxylative allylation of achiral, linear β-keto ester. This explains not only the erosion of enantiopurity of the product over time, but also the racemization of starting material.

Scheme 2.36 *Mechanism of racemization*



Another observation from ^{1}H NMR spectroscopy which had already been noted in the reaction of nitro-substituted **(*S*)-22v*** is that branched β-keto ester undergoes rearrangement to product faster than the corresponding linear isomer. This can, in part, be explained by the more facile pre-coordination of the Ru catalyst to the mono-substituted alkene found in **22** compared to the conjugated, disubstituted alkene

present in **22***. Based on this result, we surmised that the difference in reactivity between linear and branched substrates could be exploited in order to generate products with increased retention of stereochemistry by avoiding the production of racemic product through mechanism B. For example, when substrate **(*S*)-22l*** (96% ee) was allowed to react for 4 hours in order to maximize conversion to product, **(*S*)-23l** was isolated in 70% yield and 83% ee. However, ^{1}H NMR spectroscopy indicated that after 30 minutes only linear, achiral β-keto ester remained. Thus, allowing the reaction to proceed for only 30 minutes allowed us to isolate **(*S*)-23l** in 90 % ee, albeit in lower chemical yield (56%). The same strategy was used to improve the cee of **(*S*)-23x**; reducing the reaction time from three hours to one hour decreased the yield from 71% to 49%, but increased the cee to 79%.

Substrates **(*S*)-22v*** and **22v** provide the most striking example of the differential reactivity between the two isomers of starting material. In this case the reaction of **22v** is extremely slow under the conditions of catalysis (*vide supra)*, virtually eliminating the reaction pathways leading from **(*S*)-22v*** to racemic product. Presumably the dramatic difference in rate is due to the presence of the strongly withdrawing nitro group. As previously discussed, prior to oxidative addition and π-allyl formation, it has been shown that Ru pre-coordinates to the olefin. Backbonding into the π* orbital of the alkene is expected to be greatest for electron deficient aryl substituted alkenes. This in turn decreases the nucleophillicity of Ru, which will raise the barrier for oxidative addition to form the reactive π-allyl ruthenium species. This fact, coupled with the decreased reactivity of linear β-keto esters due to unfavorable

steric interactions, prevents the formation of racemic product from **22v** and decreases the overall yield of the reaction while increasing the cee.

The addition of an α-methyl group also leads to a large disparity between the reaction rates of **(*S*)-22w*** and isomeric **22w**, and allows for the isolation of **(*S*)-23w** in a 90% ee from 97% ee starting material (93% cee). This is compared to **(*S*)-23a** (nonmethylated), which was isolated in a 79% ee from 95% ee starting material (83% ee). Clearly, understanding and utilizing the differing reaction rates of isomeric allyl β-keto esters allows for the maximization of the retention of configuration.

As a result of this work we have a greater understanding of the differences in reactivity between iridium, rhodium, molybdenum, and ruthenium catalysts in decarboxylative allylation reactions. While some of these differences were expected based on the allylic alkylation literature, others, such as the ease with which ruthenium carboxylates lose CO_2 compared to iridium carboxylates, were not predicted. The survey of different transition-metal catalysts clearly demonstrates the superiority of ruthenium catalysts, especially for the decarboxylative allylation of aryl-substituted β-keto esters. The ease with which allylic alcohols can be resolved and converted into highly enantioenriched β-keto esters makes the stereospecific decarboxylative allylation reaction a very useful synthetic protocol that complements the enantioselective palladium-catalyzed reaction nicely. Following completion of this work, an enantioselective variant of the Ru-catalyzed decarboxylative allylation reaction was reported[38] and serves as an example of how ruthenium complexes have been embraced for the unique selectivity they impart in allylation reactions.[39]

2.6 Supporting Information

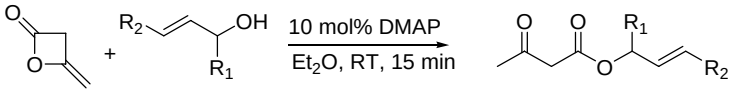
Materials

Benzene was dried over sodium metal and distilled under vacuum. THF, toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc. Acetonitrile was dried and stored over activated molecular sieves. Products were purified on silica gel from Sorbent Technologies (40-63 μm particle size, 60 Å porosity, pH 6.5-7.5). Chiral ligands were purchased from Strem with the exception of **28**, which was synthesized according to a literature procedure.[40] $[Cp^*RuCl]_4$[41] and $[Cp^*RuOMe]_2$[42] were synthesized from literature procedures; all other Ir, Mo, Rh, and Ru catalysts were purchased from Strem. NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, and HMQC spectroscopies. High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument. Gas chromatography was performed with a Shimadzu GC-17A instrument with an attached AOC-20i auto injector.

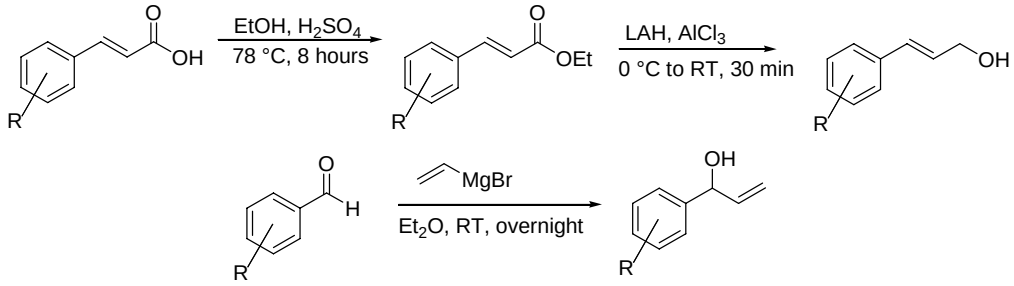
Preparation of Starting Materials

β-Keto esters **22** in which $R_1 = CH_3$ were synthesized by the DMAP-catalyzed addition of the appropriate allylic alcohol to diketene and purified by flash column

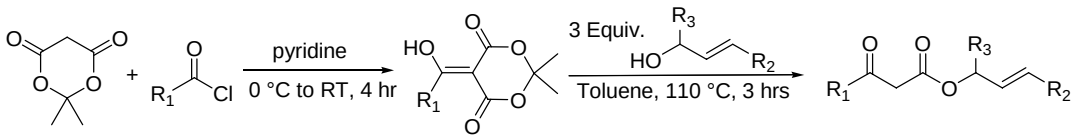
chromatography (SiO_2, 5-10% ethyl acetate in hexane).[43] Compound **22j*** degraded slightly on SiO_2 and therefore was used without further purification.



Many allylic alcohols are commercially available, although 2-cyclohexene-1-ol was prepared by reduction of the corresponding α,β-unsaturated ketone with LAH.[44] Substituted cinnamyl alcohol derivatives were prepared from the desired α,β-unsaturated carboxylic acid by esterification with ethanol, followed by reduction with LAH.[45] Branched, 2° allylic alcohols were prepared by the addition of vinyl magnesium bromide to various benzaldehyde derivatives.[46] These alcohols were enzymatically resolved by lipase AK Amano 20 for the synthesis of highly enantiopure β-keto esters employed in the studies on the stereospecificity of Ru-catalyzed reactions.[47]



β-keto esters **22** in which R_1 = Bn, ^{i}Pr, or Et were synthesized by the addition of the appropriate allylic alcohol to the desired Meldrum's acid adduct,[48] prepared by the addition of either phenylacetyl chloride, isobutyryl chloride, or propionyl chloride to Meldrum's acid in the presence of pyridine.[49]

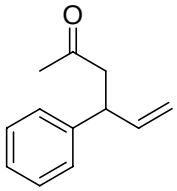


Installation of α- methyl, ethyl, or benzyl groups was accomplished by the deprotonation of the β-keto ester with potassium *tert*-butoxide, followed by addition of methyl iodide, ethyl iodide, or benzyl bromide.[50]

Procedure for the Iridium-Catalyzed Decarboxylative Allylation Reaction

In a Schlenk flask under argon, $[Ir(COD)Cl]_4$ (0.046 mmol, 31 mg) and $P(OPh)_3$ (0.092 mmol, 28 mg) were dissolved in THF (5 mL) and stirred for 30 minutes. In a separate Schlenk flask β-keto ester **22a** (0.916 mmol, 200 mg), and either sodium hydride or cesium carbonate (0.916 mmol) were dissolved in THF (5 mL). The solution of substrate was then cannula transferred to the solution of catalyst. The resulting solution was refluxed for 3 hours under argon, extracted with diethyl ether and water, and purified *via* flash chromatography (SiO_2, 10% ethyl acetate: hexane).

Spectroscopic Data



4-phenylhex-5-en-2-one

23a (eb1254)
colorless oil
Ir: 30% NMR yield
Mo: 27% yield
Rh: 50 % NMR yield
Ru: 86% yield, 83% cee (*S*)

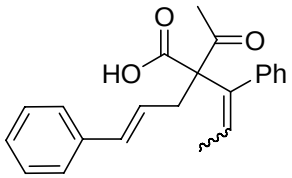
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H: aromatic CH), 5.99 (ddd, *J* = 7 Hz, 11 Hz, 17 Hz, 1H: C*H*=CH_2), 5.08 (d, *J* = 11 Hz, 1H: CH=CH(H)$_{cis}$), 5.04 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$) 3.94 (app. q, *J* = 7 Hz, 1H: CH), 2.91 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.84 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.12 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.50 (C=O), 143.19 (aromatic C), 140.94 (*C*H=CH_2), 129.04 (aromatic CH), 128.01 (aromatic CH), 127.03 (aromatic CH), 115.04 (CH=*C*H_2), 49.40 (CH_2), 44.95 (CH), 31.10 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1157, 994, 922.

HRMS calcd for $C_{12}H_{13}O$ [M-H] 173.0966, found 173.0954.

HPLC (Daicel Chiralpak AD HPLC column, 99.0% hexane/isopropanol, 0.5 mL/min) t_r = 13.3 (minor), 14.7 (major) minutes



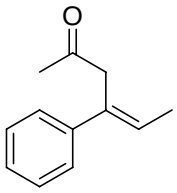
2-acetyl-2-cinnamyl-3-phenylpent-3-enoic acid

25a (eb-1-42-6)

Ir: 24% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 13.02 (s, 1 H: OH) 7.38 (d, *J*=6.9 Hz, 2 H: aromatic CH) 7.22 - 7.35 (m, 8 H: aromatic CH) 6.35 (d, *J*=16.1 Hz, 1 H: Ph-CH=) 6.26 (q, *J*=6.9 Hz, 1 H: =*CH*-CH_3) 6.04 - 6.11 (m, 1 H: =*CH*-CH_2) 4.78 (ddd, *J*=13.9, 5.7, 1.6 Hz, 1 H: diastereotopic CH_2) 4.72 (ddd, *J*=13.9, 5.7, 1.6 Hz, 1 H: diastereotopic CH_2), 1.95 (s, 3H: C=O-CH_3), 1.78 (d, *J*=6.9 Hz, 3H: =CH-*CH_3*)

HRMS calcd for $C_{22}H_{23}O_3$ [M-H] 335.1647, found 335.1669

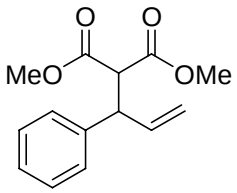


(*E*)-4-phenylhex-4-en-2-one

26a[51] (eb1056-2)

Ir: 33% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.14 - 7.39 (m, 4 H: aromatic CH) 6.11 (q, *J*=7.1 Hz, 1 H: =CH) 3.63 (s, 2 H: CH_2) 2.11 (s, 3 H: CH_3-C=O) 1.85 (d, *J*=7.1 Hz, 3 H: CH-*CH_3*)



dimethyl 2-(1-phenylallyl)malonate

27a[52] (eb1073)

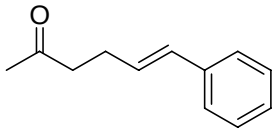
Ir: > 90% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 - 7.38 (m, 5 H: aromatic CH) 5.99 (m, 1 H: =CH) 5.15 (d, *J*=18.2 Hz, 1 H: =CH(H)$_{trans}$) 5.11 (d, *J*=10.1 Hz, 1 H: =CH(H)$_{cis}$) 4.13 (dd, *J*=8.2, 11.0 Hz, 1 H: benzylic CH) 3.89 (d, *J*=11.6 Hz, 1 H: O=C-CH) 3.51 (s, 3 H: diastereotopic OCH_3) 3.42 (s, 3 H: diastereotopic OMe)

Procedure for the Rhodium-Catalyzed Decarboxylative Allylation Reaction

In a Schlenk flask under argon, Wilkinson's catalyst ($RhCl(PPh_3)_4$) (0.0916 mmol, 85 mg) or an alternative Rh(I) source (see Table 2.2) and either $P(OPh)_3$ or $P(OBu)_3$ (0.275 mmol) were dissolved in THF (5 mL) and stirred for 30 minutes, during which time the maroon solution became yellow. In a separate Schlenk flask under argon, substrate **22a** (0.916 mmol, 200 mg) and either sodium hydride or cesium carbonate were dissolved in THF (5 mL) and cannula transferred to the solution of catalyst. The resulting solution was refluxed under argon overnight, extracted with diethyl ether and water, and purified *via* flash chromatography (SiO_2, 10% ethyl acetate: hexane).

Spectroscopic Data



(*E*)-6-phenylhex-5-en-2-one
24a[53] (eb1029-3&4)
Rh: >90% NMR yield

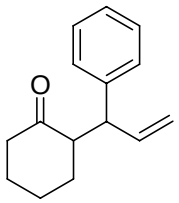
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.38 (m, 4 H: aromatic CH) 7.23 (m, 1 H: aromatic CH) 6.43 (d, *J*=15.9 Hz, 1 H: =CH-Ph) 6.16 - 6.28 (m, 1 H: CH_2-*CH*=) 2.64 (t, *J*=7.5 Hz, 2 H: CH_2-C=O) 2.46 - 2.56 (m, 2 H: =CH-*CH_2)* 2.20 (s, 3 H: CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 208.48 (C=O) 137.81 (aromatic C) 131.17 (CH) 129.24 (CH) 128.94 (CH) 127.54 (CH) 126.44 (CH) 43.61 (*CH_2*-C=O) 30.49 (CH_3) 27.54 (*CH_2*-CH)

Procedure for the Molybdenum-Catalyzed Decarboxylative Allylation Reaction

In a Schlenk flask under argon, either $(C_7H_7)Mo(CO)_3$ or $Mo(CH_3CN)_3(CO)_3$ (0.0916 mmol) and *tert*-butyl bipyridine (0.0916 mmol, 25 mg) were dissolved in toluene (5 mL) and stirred for 30 minutes. In a separate Schlenk flask under argon, β-keto ester (0.916 mmol) and either sodium hydride or cesium carbonate (0.916 mmol) was dissolved in toluene (5 mL) and cannula transferred to the solution of catalyst. The resulting solution was refluxed under argon overnight, extracted with diethyl ether and water, and purified *via* flash chromatography (SiO_2, 10% ethyl acetate: hexane).

Spectroscopic Data



2-(1-phenylallyl)cyclohexanone

23b (eb1289)

Mo: 33% NMR yield, dr = 1

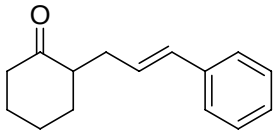
Ru: 85% isolated, dr = 1.9

^{1}H NMR (400 MHz, $CDCl_3$) Major Diastereomer: δ 7.27 (m, 5H: aromatic CH), 6.07 (ddd, J = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.06 (m, 2H: CH=C*H*$_2$), 3.75 (t, J = 9 Hz, 1H: C*H*-CH=CH_2), 2.82 (m, 1H: C=OC*H*) 1.84 (broad m, 8H: cyclohexyl CH_2's). Minor Diastereomer: δ 7.27 (m, 5H: aromatic H), 5.99 (ddd, J = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.06 (m, 2H: CH=C*H*$_2$), 3.83 (tt, J = 9 Hz, 1H: C*H*-CH=CH_2), 2.82 (m, 1H: C=OC*H*) 1.84 (broad m, 8H: cyclohexyl CH_2's).

^{13}C NMR (75 MHz, $CDCl_3$) Major and Minor Diastereomer: δ 213.15; 212.17 (C=O), 143.67;142.07 (aromatic C), 140.52; 139.64 (*C*H=CH_2), 128.98; 128.85 (aromatic CH), 128.24 (aromatic CH), 126.94; 126.66 (aromatic CH), 116.65; 115.34 (CH=*C*H_2), 55.80; 55.65 (CO*C*H), 49.76; 49.44 (*C*H-CH=CH_2), 42.76; 42.51 (cyclohexyl CH_2), 32.35; 32.03 (cyclohexyl CH_2), 28.96; 28.80 (cyclohexyl CH_2), 24.80; 24.14 (cyclohexyl CH_2).

FTIR (CH_2Cl_2): ν_{max} 1705, 1445, 1214.

HRMS calcd for $C_{15}H_{19}O$ [M+H] 215.1436, found 215.1439.

