MECHANISTIC STUDIES ON IRIDIUM CATALYZED ALLYLIC SUBSTITUTION

BY

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DISSERTATION

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Abstract

High regio- and stereocontrol will always be an essential part of developing useful reactions. A reaction that has a perfect regio- and stereocontrol is less likely to require extensive purification to obtain the product in high levels of purity. Existing reactions can be optimized in terms of selectivity by studying the factors that influence the selectivity. Thus, mechanistic studies on the origins of regio- and enantioselectivity are an integral part of developing useful reactions.

Iridium catalyzed allylic substitution has become a powerful method for the enantioselective formation of both carbon–heteroatom and carbon–carbon bonds since its discovery in 1997.\textsuperscript{1,2} The first report on iridium catalyzed allylic substitution described the reactions of stabilized carbon nucleophiles with monosubstituted allylic electrophiles.\textsuperscript{3} The method was extended to amine nucleophiles in a later report.\textsuperscript{4} Iridium catalyzed allylic substitution reaction formed the product of allylic substitution at the branched allylic terminus. This selectivity contrasts the selectivity of palladium catalyzed allylic substitution reactions which form linear organic products.\textsuperscript{5,6}

\[
\text{R}^1\text{CO}_2\text{R}^2 + \text{Nu} \xrightarrow{\text{catalyst}} \text{R}^1\text{OCO}_2\text{R}^2 + \text{Nu}
\]

\[
\text{R}^1 = \text{alkyl or aryl}
\]

\[
\text{yield} > 70 \%
\]

\[
\text{ee} > 90 \%
\]

\[
\text{b/l} > 95:5
\]

\[
\text{Ar} = \text{Ph or 2-(OMe)Ph}
\]

Allylic substitution reactions catalyzed by cyclometalated iridium phosphoramidite complexes.

Formation of branched chiral products from linear monosubstituted allylic electrophiles allows development of stereoselective versions of allylic substitution reactions. Several complexes of iridium containing chiral enantioenriched ligands catalyze enantioselective
Mechanistic studies on iridium catalyzed allylic substitution reactions catalyzed by iridium phosphoramidite complexes revealed that the active catalyst is generated through a base assisted cyclometalation of the phosphoramidite to form five-membered iridacycle. A mechanism for the reaction was proposed based on a series of kinetic experiments. According to this mechanism the product bound cyclometalated complex is the resting state of the catalyst.

First examples of allyliridium complexes containing cyclometalated phosphoramidite ligand were prepared. A series of stoichiometric experiments showed that these allyliridium complexes were chemically and kinetically competent to be intermediates in iridium catalyzed allylic substitution reactions. Double inversion mechanism for the iridium catalyzed allylic substitution reaction was also shown through a combination of catalytic and stoichiometric reactions of cyclometalated iridium complexes. A series of kinetic studies also showed that oxidative addition was the enantiodetermining step in iridium catalyzed allylic substitution.

Origins of enantioselectivity in iridium catalyzed allylic substitution.

Finally, allyliridium complexes containing cyclometalated triphenylphosphite ligand were prepared. These complexes were competent to be intermediates in non-stereoselective allylic substitution reactions catalyzed by iridium triphenylphosphite complexes. A series of kinetic experiments showed that regioselectivity of iridium catalyzed allylic substitution is likely
controlled by a larger binding affinity of terminal alkenes to iridium center over internal disubstituted alkenes.

References


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Chapter 1: Overview of iridium catalyzed allylic substitution

1. Introduction

Iridium catalyzed allylic substitution has become a method of choice for substitution of mono-substituted allylic electrophiles with a wide range of carbon and hetereoatomic nucleophiles under mild conditions and in high yields, regioselectivities and stereoselectivities.\textsuperscript{1-3} Cyclometalated catalysts C1 and C2 containing phosphoramidites L1a and L1b are the best-performing and the most widely used catalysts in iridium catalyzed allylic substitution (Scheme 1). This overview will cover development of asymmetric version of iridium catalyzed allylic substitution reaction after its initial discovery and mechanistic studies done on iridium catalyzed allylic substitution.

\begin{center}
\begin{tikzpicture}
  \node (C1) {C1: Ar = \text{o-}anisyl};
  \node (C2) [right=of C1] {C2: Ar = Ph};
  \node (L1a) [right=of C2] {L1a: Ar = Ph};
  \node (L1b) [right=of L1a] {L1b: Ar = 2-(OMe)Ph};
  \draw [->] (C1) -- (L1a);
  \draw [->] (C2) -- (L1b);
\end{tikzpicture}
\end{center}

Scheme 1.

2. Discovery of Iridium-catalyzed allylic substitution

Takeuchi and coworkers reported the first example of iridium catalyzed allylic substitution reaction in 1997.\textsuperscript{4-5} In these reports, the reaction of an allylic alcohol 1a or an allylic acetate 1b with sodium dimethylmalonate was catalyzed by combination of \([\text{Ir}(\text{COD})\text{Cl}]_2\) (Iridium cyclooctadiene chloro dimer) and triphenylphosphite (Scheme 2). The products of substitution at substituted allylic terminus, branched products (2a), were formed selectively over the products of substitution at the unsubstituted allylic terminus, linear products (2b). The reactions of allylic acetates proceeded at room temperature and formed products of allylic substitution in yields higher than 80%. The reactions of allylic alcohols required reflux conditions and formed the products of substitution in yields higher than 70%.
Scheme 2. Allylic substitution reaction catalyzed by [(COD)IrCl]₂ and P(OPh)₃

3. Development of asymmetric iridium-catalyzed allylic substitution

3.1. Iridium catalyzed asymmetric allylic substitution catalyzed by complexes containing, phosphineoxazoline, chiral phospite, bis-oxazoline and diaminophosphine ligands.

Selectivity of iridium-catalyzed allylic substitution towards the formation of the branched substitution products allows for the development of enantioselective allylic substitution reactions. Some of the asymmetric ligands reported in the early examples of enantioselective allylic substitution are shown in Scheme 3.

The first example of enantioselective iridium-catalyzed allylic substitution was reported by Helmchen and coworkers shortly after the initial report by Takeuchi. In this report a combination of chiral phosphineoxazoline (PHOX) ligand and [Ir(COD)Cl]₂ catalyzed the reaction between allylic acetates and sodium dimethylmalonate at 65°C over 24 hours (Scheme 3). Under the reported reaction conditions allylic electrophiles with aromatic substituents provided allylic substitution products in high yields (> 98%), high regioselectivities (3a/3b > 95:5) and high enantioselectivities (ee > 91%). However lower regioselectivity (3a/3b = 62:38) and enantioselectivity (ee = 78%) were observed for the reaction of allylic electrophile with aliphatic substituent.

Fuji and coworkers reported the catalysis of allylic substitution reaction between methyl cinnamyl carbonate and dimethylmalonate by a combination of [Ir(COD)Cl]₂ and a chiral phosphite ligand L₂ containing a resolved binolate. Addition of BuLi/ZnCl₂ to the reaction mixture is required to obtain the product of allylic substitution in high regioselectivity (3a/3b = 93:7) and enantioselectivity (ee = 96%).

Combination of [Ir(COD)Cl]₂ and chiral pybox ligands can catalyze the allylic substitution reactions. Takemoto and coworkers reported that iridium complex containing the Ph-Pybox ligand catalyzes the reaction between allylic phosphate electrophiles and amine,
hydroxylamine and oxime nucleophiles (Scheme 3). The substitution reaction formed products in good yields and enantioselectivities, but branched to linear selectivities were generally poor. For instance, the reaction of dibenzylamine and cinnamyl phosphate catalyzed by [Ir(COD)Cl]$_2$ and Ph-Pybox gave substitution products in combined 91% yield and 95% ee for the branched product, but only 71:29 ratio of 3a/3b was observed.

![Scheme 3. Ligands that were used in the early examples of asymmetric iridium catalyzed allylic substitutions.](image)

Chiral allylic amination reaction catalyzed by [Ir(COD)Cl]$_2$ and dianinophosphine ligand was reported by Hamada and coworkers. [Ir(COD)Cl]$_2$ and chiral dianinophosphine ligand DIAPHOX catalyzed the reaction between allylic carbonates with alkylamines (Scheme 3).
The reaction is conducted in the presence of superstoichiometric N,O-bis(trimethylsilyl)acetamide and catalytic amount of NaPF₆. Reactions of allylic electrophiles with aromatic substituents form amination products in high yields (> 90%), high regioselectivities (3a/3b > 99:1) and high enantioselectivities (ee > 90%). However, allylic electrophile with alkyl substituent forms allylic substitution product in low enantioselectivity (ee = 74%).

3.2 Asymmetric allylic substitution reactions catalyzed by iridium complexes of chiral enantiopure phosphoramidite ligands.

Chiral phosphoramidite ligands are the most widely used ligands in regio- and enantioselective allylic substitution reactions. Iridium complex of a chiral phosphoramidite ligand **monophos**, containing resolved binolate group, catalyzed allylic substitution reaction between cinnamyl acetate and sodium dimethylmalonate. The substitution reaction formed the product in quantitative yield and good regioselectivity (3a/3b > 98:2), but the enantioselectivity of the reaction was low (37%).

\[
\begin{align*}
R^1= & \text{alkyl or aryl} \\
[(\text{COD})\text{IrCl}_2\text{L2a or L2b}] & \rightarrow \\
3a & \rightarrow \begin{array}{c} R^1 \text{Nu} \\
3b & \end{array} \\
\text{yield }> 70 \% & \\
\text{ee}> 90 \% & \\
b/l> 95:5 & \\
\end{align*}
\]

**Scheme 4.** Enantioselective allylic substitution reactions catalyzed by iridium complexes containing chiral phosphoramidite ligands.

Bis-phenethylamine-derived chiral phosphoramidite ligands **L1a** and **L1b**, containing three resolved stereocenters, emerged as the ligands of choice in development of enantioselective iridium catalyzed allylic substitution reactions. The reactions catalyzed by iridium phosphoramidite complexes include nucleophilic substitution of linear monosubstituted allylic
electrophiles with aromatic and aliphatic amines, alkoxides, alcohols, imides, carbanates, ammonia, heterocyclic nucleoipiles, enolates and enolate equivalents, as well as typical stabilized carbon nucleophiles generated from malonates and cyanoesters (Scheme 4). These substitution reactions usually require less than 4% mole amount of both [Ir(COD)Cl] and chiral, enantiopure phosphoramidite ligand L1a or L1b. The phosphoramidite ligands L1a and L1b were first synthesized by Feringa and co-workers to use in conjugate addition reactions to α-β-unsaturated ketones. Iridium phosphoramidite complexes of L1b containing ortho-anisyl groups were found to catalyze allylic substitution reactions in slightly higher yields, regioselectivities and enantioselectivities than corresponding complexes of L1a containing a pair of phenyl groups. The yields observed for these substitution reactions are generally high (> 70%) and excellent regioselectivities (3a/3b > 95:5) as well as excellent enantioselectivities (> 90% and 96-99% for most cases) are observed. One notable exception to generally excellent enantioselectivities is observed when ortho-substituted cinnamyl carbonates are employed in catalytic reactions. The enantioselectivities in those substitution reactions (ee = 70-80%) are substantially lower than those observed for meta- or para- substituted allylic carbonates.

Scheme 5. Iridium catalyzed kinetic asymmetric resolution through allylic substitution of racemic allylic benzoates.

Iridium phosphoramidite complex C2 catalyzes the kinetic resolution of racemic branched allylic benzoates 4 through allylic substitution with nucleophiles (Scheme 5). The kinetic resolution method requires the use of anionic nucleophiles. These nucleophiles include stabilized carbon nucleophiles, phenoxides, 4-toluenesulfonyl and electron deficient nitrogen nucleophiles. Different reaction conditions were developed for allylic electrophiles with aliphatic and aromatic substitution. Branched allylic benzoates with aliphatic and aromatic substitution give products with opposite absolute stereochemistry under their respective reaction conditions. These opposing stereochemistries are due to fast isomerization of fast-reacting enantiomer of
branched allylic benzoates to thermodynamically more stable linear allylic benzoates in the presence of iridium catalyst. Thus, substitution product is formed from the remaining slow-reacting enantiomer. Fast-reacting enantiomer of allylic benzoates with aliphatic substitution does not undergo isomerization to a linear allylic electrophile and allylic substitution products are formed from the fast-reacting enantiomer.

4. Mechanistic studies

4.1. Identification of the active catalyst

Iridium catalyzed allylic substitution reactions work best with 1:1 ratio of iridium to phosphoramidite. This ratio was surprising initially, because very few monodentate ligands catalyze asymmetric reactions with high stereoselectivity due to free rotation around the metal ligand bond. So it was not initially clear if phosphoramidite ligands are acting as monodentate or bidentate ligands in iridium catalyzed allylic substitution.

Scheme 6.

Allylic carbonates did not oxidatively add to 16 electron square planar complex C3. Despite the lack of oxidative addition to allylic carbonates, complex C3 catalyzed the allylic substitution of alkylamines in high yields with high regioselectivity and enantioselectivity (hexylamine: 88%; b/l = 98:2; ee = 96%, Scheme 6). However, complex C3 did not catalyze allylic substitution reaction of allylic carbonates with anilines (Scheme 6). This led the researchers to question the identity of square planar complex C3 as a catalytically active species. In the presence of an alkylamine and an equivalent of phosphoramidite ligand L1a complex C3 undergoes base assisted cyclometalation to form the complex C4 (Scheme 7, part a) which was found to be catalytically active after dissociation of the monodentate L1a fragment. This cyclometalation does not take place when aniline is substituted for alkylamine. Subsequently, a method for allylic substitution of linear allylic carbonates with anilines was developed based on the mechanistic information described above. According to this method the complex C3 formed
from [Ir(COD)Cl]₂ and a phosphoramidite ligand was allowed to cyclometalate in the presence of and alkylamine prior to introduction into the reaction mixture.¹⁴

Later on, ethylene-ligated cyclometalated iridium (I) complex C2 was prepared through a similar procedure to the one described above (Scheme 7, part b).³¹ Upon introduction into the reaction mixture, complex C2 forms catalytically active species after dissociation of the labile ethylene. Ethylene-ligated complex C2 can be easily prepared in gram quantities and stored indefinitely under inert atmosphere.

**Scheme 7.** Formation of catalytically active cyclometalated iridium phosphoramidite complex from square planar complex C3 in the presence of an alkylamine.

### 4.2. Development of an iridium catalyst containing a cyclometalated phosphoramidite ligand with a single resolved stereocenter

The most commonly used phosphoramidite ligands in allylic substitution L1a and L1b contain three resolved stereocenters. Through a careful study of the base induced cyclometalation of phosphoramidite ligands Hartwig and co-workers found out that the stereochemistries of the axially chiral binolate and the phenethylamine group undergoing cyclization need to match for a successful cyclization. At the same time displacing axially chiral binolate group with an axially fluxional biphenolate does not prevent cyclization of the resolved phenethyl group. The second resolved phenethylamine group of the original L1a ligand, which does not undergo cyclization, was displaced by a bulky group without detriment to activity and selectivity of the catalyst. Based on these studies a new phosphoramidite ligand L3 that has only one resolved stereocenter was developed.³² Cyclometalated complex generated from the ligand L3 and [Ir(COD)Cl]₂ catalyzed the reaction between allylic carbonates and amines (Scheme 8). The reactions of aliphatic or aromatic, primary or secondary amines with allylic carbonates
formed substitution products in high yields (\(> 72\%\)) and selectivities (\(ee > 93\%, b:l > 95:5\)). The yields and selectivities were similar to those observed for the reactions catalyzed by complexes of L1a.

**Scheme 8.** Reactions of iridium complex containing a phosphoramidite ligand with one resolved stereocenter.

**Scheme 9.** Catalytic cycle of iridium catalyzed allylic substitution reaction.

### 4.3. Catalytic cycle

Markovic and Hartwig proposed a catalytic cycle for iridium catalyzed allylic substitution reaction based on the results of resting state and kinetic studies of the reaction between methyl cinnamyl carbonate and aniline catalyzed by cyclometalated iridium phosphoramidite complex.\(^{31}\) The resting state of the catalyst was determined to be product-coordinated cyclometalated iridium (I) complex \(\text{C5}\) based on the \(^{31}\text{P}\)-NMR spectra collected from the catalytic reaction mixture and independent synthesis of the product-coordinated complex \(\text{C5}\). The kinetic studies revealed that the reaction was first order in iridium complex, aniline and methyl cinnamyl carbonate and inverse first order in the product. A mechanism of
allylic substitution that is consistent with the outcome of resting state and kinetic studies was proposed by the authors (Scheme 9). According to this mechanism, product-coordinated complex C5 undergoes reversible product dissociation, followed by a reversible and endothermic oxidative addition of allylic carbonate to form fleeting allyliridium carbonate intermediate. This fleeting allyliridium intermediate then irreversibly reacts with the nucleophile to form the product coordinated complex C5, which is the resting state of the catalyst.

4.4. Allyliridium complexes as intermediates in allylic substitution

Although allyliridium carbonate complex C6 was proposed as intermediate in iridium catalyzed allylic substitution reaction, none of the previously known allyliridium complexes reacted with nucleophiles to give products of allylic substitution. All of the known allyliridium complexes prior to 2009 reacted at their central allylic carbon to form four-membered metallacycles. Allyliridium complex C7 prepared by Wakefield and Stryker containing a pentamethylcyclopentadienyl ligand reacted with an enolate nucleophile to give a four membered iridacycle (Scheme 10, part a). In a more relevant case to allylic substitution, allyliridium complex C8 containing a phosphineoxazoline type ligand (the ligand employed in the first reported iridium catalyzed asymmetric allylic substitution) reacted with sodium dimethylmalonate also at its central allylic carbon to form four membered iridacycle (Scheme 10, part b).

The first allyliridium complexes containing cyclometalated phosphoramidite ligands, C9 containing a plain allyl ligand and C10 containing a crotyl ligand, were reported by Hartwig and co-workers in 2009. Since oxidative addition of allylic carbonates to ethylene-ligated iridium phosphoramidite complexes C1 and C2 was found to be endergonic, allyliridium complexes C9 and C10 were prepared from allylic chlorides. These complexes were synthesized through oxidative addition of allylic chlorides to ethylene-coordinated complex C2 followed by anion exchange with silver salts of weakly coordinating anions (Scheme 11). In a later report, cinnamyliridium complex C11 and (2,6-difluoro)cinnamyliridium complex C12 were prepared by a similar procedure.
Scheme 10. Reactions of nucleophiles with allyliridium complexes known prior to 2009.

Scheme 11. Preparation of cyclometallated allyliridium phosphoramidite complexes.

In contrast to previously known allyliridium complexes, complexes C9 and C10 reacted with oxygen, nitrogen and stabilized carbon nucleophiles at terminal allylic carbon to give products of allylic substitution. Regioselectivity and enantioselectivity of the reaction of crotyliridium complex C10 with oxygen, nitrogen and stabilized carbon nucleophiles were measured. These selectivities were compared to the regio- and enantioselectivities of allylic substitution reactions of methyl crotyl carbonate 5 with corresponding nucleophiles catalyzed by the ethylene complex C2. Regioselectivities and enantioselectivities of stoichiometric reactions of crotyliridium complex C10 matched with those of catalytic reactions within 5% and 10% respectively. An example of such a comparison is shown in Scheme 12 where regio- and enantioselectivity of formation of product 6 are compared. These data showed that C9 and C10
are the first allyliridium complexes kinetically and chemically competent to be intermediates in iridium catalyzed allylic substitution reactions.

**Scheme 12.** Comparison of stoichiometric reaction of C8 with benzylamine and reaction between methyl crotyl carbonate and benzylamine catalyzed by ethylene-ligated complex C2

**Scheme 13**

Shortly after the report on the first allyliridium complexes competent to be intermediates in allylic substitution reactions, Helmchen and co-workers reported a new procedure that allows preparation of allyliridium phosphoramidite complexes in high yield and purity (Scheme 13). According to this procedure \([\text{Ir(COD)Cl}]_2\), phosphoramidite ligand, allylic carbonate and AgBF\(_4\) are allowed to stir overnight under inert atmosphere. The side products of this reaction are CO\(_2\), MeOH and AgCl.

**4.5. Stereochemical route of iridium catalyzed allylic substitution**

The initial studies on the stereochemical mechanism of iridium catalyzed allylic substitution were done on the reactions catalyzed by combination of \([\text{Ir(COD)Cl}]_2\) and triphenylphosphite. The reaction of (Z)-5-(Methoxycarbonyl)-2-cyclohexen-1-yl methyl
carbonate 7 with sodium dimethylmalonate catalyzed by combination of [Ir(COD)Cl]2 and triphenylphosphite formed the allylic substitution product 8 (Scheme 14, part a). The stereochemistry of product 8 shows that iridium catalyzed allylic substitution goes with overall retention of configuration. Helmchen and co-workers performed a similar study with acyclic allylic acetate. The reaction of enantioenriched allylic acetate 9 with sodium dimethylmalonate catalyzed by [Ir(COD)Cl]2 and triphenylphosphite formed product 10 (Scheme 14, part b). The stereochemistry and enantiomeric excess of 9 also showed that iridium catalyzed allylic substitution mostly goes with overall retention of configuration.

Overall retention of configuration in iridium catalyzed allylic substitution can correspond to a double-retention or a double-inversion mechanism for oxidative addition and reductive elimination through nucleophilic attack. The works of Takeuchi and Helmchen on global stereochemistry of catalytic reaction did not distinguish between those two stereochemical pathways.


Helmchen and co-workers attempted to distinguish between double inversion or double retention pathways for oxidative addition and reductive elimination by studying the catalytic reactions of two cyclic allylic acetates 11 and 12 with sodium dimethylmalonate (Scheme 15). According to their plan geometry of 11 would not allow oxidative addition with inversion of configuration and geometry of 12 would not allow nucleophilic attack with inversion of configuration after formation of allyliridium complex through oxidative addition with inversion of configuration. On the other hand, if the reaction proceeded with double retention mechanism cyclic allylic acetate 11 would form allylic substitution product. No reactivity with sodium
dimethylmalonate was observed for either allylic acetate 11 or 12 in the presence of iridium catalyst, so Helmchen and coworkers concluded that the reaction should be going with a double inversion mechanism. However, the researchers failed to observe formation of allyliridium complex from allylic acetate 12, which jeopardizes their conclusions on stereochemical route of individual steps of allylic substitution.

Scheme 15.

Hartwig and co-workers studied stereochemical route of iridium catalyzed allylic substitution through stoichiometric studies involving formation of a well-defined monodeuterated allyliridium complex.\(^{36}\) This complex was prepared from the reaction of monodeuterated enantioenriched cinnamyl trifluoroacetate 13 with ethylene ligated iridium phosphoramidite complex C2 in the presence of AgBF\(_4\) (Scheme 16). These studies conclusively showed that both oxidative addition and reductive elimination steps of iridium catalyzed allylic substitution occur with inversion of configuration. The results of these studies were corroborated by the outcome of catalytic reactions of enantioenriched monodeuterated allylic carbonate.

**4.6. Enantiodetermining step of iridium catalyzed allylic substitution**

The enantiodetermining step of iridium catalyzed allylic substitution was determined through kinetic studies. Rate of nucleophilic attack on allyliridium complexes and rate of interconversion between the diastereomeric allyliridium complexes were measured to identify the enantioselectivity controlling step. These studies revealed that enantioselectivity is controlled by oxidative addition that is highly selective for the formation of one diastereomer of allyliridium complex (Scheme 17).\(^{36}\)
Study of the stereochemical route of allylic substitution through formation of allyliridium intermediate from monodeuterated enantioentiched allylic trifluoroacetate.

Challenges in iridium catalyzed allylic substitution.

Over the past decade asymmetric iridium catalyzed allylic substitution became a versatile process with a wide scope of nucleophiles and allylic electrophiles that can be employed in the reaction. However, several challenges that limit the wider usage of iridium catalyzed allylic substitution still remain. These challenges include substitutions of allylic electrophiles containing more than one substituent, extending the scope of nucleophiles to include fluorides and nucleophilic trifluoromethyl sources and performing dynamic kinetic asymmetric transformation type reactions. To overcome these challenges better mechanistic understanding of iridium catalyzed allylic substitution and development of new generations of catalysts based on these mechanistic observations is necessary.

Mechanistic Studies on Palladium catalyzed allylic substitution and comparison between palladium catalyzed and iridium catalyzed allylic substitution mechanisms.

Palladium catalyzed allylic substitution reaction is the transition metal catalyzed allylic substitution reaction that was discovered first. A large variety of allylic substitutions catalyzed by palladium has been reported since its discovery. A large amount of work has also been done
studying the mechanism of Palladium catalyzed allylic substitution. Mechanism of palladium catalyzed allylic substitution will be discussed next and comparison to the mechanism of iridium catalyzed allylic substitution will be made.

6.1. Stereochemistry of oxidative addition and reductive elimination.

Catalytic cycle for palladium catalyzed allylic substitutions consists of oxidative addition and reductive elimination steps similarly to other allylic substitution reactions. An allylpalladium (II) complex forms after the oxidative addition of allylic electrophile to a palladium (0) complex. The formed allylpalladium complex undergoes a reductive elimination step to generate the organic product of allylic substitution.

Allylpalladium complexes form by oxidative addition of allylic electrophiles to palladium (0) complexes. Hayashi and coworkers studied the stereochemistry of oxidative addition through the reaction of enantioenriched allylic acetate 14 with palladium (0) complex containing a diphenylphosphinoethane (dppe) ligand (Scheme 18).^39 They explicitly showed that these oxidative additions occur by inversion of configuration based on the stereochemistry of the complex C11.

![Scheme 18. Stereochemistry of oxidative addition to palladium (0) complex.](image)

Hayashi and coworkers also studied the stereochemistry of nucleophilic attack on allylpalladium complexes. They found that, nucleophilic attack on optically active complex C12 by soft nucleophiles (sodium dimethylmalonate or dimethylamine) occurs with inversion of configuration (Scheme 19, a) and nucleophilic attack by Grignard reagents (phenyl magnesium bromide or allyl magnesium chloride), occurs with retention of configuration (Scheme 19, b). The researchers also observed that nucleophilic attack occurred almost exclusively at the less substituted terminus of the allylpalladium complex to make organic products 15 and 16.
Scheme 19. Stereochemistry of nucleophilic attack on allylpalladium complexes.

6.2. Resting state and enantiodetermining step in palladium catalyzed allylic substitution.

Bosnich and coworkers studied the mechanism of palladium catalyzed allylic substitution reaction through a series of kinetic measurements, monitored catalytic reactions and deuterium labeling experiments. Researchers did the mechanistic studies on complexes of palladium containing a chiraphos ligand as shown in Scheme 20. Rate constant for oxidative addition was much larger than the rate constant for nucleophilic attack, thus turnover determining step was nucleophilic attack and allylpalladium complex was the resting state of the catalyst. Allylpalladium complexes epimerized 10 to 100 times faster than the rate of nucleophilic attack, thus full equilibration of allylpalladium complexes was observed before the nucleophilic attack. Both oxidative addition and reductive elimination occurred with inversion of configuration and the major product of allylic substitution came from the major allylpalladium complex.

Scheme 20.
6.3. Regioselectivity of nucleophilic attack on allylpalladium complexes.