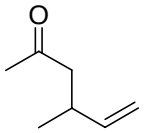


2-cinnamylcyclohexanone

24b[54] (eb1219-2)

Mo: 66% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.15 - 7.76 (m, 5 H: aromatic CH) 6.42 (d, *J*=15.7 Hz, 1 H: =CH-Ph) 6.20 (m, 1 H: CH_2-*CH*=) 2.65 - 2.75 (m, 1 H: alkyl H) 2.40 - 2.49 (m, 2 H: alkyl H) 2.15 - 2.26 (m, 2 H: alkyl H) 2.09 (m, 1 H: alkyl H) 1.90 (m, 1 H: diastereotopic cyclohexyl CH_2) 1.64 - 1.74 (m, 3 H: overlapping diastereotopic cyclohexyl CH_2) 1.43 (m, 1 H: diastereotopic cyclohexyl CH_2)

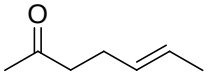


4-methylhex-5-en-2-one

23c (eb1221)

Mo: 50% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.71 - 5.82 (m, 1 H: =CH) 5.02 (d, *J*=17.2 Hz, 1 H: =CH(H)$_{trans}$) 4.95 (d, *J*=10.4 Hz, 1 H: =CH(H)$_{trans}$) 2.72 (m, 1 H: CH) 2.44 - 2.53 (m, 2 H: CH_2) 2.10 (s, 3 H: O=C-CH_3) 1.03 (d, *J*=6.8 Hz, 3 H: CH-*CH_3*)

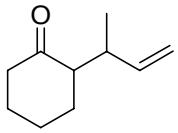


(*E*)-hept-5-en-2-one

24c (eb1221)

Mo: 50% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.43 (m, 2 H, overlapping =CH) 2.43 - 2.55 (m, 2 H: CH_2) 2.25 (m, 2 H: CH_2) 2.14 (d, *J*=indistinguishable, 3 H: CH-CH_3) 2.14 (s. 3H: CH_3)



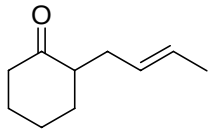
2-(but-3-en-2-yl)cyclohexanone

23d (eb1230)

Mo: 20% NMR yield, dr = 1

23d was a minor side product and was tentatively identified by its terminal alkene peaks in the ^{1}H NMR:

^{1}H NMR (400 MHz, $CDCl_3$) 5.92 (m, 0.5 H, =CH diastereomer A) 5.75 (m, 0.5 H, =CH diastereomer B) 5.09 (m, 2 H: $=CH_2$)



(*E*)-2-(but-2-enyl)cyclohexanone

24d[55] (eb1220)

Mo: 80% NMR yield

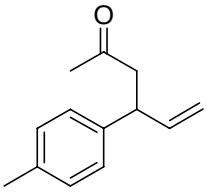
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.31 - 5.51 (m, 2 H: overlapping =CH) 2.24 - 2.52 (m, 5 H: alkyl H) 2.00 - 2.17 (m, 2 H: alkyl H) 1.80 - 1.97 (m, 2 H: alkyl H) 1.65 (s, 3 H: CH_3) 1.59 - 1.71 (m, 2 H: alkyl H)

Procedure for the Ruthenium-Catalyzed Decarboxylative Allylation Reaction

In a Schlenk tube under argon, $[RuCp^*Cl]_4$ (0.0125 mmol, 14 mg) and bipyridine (0.05 mmol, 8 mg) were dissolved in methylene chloride (2 mL). The resulting deep purple solution was allowed to stir briefly before addition of allyl β-keto ester (0.5 mmole) in methylene chloride (3 mL) *via* cannula. The reaction was allowed to stir under Ar until the resulting dark burnt orange solution returned to purple. Following solvent evaporation the crude product was purified *via* flash chromatography (SiO_2, 5% diethyl ether: hexane), providing products in >95% purity as determined by ^{1}H

NMR spectroscopy. The absolute configuration resulting from the stereospecific Ru-catalyzed reaction was verified by hydrogenation of the terminal alkene of **23a**, followed by comparison of the optical rotation to the known compound.[56]

Spectroscopic Data



4-*p*-tolylhex-5-en-2-one
23h (eb1287)
colorless oil
81% yield, 87% cee (*S*)

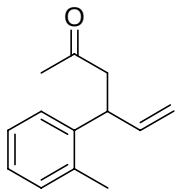
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 4H: aromatic CH), 5.97 (ddd, J = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.07 (d, J = 10 Hz, 1H: CH=CH(H)$_{cis}$), 5.03 (d, J = 17 Hz, 1H: CH=CH(H)$_{trans}$) 3.90 (app. q, J = 7 Hz, 1H: CH), 2.89 (dd, J = 7 Hz, 16Hz, 1H: diastereotopic CH_2) 2.83 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.34 (s, 3H: benzylic CH_3) 2.11 (s, 3H: O=C-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.63 (C=O), 141.18 (*C*H=CH_2), 140.161 (aromatic C), 136.57 (aromatic C), 129.73 (aromatic CH), 127.68 (aromatic CH), 114.81 (CH=*C*H_2), 49.48 (CH_2), 44.62 (CH), 31.09 (O=C-*CH_3*) 21.43 (benzylic CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1352, 1157.

HRMS calcd for $C_{13}H_{17}O$ [M+H] 189.1279, found 188.1259.

HPLC (Daicel Chiralpak AD HPLC column, 99.0% hexane/isopropanol, 0.5 mL/min) - t_r = 12.9 (minor), 14.4 (major) minutes



4-*o*-tolylhex-5-en-2-one

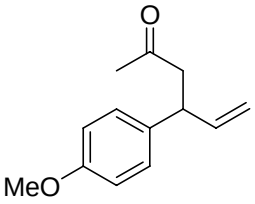
23i (eb1303)
colorless oil
81% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 4H: aromatic CH), 5.93 (ddd, J = 7 Hz, 10.3 Hz, 17 Hz, 1H: C*H*=CH_2), 5.06 (d, J = 10.3 Hz, 1H: CH=CH(H)$_{cis}$), 4.96 (d, J = 17 Hz, 1H: CH=CH(H)$_{trans}$) 4.19 (app. q, J = 7 Hz, 1H: CH), 2.93 (dd, J = 7Hz, 16.5 Hz, 1H: diastereotopic CH_2) 2.85 (dd, J = 7 Hz, 16.5 Hz, 1H: diastereotopic CH_2) 2.40 (s, 3H: benzylic CH_3) 2.14 (s, 3H: O=C-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.50 (C=O), 141.15 (aromatic C), 140.56 (*C*H=CH_2), 136.40 (aromatic C), 131.04 (aromatic CH), 126.80 (aromatic CH), 126.76 (aromatic CH), 126.62 (aromatic CH) 114.97 (CH=*C*H_2), 48.84 (CH_2), 40.21 (CH), 31.05 (O=C-*CH_3*) 19.97 (benzylic CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1270, 1152.

HRMS calcd for $C_{13}H_{17}O$ [M+H] 189.1279, found 189.1289.



4-(4-methoxyphenyl)hex-5-en-2-one

23j (eb1278)
colorless oil
83% yield, 93% cee (*S*)

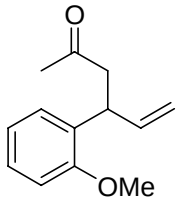
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 6.5 Hz, 2H: aromatic CH), 6.87 (d, J = 6.5 Hz, 2H: aromatic CH), 5.97 (ddd, J = 7 Hz, 10.3 Hz, 17 Hz, 1H: C*H*=CH_2), 5.06 (d, J = 10.3 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.02 (d, J = 17 Hz, 1H: CH=CH(*H*)$_{trans}$) 3.88 (app. q, J = 7 Hz, 1H: CH), 3.80 (s, 3H: OCH_3) 2.87 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.81 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.10 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.71 (C=O), 158.64 (aromatic *C*-OCH_3), 141.28 (*C*H=CH_2), 135.18 (aromatic *C*-CH_2) 128.97 (aromatic CH), 114.67 (CH=*C*H_2), 114.39 (aromatic CH), 55.65 (OCH_3), 49.55 (CH_2), 44.16 (CH), 31.11 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1710, 1244, 1117, 830.

HRMS calcd for $C_{13}H_{16}O_2$ [M+] 204.1150, found 204.1146.

HPLC (Daicel Chiralpak AD HPLC column, 97.0% hexane/isopropanol, 1.0 mL/min) - t_r = 6.8 (minor), 7.7 (major) minutes



4-(2-methoxyphenyl)hex-5-en-2-one

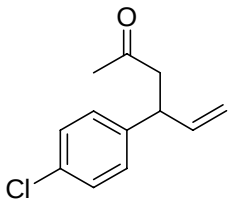
23k (eb1304)
colorless oil
93% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 2H: aromatic CH), 6.90 (d, 2H: aromatic CH), 6.04 (ddd, J = 7 Hz, 11 Hz, 17 Hz, 1H: C*H*=CH_2), 5.07 (d, J = 11 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.04 (d, J = 17 Hz, 1H: CH=CH(*H*)$_{trans}$) 4.32 (app. q, J = 7 Hz, 1H: CH), 3.86 (s, 3H: OCH_3) 2.89 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.83 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.14 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.14 (C=O), 157.11 (aromatic *C*-OCH_3), 140.20 (*C*H=CH_2), 131.45 (aromatic *C*-CH_2) 128.54 (aromatic CH), 128.06 (aromatic CH), 121.08 (aromatic CH), 115.03 (CH=*C*H_2), 111.16 (aromatic CH), 55.79 (OCH_3), 48.57 (CH_2), 38.89 (CH), 30.58 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1710, 1234, 1163.

HRMS calcd for $C_{13}H_{16}O_2$ [M+H] 204.1150, found 204.1159.



4-(4-chlorophenyl)hex-5-en-2-one

23l (eb2003)
colorless oil
70% yield, 86% cee (*S*)

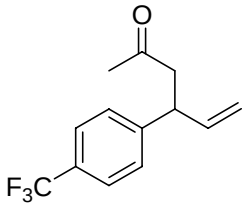
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8 Hz, 2H: aromatic CH), 7.18 (d, J = 8 Hz, 2H: aromatic CH), 5.94 (ddd, J = 7 Hz, 10.3 Hz, 17 Hz, 1H: C*H*=CH_2), 5.09 (d, J = 10.3 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.02 (d, J = 17 Hz, 1H: CH=CH(*H*)$_{trans}$) 3.92 (app. q, J = 7 Hz, 1H: CH), 2.89 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.81 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.12 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.03 (C=O), 141.67 (aromatic C), 140.50 (*C*H=CH_2), 132.73 (aromatic C) 129.46 (aromatic CH), 129.13 (aromatic CH), 115.40 (CH=*C*H_2), 49.18 (CH_2), 44.11 (CH), 31.11 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1485, 1163, 1014.

HRMS calcd for $C_{12}H_{14}OCl$ [M+H] 209.0733, found 209.0728.

HPLC (Daicel Chiralpak AD HPLC column, 99.0% hexane/isopropanol, 1.0 mL/min) - t_r = 7.7 (major), 8.9 (minor) minutes



4-(4-(trifluoromethyl)phenyl)hex-5-en-2-one

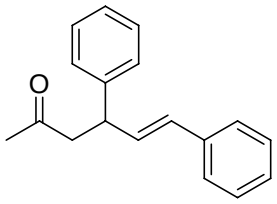
23m (eb1288)
colorless oil
90% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8 Hz, 2H: aromatic H), 7.35 (d, J = 8 Hz, 2H: aromatic H), 5.51 (ddd, J = 7 Hz, 10.3 Hz, 17 Hz, 1H: C*H*=CH_2), 5.12 (d, J = 10.3 Hz, 1H: CH=CH(H)$_{cis}$), 5.05 (d, J = 17 Hz, 1H: CH=CH(H)$_{trans}$) 4.02 (app. q, J = 7 Hz, 1H: CH), 2.94 (dd, J = 7 Hz, 17 Hz, 1H: diastereotopic CH_2) 2.86 (dd, J = 7 Hz, 17 Hz, 1H: diastereotopic CH_2) 2.13 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.67 (C=O), 147.33 (aromatic *C*-CH), 140.07 (*C*H=CH_2), 129.28 (aromatic *C*-CF_3, q, J = 54 Hz), 128.47 (aromatic CH), 125.94 (CF_3, q, J = 4 Hz), 115.84 (CH=*C*H_2), 48.98 (CH_2), 44.45 (CH), 31.06 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1613, 1326, 1168.

HRMS calcd for $C_{13}H_{12}F_3O$ [M-H] 241.0840, found 241.0840.



(*E*)-4,6-diphenylhex-5-en-2-one

23n[57] (eb2295)

yellow oil

67% yield

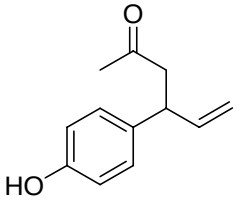
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 10H: aromatic H), 6.38 (m, 2H: C*H*=), 4.12 (app. q, *J* = 7 Hz, 1H: CH), 3.01 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.95 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic CH_2), 2.14 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.36 (C=O), 143.35 (aromatic C), 137.49 (aromatic C), 132.76 (*C*H=), 130.39 (*C*H=), 129.13 (aromatic CH), 128.91 (aromatic CH), 128.06 (aromatic CH), 127.75 (aromatic CH), 127.12 (aromatic CH), 126.65 (aromatic CH), 49.82 (CH_2), 44.36 (CH), 31.20 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1710, 1490, 1255.

HRMS calcd for $C_{18}H_{18}O$ [M+] 250.1358, found 250.1352.

HPLC (Daicel Chiralpak AD : 99:1 Hex:IPA, 0.5 mL/min) t_r = 27.1, 28.6 minutes

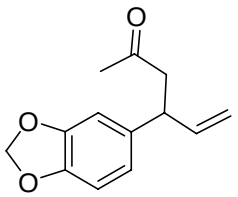


4-(4-hydroxyphenyl)hex-5-en-2-one

23o (eb2013-3)

18% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.08 (d, *J*=8.6 Hz, 2 H: aromatic CH) 6.78 (d, *J*=8.6 2 H: aromatic CH) 5.88 - 6.01 (m, 1 H: =CH) 4.93 - 5.09 (m, 2 H: =CH_2) 3.87 (app. q, *J*=7 Hz, 1 H: CH) 2.87 (dd, *J*=15.9, 9.0 Hz, 1 H: diastereotopic CH_2) 2.81 (dd, *J*=15.9, 7.6 Hz, 1 H: diastereotopic CH_2) 2.11 (s, 3 H: CH_3)



4-(benzo[*d*][1,3]dioxol-5-yl)hex-5-en-2-one

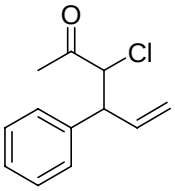
23p (eb1292)
colorless oil
91% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (m, 3H: aromatic H), 5.95 (ddd, J = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.96 (s, 2H,: O-CH_2-O) 5.06 (d, J = 10 Hz, 1H: CH=CH(H)$_{cis}$), 5.02 (d, J = 17 Hz, 1H: CH=CH(H)$_{trans}$), 3.85 (app. q, J = 7 Hz, 1H: CH), 2.85 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.79 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH_2) 2.11 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.46 (C=O), 148.16 (aromatic C), 146.55 (aromatic C), 141.04 (*C*H=CH_2), 137.05 (aromatic C) 121.00 (aromatic CH), 114.85 (O-CH_2-O), 108.73 (aromatic CH), 108.43 (aromatic CH), 101.35 (CH=*C*H_2), 49.46 (CH_2), 44.58 (CH), 31.12 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1710, 1152, 1040.

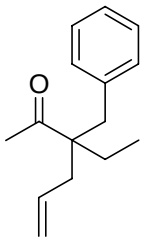
HRMS calcd for $C_{13}H_{14}O_3$ [M+] 218.0943, found 218.0926.



3-chloro-4-phenylhex-5-en-2-one

23q (eb2063-2)
>95% NMR yield, dr = 3

^{1}H NMR (400 MHz, CD_2Cl_2) *Major diastereomer:* δ ppm 7.20 - 7.45 (m, 5 H: aromatic CH) 5.94 - 6.06 (m, 1 H: =CH) 5.20 (d, *J*=17.2, 1 H: =CH(H)$_{trans}$) 5.19 (d, *J*=10.6, 1 H: =CH(H)$_{cis}$) 4.51 (d, *J*=9.6 Hz, 1 H: Cl-CH) 3.85 - 3.97 (m, 1 H: benzylic CH) 2.29 (s, 3 H) *Minor diastereomer:* δ ppm 7.20 - 7.45 (m, 5 H: aromatic CH) 6.11 - 6.22 (m, 1 H: =CH) 5.27 (d, *J*=9.6, 1 H: =CH(H)$_{cis}$) 5.21 (d, *J*=16.9, 1 H: =CH(H)$_{trans}$) 4.56 (d, *J*=8.6 Hz, 1 H: Cl-CH) 3.85 - 3.97 (m, 1 H: benzylic CH) 2.30 (s, 3 H)



3-benzyl-3-ethylhex-5-en-2-one

23s (eb3035)

>95% NMR yield

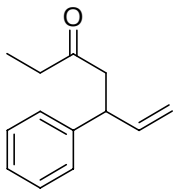
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 3H: aromatic H), 7.11 (d, *J* = 8 Hz, 2H: aromatic H), 5.77 (m, 1H: =CH), 5.14 (d, *J* = 12 Hz, 1H: =CH(H)$_{cis}$), 5.14 (d, *J* = 17 Hz, 1H: =CH(H)$_{trans}$), 2.89 (s, 2H: CH_2-Ph), 2.38 (dd, *J* = 7 Hz, 15Hz, 1H: diastereotopic CH_2-CH=), 2.28 (dd, *J* = 7 Hz, 15Hz, 1H: diastereotopic CH_2-CH=), 2.11 (s, 3H: (C=O)-CH_3), 1.64 (m, 2H: CH_2-CH_3), 0.90 (t, *J* = 7 Hz, 3H: CH_2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.40 (C=O), 138.01 (aromatic C), 134.10 (=CH), 130.45 (aromatic CH), 128.58 (aromatic CH), 126.82 (aromatic CH), 118.72 (=CH_2), 56.42 (C), 39.67 (CH$_2$-Ph), 37.81 (CH_2=CH-CH$_2$), 27.31 ((C=O)-CH$_3$), 27.26 (CH$_2$-CH_3), 8.96(CH_2-CH$_3$).