Palladium catalyzed allylic substitution reactions usually form products of substitution at the most substituted allylic terminus if there is no electronic preference.\textsuperscript{40,42} Accordingly, monosubstituted allylic electrophiles usually form linear, achiral allylic substitution products.\textsuperscript{43} In a study on the origins of regioselectivity of palladium catalyzed allylic substitution, Yudin and coworkers investigated the reaction between allylic acetates and aziridine or secondary amine nucleophiles catalyzed by palladium (0) complexes containing chiral bisphosphine ligands.\textsuperscript{44} They found that the substitution product at the more substituted allylic terminus formed as a kinetic product in these reactions. The branched substitution product quickly isomerized to thermodynamically favored linear product under reaction conditions. The isomerization from the branched product to linear product likely occurred through protonation and reversible oxidative addition of the branched substitution product. A method selective for the formation of the branched substitution products was developed by adding a strong non-nucleophilic base to the reaction.\textsuperscript{45}

6.4. Comparison between the mechanism of allylic substitution catalyzed by iridium and palladium.

There are several differences between the mechanism of palladium catalyzed allylic substitution and mechanism of iridium catalyzed allylic substitution. The first major difference is the regioselectivity of allylic substitution. Iridium complexes are highly selective toward substitution at the most substituted allylic terminus, whereas palladium complexes generally give substitution products at the least substituted allylic terminus. Rate of epimerization between the allylpalladium complexes is faster than the rate of nucleophilic attack, which allows for the development of dynamic kinetic asymmetric transformation (DKAT) type reactions. Thus, nucleophilic attack is usually the enantioselectivity determining step in palladium catalyzed allylic substitution reactions. The rate of epimerization for the studied allyliridium complexes is slower than the rate of nucleophilic attack, thus precluding the possibility of development of DKAT type reactions for the studied systems. The only similarity between the reaction mechanisms of the two metals is in stereochemical route of allylic substitution. Both metals catalyze allylic substitution reactions with double inversion mechanism for the reactions of stabilized nucleophiles.
7. References


Chapter 2:
The Allyl Intermediate in Regioselective and Enantioselective Iridium-Catalyzed
Asymmetric Allylic Substitution Reactions

1. Introduction

Iridium-catalyzed allylic substitution has become a powerful enantioselective method to
form both carbon-carbon\(^1\)\(^-\)\(^4\) and carbon-heteroatom\(^5\)\(^-\)\(^9\) bonds (eq 1). When conducted with the
proper combination of iridium precursor and phosphoramidite ligands, these reactions form
branched substitution products with high regioselectivity and enantioselectivity.

These allylic substitutions likely occur through an allyliridium intermediate, but the
composition and structure of this intermediate has been elusive. Studies from the authors’
laboratory led to the isolation of a trapped form of the active catalyst, which possesses a
cyclometalated phosphoramidite ligand\(^\text{10}\). However, kinetic studies have implied that an
allyliridium complex derived from the isolated metalacycle would be a fleeting intermediate in
the catalytic system, rather than a species that accumulates\(^\text{11}\). Here, we describe the independent
synthesis, characterization, and reactivity of allyliridium complexes that are kinetically and
chemically competent to be this allyl intermediate. Structural data help reveal the origins of
regioselectivity and suggest a remarkable, indirect relay of chirality from a stereocenter in the
catalyst that is distant from the nascent stereocenter of the product.


The most obvious route to allyliridium complexes that could be intermediates the
asymmetric allylation processes would be the reaction of an allylic ester with an isolable adduct
\([\text{Ir(COD)(P}^\text{C})\text{L}]\) of the active metalacycle catalyst. However, treatment of the \([\text{Ir(COD)(P}^\text{C})\text{L}]\)
in which \(L\) is a phosphoramidite, \(\text{PPh}_3\) or ethylene, with allyl methyl carbonate led to no apparent
reaction. We recently showed that the lack of reaction results from unfavorable thermodynamics for the addition process.\(^\text{11}\)

Thus, we tested the reactions of the iridium (I) complex \(\text{1}\) containing an ethylene ligand with more reactive allylic halides (Eq 2). Treatment of complex \(\text{1}\) with allyl chloride in benzene at room temperature led to the rapid formation of a new product corresponding to a singlet resonance at \(\delta\) 125 ppm in the \(\text{31}^\text{P}\) NMR spectrum of the crude mixture. Addition of AgOTf in THF to this complex generated \textit{in situ} formed the stable allyliridium complex \(\text{2a}\). After filtration of the AgCl, this complex deposited as single crystals from the reaction mixture in 55% yield upon standing at room temperature under inert atmosphere for 2 days.

\[
\begin{align*}
\text{(R,R,R)-1} & + \text{AgX} \rightarrow \text{2a} & \text{2a: } R=\text{H} & X=\text{OTf} \quad (2) \\
\text{R} & \quad \text{Cl} \quad \text{benzene} & \text{2b: } R=\text{Me} & X=\text{SbF}_6^- \\
\end{align*}
\]

An analogous mono-substituted allyl complex was prepared by similar methods. The reaction of ethylene complex \(\text{1}\) with \textit{trans}-crotyl chloride in benzene, followed by abstraction of the chloride with AgSbF\(_6\), generated samples of methallyl complex \(\text{2b}\). Crystals suitable for X-ray diffraction formed in 30% yield upon standing at room temperature for 2 days.

3. Characterization of allyliridium complexes

The products of these reactions were identified as allyliridium complexes containing an intact metalacycle and a cyclooctadiene ligand by one-dimensional and two-dimensional \(^1\text{H}\), \(^{13}\text{C}\) and \(^{31}\text{P}\) NMR spectroscopy, as well as X-ray diffraction. A set of \(^1\text{H}\) NMR resonances for the allyl ligand in \(\text{2a}\) were observed at 4.63, 4.22, 3.85, 3.14 and \(\delta\) 2.71 ppm. \(^1\text{H}\) resonances for the coordinated olefinic portion of the COD ligand and for the methylene protons of the metalacycle were clearly identified. Similar \(^1\text{H}\) NMR resonances for \(\text{2b}\) were observed, save for a downfield shift of the allylic proton of the substituted terminus at \(\delta\) 4.73 ppm. The \(^{31}\text{P}\) NMR spectra for \(\text{2a}\) and \(\text{2b}\) consisted of a singlet near \(\delta\) 125 ppm.
Table 1. ORTEP diagram of 2b and bond distances and angles around Iridium for complexes 2a and 2b.

<table>
<thead>
<tr>
<th>Distances (Å)</th>
<th>2a</th>
<th>2b</th>
<th>Angles (°)</th>
<th>2a</th>
<th>2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ir-P</td>
<td>2.2685(6)</td>
<td>2.280(3)</td>
<td>P-Ir-C45</td>
<td>86.96(8)</td>
<td>85.9(3)</td>
</tr>
<tr>
<td>Ir-C45</td>
<td>2.204(3)</td>
<td>2.240(10)</td>
<td>P-Ir-cent1</td>
<td>106.6</td>
<td>107.6</td>
</tr>
<tr>
<td>Ir-C47</td>
<td>2.274(3)</td>
<td>2.377(11)</td>
<td>cent1-Ir-C47</td>
<td>102.2</td>
<td>103</td>
</tr>
<tr>
<td>Ir-C21</td>
<td>2.125(3)</td>
<td>2.114(15)</td>
<td>C47-Ir-C45</td>
<td>66.4(1)</td>
<td>66.0(5)</td>
</tr>
<tr>
<td>Ir-cent1</td>
<td>2.099</td>
<td>2.097</td>
<td>cent2-Ir-P</td>
<td>103.8</td>
<td>104.6</td>
</tr>
<tr>
<td>Ir-cent2</td>
<td>2.244</td>
<td>2.215</td>
<td>cent2-Ir-C45</td>
<td>90.0</td>
<td>90.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cent2-Ir-cent1</td>
<td>82.3</td>
<td>81.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cent2-Ir-C47</td>
<td>95.8</td>
<td>97.3</td>
</tr>
<tr>
<td>C21-Ir-P</td>
<td>75.73(8)</td>
<td>75.0(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C21-Ir-C45</td>
<td>102.9(1)</td>
<td>102.5(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C21-Ir-C47</td>
<td>90.9(1)</td>
<td>89.9(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C21-Ir-cent1</td>
<td>85.6</td>
<td>86.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An ORTEP diagram of the methallyl complex 2b and metric parameters for the core of both 2a and 2b are provided in Table 1. A corresponding line drawing to clarify connectivity and a quadrant diagram to gauge steric interactions are also provided. An ORTEP diagram for the
nearly identical structure of the parent allyl complex 2a is shown in Scheme 21. These complexes can be considered to be severely distorted octahedra with the allyl ligand, an olefinic portion of the COD ligand, and the phosphorus of the metallacycle occupying one plane, and the other olefinic unit of the COD and a methylene of the metallacycle lying apical to this plane. In the complex of the parent allyl ligand, the four angles involving the olefin centroid, two allyl termini and phosphorus atom total 361.9°, indicating the relative planarity of these groups with the metal. The angles between the termini of the allyl group and the metallacycle methylene carbon are 90.9° (C21-Ir-C47) and 102.9° (C21-Ir-C45), indicating the apical positioning of this methylene group, and the angles between one of the olefin centroids and the terminal carbons of the allyl unit are 90.0° (cent2-Ir-C45) and 95.7° (cent2-Ir-C47), indicating the apical positioning of this olefin unit in the opposite direction. The metal-carbon distances to the two allyl termini are 2.204(3)Å and 2.274(3)Å. This 0.07Å difference in distance reflects the trans influence of the phosphine and olefin ligands on the metal-carbon bond lengths. The effect of a trans ligand on bond distances was stated to be small in the classic review on trans influence, and our data are consistent with this assertion.

**Scheme 21.** ORTEP diagram of 2a at 35% ellipsoids. (Protons are omitted for clarity)

The structure of methallyl complex 2b is similar to that of 2a. The major differences between the two structures involve the substituted terminal carbon (C47) of the allyl unit. The iridium-C47 bond length in 2b is 0.1 Å longer than the corresponding bond in 2a. The two angles involving the allyl termini, the iridium and the two apical ligands indicate that the allyl group in
2b is rotated by 1.5-2°, relative to the allyl group in 2a. These structural differences presumably result from greater steric interactions of the COD ligand with C47 in methylallyl 2b than with C47 of allyl complex 2a. Other bond lengths and angles in 2a and 2b agree within 0.04 Å and 1° respectively.

**Scheme 22.** Reactions of Allyl Complexes 2a,b with nucleophiles\(^{a,b}\)

\(^a\) Yields and selectivities determined for reactions at room temperature for 0.5 h in THF-\(d_8\); \(^b\) Reactions of Amines were conducted with triethylamine or Bu\(_4\)N[OC(O)CH\(_3\)] as base.

4. **Reactions of allyliridium complexes with nucleophiles.**

The competence of allyl complexes 2a and 2b in catalytic asymmetric allylic substitutions was assessed by studying their reactions with carbon and heteroatom nucleophiles. After reaction of 2a and 2b with the nucleophiles, PPh\(_3\) was added to displace the 1-alkene product and form the known [Ir(COD)(P^C)-(PPh\(_3\))].\(^{10}\) The yields of the reactions were determined through \(^1\)H-NMR spectroscopy. Regio- and enantioselectivities of products of the reaction of methallyliridium complex 2b with nucleophiles were also determined. The outcome
of those stoichiometric reactions is summarized in Scheme 22 and details of the stoichiometric reactions are provided in experimental section.

In order to compare the results of stoichiometric reactions with those of catalytic reactions, allylic substitution reactions of methallyl methyl carbonate with carbon and heteroatom nucleophiles catalyzed by ethylene ligated complex 1 were conducted. The outcomes of the catalytic reactions are provided in Table 2. The yields of the reactions varied significantly between the types of nucleophiles and were from 52% for aniline to 100% for tetrahydroquinoline. At least 9:1 ratios of branched to linear products and at least 90% ees were observed.

**Table 2.** Yields and selectivities for the reaction of methyl crotyl carbonate with different nucleophiles catalyzed by 1.

<table>
<thead>
<tr>
<th>Nu-H/M</th>
<th>cat.</th>
<th>yield(%)</th>
<th>b:l</th>
<th>ee(%)</th>
<th>time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2N</td>
<td>4%</td>
<td>52</td>
<td>99:1</td>
<td>94</td>
<td>0.5</td>
</tr>
<tr>
<td>O2Na</td>
<td>4%</td>
<td>83</td>
<td>93:7</td>
<td>90</td>
<td>0.5</td>
</tr>
<tr>
<td>O2Li</td>
<td>4%</td>
<td>60</td>
<td>99:1</td>
<td>92</td>
<td>0.5</td>
</tr>
<tr>
<td>O2N</td>
<td>4%</td>
<td>94</td>
<td>99:1</td>
<td>99</td>
<td>0.5</td>
</tr>
<tr>
<td>O2N</td>
<td>4%</td>
<td>100</td>
<td>9:1</td>
<td>94</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The yields, rates, and selectivities of the stoichiometric reactions were compared to those of the reactions of methallyl methyl carbonate catalyzed by [Ir(COD)(P^C)(C2H4)]. The branched to linear selectivities, as well as the enantioselectivities, of the stoichiometric reactions
of 2b were within 5% and 10%, respectively, of the values for the analogous catalytic reactions. Thus, 2a and 2b are chemically and kinetically competent to be intermediates in the iridium-catalyzed allylation processes.

The reaction of 2a with a soluble carboxylate was also studied to evaluate the reversibility of the oxidative addition of allylic esters to this Ir (I) system. Consistent with the endothermicity of the oxidative addition, sodium-2-methylvaleriate reacted with 2a to form Ir (I) and the allylic ester.