FTIR ($CDCl_3$): ν_{max} 1699, 1454, 1261, 1269.

HRMS calcd for $C_{15}H_{21}O$ [M+H] 217.1592, found 217.1602.

GC (Chiraldex B-TA : hold 50 ^{o}C for 5 minutes, ramp 1 ^{o}C/min to 115 ^{o}C) t_r = 67.8, 68.9 minutes



5-phenylhept-6-en-3-one

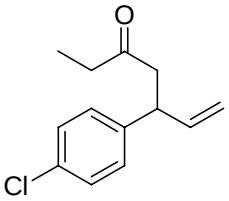
23t (eb2085)
colorless oil
80% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H: aromatic H), 6.00 (ddd, J = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.08 (d, J = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.04 (d, J = 17 Hz, 1H: CH=CH(*H*)$_{trans}$) 3.95 (app. q, J = 7 Hz, 1H: CH), 2.89 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH-C*H*$_2$) 2.82 (dd, J = 7 Hz, 16 Hz, 1H: diastereotopic CH-C*H*$_2$) 2.41 (dq, J = 7 Hz, 10 Hz, 1H: diastereotopic C*H*$_2$-CH_3) 2.33 (dq, J = 7 Hz, 10 Hz, 1H: diastereotopic C*H*$_2$-CH_3) 1.01 (t, J = 7 Hz, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 210.10 (C=O), 143.36 (aromatic C), 141.08 (*C*H=CH_2), 129.01 (aromatic CH), 128.03 (aromatic CH), 126.98 (aromatic CH), 114.97 (CH=*C*H_2), 48.22 (CH-*C*H_2), 45.00 (CH), 37.185 (*C*H_2-CH_3) 7.97 (CH_3).

FTIR (CH_2Cl_2): ν_{max} 1716, 1449, 1106.

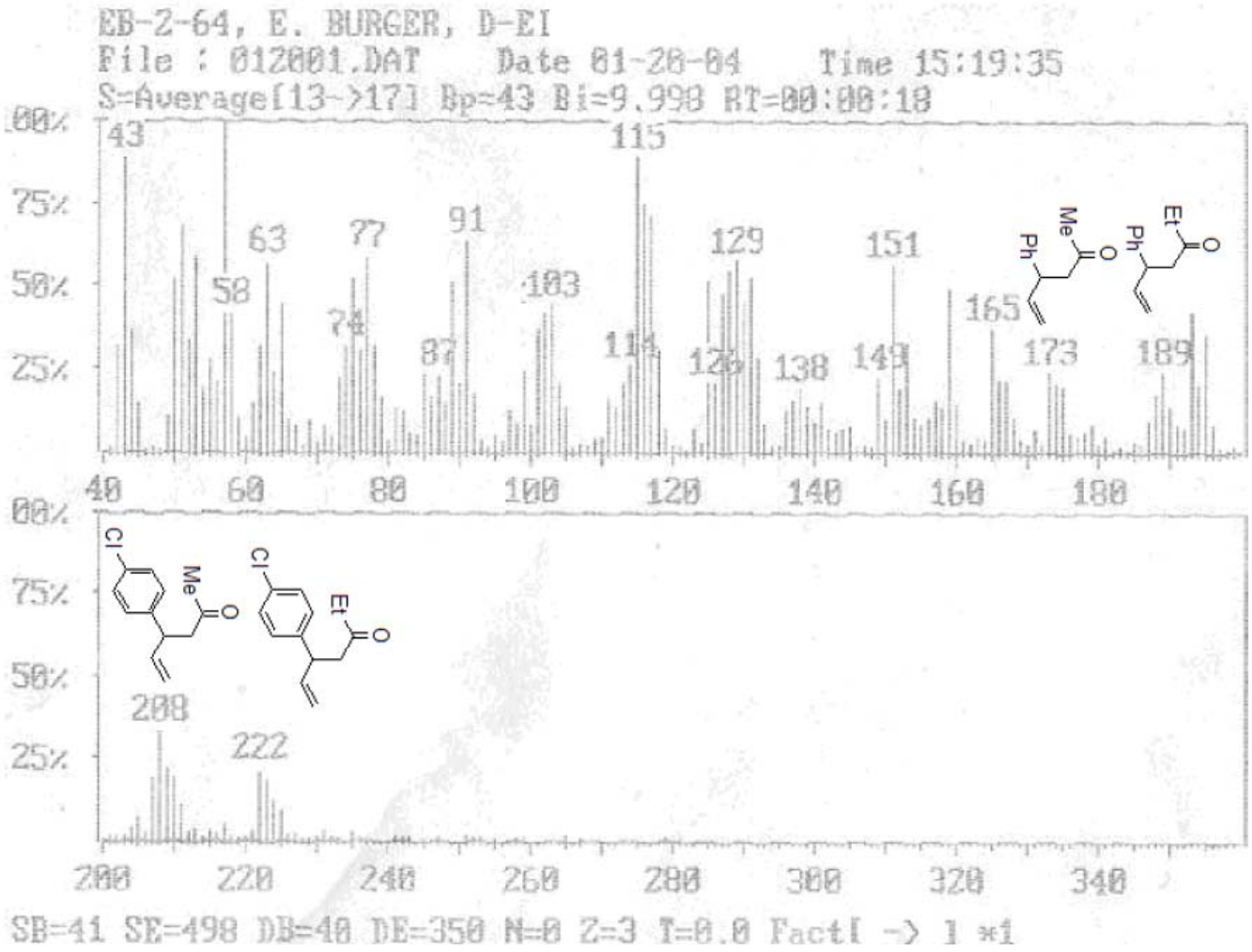
HRMS calcd for $C_{13}H_{17}O$ [M+H] 189.1279, found 189.1276.



5-(4-chlorophenyl)hept-6-en-3-one

23u

The synthesis of **23u** during the crossover experiment was confirmed by mass spectrometry ($C_{13}H_{15}ClO$ = 222.08):


EB-2-64, E. BURGER, D-EI
File : 012001.DAT Date 01-20-04 Time 15:19:35
S=Average[13->17] Bp=43 Bi=9.998 RT=00:00:10
100%
75%
50%
25%
43
58
63
77
91
103
115
129
151
165
173
189
Me
O
Ph
Et
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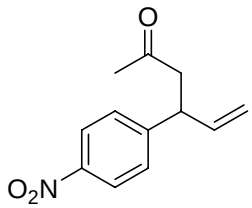
40
60
80
100
120
140
160
180
100%
75%
50%
25%
Cl
Me
O
Cl
Et
O
208
222
200
220
240
260
280
300
320
340
SB=41 SE=498 DB=40 DE=350 N=0 Z=3 T=0.0 Fact[-> 1 *1



4-(4-nitrophenyl)hex-5-en-2-one

23v (eb4183)
colorless oil
49% yield, 98% cee (*S*)

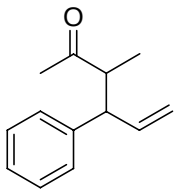
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9 Hz, 2H: aromatic H), 7.31 (d, *J* = 9 Hz, 2H: aromatic H), 5.87 (ddd, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.07 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 4.98 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 3.98 (app. q, *J* = 7 Hz, 1H: CH), 2.88 (dd, *J* = 7 Hz, 17 Hz, 1H: diastereotopic CH_2), 2.80 (dd, *J* = 7 Hz, 17 Hz, 1H: diastereotopic CH_2), 2.05 (s, 3H: CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 205.76 (C=O), 150.57 (aromatic C), 146.72 (aromatic C), 139.06 (*C*H=CH_2), 128.66 (aromatic CH), 124.08 (aromatic CH), 116.02 (CH=*C*H_2), 48.52 (CH_2), 43.94 (CH), 30.63 (CH_3).

FTIR ($CDCl_3$): ν_{max} 1716, 1522, 1348.

HRMS calcd for $C_{12}H_{14}NO_3$ [M+H] = 220.0974, found 220.0976.

HPLC (Daicel Chiralpak AD HPLC column, 94.0% hexane/isopropanol, 1.0 mL/min) - t_r = 10.3 (minor), 11.5 (major) minutes



3-methyl-4-phenylhex-5-en-2-one

23w (eb4157)

colorless oil

76% yield, dr = 1.5, 93% cee (*S*)

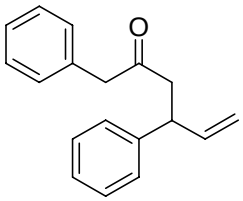
^{1}H NMR (500 MHz, $CDCl_3$) *Major diastereomer*: δ 7.28 (broad overlapping m, 5H: aromatic H), 5.96 (overlapping m, 1H: C*H*=CH_2), 5.09 (overlapping m, 1H: CH=CH(H)$_{cis}$), 5.09 (overlapping m, 1H: CH=CH(H)$_{trans}$), 3.49 (overlapping m, 1H: Ph-CH), 2.99 (overlapping dq, J = 7 Hz, 10 Hz, 1H: C*H*-CH_3), 2.20 (s, 3H: (CO)CH_3), 0.91 (d, J = 7 Hz, 3H: CH-CH_3). *Minor diastereomer*: δ 7.28 (broad overlapping m, 5H: aromatic H), 5.96 (overlapping m, 1H: C*H*=CH_2), 5.09 (overlapping m, 1H: CH=CH(H)$_{cis}$), 5.09 (overlapping m, 1H: CH=CH(H)$_{trans}$), 3.49 (overlapping m, 1H: Ph-CH), 2.99 (overlapping dq, J = 7 Hz, 10 Hz, 1H: C*H*-CH_3), 1.90 (s, 3H: (CO)CH_3), 1.74 (d, J = 7 Hz, 3H: CH-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) *Major diastereomer* δ 212.17 (C=O), 141.44 (aromatic C), 139.69 (*C*H=CH_2), 128.71 (aromatic CH), 128.10 (aromatic CH), 126.73 (aromatic CH), 115.68 (CH=*C*H_2), 53.07 (CH-Ph), 52.00 (*C*H-CH_3), 29.48 (*C*H_3-(CO)), 15.58 (CH-*C*H_3). *Minor diastereomer* δ 212.00 (C=O), 142.52 (aromatic C), 138.85 (*C*H=CH_2), 128.53 (aromatic CH), 127.63 (aromatic CH), 126.08 (aromatic CH), 116.57 (CH=*C*H_2), 53.41 (CH-Ph), 51.60 (*C*H-CH_3), 29.68 (*C*H_3-(CO)), 15.33 (CH-*C*H_3).

FTIR ($CDCl_3$): ν_{max} 1711, 1454, 1356.

HRMS calcd for $C_{13}H_{17}O$ [M+H] = 189.1279, found 189.1278.

HPLC (Daicel Chiralpak OD-H HPLC column, 99.8% hexane/isopropanol, 0.5 mL/min) - t_r major diastereomer = 21.7 (minor enantiomer), 22.9 (major enantiomer) minutes, t_r minor diastereomer = 25.4 (minor enantiomer), 25.9 (major enantiomer) minutes



1,4-diphenylhex-5-en-2-one
23x (eb4172)
colorless oil
71% yield, 72% cee (*S*)

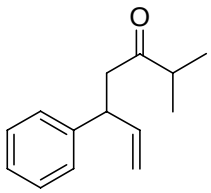
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H: aromatic H), 7.24 (m, 1H: aromatic CH), 7.17 (d, *J* = 7 Hz, 2H: aromatic CH), 7.12 (d, *J* = 7 Hz, 2H: aromatic CH), 5.95 (ddd, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.05 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 4.98 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 3.94 (app. q, *J* = 7 Hz, 1H: CH), 3.64 (d, *J* = 15 Hz, 1H: diastereotopic benzylic CH_2), 3.61 (d, *J* = 15 Hz, 1H: diastereotopic benzylic CH_2), 2.91 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic (CO)CH_2), 2.86 (dd, *J* = 7 Hz, 16 Hz, 1H: diastereotopic (CO)CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.40 (C=O), 142.71 (aromatic C), 140.45 (*C*H=CH_2), 133.82 (aromatic CH), 129.47 (aromatic CH), 128.72 (aromatic CH), 128.60 (aromatic CH), 127.65 (aromatic CH), 127.04 (aromatic CH), 126.60 (aromatic CH), 114.65 (CH=*C*H_2), 50.89 (benzylic CH_2), 47.17 ((CO)*C*H_2), 44.49 (CH).

FTIR ($CDCl_3$): ν_{max} 1715, 1495, 1454.

HRMS calcd for $C_{18}H_{19}O$ [M+H] = 251.1436, found 251.1432.

HPLC (Daicel Chiralpak AD HPLC column, 99.0% hexane/isopropanol, 0.5 mL/min) - t_r = 18.4 (minor), 20.2 (major) minutes



2-methyl-5-phenylhept-6-en-3-one

23y (eb4173)
colorless oil
68% yield, 58% cee (*S*)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (m, 2H: aromatic H), 7.13 (m, 3H: aromatic H), 5.91 (ddd, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 4.98 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 4.94 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 3.88 (app. q, *J* = 7 Hz, 1H: benzylic CH), 2.83 (dd, *J* = 7 Hz, 17 Hz, 1H: diastereotopic CH_2), 2.77 (dd, *J* = 7 Hz, 17 Hz, 1H: diastereotopic CH_2), 2.43 (sep., *J* = 7 Hz, 1H: C*H*-$(CH_3)_2$), 0.97 (d, *J* = 7 Hz, 3H: diastereotopic CH_3), 0.90 (d, *J* = 7 Hz, 3H: diastereotopic CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.65 (C=O), 143.15 (aromatic C), 140.77 (*C*H=CH_2), 128.56 (aromatic CH), 127.69 (aromatic CH), 126.52 (aromatic CH), 114.53 (CH=*C*H_2), 45.94 (CH_2), 44.30 (*C*H-$(CH_3)_2$), 41.37 (benzylic CH), 17.94 (diastereotopic CH_3), 17.83 (diastereotopic CH_3).

FTIR ($CDCl_3$): ν_{max} 1709, 1452, 1385, 1364.

HRMS calcd for $C_{14}H_{19}O$ [M+H] = 203.1436, found 203.1433.

HPLC (Daicel Chiralpak AD HPLC column, 99.0% hexane/isopropanol, 0.5 mL/min) - t_r = 9.5 (minor), 10.5 (major) minutes

2.7 References

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Chapter 3

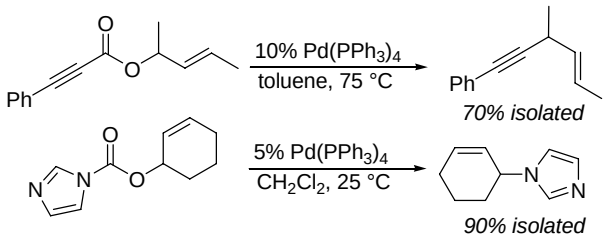
The Synthesis of Homoallylic Amines *via* the Palladium-Catalyzed Decarboxylative Coupling of Amino Acid Derivatives

3.1 Introduction

3.1.1 Expanding the Scope of Nucleophiles Generated via Decarboxylation

The successful development of methodology which effectively generates ketone enolate nucleophiles following a palladium- or ruthenium-catalyzed decarboxylation step encouraged us to explore a decarboxylative strategy for the *in situ* generation of other reactive nucleophiles. Shortly after the publication of our research on the decarboxylative allylation of ketone enolates, results from our group demonstrated that this was a reasonable goal; acetylide and amide nucleophiles were successfully revealed following the decarboxylation of the corresponding allylic esters or carbamates.[1] Allylation of these nucleophiles provided 1,4-enynes and allylic amines in very good yields (Scheme 3.1).

Scheme 3.1 *Decarboxylative allylation of non-ketone enolates*

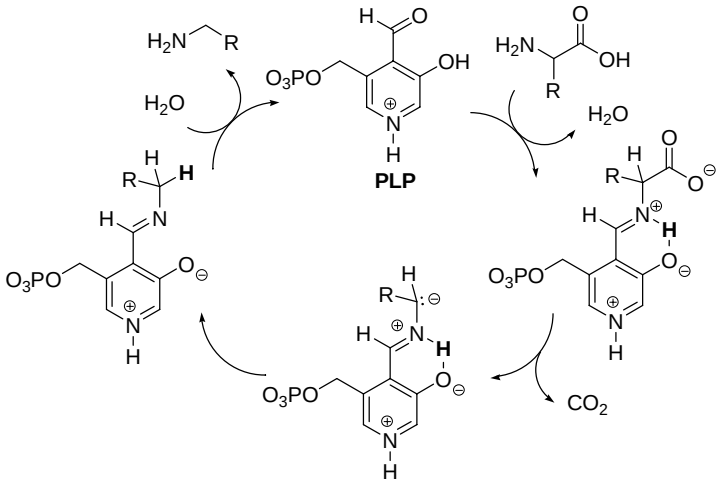


3.1.2 Decarboxylation in Biological Systems

We turned to biological systems for inspiration when choosing a new class of nucleophiles to pursue using our decarboxylative strategy. Decarboxylation reactions are prevalent in biological systems,[2] with many decarboxylases relying on pyridoxal-5-phosphate (PLP), also known as vitamin B_6, as a coenzyme.[3] PLP, illustrated in Scheme 3.2, facilitates the decarboxylation of α-amino acids by first forming a Schiff

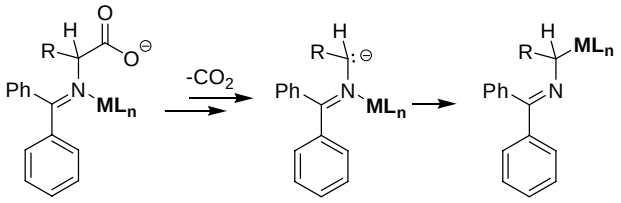
base with the amino acid. Decarboxylation of this intermediate is facile due to the formation of a resonance-stabilized anion following the loss of CO_2. Protonation of the decarboxylated intermediate, followed by hydrolysis of the imine, liberates amine and regenerates PLP.