The reactivity of 2a and 2b contrasts with that of previous allyliridium complexes, and the structural data provide insights into the selectivity of the allyl intermediates. First, in contrast to 2a and 2b, previous allyliridium complexes have undergone reactions with nucleophiles at the central carbon of the allyl unit.\textsuperscript{13-14} Second, consistent with previous correlations between structure and regioselectivity,\textsuperscript{15-17} attack on 2b occurs at the carbon atom containing the longer Ir-C bond. This carbon is located trans to the ligand with the stronger trans influence.\textsuperscript{12} However, a comparison of the structures of 2a and 2b imply that the effect of the trans ligand on the bond distances is smaller than the effect of the methyl substituent on this distance.

5. **Insight into the origin of enantioselectivity**

Finally, the structure of 2b helps explain the origin of enantioselectivity. The stereochemistry of the allyl ligand and products is consistent with attack of the nucleophile anti to the metal center. The enantioselectivity by iridium catalyst 1 has been shown to originate from the stereochemistry of the $\beta$-carbon in the metallacycle,\textsuperscript{18} but this sterocenter is located far from the expected trajectory of the nucleophile. The quadrant diagram in Table 1 implies that the relay of stereochemistry from this site to the metal center to the allyl ligand occurs by orientation of the aryl group of the phenethyl substituent by the aryl group on the $\beta$-carbon. The phenethyl aryl group then blocks, in combination with the binolate group, adoption of the stereoisomer in which the methyl group of the allyl ligand would be oriented in either of the two western quadrants. The difference in steric properties of the COD and metallacycle methine hydrogen causes the allyl methyl group to occupy the southeastern quadrant that contains the methine hydrogen. The allyl methyl substituent extends into solution, and this structural feature allows the reaction to occur in a similar fashion with many allylic electrophiles.
6. Conclusions

Allyliridium complexes 2a and 2b were prepared and characterized by one and two
dimensional multinuclear NMR spectroscopy and solid state structural analysis. Stoichiometric
reactions of these allyliridium complexes were conducted. The regio- and enantioselectivities of
the stoichiometric reactions were determined and compared to those of catalytic reactions. The
outcome of stoichiometric reactions and comparisons show that allyliridium complexes 2a and
2b are the first complexes chemically and kinetically competent to be intermediates of iridium
catalyzed allylic substitution. An insight into the stereo- and enantioselectivity of nucleophilic
attack was provided based on the analysis of the solid state structure of allyliridium complexes
and absolute stereochemistry of the products of nucleophilic attack.

7. Experimental Section

7.1. General Procedures.

All reactions were conducted in flame or oven-dried round-bottomed flasks fitted with
rubber septa under a positive pressure of argon or nitrogen, or in 1-gram vials sealed with a
screw cap fitted with PTFE silicon septum under an atmosphere of Argon, unless otherwise
stated. Air- and moisture-sensitive reagents were transferred via syringe, or were handled in an
argon-filled drybox (Innovative Technologies, Newburyport, Massachusetts) equipped with an
oxygen sensor (working oxygen level <1 ppm) and low-temperature refrigeration unit (−35 °C).
Organic solutions were concentrated by rotary evaporation at 23–35 °C. Flash-column
chromatography was performed as described by Still et. al.19 employing silica gel (40–63 μm
particle size) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was
performed using glass plates pre-coated with silica gel (0.25 mm). TLC plates were visualized by
exposure to ultraviolet light (UV) or submersion in aqueous potassium permanganate solution
(KMnO₄), followed by brief heating by a heat gun (175 °C, 3–5 s).


Commercial solvents and reagents were used as received with the following exceptions.
Tetrahydrofuran and benzene were deoxygenated by sparging with argon and then were purified
according to the method of Pangborn et al.20 Both enantiomers of 1 were synthesized according
to procedures described in the literature.21 (E)-but- 2-enyl methyl carbonate was synthesized by
the reaction of corresponding allylic alcohol with methyl chloroformate in the presence of pyridine. Sodium 2-methylpentanoate was prepared by the reaction of 2-methylpentanoic acid with NaOH in THF and drying the solid under vacuum at 100 °C overnight after removing the volatile materials. Aniline, N-ethylaniline, benzylamine, and 1,2,3,4-tetrahydroquinoline were all dried over KOH, distilled under reduced pressure and freeze pump thawed before transferring into the drybox. Sodium dibenzylmalonate and sodium dimethylmalonate were prepared by the reaction of 1 equiv of the corresponding malonate with 1 equiv NaH in THF or THF-d8 directly before use. Lithium phenolate, lithium benzoate and lithium 3-(dimethylamino)phenolate were all prepared by 1 equiv of the corresponding alcohol with 1 equiv of a 2.5 molar solution of n-butyllithium in hexanes at 0 °C.

7.3. Instrumentation.

Proton nuclear magnetic resonance spectra (1H NMR) were recorded at 500 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl3, δ 7.26; THF, δ 1.73, 3.58). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz. Proton-decoupled carbon nuclear magnetic resonance spectra (13C NMR) were recorded at 125 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl3, δ 77.0). Two-dimensional COSY (Correlation Spectroscopy) and Heteronuclear Multiple Quantum Coherence (HMQC) were recorded at 500 MHz at 22 °C. Gas chromatography was performed using an HP 6890 series gas chromatograph equipped with an HP-5 column (25 m, 0.2 mm I.D., 0.33 μm film). GC/MS analysis were performed on an Agilent 6890N GC equipped with a 5973 MS and an HP-5ms column (30 m x 0.25 mm ID x 0.25 μm film). HPLC analyses were carried out on a Waters chromatography system (1525 binary pump, 717+ autosampler, 2487 dual wavelength detector). Elemental analyses were obtained at the University of Illinois Microanalysis Laboratory. High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.
7.4. Synthetic Procedures

**Products of reactions of 2a**: All of the products of stoichiometric reactions of 2a were bought from commercial sources with following exceptions. N-allylbenzylamine and N-allyl-N-ethylaniline were prepared according to previously published methods.22-23 Allyl 2-methylpentanoate was made by refluxing sodium 2-methylpentanoate with allyl bromide in acetonitrile.

**GC retention times of linear products of reactions of 2b**: The GC retention times for all linear products were obtained by reacting 1 equiv crotyl chloride with the respective nucleophiles for 1 hour at 50 °C and running GC on crude reaction mixtures.

**Preparation of complex 2a**: In a 20 mL glass vial containing a magnetic stirbar, 400.0 mg of complex 1 (0.4617 mmol) was dissolved in 10.0 mL of C₆H₆, and 37.5 μL (0.460 mmol) of allyl chloride were added to the resulting solution while stirring. After 5-15 min 115.6 mg of AgOTf (0.4499 mmol) dissolved in 3.0 mL of THF was added to the stirring solution. The AgCl, which precipitated, was removed by filtration through a 0.2 μm syringe filter. The resulting solution was concentrated to about 10 mL and allowed to stand at room temperature. After 24 h, the solid was isolated by removing the mother liquor with a pipette and washing the resulting crystals with benzene to give 290 mg of 2a (55% yield). Complex 2a crystallized with two molecules of benzene. Anal. Calc. for C₆₀H₅₈F₃O₅IrNPS: C, 60.79; H, 4.93; N 1.18. Found: C, 60.77; H, 4.90; N, 1.35. 1H NMR (500 MHz, THF) δ 8.33 (m, 2H), 8.05 (m, 4H), 7.51 (m, 4H), 7.30 (m, 10H), 7.14 (d, J = 7.4, 2H), 5.22 (m, 1H), 4.63 (m, 1H), 4.22 (app, t, J = 6.9, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.87 (m, 3H), 3.54 (m, 1H), 3.31 (m, 1H), 3.14 (app, t, J = 7.9, 1H), 2.87 (m, 1H), 2.71 (d, J = 12.0, 1H), 2.31 (m, 2H), 2.11 (m, 1H), 1.74 (m, 1H), 1.63 (m, 2H), 1.44 (m, 1H), 1.08 (t, J = 11.7, 1H), 0.59 (d, J = 7.4, 3H). 31P NMR (202 MHz, THF) δ 124.99.

**Preparation of complex 2b**: In a 20 mL glass vial containing a magnetic stirbar, 118 mg of complex 1 (0.136 mmol) was dissolved in 5.0 mL of C₆H₆, and 18.8 μL (0.193 mmol) of crotyl chloride was added to the resulting solution while stirring. After 5-15 min, 46.6 mg of AgSbF₆ (0.136 mmol) dissolved in 2.0 mL of THF was added to the stirring solution. The AgCl, which
precipitated, was removed by filtration through a 0.2 μm syringe filter. The resulting solution was concentrated to about 5 mL and allowed to stand at room temperature. After 48 h, the solid was isolated by removing the mother liquor with a pipette and washing the resulting crystals with benzene to give 60 mg (35% yield) of \( \text{2b} \). Complex \( \text{2b} \) crystallized with two molecules of benzene. In THF solution, \( \text{2b} \) exists as two isomers in a ratio of 97/3. Anal. Calc. for C\(_{60}\)H\(_{60}\)F\(_2\)IrNPSb: C, 56.03; H, 4.70; N 1.09. Found: C, 55.89; H, 4.78; N, 1.34. \(^1\)H NMR (500 MHz, THF) 8.36 (d, \( J = 8.9 \), 1H), 8.27 (d, \( J = 8.9 \), 1H), 8.10 (m, \( J = 4.5 \), 2H), 8.01 (d, \( J = 8.9 \), 1H), 7.86 (d, \( J = 8.8 \), 1H), 7.55 (m, 2H), 7.36 (m, 2H), 7.16 (d, \( J = 7.0 \), 2H), 5.12 (m, 1H), 4.73 (m, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 3.88 (m, 2H), 3.28 (m, 2H), 3.17 (m, 1H), 2.94 (m, 2H), 2.42 (m, 1H), 2.32 (m, 1H), 2.10 (m, 2H), 1.89 (m, 1H), 1.84 (m, 3H), 1.69 (m, 1H), 1.59 (m, 2H), 1.13 (t, \( J = 12.25 \), 1H), 0.56 (d, \( J = 7.4 \), 3H). \(^{31}\)P NMR (202 MHz, THF) δ 128.55 (minor), 124.93 (major) in a ratio of 97/3.

**General procedure for stoichiometric reactions of \( \text{2a} \):** Complex \( \text{2a} \) (20.0 mg, 0.0169 mmol) and Si\(_2\)Me\(_6\) (1.0 μL) were dissolved in 0.4 mL of THF-d8. A \(^1\)H-NMR spectrum was acquired. To this solution was added the combination of a primary or secondary amine and triethylamine, an alkali metal alkoxide, sodium 2-methylpentanoate, or an alkali metal malonate as nucleophile. Reactions of the primary amines were conducted with 5.0 equiv of the primary amine and 1.2 equiv of the tertiary amine; the other reactions were conducted with 1.2 equiv of the nucleophile. The resulting mixture was stirred for 5 min. A solution of PPh\(_3\) (4.9 mg, 0.019 mmol) in 0.1 mL of THF-d8 was then added, at which point the solution turned yellow. A second \(^1\)H-NMR spectrum was acquired, and the yields of the organic product were determined by integration of the two 1H-NMR spectra vs the Si\(_2\)Me\(_6\) internal standard. The identity of the allylation products was confirmed by comparing the GC retention times with commercially available material or independently synthesized products.

**General procedures for stoichiometric reactions of \( \text{2b} \):** Complex \( \text{2b} \) (20.0 mg, 0.0156 mmol) and Si\(_2\)Me\(_6\) (1.0 μL) were dissolved in 0.4 mL of THF-d8. A \(^1\)H-NMR spectrum was acquired. To this solution was added a combination of a primary amine and triethylamine, 1,2,3,4-tetrahydroquinoline and tert-butylmethylcarbonate, or an alkali metal alkoxide. Reactions of the primary amines were conducted with 5.0 equiv of the primary amine and 1.2 equiv of the tertiary
amine; the other reactions were conducted with 1.2 equiv of the nucleophile. The resulting solution was stirred for 5 min, and a solution of PPh$_3$ (8.1 mg, 0.032 mmol) in THF-$d_8$ was added to the stirred solution. A second $^1$H-NMR spectrum was acquired, and the yields of the organic product were determined by integration of the two $^1$H-NMR spectra versus the Si$_2$Me$_6$ internal standard. The crude reaction was concentrated under vacuum. The product was isolated by preparative TLC, eluting with 20:1 hexanes:ethyl acetate in all cases, except for the isolation of $N$-benzyl but-3-en-2-amine, which was isolated by elution with 3:1 hexanes:acetone. Formation of the allylation products was confirmed by comparing the GC retention times with products prepared independently by catalytic reactions described in the next procedure. Branched-to-linear ratios were measured by GC prior to purification by TLC, and enantiomeric excesses of samples purified by TLC were obtained by chiral HPLC or with chiral lanthanide shift reagents using the same conditions determined for the products obtained by the catalytic reactions. The major enantiomer was always found to correspond to the major enantiomer obtained using $1(R,R,R)$ catalyst.

**General procedures for catalytic reactions using trans-crotyl methyl carbonate:** Methyl crotyl carbonate (130 mg, 1.00 mmol) was dissolved in 2 mL of THF. To this solution was added the nucleophile (1.20 mmol), followed by complex 1 (34.7 mg, 0.0400 mmol). The solution was stirred for 30 min. The volatile materials from the crude reaction solution were evaporated under vacuum. Mesitylene 7.0 μL (0.050 mmol) and CDCl$_3$ were added. A $^1$H-NMR spectrum was acquired, and the yield was determined by integration of the signals due to the organic product versus the mesitylene standard. The chloroform solvent was then evaporated, and the product was isolated by silicagel chromatography as described for the individual products. Branched-to-linear ratios were measured by GC. Enantioselectivities were determined by chiral HPLC of the products isolated after chromatography, or with chiral lanthanide shift reagents. The retention times of the enantiomeric products were determined from racemic mixtures obtained by mixing the products of separate catalytic reactions conducted with the two enantiomers of 1. The yields, enantioselectivities and branched-to-linear ratios for each reaction are given in Table 2.

**Conditions for Isolation and spectral data of the organic products prepared by the catalytic reactions. $N$-(but-3-en-2-yl)aniline**
The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.18 (dd, J = 7.3, 7.6, 2H), 6.70 (t, J = 7.3, 1H), 6.63 (d, J = 7.6, 2H), 5.84 (ddd, J = 5.6, 10.3, 17.2, 1H), 5.23 (dd, J = 1.4, 17.2, 1H), 5.09 (dd, J = 1.4, 10.3, 1H), 3.99 (dq, J = 5.6, 6.7 1H), 3.63 (br, 1H) 1.32 (d, J = 6.7, 3H).

$^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$ 147.30, 141.35, 129.10, 117.07, 114.08, 113.31, 51.00, 21.61. HRMS-ESI (m/z): [MH]+ calcd for C$_{10}$H$_{14}$N, 148.1126; found, 148.1122.

HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99.5/0.5; flow rate = 1 mL/min; detection wave length = 220 nm; TR = 17.1 (major), 20.3 (minor) min. $[^{\alpha}]_{D}^{RT} = -1.6 (c 0.2, CHCl$_3$), (S)-(−)-N-(but-3-en-2-yl)aniline.

**Dimethyl 2-(but-3-en-2-yl)malonate**

The reaction was conducted according to the general procedure. The crude product was passed through a fritted glass filter packed with Celite layered on silica gel and eluted with 20 ml of EtOAc. The solvents were removed under reduced pressure, and the product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). $^1$H-NMR (499 MHz, CDCl$_3$) $\delta$ 5.77 (ddd, J = 8.0, 10.3, 17.2, 1H), 5.09 (d, J = 17.1, 1H), 5.01 (d, J = 10.3, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.32 (d, J = 8.9, 1H), 2.95 (m, 1H), 1.10 (d, J = 6.8, 3H). $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$ 168.42, 168.36, 139.49, 115.24, 57.28, 52.10, 52.00, 37.89, 17.67. The enantiomeric excess was determined by GC: Chiraldex γ-CDTA 30 m column, 50-100 °C, 1 °/min, 90 kPa H2, $tR = 37.3$ (minor) min, $tR = 37.6$ (major) min. $[^{\alpha}]_{D}^{21} = -18.8 (c 1.25, CHCl$_3$), (S)-(−) Dimethyl 2-(but-3-en-2-yl)malonate.

**3-(but-3-en-2-yl)-O,N,N-dimethylaniline**

The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.11 (dd, J = 4.4, 12.1, 1H), 6.33 (m, 3H), 5.94 (ddd, J = 5.8, 10.6, 17.3, 1H), 5.28 (app. dt, J = 1.3, 17.3, 1H), 5.16 (app. dt, J = 1.3, 10.6, 1H), 4.81 (dq, J = 5.8, 6.4 1H), 2.94 (s, 6H), 1.43 (d, J = 6.4, 3H). $^{13}$C-NMR (126 MHz, CDCl$_3$) $\delta$ 159.01, 151.99, 139.58, 129.51, 115.28, 105.73, 103.53, 101.16, 74.32, 40.58, 21.30. HRMS-ESI (m/z): [MH]+ calcd for C$_{12}$H$_{18}$NO, 192.1388; found, 192.1386. HPLC conditions: Daicel CHIRALCEL OD-H (0.46 cm x 25 cm); hexane/2-
propanol = 99.5/0.5; flow rate = 1 mL/min; detection wave length = 220 nm; TR = 29.4 (major), 39.4 (minor) min.

**N-benzylbut-3-en-2-amine**

The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography eluting with 3:1 (hexane:acetone). $^1$H-NMR (500 MHz, CDC$_3$) δ 7.32 (m, 4H), 7.24 (m, 1H), 5.72 (ddd, J = 7.7, 10.2, 17.2, 1H), 5.13 (d, J = 17.2, 1H), 5.09 (d, J = 10.2, 1H), 3.81 (d, J = 13.1, 1H), 3.69 (d, J = 13.1, 1H), 3.22 (dq, J = 7.7, 6.5, 1H), 1.41 (br, 1H), 1.18 (d, J = 6.5, 3H). $^{13}$C-NMR (126 MHz, CDC$_3$) δ 142.50, 140.78, 128.37, 128.14, 126.81, 114.73, 56.01, 51.35, 21.78. HRMS-ESI (m/z): [MH]+ calcd for C$_{11}$H$_{16}$N, 162.1283; found, 162.1276. Daicel CHIRALCEL AD-H (0.46 cm x 25 cm); hexane/2-propanol/diethylamine = 99.75/0.24/0.01; flow rate = 0.5 mL/min; detection wave length = 220 nm; TR = 12.5 (minor), 13.3 (major) min.

**1-(but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline**

The reaction was conducted according to the general procedure. The product was purified by silica gel chromatography, eluting with 9:1 (hexane:EtOAc). $^1$H-NMR (499 MHz, CDC$_3$) δ 7.10 (t, J = 7.0, 1H), 7.01 (d, J = 7.3, 1H), 6.73 (d, J = 8.3, 1H), 6.62 (t, J = 7.3, 1H), 5.96 (ddd, J = 4.1, 10.2, 17.7, 1H), 5.23 (m, 1H), 5.20 (m, 1H), 4.55 (dq, J = 4.1, 6.8, 1H), 3.20 (m, 2H), 2.80 (t, J = 6.4, 2H), 1.96 (m, 2H), 1.35 (d, J = 6.8, 3H). $^{13}$C-NMR (126 MHz, CDC$_3$) δ 145.09, 139.02, 129.19, 126.96, 123.08, 115.46, 114.83, 110.79, 53.19, 41.98, 28.45, 22.38, 15.21. [MH]+ calcd for C$_{13}$H$_{18}$N, 188.1439; found, 188.1437. Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/propanol =99.75/0.25; flow rate = 0.5 mL/min; detection wave length = 220 nm; TR = 11.9 (major), 14.5 (minor) min.

8. **References**


Chapter 3:
Origins of Enantioselectivity during Allylic Substitution Reactions Catalyzed by Metallacyclic Iridium Complexes

1. Introduction

Iridium-catalyzed allylic substitution has become a powerful method for the enantioselective formation of both carbon–heteroatom\(^1\)–\(^8\) and carbon–carbon\(^9\)–\(^15\) bonds. The catalysts developed for this transformation (Figure 1) contain a diolefin ligand bound to a metallacyclic core that is formed by cyclometalation of an iridium–phosphoramidite complex in the presence of base.\(^16\)–\(^17\) This class of catalyst converts linear allylic carbonates to substitution products with high regioselectivity for the branched isomers and with high enantiomeric excess. Recently, \(1b\) was also shown to be exquisitely selective for the conversion of one enantiomer of a racemic mixture of branched allylic benzoates to the allylic substitution products with overall retention of configuration. This reaction of racemic benzoates leads to high enantiomeric excess of both the substitution product and the unreacted ester.\(^18\)

![Figure 1](image)

**Figure 1** Catalysts and ligands commonly used for iridium catalyzed allylic substitution reactions

During the early mechanistic studies of iridium-catalyzed allylic substitution with catalysts derived from phosphoramidite ligands, the identity of the active species was revealed,\(^19\) and a catalytic cycle, along with information on relative rates and equilibria of the sequential steps, was deduced.\(^20\) As part of these studies, a method for isolation and characterization of an allyliridium complex that is an intermediate in this reaction was developed.\(^16\) Following this work, an alternative method for preparing analogous allyliridium complexes directly from \([\text{Ir(COD)}\text{Cl}]_2\) (COD=1,5-cyclooctadiene) and the phosphoramidite ligand was published.\(^21\)
Early studies on the stereochemical course of iridium-catalyzed allylic substitution showed that the overall reaction of 1-phenylallyl acetate or cyclic allylic carbonates occurs with predominant net retention of configuration when conducted with the combination of [Ir(COD)Cl]₂ and P(OPh)₃ as catalyst precursors. This overall stereochemical outcome could result from either two steps occurring by inversion of configuration or by all steps occurring with retention of configuration. Reactions of substrates that discourage additions or eliminations with inversion of configuration with the catalyst derived from [Ir(COD)Cl]₂ and P(OPh)₃ gave low yields of substitution product. However, these substrates are more sterically demanding than those commonly used in iridium-catalyzed allylic substitutions, and the catalyst contains a ligand that is much different from those now used most commonly for the iridium-catalyzed asymmetric allylic substitutions. Most important, little information on the origins of enantioselectivity has been gained during any of the prior studies. For example, the enantioselectivity-determining step of the catalytic cycle, the relative rates for epimerization of diastereomeric intermediates versus the reactions of the nucleophiles with the allyl intermediates, the relative reactivity of the diastereomeric intermediates leading to different enantiomers of the substitution product, and the determination of the configurations of both intermediates and products that reveal the stereochemical outcome of individual steps of the catalytic cycle have not been determined.

We report the results of mechanistic studies conducted with catalysts containing cyclometallated phosphoramidite ligands that are the active form of the most commonly used iridium catalysts for allylic substitution. These studies provide information on 1) the stereochemistry of the individual oxidative addition and nucleophilic substitution steps; 2) isolation of the major allyliridium diastereomer in the catalytic cycle and direct observation of both major and minor diastereomers generated from alkyl- and aryl-substituted allylic electrophiles, and 3) the relative rates for epimerization of allyliridium complexes versus nucleophilic attack on the major and minor diastereomers. These studies provide deep-seated conclusions about the origins of the high stereoselectivity of iridium-catalyzed allylic substitution. Our data show that the factors controlling enantioselectivity in these iridium-catalyzed reactions are distinct from those controlling enantioselectivity in both palladium-catalyzed and molybdenum-catalyzed asymmetric allylic substitutions and that the relationships
between diastereomeric intermediates and enantiomeric products are distinct from those of prior catalytic asymmetric systems studied mechanistically.


Our previous studies showed that the stoichiometric reactions of allylic carbonates with the Ir (I) ethylene complex in Scheme 23 do not generate observable amounts of allyliridium complexes. Thus, we prepared allyliridium complex 2a and crotyliridium complex 2b previously by the route shown in part a of Scheme 23 involving the reaction of iridium-ethylene complex 1a-(R,R,R), allyl or crotyl chloride, and silver salts containing non-coordinating anions.\textsuperscript{16} Subsequent work by Helmchen showed that crotyl complex 3a, and cinnamyliridium complex 3b could be isolated from the route in part b of Scheme 23 starting from [Ir(COD)Cl]\textsubscript{2}, the phosphoramidite, allylic carbonates, and silver perchlorate.\textsuperscript{21} In addition, we prepared allyliridium complex 3b, generated from ligand L2, by a procedure similar to that reported by Helmchen and coworkers.\textsuperscript{21} However, the mechanistic studies reported here required a route to allyliridium complexes that occurred under sufficiently mild conditions to observe directly both minor and major diastereomers containing the metal bound to the two different faces of the allyl unit.

Scheme 23

After conducting further studies with allylic chlorides, we identified an alternative route to the allyl intermediates involving the reaction of iridium-ethylene complexes with allylic trifluoroacetates or with the combination of allylic carbonates and AgBF\textsubscript{4} (Scheme 24a). Both of
these reactions allowed the isolation of pure allyliridium products in high yields and, in specific cases discussed later, as the mixtures of diastereomeric allyliridium complexes needed for the envisioned mechanistic studies. The reaction of ethylene complex 1a-(R,R,R) with cinnamyl trifluoroacetate 4a in THF, followed by the replacement of the trifluoroacetate anion by tetrafluoroborate anion, formed cinnamyliridium complex 2c in 75% isolated yield. Similarly, reaction of the mixture of 1a-(R,R,R) and methyl cinnamyl carbonate 4b with AgBF₄ in THF led to the precipitation of silver methyl carbonate and formation of 2c as the BF₄⁻ salt in 80% isolated yield. The substituted cinnamyliridium complex 2d containing 2,6-difluoro substituents was prepared from the cinnamyl chloride (Part b of Scheme 24). The reaction of 1a-(R,R,R) with 2,6-difluorocinnamyl chloride 4c, followed by exchange of the chloride anion by the tetrafluoroborate anion, gave allyliridium complex 2d in 65% isolated yield.

Scheme 24

As noted in the introduction to this section, the combination of ethylene complex 1a-(R,R,R) and an excess amount of methyl cinnamyl carbonate 4b did not form the allyliridium complex in detectable quantities in the absence of AgBF₄; 1a-(R,R,R) remained unreacted. Thus, a small quantity of allyliridium complex formed in an unfavorable equilibrium appears to react irreversibly with AgBF₄ to form thermodynamically-stable allyliridium complex with a non-nucleophilic counterion 2c-BF₄, or the allylic carbonate is activated by association with the
silver cation. The potential that the carbonate is activated by association with silver cation was tested by combining ethyl cinnamyl carbonate with AgBF\textsubscript{4} in THF-\textit{d}_8 and comparing the \textit{^1}H-NMR spectrum of the resulting solution with that of ethyl cinnamyl carbonate. No difference was observed between the two spectra, showing that little if any adduct is formed. A small amount of Lewis acid-base complex formed in an unfavorable equilibrium could be the species that reacts with the Ir(I) complex, but the absence of an observable adduct is at least consistent with reaction of the silver salt with a small amount of allyliridium carbonate complex.