Scheme 3.2 *Mechanism of decarboxylation with PLP*



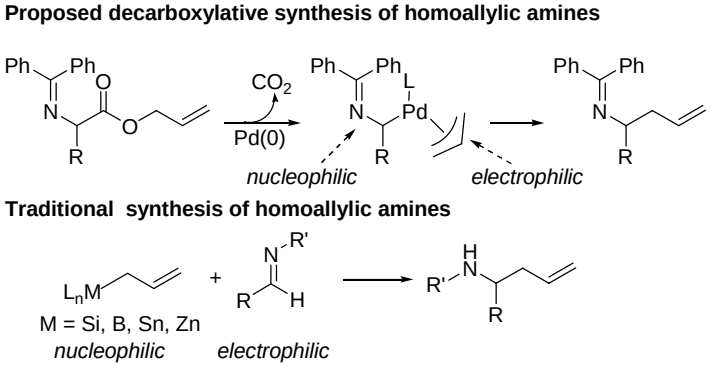
We reasoned that amino acids protected as diphenylketimines should decarboxylate in the presence of a transition-metal catalyst to form stabilized α-imino anions in a similar fashion to the PLP-catalyzed decarboxylation of amino acids (Scheme 3.3). The diphenylketimine protecting group has previously been used to stabilize α-anions in various alkylation reactions.[4] Rather than protonation of the imino anion intermediate, we envisioned utilizing it as a nucleophile which could be allylated in the presence of an electrophilic transition metal π-allyl. Given the wide accessibility of enantioenriched amino acids, we were also interested in the stereochemical outcome of the proposed transformation.

Scheme 3.3 *Analogous transition-metal catalyzed decarboxylation of amino acids*



The successful execution of this strategy, depicted in Scheme 3.4, would provide for the decarboxylative synthesis of homoallylic amines following hydrolysis of the ketimine protecting group. This would be a noteworthy accomplishment as conceptually it would be very different from the traditional methods for the synthesis of homoallylic amines.[5] Whereas traditional synthetic methods rely on the addition of *nucleophilic* metal allyls to electrophilic aldimines, our proposed decarboxylative strategy would be expected to operate through a mechanism in which a nucleophilic α-imino anion adds to an *electrophilic* metal allyl.

Scheme 3.4 *Proposed and traditional syntheses of homoallylic amines*

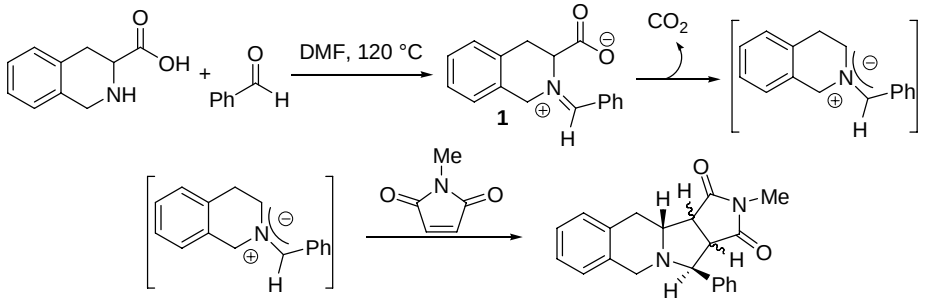


3.1.3 Thermal Decarboxylation of Imine Protected α-Amino Acids

The Strecker degradation is one of the earliest examples of imine formation facilitating the thermal decarboxylation of α-amino acids.[6] More recently, Ronald

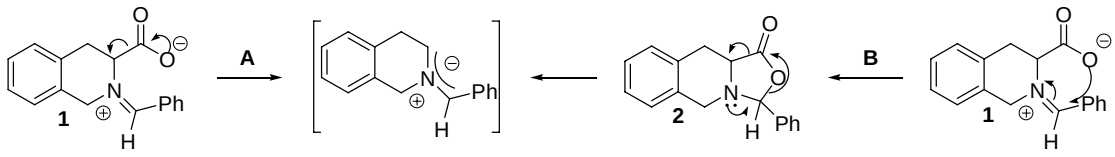
Grigg's group has successfully capitalized on the formation of aldimines of amino acids as a way of generating 1,3-dipolar azomethine ylide intermediates following loss of CO_2. The azomethine ylides formed *in situ* were trapped with various dipolarophiles to generate fused ring systems (Scheme 3.5).[7]

Scheme 3.5 *Thermal decarboxylative formation of azomethine ylides*



Initially it was assumed that the decarboxylation step occurred by mechanism **A**, outlined in Scheme 3.6. A more thorough investigation of the stereochemical course of the reaction led the researchers to perform theoretical calculations on the decarboxylation of imine **1**.[8] It was found that, despite being a 5-*endo*-trig process, the cyclization of **1** to yield the oxazolin-5-one **2** was a highly favorable process (mechanism **B**). A retro cycloaddition of **2** expels CO_2 and generates the 1,3-dipole.

Scheme 3.6 *Mechanism of thermal decarboxylation*



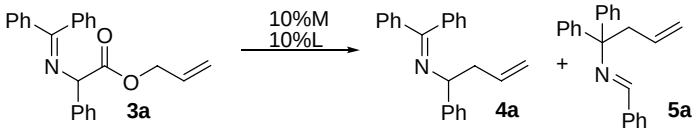
3.2 The Decarboxylative Coupling of Amino Acid Derivatives

3.2.1 Racemic Reactions

We chose to begin our studies on the decarboxylative allylation of α-imino anions by synthesizing diphenyl ketimine protected allylic esters of phenylglycine and phenylalanine.[9] α-Amino allylic esters were synthesized in a very expedient manner from the desired Boc-protected amino acid through an EDCI/DMAP coupling with allyl alcohol.[10] Formation of the imine functionality by condensation of the free amine with benzophenenone has been reported to be quite difficult and indeed proved to be problematic.[11,b] Fortunately, condensation of the amine HCl salt with benzophenone imine has been routinely used to form diphenyl ketimines and cleanly converted the allylic esters of amino acids to the protected imines.[12]

The ketimine derivative of phenylglycine, **3a**, was subjected to a variety of conditions aimed at identifying the optimal catalyst, ligand, solvent, and reaction temperature (Table 3.1). The combination of $[Cp^*RuCl]_4$ and bpy was ineffective at room temperature in methylene chloride, although the reaction went to complete conversion after 2 hours in refluxing toluene. The major product observed by ^1H NMR was the desired coupling product **4a**, however significant amounts of side product, identified by ^{13}C and ^1H NMR to be **5a**, were also present.

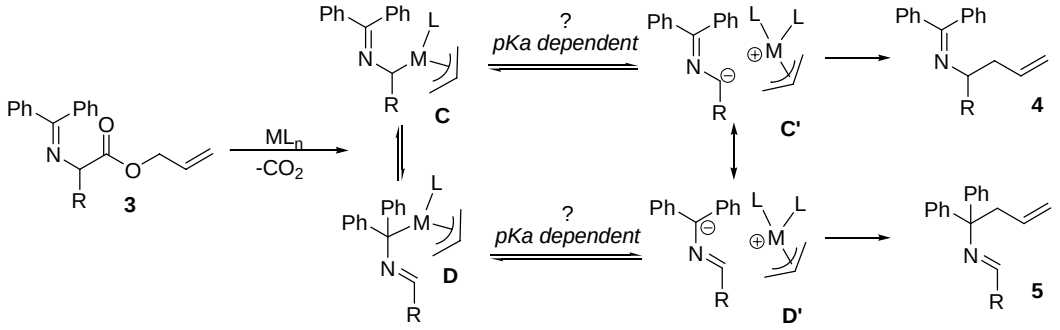
Table 3.1 *Optimizaton of reaction conditions for **3a***



Entry	Catalyst	Ligand	Solvent	Temperature	%Conversion	4a:5a
1	$[Cp^*RuCl]_4$	bpy	CH_2Cl_2	25 °C	0	---
2	$[Cp^*RuCl]_4$	bpy	Toluene	110 °C	100	4.8:1
3	$Pd(PPh_3)_4$	---	Benzene	80 °C	100	2.3:1
4	Pd_2dba_3	dppb	THF	25 °C	100	4.8:1
5	Pd_2dba_3	dppf	THF	25 °C	100	5.3:1
6	Pd_2dba_3	dppf	Benzene	80 °C	100	2.3:1
7	Pd_2dba_3	dppf	Benzene	40 °C	100	2.6:1
8	Pd_2dba_3	dppf	CH_3CN	82 °C	100	5.3:1
9	Pd_2dba_3	dppf	CH_2Cl_2	25 °C	65	5.1:1
10	Pd_2dba_3	dppf	Toluene	110 °C	100	2:1

Although clean conversion to the desired product **4a** would be ideal, the observation of **5a** in the reaction mixture provides some insight into the reaction mechanism and lends support to the hypothesis that α-imino anions are generated in the reaction. Presumably **5a** arises from the allylation of intermediate **D** or **D'** (Scheme 3.7). While the benzylic α-imino anion **C'** generated after the loss of CO_2 from **3a** has a pK_a of 24.3 in DMSO[13] and could conceivably exist as a resonance stabilized anion in solution (**C'** or **D'**), the pK_a of alkyl substituted imines is expected to increase by approximately 7 pK_a units[14] and may behave like a hard nucleophile and remain metal-bound (**C** or **D**).

Scheme 3.7 *Resonance-stabilized intermediates*

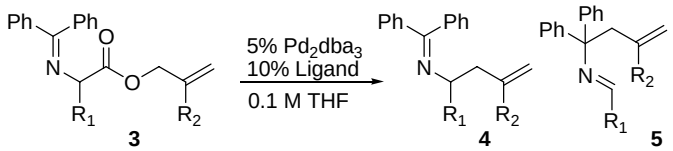


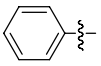
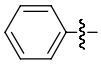
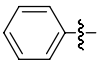
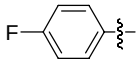
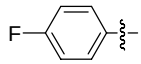
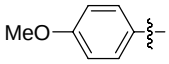
Palladium was also an effective catalyst for the reaction. At temperatures above 80 °C in non-polar solvents, regardless of the palladium source or ligand, a 2:1 mixture of **4a** and **5a** were formed after several hours (entries 3,6 and 10). When the reaction was run in refluxing acetonitrile overnight the product ratio increased to 5.3:1 (entry 8). A similar product ratio was obtained in methylene chloride at room temperature, although the reaction proceeded to only 65% conversion in 24 hours (entry 9). Changing the solvent to THF increased the rate of reaction at room temperature considerably; reactions run with dppf or dppb as the ligand were complete in only 3 hours (entries 4 and 5). The catalytic system of 5 mol% $Pd_2(dba)_3$ and 10 mol% dppf afforded the best selectivity for **4a** (5.3:1) and was selected for further studies.

A variety of phenylglycine derivatives were synthesized in order to investigate the scope of the transformation (Table 3.2). The reaction tolerates the introduction of a methyl or phenyl group in the *2* position of the allyl fragment; in fact, substitution at this position facilitates the isolation of higher yields, although it is necessary to increase the reaction temperature to 40 °C. The higher yields reflect that fact that

formation of **5** is inhibited when there is substitution on the allyl group, presumably due to unfavorable steric interactions For instance, whereas **3d** reacted to give a 5:1 mixture of **4d** and **5d**, **3e** yielded a 13:1 mixture of regioisomers.

Table 3.2 *Isolated yields of phenylglycine derivatives*



Substrate	R_1	R_2	Ligand	Temp	Time (h)	Yield (4)	4:5
3a		H	dppf	25 °C	3	67%	5:1
3b		CH_3	dppf	40 °C	3	81%	7.5:1
3c		Ph	dppf	40 °C	2	75%	9:1
3d		H	dppb	25 °C	2	66%	5:1
3e		CH_3	dppb	40 °C	3	93%	13:1
3f		CH_3	dppb	40 °C	12	85%	4.5:1

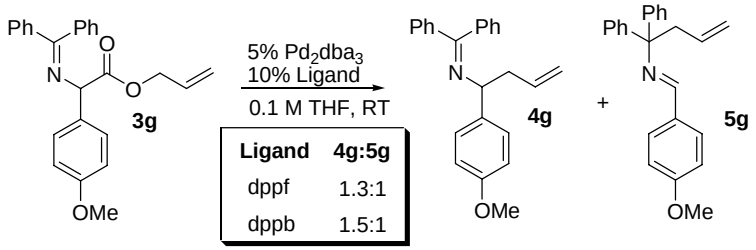
The favorable outcome in reactions of substrates bearing substituted allyls encouraged us to pursue the cyclohexenyl derivative of **3a**. Unfortunately the reaction temperature had to be increased to 100 °C, and the only product tentatively identified by ^{1}H NMR arises from protonation of the α-imino anion generated in the reaction. The 2-pentenyl derivative displayed a similar lack of reactivity and did not yield any allylation product.

It was noted that for substrates **3d**-**3f**, a catalytic system employing dppb as the ligand was found to provide superior regiochemical control when compared to dppf. Compound **3d** reacted to yield a 3.7:1 mixture of regioisomers when dppf was the ligand on palladium, compared to the 5:1 ratio obtained with dppb. It was

difficult to explain this increased selectivity or rationalize which reactions would benefit from switching to dppb from dppf, therefore both ligands were screened for activity in subsequent reactions.

The presence of an electron-donating methoxy group also slowed the reaction considerably, further supporting the necessity of forming a proposed anionic intermediate. Despite this, **4f** was still isolated in an 85% yield after 12 hours at 40 °C. The unsubstituted allyl analog of **3f**, **3g**, also reacted under standard conditions, but the reaction was plagued by poor regioselectivity (Scheme 3.8). Attempted isolation of **4g** always yielded samples contaminated with small amounts of *p*-methoxy benzaldehyde, which arises from the hydrolysis of **5g** on the silica chromatography column. Samples of **4g** that did not contain any **5g** were resubjected to the conditions of catalysis in order to test if **5g** could be arising from a [3,3] rearrangement of **4g**, however **5g** was never observed by ^{1}H NMR, even at 110 °C in toluene. Unfortunately the conversion of **5g** to **4g** could not be tested due to the hydrolysis of aldimines such as **5g** upon purification.

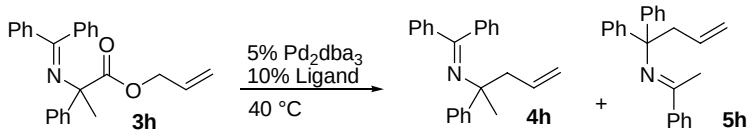
Scheme 3.8 *Regioselectivity in the reaction of* **3g**



The bulky, tertiary α-imino anion generated following the decarboxylation of the phenylglycine analog **3h** was also allylated with low levels of selectivity.

Regardless of ligand or solvent, the ratio of **4h**:**5h** failed to increase beyond a 1:1 mixture (Table 3.3). Despite the low selectivity of the reaction, successful conversion of **3h** to allylated products requires that decarboxylation precedes allylation and lends support to our proposed mechanism (*vida infra*).

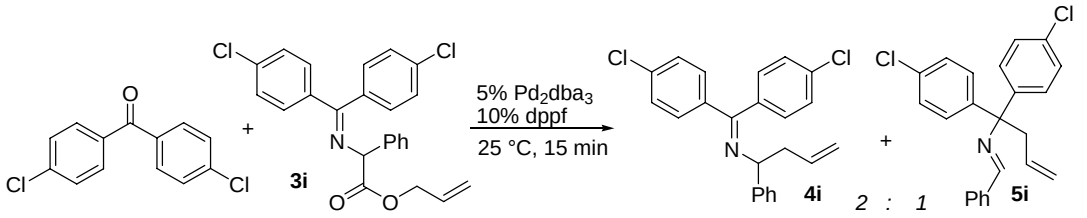
Table 3.3 *α-Disubstituted substrate*



Ligand	Solvent	4h:5h
dppf	CD_3CN	1:1.2
dppb	CD_3CN	1:1.2
P(*o*-Tol)$_3$	CD_3CN	1:1.2
dppb	Toluene, Δ	1:1.4
dppf	THF	1:1 *65% combined yield*

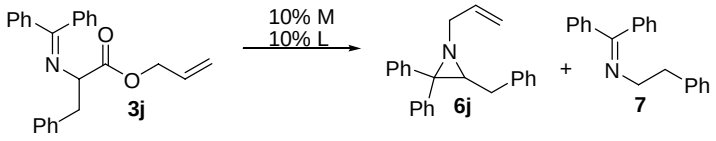
The effects of an electron withdrawing chloro group on the phenyl substituents of the imine were probed by preparing **3i** (Scheme 3.9). Unfortunately, condensation of the amino ester with *p*-chloro benzophenone in the presence of $TiCl_4$ was sluggish and attempts to purify **3i** were met with only modest success. Compound **3i** was isolated with a significant portion of *p*-chloro benzophenone; a 1:2 mixture of imine and ketone was obtained. When this mixture was subjected to the conditions of catalysis a 2:1 ratio of **4i** and **5i** was observed in the crude ^{1}H NMR. By comparing this product ratio to the 5:1 mixture of regioisomers obtained in the reaction of **3a** it is clear that introduction of *p*-chloro groups decreases the regioselectivity of the reaction. Attempts at exploring the effects of other substituents on the aryl rings of the imine were severely hampered by the lack of methods for the synthesis of diaryl imines from diaryl ketones (*vida supra*).

Scheme 3.9



The decarboxylation of **3j**, derived from phenylalanine, was also examined. Table 3.4 indicates that, unlike the phenylglycine analog **3a**, the reaction does not proceed at room temperature in THF (Entry 2). This most likely reflects the higher activation energy required to form an α-imino anion that is no longer benzylic. At elevated temperatures aziridine **6j** was formed, along with protonated imino anion **7**. While this result was quite unexpected, the cyclization of diphenylketimine protected glycine anions has been reported to occur upon the addition of acid chlorides.[15] Extensive optimization studies were conducted in an attempt to maximize the formation of aziridine.

Table 3.4 *Optimization of reaction conditions for **3j***

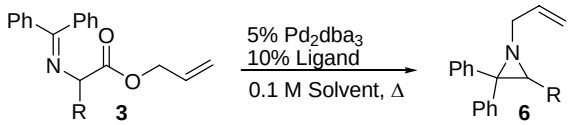


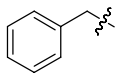
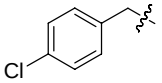
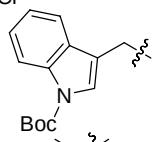
Entry	Catalyst	Ligand	Solvent	Temperature	% Conversion	6j:7j
1	$[Cp^*RuCl]_4$	bpy	Toluene	110 °C	17	0:1
2	Pd_2dba_3	dppf	THF	25 °C	0	---
3	$Pd(PPh_3)_4$	---	Benzene	40 °C	0	---
4	$Pd(PPh_3)_4$	---	Benzene	80 °C	100	2:1
5	Pd_2dba_3	dppf	Benzene	40 °C	100	0:1
6	Pd_2dba_3	dppb	Benzene	80 °C	100	3.8:1
7	Pd_2dba_3	dppf	Benzene	80 °C	100	11:1
8	Pd_2dba_3	dppf	dioxane	102 °C	100	6:1
9	Pd_2dba_3	dppb	Toluene	110 °C	100	4:1
10	Pd_2dba_3	3 $P(OPh)_3$	Toluene	110 °C	0	---

The survey of reaction conditions indicated that at low temperatures the catalytic system of $Pd_2(dba)_3$ and dppf affords only protonation product **7** after 24 hours, although in refluxing benzene aziridine becomes the predominate product and is formed in a very high 11:1 ratio after only two hours (entries 5 and 7). Benzene was the optimal solvent for this catalytic system; substituting dioxane decreased the product ratio to 6:1 (entry 8). Changing the ligand to dppb results in a significant drop in selectivity (entries 6 and 9). Employing triphenyl phosphite as the ligand was ineffective in the reaction, as was the ruthenium catalyst.

The formation of aziridine products was observed in the reaction of amino acid derivatives that had been esterified with allyl alcohol and in which a stabilized benzylic anion is not formed following decarboxylation (Table 3.5). As observed for substrates **3d-f**, substitution of dppb for dppf was necessary to obtain high product yields of **6k** and **6l**. The identity of the solvent also was vital for clean product formation. For instance, when **3k** was subjected to 5 mol% $Pd_2(dba)_3$ and 10 mol% dppb in refluxing toluene, a 1.5:1 mixture of **6k** and **7** was formed. When the solvent was changed to dioxane the product ratio increased to 2.2:1. It was also necessary to Boc protect the nitrogen in the tryptophan derivative **3l**. The free amine analog afforded a complex mixture of products, as did a substrate synthesized from tyrosine. Finally, we were pleased to find that the valine based imino ester, **3m**, was cleanly converted to aziridine product and afforded a greater than 95% yield of **6m**.

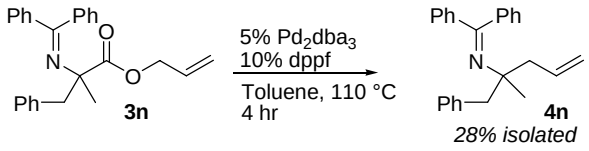
Table 3.5 *Scope of aziridine formation*



Substrate	R	Ligand	Solvent	Time	Yield
3j		dppf	Toluene	2 h	68%
3k		dppb	Dioxane	3 h	59%
3l		dppb	Dioxane	12 h	87%
3m		dppf	Toluene	2 h	>95%

In contrast to the α-monosubstituted amino acid derivatives **3j**-**3m**, α-disubstituted **3n** did not react to yield aziridine **6n**, but rather **4n** was produced in a 1:1.7 mixture with another product (not aziridine) that remains unidentified. A 28% yield of **4n** was isolated following flash column chromatography.

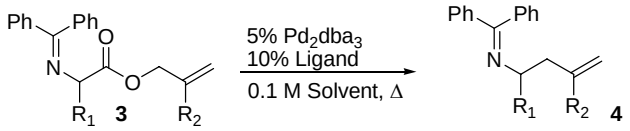
Scheme 3.10

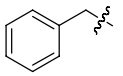
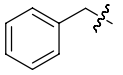
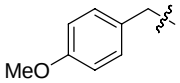
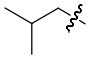


The presence of a substituent on the allyl group also inhibited aziridine formation and allowed for the isolation of allylated products **4o**-**4r** (Table 3.6). The exception to this was **3q**, which yielded **4q** despite the fact that **3q** was esterified with unsubstituted allyl alcohol. In contrast to the exclusive formation of aziridine from unsubstituted allyl **3m**, **3r** decarboxylated to yield an equimolar mixture of aziridine **6r** and **4r**, which was isolated in only a 26% yield. Unfortunately, the methallyl

analog of tryptophan derivative **3l** failed to react in refluxing toluene. The methallyl ester analog of *p*-chloro phenylalanine derivative **3k** yielded only protonation product **7**.

Table 3.6 *Substrate scope*

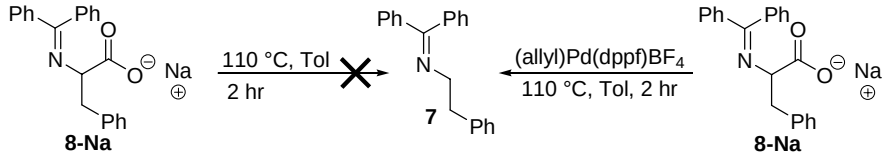


Substrate	R_1	R_2	Ligand	Solvent	Time	Yield
3o		CH_3	dppf	Toluene	6 h	63%
3p		Ph	dppf	Toluene	3 h	46%
3q		H	dppb	Dioxane	2 h	67%
3r		CH_3	dppf	Toluene	18 h	26%

To probe the role of palladium in the decarboxylation process, sodium carboxylate **8-Na** was heated in the absence of palladium for 12 hours at 110 °C in toluene (Scheme 3.11). It was found that, in contrast to the analogous carboxylic acid **8-H**, no decarboxylation took place. Similar treatment of **8-Na** with one equivalent of (allyl)Pd(dppf)BF_4 resulted in quantitative decarboxylation, however, the major product resulted from decarboxylative protonation. We have speculated that the protons may originate from the ligand, which helps to explain the observation of protonation products when the catalytic reactions were run in rigorously dried solvents. After the mixture of **8-Na** and (allyl)Pd(dppf)BF_4 was refluxed for 2 hours imino ester **3j** was added to the reaction mixture and heating continued. Following an additional hour at reflux ^{1}H NMR indicated formation of **6j**, confirming the existence

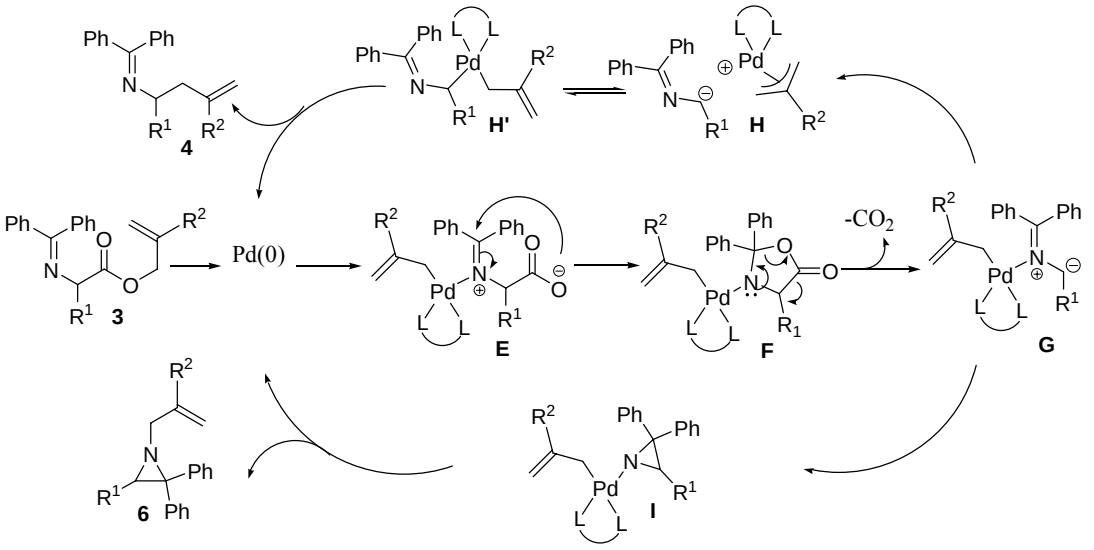
of a catalytically active system derived from [Pd(allyl)(dppf)]BF_4. These experiments indicate that palladium plays a role in activating the substrate for decarboxylation.

Scheme 3.11 *Palladium-facilitated decarboxylation*



A proposed mechanism that accounts for the formation of aziridine and protected homoallylic amine is illustrated in Scheme 3.12. Oxidative addition of **3** to Pd(0) yields the π-allyl Pd(II) intermediate **E**. Coordination of palladium to nitrogen can facilitate the decarboxylation of intermediate **E** through formation of the cycloaddition adduct **F**, as described by Grigg in the proton mediated decarboxylation of protected amino acids (*vida supra*). The fate of **G** is expected to be pK_a dependent. For substrates possessing a more acidic α position, simple ionization of **G** yields **H**. Nucleophilic attack of the imino anion on the electrophilic π-allyl yields **4**. Alternatively, for less acidic substrates, a 1,2 shift of palladium may yield **H'**, which can undergo reductive elimination to yield **4** and regenerate palladium (0). A third possibility is that **G** can undergo electrocyclization to yield intermediate **I**, which furnishes aziridine **6** upon reductive elimination.

Scheme 3.12 *Proposed catalytic cycle*



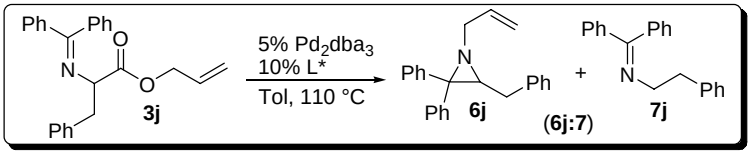
3.2.2 Enantioselective Reactions

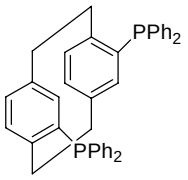
The stereochemical course of the reaction was probed by treatment of allyl ester **3b,** derived from (*R*)-phenylglycine (83% ee), under standard reaction conditions. The resulting product (**4b**) was racemic. Importantly, remaining **3b** was still enantiomerically enriched at 75% conversion (82% ee). Racemic **4o** was also isolated from the reaction of (*S*)-phenylalanine derivative **3o**, prepared with over 98% ee. Thus an achiral intermediate, such as **G**, that is not in equilibrium with α-imino ester is formed under the reaction conditions. This implies that the stereochemical determining step occurs after decarboxylation and that appropriate chiral ligands may promote enantioselective coupling.

In light of these results, the enantioselective synthesis of aziridine **6j** was explored with a variety of chiral ligands (Scheme 3.13). PhanePhos induced the

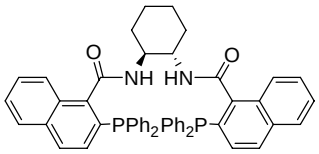
highest level of selectivity in the reaction, although **6j** was only isolated with a disappointing 18% ee.

Scheme 3.13 *Enantioselective aziridine synthesis*

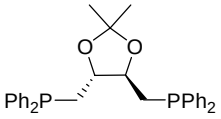




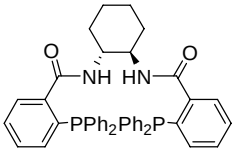
(*S*)-PhanePhos
18% ee
(6.4:1)



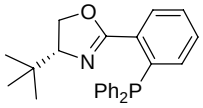
(*S*,*S*)-Napthyl Trost Ligand
12.5 % ee
(1.2:1)



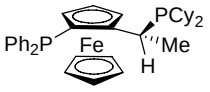
(*S*,*S*)-DIOP
5% ee
(8:1)



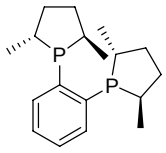
(*R*,*R*)-Trost Ligand
5% ee
(1:1.2)



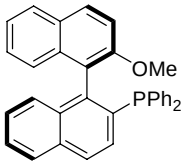
(*S*)-^{t}Bu PHOX
no reaction



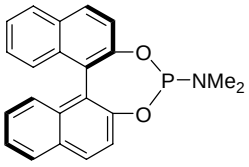
(*R*,*S*)-JosiPhos
(0:1)



(*R*,*R*)-MeDuPhos
no reaction



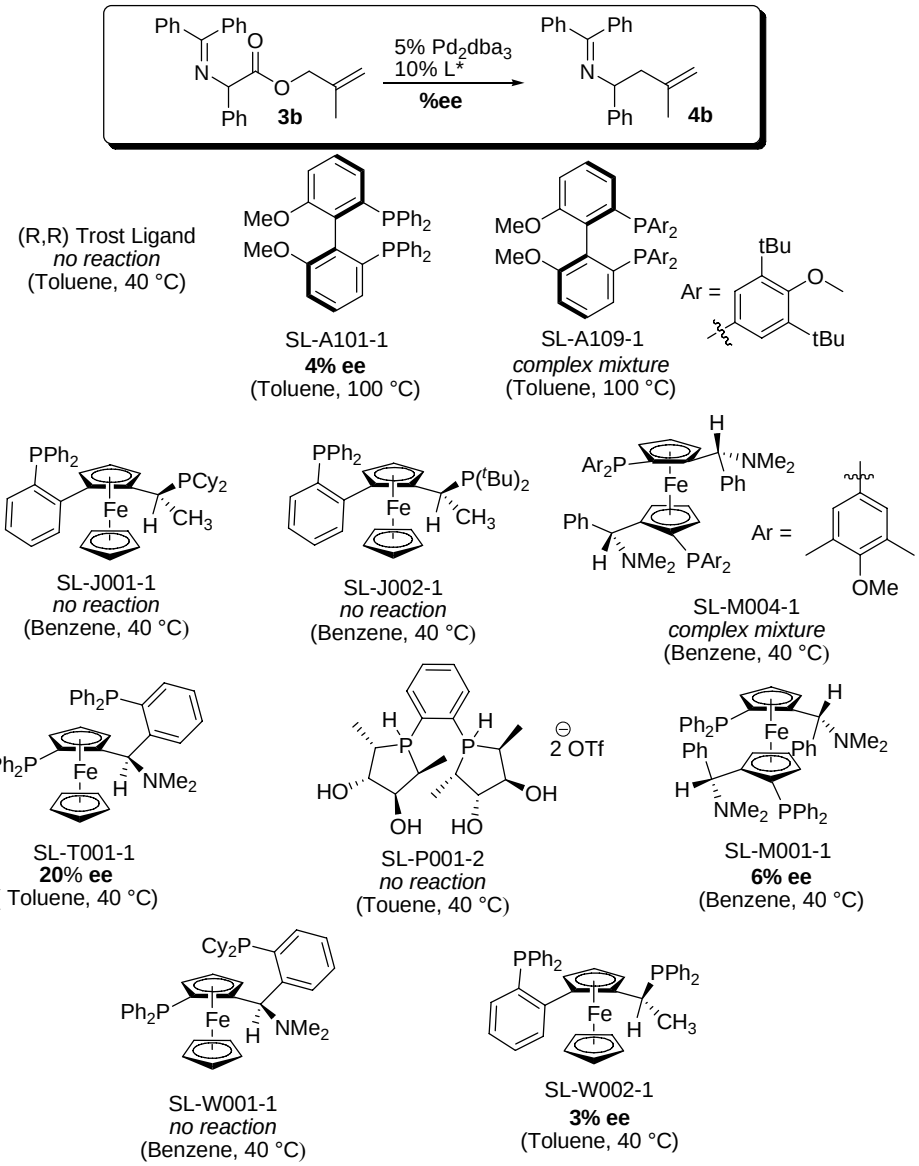
(*R*)-MOP
no reaction



(*R*)-MonoPhos
(0:1)

The low levels of enantioselectivity obtained in the synthesis of aziridine **6j** led us to quickly turn our attention to the development of an enantioselective synthesis of homoallylic imines. However, only one ligand, SL-T001-1, generated **4b** with greater than 10% ee, although the enantiomeric ratio was still low (60:40).