Two synthetic routes provided access to samples of allyliridium complexes containing observable amounts of the less stable diastereomer. A mixture of diastereomers of cinnamyl complex 2e was generated from reaction of 2-bromocinnamyl chloride, followed by addition of a silver salt containing a non-nucleophilic anion. Because ortho-substituted cinnamyl carbonates undergo iridium-catalyzed allylic substitution with lower enantiomeric excess than meta- or para-substituted cinnamyl carbonates (typically 70%-80% ee for 2-methoxy cinnamylcarbonates),\textsuperscript{1,8,15,23} we considered that the stoichiometric reaction of the Ir(I) species with an ortho-substituted allylic electrophile might generate a mixture of diastereomers. Indeed, reaction of the ethylene complex 1a-(\textit{R},\textit{R},\textit{R}) with 2-bromocinnamyl chloride, followed by addition of AgBF\textsubscript{4}, gave a mixture of diastereomers of 2e. The ratios of diastereomers obtained from this process depended on solvent; preparation of 2e in benzene gave a 60:40 ratio of diastereomers, preparation of 2e in THF gave an 80:20 ratio of diastereomers, and preparation in CH\textsubscript{2}Cl\textsubscript{2} gave a 90:10 ratio of diastereomers (part b of Scheme 24).

An alternative method to prepare a mixture of diastereomeric allyliridium complexes involves the reaction of one enantiomer of a branched allylic trifluoroacetate with the enantiomer of ethylene complex 1a that generates the less stable diastereomeric allyl complex. As shown in Scheme 25, the reaction of the branched phenethyl-substituted allylic trifluoroacetic acid ester 5b-(\textit{S})\textsuperscript{24,25} with ethylene-ligated iridium complex 1a-(\textit{S},\textit{S},\textit{S}) (Scheme 25) at −40 °C gave the less stable diastereomer 2f-TFA-(\textit{S},\textit{S},\textit{S},\textit{R}) of the corresponding allyliridium complex as the initial product of this oxidative addition. Over the course of several hours at −40 °C, 2f-TFA-(\textit{S},\textit{S},\textit{S},\textit{R}) converted to the more stable allyliridium diastereomer 2f-TFA-(\textit{S},\textit{S},\textit{S},\textit{S}). When the same reaction between 5b-(\textit{S}) and 1a-(\textit{S},\textit{S},\textit{S}) was conducted at 25 °C, 2f-TFA-(\textit{S},\textit{S},\textit{S},\textit{R}) was not observed by NMR spectroscopy; the more stable allyliridium complex 2f-TFA-(\textit{S},\textit{S},\textit{S},\textit{S}) was formed quantitatively.
The new allyliridium complexes 2c, 2d and 2e prepared by the methods in Scheme 24, and the new complex 2f-BF$_4$ prepared as shown in Scheme 23, were characterized by multinuclear 1D and 2D NMR spectroscopy. Complexes 2c, 2d and 2e were also characterized by single-crystal X-ray diffraction analysis. The related complex 3b was characterized by multinuclear 1D–NMR spectroscopy. The $^{31}$P-NMR spectrum of cinnamyliridium complex 2c in THF-$d_8$ consisted of a single resonance at $\delta$ 118.5 ppm, consistent with the presence of a single observable diastereomer. Each of the $^1$H NMR signals of the allylic protons of 2c was well resolved. The chemical shifts of the allyl group are $\delta$ 5.61 ppm (substituted terminus), $\delta$ 4.85 ppm (proton on central allylic carbon), $\delta$ 2.83 ppm (syn proton on the terminal allylic carbon) and $\delta$ 2.05 ppm (anti proton on the terminal allylic carbon) in THF-$d_8$. Similarly, 2,6-difluorocinnamyliridium complex 2d was characterized by $^1$H-NMR, $^{13}$C-NMR, $^{31}$P NMR, and 2D gCOSY-NMR spectroscopy, as well as X-ray crystallography (vide infra). Again, a single $^{31}$P-NMR resonance ($\delta$ 115.6 ppm) was observed for samples in THF solvent. The $^1$H NMR signals of the allylic protons for 2d in THF-$d_8$ were also well-resolved and resonated at chemical shifts similar to those of the allyl group in 2c. The solid-state structures of complexes 2c and 2d are shown in Figure 2. The $^{31}$P-NMR spectrum of 2f-BF$_4$ consisted of a singlet at $\delta$ 120.6 ppm, and the $^{31}$P-NMR spectrum of 3c consisted of a singlet at $\delta$ 121.9 ppm which matches the value reported by Helmchen et al.21

The 2-bromocinnamyl complex 2e-BF$_4$ was characterized after synthesis in a solvent that favored one diastereomer, followed by recrystallization. Synthesis of 2-bromocinnamyl complex 2e-BF$_4$ in THF or CH$_2$Cl$_2$ from 2-bromocinnamyl chloride, ethylene complex 1a-(R,R,R) and
AgBF$_4$, followed by recrystallization from benzene gave samples containing the two diastereomers with ratios as high as 95:5. The $^{31}$P-NMR spectra of samples of 2e consisted of two signals at $\delta$ 115.4 and 114.5 ppm for the major and minor diastereomers, respectively. The sample containing a 95:5 ratio of diastereomers was characterized by 1D $^1$H-NMR, 1D $^{13}$C-NMR, and 2D gCOSY-NMR spectroscopy. The ratios of diastereomers of the 2-bromocinnamyl iridium complex 2e generated in benzene, CH$_2$Cl$_2$ and THF were determined by $^{31}$P-NMR spectroscopy. Preparation of 2e in benzene and recrystallization from the same solution gave crystals containing an 80:20 ratio of diastereomers that were suitable for single-crystal X-ray diffraction (Figure 3). A $^{31}$P NMR spectrum of the individual crystal was not obtained, but the same ratio of diastereomers was observed by $^{31}$P-NMR spectroscopy of the bulk sample from which the crystal was selected for X-ray crystallography.

The identity of 2f-TFA-(S,S,S,R) containing a phenethyl-substituted allyl group was deduced from several pieces of information. First, the $^{31}$P NMR spectra of the iridium-allyl complexes consist of singlets near $\delta$ 120-125 ppm and a resonance assigned to 2f-TFA-(S,S,S,R) was observed at $\delta$ 120.2 ppm. Second, the signal at $\delta$ 120.2 ppm decays as the intensity of the signal at $\delta$ 123.8 ppm increases. (The assignment of the $^{31}$P-NMR resonance at $\delta$ 123.8 ppm to 2f-TFA-(S,S,S,S) was corroborated by the reaction of 1a-(S,S,S) with linear electrophile 5l to form the same species, as shown in Scheme 25). Finally, studies described later in this paper show that oxidative addition of the allylic esters occurs with inversion of configuration, and the identity of 2f-TFA-(S,S,S,R) as the kinetic product of oxidative addition is consistent with this inversion of configuration.

3. **Structural characterization of cinnamyliridium 2c, 2,6-difluorocinnamyliridium 2d and 2-bromocinnamyliridium 2e.**

The solid-state structural data of the complexes 2c, 2d (Figure 2) and 2e-(R,R,R,S) (Figure 3), as well as that of previously reported allyliridium complex 2a, crotyliridium complex 2b,$^{16}$ and crotyliridium complex 3a (which contains a phosphoramidite ligand with 2-methoxyphenyl groups L1b$^{21}$) are listed in Table 3. An overlay of the structures of 2b and 2c is provided in Figure 4. The position of C47 (the carbon of the substituted allylic terminus) varies significantly among this series of compounds (Table 3 and Figure 4). The position of C45 (the carbon of the unsubstituted allylic terminus) varies to a lesser degree. More subtle differences are
found in the bond angles, and these changes are analyzed in a footnote. The Ir-C47 bond lengths increase with an increase in the size of the substituent on the allyl group, from 2.27 Å for parent allyliridium 2a to 2.38 Å for crotyliridium 2b and 2.32 Å for crotyliridium 3a to 2.46 Å for cinnamyl, 2-bromocinnamyl, and 2,6-difluorocinnamyliridium complexes 2c-e. Although large, this difference in metal-carbon bond lengths does not affect the other bond lengths around iridium; the other distances are within 0.05 Å of each other. Moreover, this difference in Ir-C47 distance does not lead to differences in the C-C bond lengths of the allyl unit that would reflect varying degrees of contribution of ene-y1 resonance forms. As the difference between Ir-C47 and Ir-C45 bond lengths in the series of complexes increases from the small value of 0.07 Å for 2a to the larger value of 0.14 Å for 2b and 0.11 Å for 3a and largest value of 0.27 Å for 2c-e, the C45-C46 bond lengths remain between 1.40-1.44 Å for all complexes, and the C46-C47 bond lengths remain between 1.39-1.41 Å, with one exception – the C46-C47 distance is only 1.368(9) Å for the 2,6-difluorocinnamyliridium complex 2d. This shorter C46-C47 bond length in 2e could be due to the presence of two strongly electron withdrawing units on the phenyl group, which would weaken the sigma donation from the π system to the metal. Considering the proposed connection between the ene-y1 form of an allyl unit and the regioselectivity for attack at the more substituted vs. unsubstituted termini of an allyl group, the observation of high regioselectivity for formation of a branched isomer, despite the large changes in the difference between the two Ir-C bond lengths is noteworthy. In addition, the structure of crotyliridium complex 3a is similar to that of crotyliridium complex 2b, which contains the phosphoramidite ligand L1a having plain phenyl groups, despite the often distinct reactivity and selectivity.

Figure 2. ORTEP diagrams of 2c and 2d (counterions and hydrogens are omitted for clarity, ellipsoids are drawn to 35% probability)
Table 3. Bond distances and angles around Ir for allyliridium complexes $2a$–d,e-$\langle R,R,R,S \rangle$ and $3a$.

![Diagram of molecular structure]

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<th>$2c$</th>
<th>$2d$</th>
<th>$2e$-$\langle R,R,R,S \rangle$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P–Ir–C45</td>
<td>86.96(8)</td>
<td>85.9(3)</td>
<td>85.28</td>
<td>85.2(2)</td>
<td>85.83(17)</td>
</tr>
<tr>
<td>P–Ir–cent1</td>
<td>106.6</td>
<td>107.6</td>
<td>106.82</td>
<td>107.16</td>
<td>106.87</td>
</tr>
<tr>
<td>cent1–Ir–C47</td>
<td>102.2</td>
<td>103</td>
<td>105.23</td>
<td>106.11</td>
<td>105.13</td>
</tr>
<tr>
<td>C47–Ir–C45</td>
<td>66.4(1)</td>
<td>66.0(5)</td>
<td>63.2(3)</td>
<td>62.3(3)</td>
<td>62.8(2)</td>
</tr>
<tr>
<td>cent2–Ir–P</td>
<td>103.8</td>
<td>104.6</td>
<td>103.22</td>
<td>103.82</td>
<td>102.92</td>
</tr>
<tr>
<td>cent2–Ir–C45</td>
<td>90.0</td>
<td>90.9</td>
<td>94.26</td>
<td>92.65</td>
<td>94.34</td>
</tr>
<tr>
<td>cent2–Ir–cent1</td>
<td>82.3</td>
<td>81.4</td>
<td>81.87</td>
<td>82.63</td>
<td>81.37</td>
</tr>
<tr>
<td>cent2–Ir–C47</td>
<td>95.8</td>
<td>97.3</td>
<td>91.79</td>
<td>92.11</td>
<td>91.85</td>
</tr>
<tr>
<td>C21–Ir–P</td>
<td>75.73(8)</td>
<td>75.0(4)</td>
<td>76.39(14)</td>
<td>75.94(18)</td>
<td>76.59(15)</td>
</tr>
<tr>
<td>C21–Ir–C45</td>
<td>102.9(1)</td>
<td>102.5(5)</td>
<td>99.81</td>
<td>100.2(3)</td>
<td>99.8(3)</td>
</tr>
<tr>
<td>C21–Ir–C47</td>
<td>90.9(1)</td>
<td>89.9(5)</td>
<td>96.09</td>
<td>95.2(3)</td>
<td>96.1(2)</td>
</tr>
<tr>
<td>C21–Ir–cent1</td>
<td>85.6</td>
<td>86.4</td>
<td>84.7</td>
<td>85.06</td>
<td>85.20</td>
</tr>
<tr>
<td>C45–C46–C47</td>
<td>121.3(3)</td>
<td>127.5(3)</td>
<td>122.1(2)</td>
<td>121.2(2)</td>
<td>122.1(4)</td>
</tr>
</tbody>
</table>

$2a$: R" = H, Ar = Ph  
$2b$: R" = Me, Ar = Ph  
$2c$: R" = Ph, Ar = Ph  
$2d$: R" = 2,6-difluorophenyl, Ar = Ph  
$2e$: R" = 2-bromophenyl, Ar = Ph  
$3a$: R" = Me, Ar = 2-(OMe)-C₆H₄
**Figure 3.** ORTEP diagrams of major and minor diastereomers of 2e (counterions and hydrogens are omitted for clarity, ellipsoids are drawn to 35% probability) determined by X-ray diffraction of a crystal containing an 80:20 ratio of the major and minor diastereomers.

**Figure 4.** Overlay of solid state structures of 2b and 2c

### 4. Kinetic studies of the reactions of the allyliridium complexes.

To elucidate the origin of enantioselectivity by the iridium catalyst in these substitution reactions, we measured the rate constants for epimerization of allyliridium complexes and the rate constants for nucleophilic attack on allyliridium complexes. Direct comparison of this set of rate constants would allow us to determine the enantioselectivity-determining step. Our synthetic route to a non-equilibrium ratio of diastereomeric allyl complexes allowed us to determine explicitly the values of these rate constants.