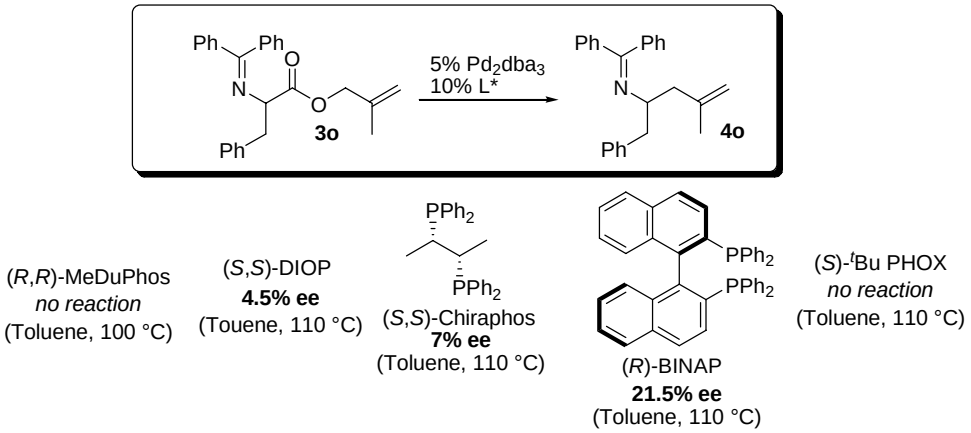
Scheme 3.14 *Enantioselective synthesis of* **4b**



The highest enantioselectivities obtained in the decarboxylative allylation of α-imino anions were in the conversion of **3o** to **4o**. Preliminary findings indicated that BINAP provided the highest levels of selectivity in the reaction (Scheme 3.15). The temperature and solvent were also shown to impact the enantioselectivity of the reaction. When the reaction temperature was decreased from 110 °C to 100 °C the ee

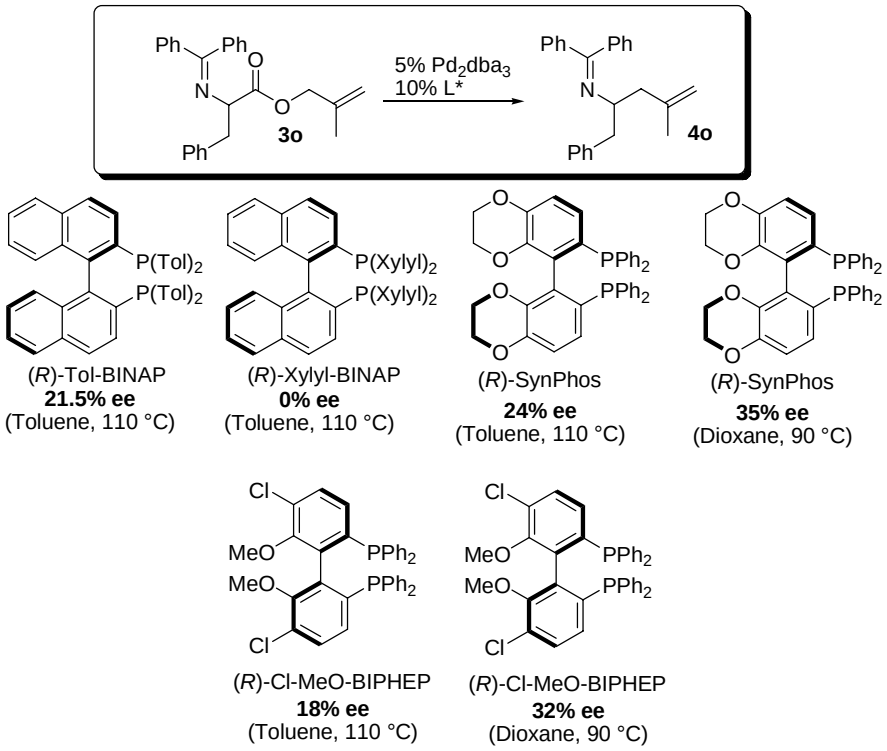
of **4o** increased from 21.5% to 26%. Changing the solvent to dioxane increased the ee as well; when the reaction was run at 100 °C in dioxane the ee improved to 30%. Running the reaction in dichloroethane and decreasing the reaction temperature to 83 °C shut down the reaction completely.

Scheme 3.15



Several BINAP analogs were acquired in an attempt to improve the enantioselectivity of the reaction. While xylyl-BINAP led to the production of racemic products, SynPhos and Cl-MeO-BIPHEP led to slightly improved ee's (35% and 32%).

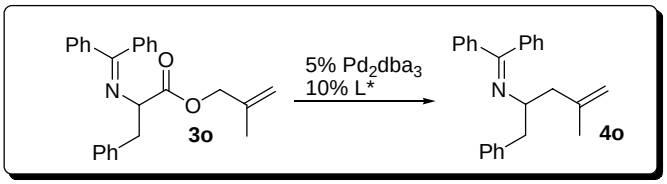
Scheme 3.16 *Screening of BINAP analogs*

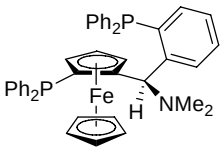


Further screening was conducted with the ligands shown in Scheme 3.17. The BIPHEP analog SL-A101-1 performed as expected based on the data obtained in Scheme 3.16, however, SL-A109-1 was apparently too bulky to effectively bind to palladium and catalyze the reaction. Even better results were obtained with SL-T001-1, which had previously been shown to induce the highest enantioselectivity in the conversion of **3b** to **4b**. When **3o** was allowed to react at 80 °C in dioxane in the presence of 10 mol% SL-T001-1 and 5 mol% $Pd_2(dba)_3$, **4o** was isolated in a 34% yield with a 58% ee. The crude NMR of the reaction mixture indicated that the low yield was a result of the formation of protonated imine **7** in a 1:1 mixture with homoallylic imine. The same ratio of products was observed when the reaction was

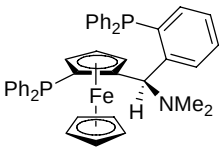
conducted at 100 °C. We attempted to run the reaction at 60 °C in order to further increase the enantioselectivity of the reaction, although at this temperature no reaction occurred.

Scheme 3.17

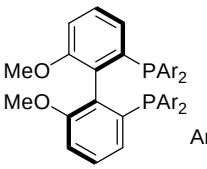




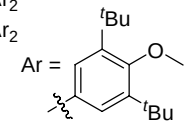
SL-T001-1
48% ee
(Dioxane 100 °C)

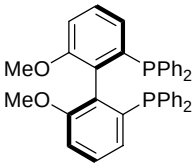


SL-T001-1
58% ee
(Dioxane 80 °C)



SL-A109-1
no reaction
(Dioxane 100 °C)

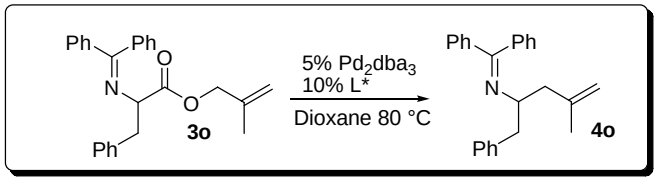


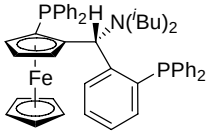


SL-A101-1
37% ee
(Dioxane 100 °C)

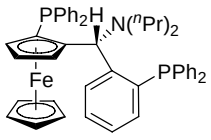
Finally, several analogs of SL-T001-1 were synthesized and screened in the conversion of **3o** to **4o** (Scheme 3.18).[16] Unfortunately, catalytic systems based on these ligands failed to produce **4o** with higher selectivity than was obtained with SL-T001-1, and the 58% ee obtained with this ligand is the best result we were able to obtain for the decarboxylative allylation of amino acid derivatives.

Scheme 3.18 *Synthesized analogs of SL-T001-1*

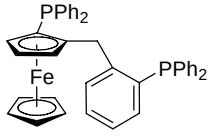




38% ee



37% ee



30% ee

With these results we have shown that the decarboxylative coupling reaction is not limited only to ketone enolates, but can encompass a variety of nucleophiles generated following the loss of CO_2. By avoiding a transmetallation step commonly found in many popular coupling reactions, decarboxylative coupling reactions are an important and environmentally beneficial addition to the chemist's arsenal of carbon-carbon bond forming reactions, especially as the range of suitable nucleophiles continues to grow. Ongoing research aimed at broadening the scope of the reaction to include electrophiles other than an allyl group, such as benzyl and napthyl groups, is an important future direction and promises to further increase the utility of the transformation.

3.3 Supporting Information

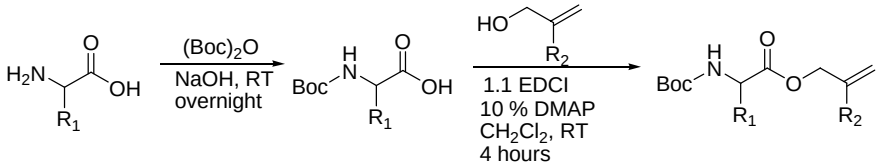
Materials

Benzene was dried over sodium metal and distilled under vacuum. THF, toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc. Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Products were purified on silica gel from Sorbent Technologies (40-63 μm particle size, 60 Å porosity, pH 6.5-7.5). Josiphos (SL-J001-1 through SL-J005-1), Taniaphos (SL-T001-1 and SL-T002-1), Walphos (SL-W001-1 and SL-W002-1), Mandyphos (SL-M001-1 and SL-M004-1), Rophos (SL-P001-2), and MeOBIPHEP (SL-A101-1 and SL-A109-1) chiral ligands were a gift from Solvias. The Taniaphos ligand derivatives illustrated in Scheme 3.18 were synthesized according to a literature

procedure.[17] All other chiral ligands were purchased from Strem. $[Cp^*RuCl]_4$ was synthesized according to the reported literature procedure.[18] All palladium compounds were purchased from Strem with the exception of $[Pd(allyl)(dppf)]BF_4$, which was synthesized as described by Amatore.[19] NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, and HMQC spectroscopies. High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument. Gas chromatography was performed with a Shimadzu GC-17A instrument with an attached AOC-20i auto injector.

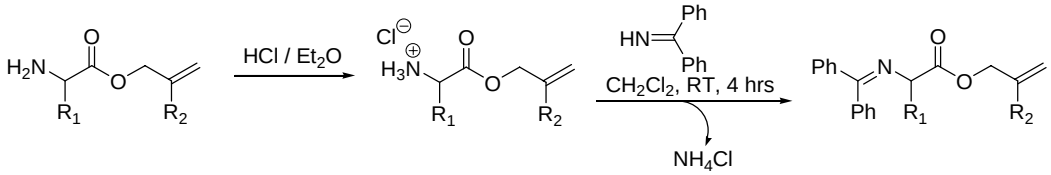
Preparation of Starting Materials

The synthesis of allyl imino esters **3** began with the Boc protection of α-amino acids.[20] The protected amino acids were then esterified with the desired allylic alcohol by utilizing an EDCI/DMAP coupling.[21]

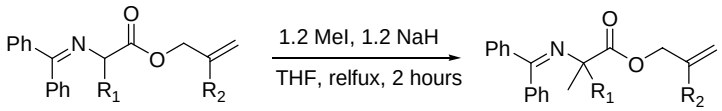


Most allylic alcohols were commercially available, although it was necessary to synthesize 2-phenyl allyl alcohol by the addition of $ClICH_2$, MeI, LiI, and LiBr to benzoyl chloride.[22] Following esterification the allylic esters were deprotected with TFA.[23] Exposure of the cyclohexenyl and 2-pentenyl esters to TFA resulted in

decomposition of the ester, therefore TMSI was used to remove the Boc group.[24] Alternatively, allyl esters could be obtained directly from the unprotected amino acid and allylic alcohol by toluenesulfonic acid-catalyzed esterification with azeotropic removal of water.[25] The HCl salt of the deprotected amino ester was isolated following slow addition of 2M HCl in ether. Benzophenone imine was added to a solution of the amine salt in methylene choride.[26] After four hours filtration of NH_4Cl from the reaction mixture and evaporation of the solvent yielded imino ester in a quantitative yield; no further purification was necessary.



The Boc-protected tyrosine derivative **31** was synthesized from the imino allyl ester by the addition of Boc_2O and a catalytic amount of DMAP.[27] It was necessary to purify **3l** on a neutral alumina column with 3% ethyl acetate / hexane in order to avoid hydrolysis of the imine. **3i** was prepared by the condensation of *p*-chlorobenzophenone with amino ester in the presence of $TiCl_4$.[28] Purification was attempted on a neutral alumina column, unfortunately, regardless of the solvent polarity, the product was always contaminated with *p*-chlorobenzophenone. α-Disubstituted imino esters were synthesized by the addition of 1.2 equivalents of methyl iodide and 1.2 equivalents of sodium hydride to the imino ester of phenylglycine or phenylalanine. The reaction was refluxed for two hours in dry THF under argon. The crude product was purified on a neutral alumina column with 5% ethyl acetate / hexane.

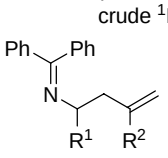
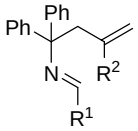
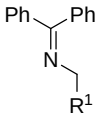
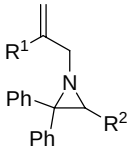
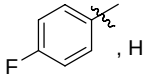
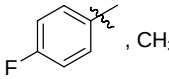
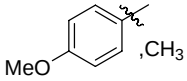
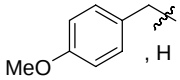
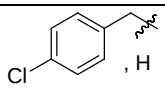
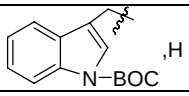


Imino acid **8** was prepared by the addition of 1 equivalent of benzophenone imine to a 0.1M solution of phenylalanine HCl in methylene chloride with molecular sieves. After the reaction was stirred for 24 hours, the resulting yellow suspension of NH_4Cl was filtered. Evaporation of solvent yielded the desired product.

Procedure for the synthesis of protected homoallylic amines and N-allyl aziridines:

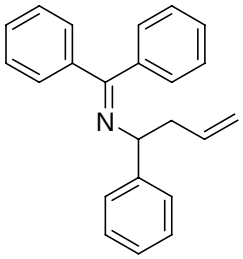
Allylic ester (0.5 mmole) was added to a flame-dried Schlenk tube under argon. $Pd_2(dba)_3$ (0.025 mmol, 23mg) and the appropriate ligand (0.05 mmol) were dissolved in the optimal solvent (5 mL) (see Tables 3.2, 3.5, and 3.6) in a separate Schlenk tube under argon. The catalyst solution was stirred briefly and added *via* cannula addition to the substrate flask. The solution was stirred under argon for the indicated reaction time at the appropriate temperature. The solvent was then removed under reduced pressure and the crude material was purified by flash chromatography (0.5 to 1% ethyl acetate in hexane on SiO_2).

Detailed Product Distributions

Substrate	R^1 , R^2	**Yields** (estimated from crude ^{1}H NMR) 			
3a	Ph, H	67%	(17%)	----	----
3b	Ph, CH_3	81%	(10%)	----	----
3c	Ph, Ph	75%	(10%)	----	----
3d	 , H	66%	(17%)	----	----
3e	 , CH_3	93%	(7%)	----	----
3f	 ,CH_3	85%	(15%)	----	----
3o	Bn, CH_3	63%	(17%)	(12%)	----
3p*	Bn, Ph	43%	---	(14%)	
3q	 , H	67%	----	(16%)	(5%)
3r*	 , CH_3	26%	----	----	(25%)
3j	Bn, H	(13%)	----	(8%)	68%
3k	 , H	(31%)	----	----	59%
3l*	 ,H	----	----	----	87%
3m	 , H	----	----	----	>95%

* crude ^{1}H NMR also indicated a significant amount of unidentifiable side products

Spectroscopic Data



N-(diphenylmethylene)-1-phenylbut-3-en-1-amine

4a[29] (eb6191)

colorless solid

67% yield

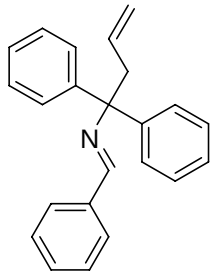
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H: arom. CH), 7.59 (m, 2H: aromatic CH), 7.52 (t, *J* = 7 Hz, 1H: aromatic CH), 7.41 (t, *J* = 8 Hz, 2H: aromatic CH), 7.35 (overlapping m, 3H: aromatic CH), 7.21 (overlapping m, 3H: aromatic CH), 6.99 (m, 2H: aromatic CH), 5.57 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 4.90 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 4.88 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 4.36 (dd, *J* = 5 Hz, 8 Hz, 1H: CH), 2.61 (ddd, *J* = 7 Hz, 8 Hz, 14 Hz, 1H: diastereotopic allylic CH_2), 2.50 (ddd, *J* = 5 Hz, 7 Hz, 14 Hz, 1H: diastereotopic allylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.69 (C=N), 145.50 (aromatic C), 140.06 (aromatic C), 137.61 (aromatic C), 135.78 (=CH), 132.45 (aromatic CH), 130.10 (aromatic CH), 129.87 (aromatic CH), 128.60 (aromatic CH), 128.30 (aromatic CH), 127.99 (aromatic CH), 127.92 (aromatic CH), 127.16 (aromatic CH), 126.72 (aromatic CH), 116.70 (=CH_2), 66.49 (CH), 43.96 (CH_2).

FTIR (CD_2Cl_2): ν_{max} 1658, 1622, 1446, 999, 920.

HRMS calcd for $C_{23}H_{22}N$ [M+H] = 312.1752, found 312.1721.

HPLC (Daicel Chiralpak OD-H column, 99.5% hexane:isopropanol, 1.0 mL/min) t_r = 4.18, 4.58 minutes



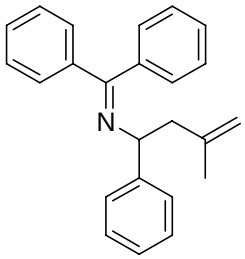
(*E*)-*N*-benzylidene-1,1-diphenylbut-3-en-1-amine

5a (eb6043)

16% NMR yield

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.75 (s, 1 H: N=CH) 6.95 - 7.62 (m, 15 H: aromatic CH) 5.67 - 5.78 (m, 1 H: C=CH) 4.84 - 4.94 (m, 2 H: $=CH_2$) 3.06 (d, *J*=6.9 Hz, 2 H: CH_2)

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.77 (N=CH) 146.35 (aromatic C) 137.12 (aromatic C) 136.92 (CH) 134.55 (CH) 130.60 (CH) 128.53 (CH) 128.31 (CH) 127.96 (CH) 126.57 (CH) 117.54 ($=CH_2$) 72.05 (C) 46.82 (CH_2)



N-(diphenylmethylene)-3-methyl-1-phenylbut-3-en-1-amine

4b (eb6180)
colorless solid
81% yield

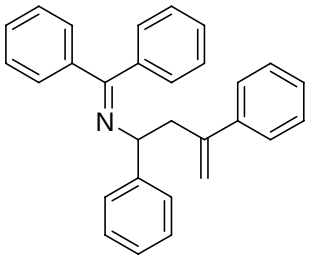
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7 Hz, 2H: aromatic CH), 7.34 (overlapping m, 4H: aromatic CH), 7.26 (overlapping m, 7H: aromatic CH), 7.19 (d, *J* = 3 Hz, 2H: aromatic CH), 4.61 (s, 1H: diastereotopic $=CH_2$), 4.54 (s, 1H: diastereotopic $=CH_2$), 4.44 (m, 1H: CH), 2.60 (dd, *J* = 8 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.39 (dd, *J* = 5 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 1.42 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.48 (C=N), 144.92 (aromatic C), 142.72 (aromatic C), 140.13 (aromatic C), 136.96 (=C), 130.09 (aromatic CH), 129.79 (aromatic CH), 128.60 (aromatic CH), 128.27 (aromatic CH), 128.20 (aromatic CH), 128.08 (aromatic CH), 127.95 (aromatic CH), 127.12 (aromatic CH), 126.65 (aromatic CH), 113.14 ($=CH_2$), 65.21 (CH), 48.13 (CH_2), 22.86 (CH_3).

FTIR (CD_2Cl_2): ν_{max} 1647, 895, 696.

HRMS calcd for $C_{24}H_{23}N$ [M+H] = 326.1909, found 326.1883.

HPLC (Daicel Chiralpak OD-H HPLC column, 99.5% hexane/isopropanol, 1.0 mL/min) - t_r = 3.8, 4.4 minutes



N-(diphenylmethylene)-1,3-diphenylbut-3-en-1-amine

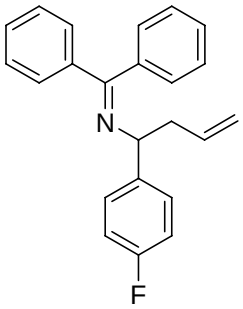
4c (eb7033)
colorless, viscous oil
75% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 2H: aromatic CH), 7.52 (overlapping m, 3H: aromatic CH), 7.42 (t, *J* = 8 Hz, 2H: aromatic CH), 7.20 (overlapping m, 11H: aromatic CH), 6.73 (d, *J* = 7 Hz, 2H: aromatic CH) 5.12 (s, 1H: diastereotopic $=CH_2$), 4.89 (s, 1H: diastereotopic $=CH_2$), 4.41 (dd, *J* = 6 Hz, 8 Hz, 1H: CH), 3.06 (dd, *J* = 8 Hz, 14 Hz, 1H: diastereotopic allylic CH_2), 2.95 (dd, *J* = 6 Hz, 14 Hz, 1H: diastereotopic allylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.95 (C=N), 145.12 (aromatic C), 144.66 (aromatic C), 140.68 (aromatic C), 140.05 (aromatic C), 136.70 (=C), 132.45 (aromatic CH), 130.09 (aromatic CH), 129.79 (aromatic CH), 128.57 (aromatic CH), 128.30 (aromatic CH), 128.22 (aromatic CH), 128.13 (aromatic CH), 128.00 (aromatic CH), 127.90 (aromatic CH), 127.73 (aromatic CH), 127.19 (aromatic CH), 126.17 (aromatic CH), 115.14 ($=CH_2$), 65.21 (CH), 45.49 (CH_2).

FTIR (CD_2Cl_2): ν_{max} 1658, 1622, 1446, 894.

HRMS calcd for $C_{29}H_{26}N$ [M+H] = 388.2065, found 388.2051.



N-(diphenylmethylene)-1-(4-fluorophenyl)but-3-en-1-amine

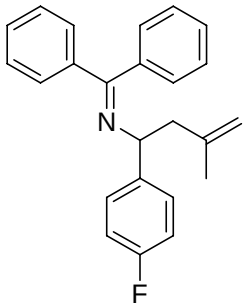
4d (eb6231)
colorless solid
66% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (m, 2H: aromatic CH), 7.59 (m, 2H: aromatic CH), 7.52 (t, *J* = 7 Hz, 1H: aromatic CH), 7.30 (overlapping m, 5H: aromatic CH) 6.97 (m, 2H: aromatic CH), 6.90 (t, *J* = 7 Hz 2H: aromatic CH), 5.55 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 4.89 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 4.88 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 4.33 (dd, *J* = 6 Hz, 8 Hz, 1H: CH), 2.57 (ddd, *J* = 7 Hz, 7 Hz, 14 Hz, 1H: diastereotopic allylic CH_2), 2.46 (ddd, *J* = 6 Hz, 7 Hz, 14 Hz, 1H: diastereotopic allylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.84 (C=N), 161.67 (d, *J* = 244 Hz, C-F), 140.18 (aromatic C), 137.61 (aromatic C), 137.00 (aromatic C), 135.46 (=CH), 132.45 (aromatic CH), 130.10 (aromatic CH), 128.58 (aromatic CH), 128.37 (aromatic CH), 128.31 (aromatic CH), 128.03 (aromatic CH), 127.80 (aromatic CH), 116.92 (=CH_2), 115.04 (d, *J* = 21 Hz, arom CH), 65.74 (CH), 44.02 (CH_2).

FTIR (CD_2Cl_2): ν_{max} 1639, 1600, 995.

HRMS calcd for $C_{23}H_{21}FN$ [M+H] = 330.1658, found 330.1641.



N-(diphenylmethylene)-1-(4-fluorophenyl)-3-methylbut-3-en-1-amine

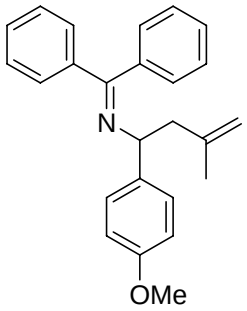
4e (eb6236)
colorless solid
93% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H: aromatic CH), 7.54 (d, *J* = 8 Hz, 2H: aromatic CH), 7.31 (overlapping m, 7H: aromatic CH), 6.98 (m, 2H: aromatic CH), 6.90 (t, *J* = 8 Hz, 2H: aromatic CH), 4.61 (s, 1H: diastereotopic $=CH_2$), 4.51 (s, 1H: diastereotopic $=CH_2$), 4.24 (dd, *J* = 5 Hz, 8 Hz, 1H: CH), 2.55 (dd, *J* = 8 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.36 (dd, *J* = 5 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 1.42 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.62 (C=N), 161.64 (d, *J* = 244 Hz, C-F), 142.44 (aromatic C), 140.57 (aromatic C), 139.97 (C), 136.87 (=C), 132.45 (aromatic CH), 130.10 (aromatic CH), 129.92 (aromatic CH), 128.59 (aromatic CH), 128.28 (aromatic CH), 128.00 (aromatic H), 127.96 (aromatic CH), 115.02 (d, *J* = 21 Hz, aromatic CH), 113.32 ($=CH_2$), 64.51 (CH), 48.19 (CH_2), 22.85 (CH_3).

FTIR (CD_2Cl_2): ν_{max} 1620, 894, 761, 696.

HRMS calcd for $C_{24}H_{23}FN$ [M+H] = 344.1815, found 344.1800.



N-(diphenylmethylene)-1-(4-methoxyphenyl)-3-methylbut-3-en-1-amine

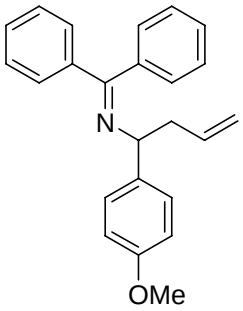
4f (eb6266)
colorless, viscous oil
85% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7 Hz, 2H: aromatic CH), 7.34 (overlapping m, 3H: aromatic CH), 7.26 (overlapping m, 3H: aromatic CH), 7.17 (d, *J* = 8 Hz, 2H: aromatic CH), 6.98 (m, 2H: aromatic CH), 6.77 (d, *J* = 8 Hz, 2H: aromatic CH), 4.61 (s, 1H: diastereotopic $=CH_2$), 4.53 (s, 1H: diastereotopic $=CH_2$), 4.40 (dd, *J* = 5 Hz, 8 Hz, 1H: CH), 3.72 (s, 3H: O-CH_3), 2.57 (dd, *J* = 8 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.37 (dd, *J* = 5 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 1.42 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.16 (C=N), 158.28 (aromatic C), 142.82 (aromatic C), 140.17 (aromatic C), 137.09 (C), 137.02 (C), 132.45 (aromatic CH), 130.09 (aromatic CH), 129.74 (aromatic CH), 128.58 (aromatic CH), 128.20 (aromatic CH), 128.07 (aromatic CH), 127.94 (aromatic CH), 113.64 (aromatic CH), 113.05 ($=CH_2$), 64.58 (CH), 55.24 (O-CH_3), 48.09 (CH_2), 22.89 (CH_3).

FTIR (CD_2Cl_2): ν_{max} 1647, 1443, 897, 762.

HRMS calcd for $C_{25}H_{26}NO$ [M+H] = 356.2014, found 356.2000.

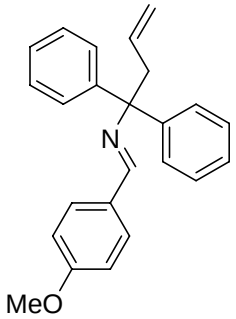


N-(diphenylmethylene)-1-(4-methoxyphenyl)but-3-en-1-amine

4g (eb6233-2)

60% NMR yield

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.78 - 7.89 (m, 14 H: aromatic CH) 5.59 - 5.73 (m, 1 H: =CH) 5.00 (d, *J*=17.2 Hz, 1 H: =CH(H)$_{trans}$) 4.95 (d, *J*=10.1 Hz, 1 H) 4.36 - 4.44 (m, 1 H: CH) 3.81 (s, 3 H: CH_3) 2.62 - 2.75 (m, 1 H: diastereotopic CH_2) 2.56 (m, 1 H: diastereotopic CH_2)

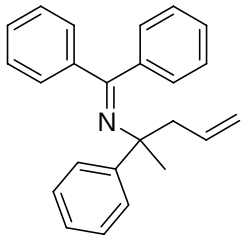


(*E*)-*N*-(4-methoxybenzylidene)-1,1-diphenylbut-3-en-1-amine

5g (eb6224-2)

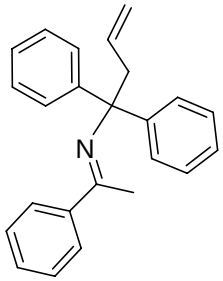
40% NMR yield

^{1}H NMR (400 MHz, ^{d}THF) δ ppm 7.80 (s, 1 H: N=CH) 6.77 - 7.72 (m, 14 H: aromatic CH) 5.70 - 5.82 (m, 1 H: C=CH) 4.80 - 4.88 (m, 2 H: =CH_2) 3.80 (s, 3 H: CH_3) 3.14 (d, *J*=6.8 Hz, 2 H: CH_2)



N-(diphenylmethylene)-2-phenylpent-4-en-2-amine

4h (eb7064)



(*E*)-1,1-diphenyl-*N*-(1-phenylethylidene)but-3-en-1-amine

5h (eb7064)

viscous, yellow oil

65% combined yield

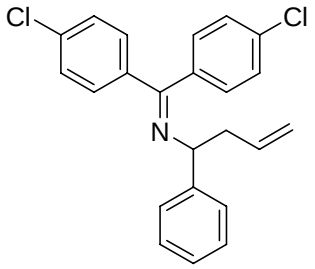
4h and **5h** isolated and characterized as a 1:1 mixture:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (m, 2H: aromatic CH), 7.53 (d, *J* = 7 Hz, 2H: aromatic CH), 7.43 (d, *J* = 8 Hz, 4H: aromatic CH), 7.34 (m, 3H: aromatic CH), 7.21 (overlapping m, 7H: aromatic CH), 7.09 (overlapping m, 8H: aromatic CH), 6.99 (t, *J* = 8 Hz, 2H: aromatic CH), 6.51 (d, *J* = 8 Hz, 2H: aromatic CH), 5.76 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.56 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 4.97 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 4.94 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 4.81 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 4.78 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 3.18 (d, *J* = 7 Hz, 2H: CH_2 of **5h**), 2.85 (dd, *J* = 7 Hz, 13 Hz, 1H: diastereotopic CH_2 of **4h**), 2.61 (dd, *J* = 7 Hz, 13 Hz, 1H: diastereotopic CH_2 of **4h**), 1.79 (s, 3H: CH_3), 1.23 (s, 3H: CH_3) .

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.40 (C=N), 164.86 (C=N), 149.28 (aromatic C), 148.91 (aromatic C), 142.57 (aromatic C), 141.71 (aromatic C), 139.03 (aromatic C), 135.77 (=CH), 134.30 (=CH), 130.11 (aromatic CH), 129.69 (aromatic CH), 129.51 (aromatic CH), 128.24 (aromatic CH), 128.15 (aromatic CH), 128.08 (aromatic CH), 127.92 (aromatic CH), 127.79 (aromatic CH), 127.48 (aromatic CH), 127.29 (aromatic CH), 127.24 (aromatic CH), 126.86 (aromatic CH), 126.36 (aromatic CH), 125.98 (aromatic CH), 117.21 (=CH_2), 116.81 (=CH_2), 68.69 (C), 63.37 (C), 52.63 (CH_2), 45.41 (CH_2), 24.97(CH_3), 20.37 (CH_3).

FTIR (CD_2Cl_2): ν_{max} 1637, 1445, 977, 894.

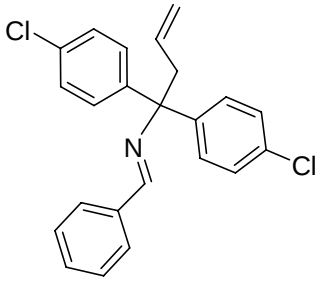
HRMS calcd for $C_{24}H_{24}N$ [M+H] = 326.1909, found 326.1909.



N-(bis(4-chlorophenyl)methylene)-1-phenylbut-3-en-1-amine

4i (eb6218-2)

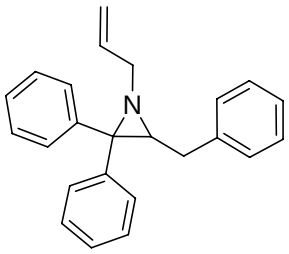
^{1}H NMR (400 MHz, ^{d}THF) δ ppm 7.05 - 7.89 (m, 13 H: aromatic CH) 5.60 - 5.71 (m, 1 H: =CH) 4.91 - 5.02 (m, 2 H: $=CH_2$) 4.42 (dd, *J*=8.0, 5.2 Hz, 1 H: CH) 2.64 - 2.75 (m, 1 H: diastereotopic CH_2) 2.55 - 2.62 (m, 1 H: diastereotopic CH_2)



(*E*)-*N*-benzylidene-1,1-bis(4-chlorophenyl)but-3-en-1-amine

5i (eb6218-2)

^{1}H NMR (400 MHz, ^{d}THF) δ ppm 7.95 (s, 1 H: N=CH) 7.05 - 7.86 (m, 13 H: aromatic CH) 5.70 - 5.82 (m, 1 H: =CH) 4.88 - 4.98 (m, 2 H: $=CH_2$) 3.17 (d, *J*=6.8 Hz, 2 H: CH_2)



1-allyl-3-benzyl-2,2-diphenylaziridine

6j (eb6117)
colorless solid
68% yield

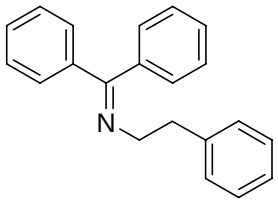
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7 Hz, 2H: aromatic CH), 7.17 (overlapping m, 11H: aromatic CH), 7.03 (d, *J* = 7 Hz, 2H: aromatic CH), 5.77 (ddt, *J* = 6 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.05 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 4.95 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 2.84 (dd, *J* = 6 Hz, 17 Hz, 1H: diastereotopic allylic CH_2), 2.53 (overlapping m, 1H: diastereotopic allylic CH_2), 2.53 (overlapping m, 1H: CH), 2.53 (overlapping m, 1H: diastereotopic benzylic CH_2), 2.37 (dd, *J* = 6 Hz, 13 Hz, 1H: diastereotopic benzylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.83 (aromatic C), 139.79 (aromatic C), 138.85 (aromatic C), 136.29 (=CH), 131.30 (aromatic CH), 129.10 (aromatic CH), 128.87 (aromatic CH), 128.62 (aromatic CH), 127.97 (aromatic CH), 127.82 (aromatic CH), 127.73 (aromatic CH), 126.58 (aromatic CH), 126.04 (aromatic CH), 115.84 (=CH_2), 56.86 (allylic CH_2), 55.77 (C), 50.35 (CH), 35.31 (benzylic CH_2).