**4.1. Rates for epimerization of allyliridium complexes**

As described in section 2, the less thermodynamically stable allyliridium complex 2f-TFA-(S,S,S,R) was obtained by the oxidative addition of 5b-(S) (6 equiv.) to 1a-(S,S,S) (Scheme 25). The conversion of 5b-(S) and 1a-(S,S,S) to the diastereomeric allyl complexes was monitored at -40 °C and at -30 °C. The initial >25:1 ratio of diastereomers of 2f favoring the less
stable isomer \(2f\)-TFA-\((S,S,R)\) converts over the course of 5.5 hours to a 5:3 (60:40) ratio of diastereomers favoring the more stable isomer \(2f\)-TFA-\((S,S,S)\) and eventually leads to exclusive formation of thermodynamically favored \(2f\)-TFA-\((S,S,S)\). The rate constant for this isomerization process was assessed by monitoring the decay of the signal at \(\delta\) 151.0 ppm in the \(^{31}\)P NMR spectrum of the initial reaction mixture, the changes in the intensity of the signal at \(\delta\) 120.2 ppm for the less stable diastereomer, and the appearance of the signal at \(\delta\) 123.8 ppm corresponding to the more stable diastereomer.

Figure 5. Plot of concentration vs. time for the oxidative addition of \(5b\)-(S) to \(1a\)-(S,S,S) and isomerization of \(2f\)-TFA-\((S,S,R)\) to \(2f\)-TFA-\((S,S,S)\) at -40 °C in THF.

The plot showing the species present during the oxidative addition of \(5b\)-(S) to \(1a\)-(S,S,S) and during conversion of \(2f\)-TFA-\((S,S,R)\) to \(2f\)-TFA-\((S,S,S)\) at -40 °C are shown in Figure 5, and the plot corresponding to the same reaction monitored at -30 °C is presented in the Experimental Section. This process follows a consecutive irreversible reaction sequence in which the two steps occur at similar rates.\(^{27-28}\) The decay of \(1a\)-(S,S,S) versus time corresponds to the oxidative addition of the branched allylic ester \(5b\)-(S) to \(1a\)-(S,S,S). A large excess of allylic ester \(5b\)-(S) ensures that the oxidative addition occurs under pseudo first-order conditions in \(1a\)-(S,S,S). This process occurs with an exponential, first-order decay with a rate constant of \(2.2 \times 10^{-4} \text{ s}^{-1}\) at -40 °C and with a rate constant of \(5.8 \times 10^{-4} \text{ s}^{-1}\) at -30 °C. These pseudo first-order rate constants for oxidative addition \((k_1)\) were used to determine the rate constant for isomerization of the allyliridium complex \((k_2)\).
The change in the concentration of \(2f-(S,S,S,R)\) over time is expressed in eq 1.

\[
d[2f-(S,S,S,R)]/dt = k_1[1a-(S,S,S)] - k_2[2f-(S,S,S,R)] \quad (1)
\]

The change in the concentration of \(2f\)-TFA-(S,S,S,R) over time is expressed in eq 1. Integration and approximation of eq 1, according to Swain’s treatment,\textsuperscript{27} gives eq 2. By iteratively fitting the experimental data to this equation, we determined that the rate constant for conversion of the minor to the major diastereomer is \(5.4 \times 10^{-5} \text{s}^{-1}\) at \(-40 \degree\)C and \(3.4 \times 10^{-4} \text{s}^{-1}\) at \(-30 \degree\)C. Further details of this treatment of the data are provided in the Experimental Section.

\[
[2f-(S,S,S,R)]_{\text{max}}/[1a-(S,S,S)]_0 = (k_2/k_1)^{(k_2/k_1)/(1-(k_2/k_1))} \quad (2)
\]

4.2. Rates of nucleophilic attack on the allyliridium complexes

The rate constants for nucleophilic attack on allyliridium complexes \(2c\), \(2d\), \(2f-(S,S,S,S)\) and \(3b\) were determined by conducting reactions of the complexes with 25 equiv of a primary or a secondary amine nucleophile and 25 equiv of triethylamine as proton acceptor. The large excess of nucleophile creates pseudo first-order conditions for the reaction of the nucleophile with the allyliridium complexes. Because the rate of these reactions surely depends on the concentration of nucleophile, it is important to consider the relative concentration of nucleophile in these stoichiometric reactions and a typical iridium-catalyzed allylic substitution reaction. The concentration of nucleophile in these stoichiometric reactions (0.75 to 1.15 M) is similar to that in the middle of a typical iridium-catalyzed allylic substitution (after one to two half-lives).\textsuperscript{29}

Thus, the conclusions about the relative rates for nucleophilic attack on the allyl intermediate versus epimerization of the minor allyl diastereomer to the major diastereomer apply to the catalytic reactions. Moreover, data presented later in this paper imply that these relative rates are maintained throughout a catalytic reaction conducted under the standard conditions with a small excess of the nucleophile. The rate constants were determined by measuring the decay of the \(^{31}\text{P}\)-NMR signal of the starting iridium complex. The reaction progress curves are provided in the Experimental Section, and the rate constants are provided in Table 4.

The data in Table 4 reveal several trends: (1) The rate of nucleophilic attack is sensitive to the polarity of the solvent. A slight increase in the polarity of the solvent led to a large increase in the rate of nucleophilic attack (entry 1 vs entry 2); (2) Alkylamines react much faster than arylamines (entries 2 and 3); (3) \(N\)-Methylaniline and aniline react with nearly identical rate constants (entries 4 and 5), (4) Nucleophilic attack on cinnamyliridium complex \(3b\), which bears
the phosphoramidite ligand containing an anisyl group, is slower than nucleophilic attack on cinnamyliridium complex 2c (entries 2 and 6), which bears the phosphoramidite ligand containing a phenyl group. This slower rate for attack on complex 3b contrasts the often faster rate for catalytic allylic substitution with the anisyl-substituted system, suggesting that the origin of the difference in rate of the catalytic reactions as a function of the substituent on the phosphoramidite is more subtle than affecting the rate of the turnover-limiting C-N bond-forming step within the catalytic cycle.

Table 4. Rate constants of nucleophilic attack on allyliridium complexes 2c,d, f and 3b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Complex a (M)</th>
<th>NHR(^1)R(^2) or TBAOAc</th>
<th>Solvent</th>
<th>T, °C</th>
<th>(k_{obs}, s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2c (0.030)</td>
<td>PhNH(_2)</td>
<td>CH(_2)Cl(_2)</td>
<td>−30</td>
<td>6.0 × 10(^{-4})</td>
</tr>
<tr>
<td>2</td>
<td>2c (0.043)</td>
<td>PhNH(_2)</td>
<td>THF</td>
<td>−40</td>
<td>3.4 × 10(^{-3})</td>
</tr>
<tr>
<td>3</td>
<td>2c (0.030)</td>
<td>PrNH(_2)</td>
<td>THF</td>
<td>−60</td>
<td>too fast to measure</td>
</tr>
<tr>
<td>4</td>
<td>2d (0.030)</td>
<td>PhNH(_2)</td>
<td>CH(_2)Cl(_2)</td>
<td>−30</td>
<td>2.8 × 10(^{-4})</td>
</tr>
<tr>
<td>5</td>
<td>2d (0.043)</td>
<td>PhNH(Me)</td>
<td>CH(_2)Cl(_2)</td>
<td>−30</td>
<td>2.0 × 10(^{-4})</td>
</tr>
<tr>
<td>6</td>
<td>3b (0.030)</td>
<td>PhNH(_2)</td>
<td>THF</td>
<td>−40</td>
<td>9.9 × 10(^{-4})</td>
</tr>
<tr>
<td>7</td>
<td>2c (0.030)</td>
<td>TBAOAc</td>
<td>THF</td>
<td>−60</td>
<td>too fast to measure</td>
</tr>
<tr>
<td>8</td>
<td>2f-TFA (0.046)</td>
<td>PhNH(_2)</td>
<td>THF</td>
<td>−40</td>
<td>2.5 × 10(^{-3})</td>
</tr>
<tr>
<td>9</td>
<td>2f-BF(_4) (0.037)</td>
<td>PhNH(_2)</td>
<td>THF</td>
<td>−40</td>
<td>9.9 × 10(^{-3})</td>
</tr>
</tbody>
</table>

\(^a\) The reactions of complexes 2c, 2d, 2f-BF\(_4\) and 3b were conducted with the \(R,R,R,R\) diastereomers shown in the graphic. The reaction of 2f-TFA was conducted with the \(S,S,S,S\) diastereomer.

Most important for the current study is the conclusion one can draw by comparing the rate constants for interconversion of the diastereomeric allyliridium complexes with the rate constants for nucleophilic attack on allyliridium complexes. Nucleophilic attack of alkylamines
on the allyliridium complexes was too fast to measure at -60 °C (Table 4: entry 3), whereas conversion of the minor to the major diastereomer of the allyliridium complexes required hours at -40 °C. The rate constants for nucleophilic attack by arylamines in THF (Table 4, entries 2, 6 and 8) were found to be more than an order of magnitude larger than the rate constants for conversion of the minor to major diastereomers. For example, the rate constant for nucleophilic attack on the major diastereomer of 2f-TFA-(S,S,S,S) was about fifty times faster than the 5.4 × 10^{-5} s^{-1} rate constant at -40 °C for epimerization of the minor diastereomer of 2f-(S,S,S,S) deduced from the data in Figure 5. The rate constants for nucleophilic attack by arylamines on 2c and 2d in CH₂Cl₂ (Table 4, entries 1, 4, and 5) were found to be comparable to the rate constant for isomerization of the minor diastereomer of 2f to the major diastereomer of 2f at -30 °C. The identity of the anion of the allyliridium complex had a strong influence on the rate of nucleophilic attack; more than an order of magnitude difference was observed between the rate constant for nucleophilic attack on 2f-TFA and 2f-BF₄ (Table 4, entries 8 and 9). Nucleophilic attack by acetate was too fast to measure at -60 °C (Table 4, entry 7). This final result agrees with our conclusion published previously in communication form on the reactions of amines with allylic carbonates¹⁶,²⁰ indicating that oxidative addition of allylic esters is reversible, as discussed further later in this paper.

These rate constants were measured at temperatures that were lower than those of the catalytic reactions conducted at room temperature. Thus, we determined the activation parameters for the nucleophilic attack of aniline on the major diastereomer of 2f-BF₄ and extrapolated the rate constants to the 25-50 °C temperatures of the catalytic reactions. Because data from the appearance and decay curves (Figure 5) would not give data sufficiently accurate for this analysis of the relative rates for epimerization and nucleophilic attack, we assessed the temperature dependence of this process by assuming that the entropy of activation for this intramolecular reaction was small. The details of the analysis can be found in the Experimental Section. This analysis shows that the rate for attack of aniline on the major diastereomer of the allyliridium complex 2f-TFA is similar to the rate for epimerization of the minor diastereomer of 2f-TFA to corresponding major diastereomer.³¹ Because we showed that nucleophilic attack on the minor diastereomer is much faster than attack on the major diastereomer (vide infra), this analysis implies that nucleophilic attack on the minor diastereomer is faster than epimerization of the minor to major diastereomer. Moreover, we have shown that the major diastereomer is much
more stable than the minor diastereomer, so the rate of conversion of the major diastereomer to the minor diastereomer is roughly two orders of magnitude or more slower than the rate of conversion of the minor diastereomer to the major diastereomer. Thus, attack of an arylamine on the major diastereomer should be faster than epimerization of this stereoisomer to the minor diastereomer under the catalytic conditions.

5. Reactions of diastereomeric allyliridium complexes.

5.1. Relationship between diastereomeric excesses of the allyliridium complexes and enantiomeric excesses of the products of nucleophilic attack on the allyliridium complexes. The samples of 2-bromocinnamyliridium complex 2e and phenethyl-substituted allyliridium complex 2f containing mixtures of diastereomers allowed us to gain direct information on the relative rates for reaction of diastereomeric allyliridium complexes with an amine as nucleophile. The enantiomeric excess from the reactions of mixtures of 2e-(R,R,R,S) and 2e-(R,R,R,R) with aniline and the sodium salt of dimethyl malonate are summarized in Scheme 26. The reaction of aniline with an 80:20 ratio of diastereomers of 2e-BF$_4$ generated by exchanging the chloride anion with a more weakly coordinating BF$_4^-$ anion formed the N-phenyl allylic amine product in 60% ee. The enantioselectivity of this reaction corresponds precisely to the ratio of diastereomers. The reaction of aniline with a sample of complex 2e-BF$_4$ consisting of a higher 95:5 ratio of diastereomers obtained after recrystallization from benzene formed the substitution product in a higher 92% ee. This enantioselectivity also corresponds well with the initial ratio of diastereomers in the sample of 2e-BF$_4$. When the same sample of 2e-BF$_4$ consisting of a 95:5 ratio of diastereomers was allowed to react with sodium dimethylmalonate the product of nucleophilic attack was formed in a slightly lower 83% ee, but this ratio of products (91.5:8.5 er) remains similar to that of the ratio of diastereomers. These results are consistent with the conclusion from kinetic measurements that the diastereomeric complexes 2e containing non-coordinating anions react with the nucleophiles faster than they interconvert.

5.2. Rate constants for reactions of individual diastereomeric allyliridium complexes with amine nucleophiles.

The ability to generate mixtures of diastereomers that do not interconvert allowed us to measure directly the rate constants for reactions of the major and minor diastereomers of 2-bromocinnamyl complex 2e with amine nucleophiles. The rates of these reactions were measured
at -60 °C in CH₂Cl₂. The data were collected with 10 equiv of PhNH₂ as nucleophile and triethylamine to quench the acid formed by the substitution process. We were unable to collect full reaction progress curves for nucleophilic attack on both diastereomers because the signal-to-noise ratio for the resonance of the minor isomer was low after the first half-life. However, we were able to gain information on the relative reactivity of the two diastereomers toward nucleophilic attack from the initial rates.