FTIR (CD_2Cl_2): ν_{max} 1421, 895, 758.

HRMS calcd for $C_{24}H_{23}N$ [M+H] = 326.1909, found 326.1867.

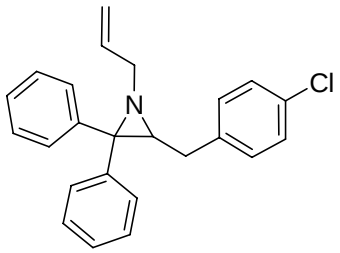
HPLC (Daicel Chiralpak AD HPLC column, 99.8% hexane/isopropanol, 0.5 mL/min) - t_r = 9.0, 9.8 min.



N-(diphenylmethylene)-2-phenylethanamine

7 (eb6133-2)

^{1}H NMR (400 MHz, ^{d}Toluene) δ ppm 7.01 - 7.11 (m, 15 H: aromatic CH) 3.64 (t, *J*=7.1 Hz, 2 H: N-CH_2) 3.02 (t, *J*=7.1 Hz, 2 H: benzylic CH_2)



1-allyl-3-(4-chlorobenzyl)-2,2-diphenylaziridine

6k (eb6215)

viscous, pale yellow oil

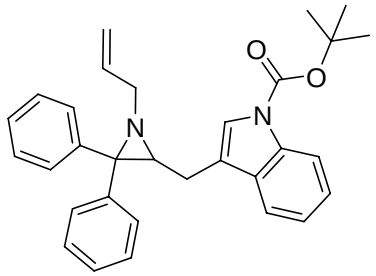
59% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (m, 2H: aromatic CH), 7.48 (t, *J* = 8 Hz, 1H: aromatic CH), 7.42 (t, *J* = 8 Hz, 3H: aromatic CH), 7.31 (d, *J* = 7 Hz, 2H: aromatic CH), 7.21 (m, 3H: aromatic CH), 7.14 (m, 2H: aromatic CH), 6.95 (d, *J* = 8 Hz, 1H: aromatic CH), 5.76 (ddt, *J* = 6 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.04 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 4.95 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 2.85 (dd, *J* = 6 Hz, 15 Hz, 1H: diastereotopic allylic CH_2), 2.48 (overlapping m, 1H: diastereotopic allylic CH_2), 2.48 (overlapping m, 1H: CH), 2.48 (overlapping m, 1H: diastereotopic benzylic CH_2), 2.34 (dd, *J* = 5 Hz, 13 Hz, 1H: diastereotopic benzylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.66 (aromatic C), 138.65 (aromatic C), 138.20 (aromatic C), 137.60 (aromatic C), 136.18 (=CH), 132.44 (aromatic CH), 130.24 (aromatic CH), 130.09 (aromatic CH), 129.04 (aromatic CH), 128.29 (aromatic CH), 128.03 (aromatic CH), 127.78 (aromatic CH), 126.67 (aromatic CH), 115.94 (=CH_2), 56.84 (allylic CH_2), 55.74 (C), 50.11 (CH), 34.70 (benzylic CH_2).

FTIR (CD_2Cl_2): ν_{max} 1492, 1446, 895.

HRMS calcd for $C_{24}H_{23}ClN$ [M+H] = 360.1519, found 360.1490.



tert-butyl 3-((1-allyl-3,3-diphenylaziridin-2-yl)methyl)-1*H*-indole-1-carboxylate

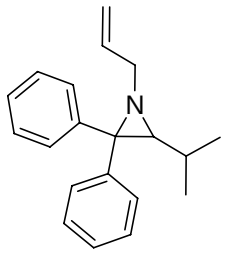
6l (eb6253)
viscous, pale yellow oil
87% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H: aromatic CH), 7.40 (d, *J* = 7 Hz, 1H: aromatic CH), 7.35 (d, *J* = 7 Hz, 2H: aromatic CH), 7.19 (overlapping m, 11H: aromatic CH), 5.82 (ddt, *J* = 6 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.07 (d, *J* = 17 Hz, 1H: CH=CH(H)$_{trans}$), 4.97 (d, *J* = 10 Hz, 1H: CH=CH(H)$_{cis}$), 2.84 (dd, *J* = 6 Hz, 15 Hz, 1H: diastereotopic N-CH_2), 2.61 (overlapping m, 1H: diastereotopic N-CH_2), 2.61 (overlapping m, 1H: CH), 2.61 (overlapping m, 1H: diastereotopic CH-*C*H_2), 2.41 (dd, *J* = 9 Hz, 18 Hz, 1H: diastereotopicCH-CH_2), 1.59 (s, 9H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.78 (C=O), 141.66 (aromatic C), 138.71 (aromatic C), 136.25 (=CH), 131.25 (aromatic CH), 130.70 (aromatic C), 129.09 (aromatic CH), 128.01 (aromatic CH), 127.79 (aromatic CH), 127.58 (aromatic CH), 126.64 (aromatic CH), 124.28 (aromatic CH), 123.04 (aromatic CH), 122.33 (aromatic CH), 119.32 (aromatic CH), 118.44 (aromatic C), 115.99 (=CH_2), 115.10 (aromatic CH), 83.28 (O-C), 56.70 (N-CH_2), 55.76 (C), 48.49 (CH), 28.26 (CH_3), 25.04 (CH-*C*H_2).

FTIR (CD_2Cl_2): ν_{max} 1713, 1420, 1367, 982.

HRMS calcd for $C_{31}H_{33}N_2O_2$ [M+H] = 465.2542, found 465.2518.



1-allyl-3-isopropyl-2,2-diphenylaziridine

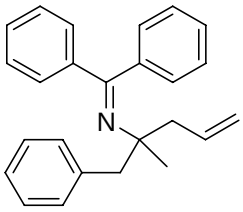
6m (eb6059)
viscous colorless oil
>95% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7 Hz, 2H: aromatic CH), 7.20 (overlapping m, 5H: aromatic CH), 7.16 (t, *J* = 8 Hz, 2H: aromatic CH), 7.09 (t, *J* = 7 Hz, 1H: aromatic CH), 5.90 (ddt, *J* = 6 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.03 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 5.00 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 2.90 (dd, *J* = 6 Hz, 14 Hz, 1H: diastereotopic CH_2), 2.38 (dd, *J* = 6 Hz, 14 Hz, 1H: diastereotopic CH_2), 1.89 (d, *J* = 9 Hz, 1H: N-CH), 0.94 (d, *J* = 6 Hz, 3H: diastereotopic CH_3), 0.89 (m, 1H: ^{i}*pr* CH), 0.77 (d, *J* = 6 Hz, 3H: diastereotopic CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.28 (aromatic C), 139.45 (aromatic C), 136.65 (=CH), 131.33 (aromatic CH), 128.89 (aromatic CH), 127.94 (aromatic CH), 127.56 (aromatic CH), 127.41 (aromatic CH), 126.24 (aromatic CH), 116.16 (=CH_2), 57.73 (CH_2), 56.91 (N-CH), 55.97 (C), 27.54 (^{i}*pr* CH), 21.05 (diastereotopic CH_3), 19.51 (diastereotopic CH_3).

FTIR (CD_2Cl_2): ν_{max} 1600, 1444, 1363, 997.

HRMS calcd for $C_{20}H_{24}N$ [M+H] = 278.1909, found 278.1877.

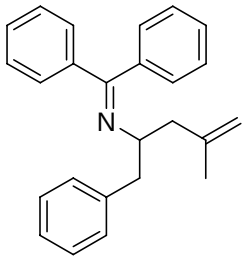


N-(diphenylmethylene)-2-methyl-1-phenylpent-4-en-2-amine

4n (eb6273)
viscous, pale yellow oil
28% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.46 - 7.53 (m, 2 H: aromatic CH) 7.03 - 7.32 (m, 13 H: aromatic CH) 5.88 (dddd, *J*=17.3, 10.0, 7.3, 7.1 Hz, 1 H: =CH) 5.01 (d, *J*=10.1 Hz, 1 H: =CH(H)$_{cis}$) 4.97 (d, *J*=17.0 Hz, 1 H: =CH(H)$_{trans}$) 3.03 (d, *J*=12.9 Hz, 1 H: diastereotopic benzylic CH_2) 2.70 (d, *J*=12.9 Hz, 1 H: diastereotopic benzylic CH_2) 2.46 (dd, *J*=13.4, 6.8 Hz, 1 H: diastereotopic allylic CH_2) 2.21 (dd, *J*=13.6, 7.6 Hz, 1 H: diastereotopic allylic CH_2) 0.63 (s, 3 H: CH_3)

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 161.78 (C=N) 140.28 (aromatic C) 138.19 (aromatic C) 134.11 (=CH) 129.45 (aromatic CH) 126.55 (aromatic CH) 126.30 (aromatic CH) 126.12 (aromatic CH) 125.94 (aromatic CH) 124.45 (aromatic CH) 115.73 (=CH_2) 61.86 (C) 47.68 (benzylic CH_2) 47.07 (allylic CH_2) 23.11 (CH_3)



N-(diphenylmethylene)-4-methyl-1-phenylpent-4-en-2-amine

4o (eb6189)
viscous, pale yellow oil
63% yield

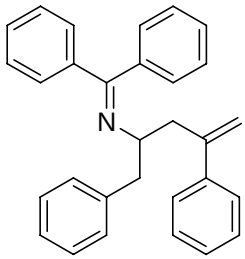
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H: aromatic CH), 7.47 (m, 3H: aromatic CH), 7.18 (overlapping m, 7H: aromatic CH), 6.95 (d, *J* = 8 Hz, 1H: aromatic CH) 6.41 (m, 2H: aromatic CH), 4.69 (s, 1H: diastereotopic $=CH_2$), 4.65 (s, 1H: diastereotopic $=CH_2$), 3.52 (m, 1H: CH), 2.83 (dd, *J* = 8 Hz, 13 Hz, 1H: diastereotopic benzylic CH_2), 2.78 (dd, *J* = 4 Hz, 13 Hz, 1H: diastereotopic benzylic CH_2), 2.30 (dd, *J* = 7 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.24 (dd, *J* = 6 Hz, 13 Hz, 1H: diastereotopic allylic CH_2),1.43 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.08 (C=N), 142.98 (aromatic C), 140.11 (aromatic C), 139.88 (aromatic C), 137.09 (=C), 129.88 (aromatic CH), 129.59 (aromatic CH), 128.35 (aromatic CH), 128.08 (aromatic CH), 127.97 (aromatic CH), 127.85 (aromatic CH), 127.76 (aromatic CH), 127.74 (aromatic CH), 125.86 (aromatic CH), 113.18 ($=CH_2$), 62.71 (CH), 45.17 (allylic CH_2), 42.83(benzylic CH_2), 22.97 (CH_3).

FTIR (CD_2Cl_2): ν_{max} 1624, 895, 696.

HRMS calcd for $C_{25}H_{26}N$ [M+H] = 340.2065, found 340.2047.

HPLC (Daicel Chiralpak OD-H HPLC column, 99.8% hexane/isopropanol, 1.0 mL/min) - t_r = 5.4, 5.9 min.



N-(diphenylmethylene)-1,4-diphenylpent-4-en-2-amine

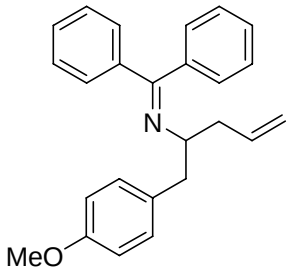
4p (eb7030)
viscous, pale yellow oil
46% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 2H: aromatic CH), 7.23 (overlapping m, 6H: aromatic CH), 7.09 (overlapping m, 6H: aromatic CH), 7.01 (t, *J* = 8 Hz, 1H: aromatic CH) 6.82 (d, *J* = 6 Hz, 2H: aromatic CH), 6.28 (d, *J* = 7 Hz, 2H: aromatic CH), 5.28 (s, 1H: diastereotopic $=CH_2$), 5.04 (s, 1H: diastereotopic $=CH_2$), 3.50 (p, *J* = 7 Hz, 1H: CH), 2.79 (overlapping m, 2H: benzylic CH_2), 2.79 (overlapping m, 2H: allylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.45 (C=N), 145.46 (aromatic C), 140.58 (aromatic C), 139.99 (aromatic C), 139.66 (aromatic C), 136.82 (=C), 132.45 (aromatic CH), 129.79 (aromatic CH), 128.33 (aromatic CH), 128.13 (aromatic CH), 128.06 (aromatic CH), 127.93 (aromatic CH), 127.76 (aromatic CH), 127.59 (aromatic CH), 127.43 (aromatic CH), 127.20 (aromatic CH), 126.10 (aromatic CH), 125.86 (aromatic CH), 114.99 ($=CH_2$), 49.53 (CH), 42.46 (CH_2), 42.10 (CH_2).

FTIR (CD_2Cl_2): ν_{max} 1600, 895, 760, 696.

HRMS calcd for $C_{30}H_{28}N$ [M+H] = 402.2222, found 402.2210.



N-(diphenylmethylene)-1-(4-methoxyphenyl)pent-4-en-2-amine

4q (eb6278)

viscous, pale yellow oil

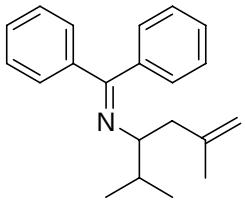
67% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7 Hz, 2H: aromatic CH), 7.17 (overlapping m, 8H: aromatic CH), 6.94 (d, *J* = 8 Hz, 2H: aromatic CH), 6.73 (d, *J* = 8 Hz, 2H: aromatic CH), 5.78 (ddt, *J* = 6 Hz, 10 Hz, 17 Hz, 1H: C*H*=CH_2), 5.07 (d, *J* = 17 Hz, 1H: CH=CH(*H*)$_{trans}$), 4.96 (d, *J* = 10 Hz, 1H: CH=CH(*H*)$_{cis}$), 3.71 (s, 3H: OCH_3), 2.84 (dd, *J* = 6 Hz, 15 Hz, 1H: CH), 2.53 (dd, *J* = 6 Hz, 15 Hz, 1H: diastereotopic allylic CH_2), 2.47 (m, 1H: CH), 2.47 (m, 1H: diastereotopic CH_2), 2.30 (dd, *J* = 6 Hz, 13 Hz, 1H: diastereotopic benzylic CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.93 (C=N), 141.87 (aromatic C), 138.91 (aromatic C), 136.33 (=CH), 132.45 (aromatic C), 131.82 (aromatic C), 131.32 (aromatic CH), 129.79 (aromatic CH), 129.11 (aromatic CH), 127.97 (aromatic CH), 127.72 (aromatic CH), 127.52 (aromatic CH), 126.56 (aromatic CH), 115.84 (=CH_2), 113.70 (aromatic CH), 56.88 (benzylic CH_2), 55.25 (CH_3), 50.61 (CH), 34.36 (allylic CH_2).

FTIR (CD_2Cl_2): ν_{max} 1610, 1161, 761.

HRMS calcd for $C_{25}H_{25}NO$ [M+H] = 356.2014, found 356.1980.



N-(diphenylmethylene)-2,5-dimethylhex-5-en-3-amine

4r (eb7050)
viscous, pale yellow oil
26% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8 Hz, 2H: aromatic CH), 7.29 (overlapping m, 6H: aromatic CH), 7.06 (d, *J* = 8 Hz, 2H: aromatic CH), 4.64 (s, 1H: diastereotopic $=CH_2$), 4.58 (s, 1H: diastereotopic $=CH_2$), 3.18 (dt, *J* = 5 Hz, 8 Hz, 1H: N-CH), 2.24 (dd, *J* = 5 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 2.17 (dd, *J* = 8 Hz, 13 Hz, 1H: diastereotopic allylic CH_2), 1.73 (dq, *J* = 5 Hz, 7 Hz, 1H: ^{i}*pr* CH), 1.37 (s, 3H: CH_3), 0.92 (d, *J* = 7 Hz, 3H: diastereotopic CH_3), 0.79 (d, *J* = 7 Hz, 3H: diastereotopic CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.21 (C=N), 143.46 (aromatic C), 140.52 (aromatic C), 137.39 (=C), 132.45 (aromatic CH), 130.09 (aromatic CH), 129.49 (aromatic CH), 128.42 (aromatic CH), 128.03 (aromatic CH), 127.95 (aromatic CH), 127.95 (aromatic CH), 112.97 ($=CH_2$), 65.16 (N-CH), 42.26 (CH_2), 32.90 (^{i}*pr* CH), 22.98 (CH_3), 20.03 (0.79)(diastereotopic CH_3), 18.13 (0.92)(diastereotopic CH_3).

FTIR (CD_2Cl_2): ν_{max} 1658, 1444, 1363, 894.

HRMS calcd for $C_{21}H_{26}N$ [M+H] = 292.2065, found 292.2053.

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