**Scheme 26.** Stoichiometric reactions of 2e.

Plots showing the initial rates for reaction of the major and minor diastereomers are shown in Figure 6. The initial rate of reaction of the major diastereomer was 6.5 x 10⁻⁶ M•s⁻¹, and the initial rate of reaction of the minor diastereomer was 1.1 x 10⁻⁶ M•s⁻¹. The pseudo first-order rate constants (k_{obs}) for the nucleophilic attack on each of the diastereomers can be calculated from these rates by dividing them by the initial concentrations of the two diastereomers. The two rate constants are k_{major} = 1.2 x 10⁻⁴ s⁻¹ and k_{minor} = 2 x 10⁻⁴ s⁻¹. These values calculated from initial rates show that the rate constant for reaction of the minor diastereomer is about two times larger than that for reaction of the major diastereomer when the reaction is conducted under same conditions for both major and minor allyliridium complexes.

The similarity of these rate constants for nucleophilic attack on the two diastereomers (with reaction of the diastereomer that forms the minor enantiomer being slightly larger) suggest that the high enantioselectivity of the catalytic reaction must result from a highly selective oxidative addition of the allylic ester. This oxidative addition could be irreversible under the
catalytic conditions, in which case the enantioselectivity would result from the kinetic ratio of diastereomers formed by this initial step, or it could be reversible under the catalytic conditions. In the latter case, Curtin-Hammett conditions would be established through reversible oxidative addition. We have shown that carboxylates react with the allyliridium intermediate to form free allylic esters, showing that the oxidative addition can be reversible (Table 4, entry 7). The reversibility of the oxidative addition step likely depends on the nucleophile. This step is clearly reversible for the reactions of amines, but could be irreversible for reactions with anionic nucleophiles or reactions conducted with a precatalyst containing a weakly coordinating anion that would exchange with the carbonate anion.\(^{21}\) In either case, the enantioselectivity is based on a high stereoselectivity for oxidative addition, and this mode of enantioselection is different from that proposed to control enantioselectivity with palladium complexes that undergo facile \(\eta^3-\eta^1-\eta^3\) interconversions.\(^{32-33}\)

![Diagram of the reaction](image)

**Figure 6.** Initial rates of reaction of aniline with the major and minor diastereomers of 2e-BF\(_4\) at -60 °C.
If the high enantioselectivity results from a high stereoselectivity for oxidative addition, then the catalytic reactions of 2-bromocinnamyl carbonates should occur with ee’s that are modest (the stereoselectivity for oxidative addition is low, as described earlier in this paper). Consistent with this assertion, the reactions of 2-bromocinnamyl ethyl carbonate 6 with aniline, sodium dimethylmalonate, and lithium phenoxide catalyzed by 1a-(R,R,R) form the substitution product with 25% to 29% ee (Table 5).³⁴

Table 5. Catalytic reactions of 2-bromocinnamyl carbonate 6 with aniline, lithium phenoxide, and Na-dimethylmalonate.

<table>
<thead>
<tr>
<th>Nucleophile (Product)</th>
<th>Yield, %</th>
<th>7:8</th>
<th>ee, %</th>
<th>T, °C</th>
<th>Time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhNH₂ (7a)</td>
<td>26</td>
<td>99:1</td>
<td>29</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>(CH₃CO₂)₂CHNa (7b)</td>
<td>90</td>
<td>99:1</td>
<td>25</td>
<td>RT</td>
<td>12</td>
</tr>
<tr>
<td>PhOLi (7c)</td>
<td>53</td>
<td>99:1</td>
<td>26</td>
<td>50</td>
<td>0.5</td>
</tr>
</tbody>
</table>

We also sought to determine the relative rates for nucleophilic attack on the two diastereomeric allyl complexes in cases in which the enantioselectivity for the corresponding catalytic reaction was high. To do so, we measured the rates of nucleophilic attack on major and minor isomers of phenethylallyl complex 2f (Scheme 27). A 1:1 ratio of 2f-TFA-(S,S,S,S) and 2f-TFA-(S,S,S,R) was generated by the reaction of Ir(I) ethylene complex 1a-(S,S,S) and branched allylic trifluoroacetate 5b-(S). Reactions of the two diastereomeric allyl complexes 2f with aniline as nucleophile and triethylamine as proton acceptor revealed that the nucleophilic attack of aniline on 2f-TFA-(S,S,S,R) is much faster than the nucleophilic attack on 2f-TFA-(S,S,S,S) and that nucleophilic attack on both diastereomers is faster than interconversion of the two diastereomers containing the trifluoroacetate counterion (vide supra). The reaction of 2f-TFA-(S,S,S,R) occurred to completion in less than 3 minutes at -60 °C, while the reaction of 2f-
(S,S,S,S) occurred to less than 5% conversion over the same time. The rate constant for nucleophilic attack by aniline on the more stable allyliridium diastereomer 2f-(S,S,S,S) was determined quantitatively with the material prepared from the reaction of ethylene ligated complex 1a-(S,S,S) and linear allylic trifluoroacetate 5l (Scheme 25). The rate constant at -40 °C in the presence of triethylamine as base was found to be 2.5 × 10^{-3} s^{-1} (Table 4, entry 8). The difference in rate constants for attack on these diastereomers is larger than that for attack on the 2-bromocinnamyl diastereomer and, again, favors formation of the minor enantiomer, but the stereoselectivity of the oxidative addition step is sufficiently high to cause the overall process to occur with high enantioselectivity.

**Scheme 27. Relative rates of nucleophilic attack on 2f-TFA-(S,S,S,S) and 2f-TFA-(S,S,S,R)**

6. **Investigation of the stereochemistry of the individual steps of the catalytic reaction**

Prior studies of the stereochemistry of iridium-catalyzed allylic substitution reactions have shown that the reaction occurs with overall retention of configuration.\(^\text{9,22}\) To determine if this stereochemical outcome results from two steps of the catalytic cycle occurring by inversion of configuration or two steps occurring by retention of configuration, we determined the stereochemical changes that occur during the reaction of ethylene ligated complex 1a-(R,R,R) with an enantioenriched, deuterium-labeled linear allylic trifluoroacetate 4a-D. In addition, we determined the stereochemical outcome of nucleophilic attack on the isolated allyliridium complexes that result from this oxidative addition. Finally, we conducted the reactions of enantioenriched, monodeuterated allylic carbonate 4b-D\(^2\text{5}\) catalyzed by the two enantiomers of the cyclometallated iridium catalysts 1a and 1b to determine the relationship between the data gained on the stoichiometric reactions of the allylic trifluoroacetate and the data gained on the true catalytic system with allylic carbonates.

The changes in configuration from the oxidative addition and reductive elimination steps were determined directly by conducting reactions of enantioenriched, mono-deuterated, linear allylic trifluoroacetate 4a-D-(S) (eq 3). The position of deuterium in the products of nucleophilic addition to these allyliridium complexes, coupled with the absolute configuration of the products, reveals the stereochemistry of the reaction of the allyl complex with nucleophiles. These studies are based on the system developed by Lloyd-Jones for determining the stereochemistry of the individual steps of molybdenum-catalyzed allylic substitution reactions.25,35

Reaction of the Ir(I) complex 1a-(R,R,R) with the monodeuterated, enantioenriched cinnamyl trifluoroacetate 4a-D (the enantiomeric ratio of the precursor alcohol was > 95:5),24,35,36 followed by anion exchange with AgBF₄, formed an 83:17 ratio of allyliridium complexes containing the deuterium label syn and anti to the metal center, respectively (eq. 3). The ratio of the complexes was determined by integration of the ¹H-NMR signals corresponding to syn and anti protons at the terminal carbon of the allyl unit. This result is consistent with an oxidative addition process that occurs with inversion of configuration. The lack of exclusive formation of one stereoisomer is likely due to partial racemization of the substrate during esterification of the alcohol. We cannot determine the enantiomeric excess of the trifluoroacetate directly, but this result shows that the reaction occurs, at least predominantly, with inversion of configuration.

The stereochemistry of nucleophilic attack on the allyliridium intermediate was determined by reaction of aniline with the cinnamyliridium complex consisting of an 83:17 ratio of syn and anti isomers. This stoichiometric reaction gave the (R) enantiomer of the allylic substitution product 9 in 96% ee. The ratio of products Z-9-(R):E-9-(R) was 8:1, with a small
amount of product formed that lacked the deuterium label. This result is consistent with nucleophilic attack occurring with almost complete inversion of configuration. These two results show that the mechanism of iridium-catalyzed allylic substitution involves two inversions of configurations, one during oxidative addition of the allylic ester and one during reductive elimination that occurs by nucleophilic attack of the nucleophile on the allyl intermediate.

6.2. Catalytic reactions of enantioenriched, deuterium-labeled linear and branched allylic electrophiles

Several differences between the stoichiometric reactions of section 5a and the catalytic system could compromise the conclusions drawn from the reactions of the trifluoroacetate. First, the stoichiometric reactions were conducted with the highly reactive cinnamyl trifluoroacetate 4a-D, whereas catalytic reactions are typically conducted with the less reactive alkyl carbonates or acetates. Second, the stoichiometric reactions of the allylic electrophiles with amine and malonate nucleophiles were conducted with the cinnamyliridium complex containing a weakly coordinating BF$_4^-$ counterion and with added amine as the proton acceptor, whereas the nucleophilic attack that takes place during the catalytic reactions occurs on an intermediate containing either a carbonate, acetate or an alkoxide counterion without an external base.

Thus, we studied catalytic reactions of methyl cinnamyl carbonate 4b-D-(R), an enantioenriched, deuterium-labeled version of the allylic carbonate used in the catalytic process. This substrate was prepared from the enantioenriched, labeled allylic alcohol we had prepared for synthesis of the allylic trifluoroacetate. The potential products of the reactions of this labeled linear allylic carbonate are shown in Scheme 28. Oxidative addition with retention of configuration would generate the allyl intermediate with deuterium in the position anti to the central hydrogen of the allyl unit (labeled as anti–D-major), and oxidative addition with inversion of configuration would generate the allyl intermediate with deuterium in the position syn to the central hydrogen (labeled as syn–D-major). In addition, the minor allyliridium diastereomers similar to those of 2-bromocinnamyl and phenethylsubstituted allyl complexes 2e and 2f, respectively, can be formed (labeled as anti–D-minor and syn–D-minor) through η$^1$-η$^1$-η$^3$ interconversion. An interconversion from the η$^3$ form of anti-D-major to the η$^1$ isomer and back to the η$^3$ forms generates syn-D-minor, and an interconversion from the η$^3$ form of syn-D-major to the η$^1$ isomer and back to the η$^3$ form generates anti-D-minor. Nucleophilic attack with
retention of configuration on the anti-D-major isomer shown would give \((Z)-9\text{-D-}(S)\) as the organic product. Nucleophilic attack on anti-D-major with inversion of configuration would give \((Z)-9\text{-D-}(R)\) as the major product.

**Scheme 28**

The opposite outcome would be expected from nucleophilic attack on anti-D-minor. Nucleophilic attack on anti-D-minor with retention of configuration would give \((Z)-9\text{-D-}(R)\) and nucleophilic attack on anti-D-minor with inversion of configuration would give \((Z)-9\text{-D-}(S)\). Similarly, two different products would form from nucleophilic attack on the syn-D-major and syn-D-minor allyliridium complexes. Nucleophilic attack on syn-D-major with retention of configuration would give \((E)-9\text{-D-}(S)\) as the major product, and nucleophilic attack on syn-D-
major with inversion would give \((E)-9\text{-D-(R)}\) as the major product. Nucleophilic attack on syn-D-minor with retention would give \((E)-9\text{-D-(R)}\) as the major product, and nucleophilic attack on syn-D-minor with inversion would give \((E)-9\text{-D-(S)}\) as the major product.

Results from the catalytic allylic substitution of enantioenriched monodeuterated linear substrate \(4\text{b-D-(R)}\) are provided in Table 6. The reaction of \(4\text{b-D-(R)}\) with aniline catalyzed by \(1\text{a-(R,R,R)}\) gave \((E)-9\text{-D-(R)}\) with 96% ee and a 18:1 ratio of E:Z isomers (Table 6: entry 1). The observed \((R)\) and \((E)\) configurations of the major product from the reaction catalyzed by the complex with \((R,R,R)\) configurations is consistent with the sequence involving two inversions or two retentions (Scheme 28). The sequence involving two retentions can be ruled out, based on the outcome of the stoichiometric reactions (vide supra).

Table 6. Catalytic reactions of enantioenriched, monodeuterated allylic carbonates with aniline catalyzed by ethylene-ligated iridium catalysts 1a and 1b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>((Z))-9:(E)-9</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a-(R,R,R)</td>
<td>4b-D-(R)</td>
<td>1:18</td>
<td>96 (R)</td>
</tr>
<tr>
<td>2</td>
<td>1a-(S,S,S)</td>
<td>4b-D-(R)</td>
<td>18:1</td>
<td>96 (S)</td>
</tr>
<tr>
<td>3</td>
<td>1b-(S,S,S)</td>
<td>4b-D</td>
<td>19:1</td>
<td>98 (S)</td>
</tr>
</tbody>
</table>

A similar stereochemical scenario can be proposed for the allylic substitution of the same monodeuterated, enantioenriched linear allylic electrophile \(4\text{b-D-(R)}\) with aniline catalyzed by the antipodal catalysts 1a or 1b possessing \((S,S,S)\) absolute configuration. In this case, the opposite set of stereoisomers to those in Scheme 28 would be expected to form by each of the eight mechanisms. In the event, the reaction of \(4\text{b-D-(R)}\) with aniline catalyzed by 1a-(S,S,S) gave the allylic substitution product \((Z)-9\text{-D-(S)}\) with 96% ee and a 18:1 Z:E ratio (Table 6: entry 2), and the same reaction catalyzed by 1b-(S,S,S) formed the substitution product \((Z)-9\text{-D-(S)}\) with 98% ee and a 19:1 Z:E ratio (Table 6: entry 3). These results are also consistent with an
iridium catalyzed allylic substitution by the sequence involving two inversions. Thus, our data from the stoichiometric reactions and from the catalytic reaction are consistent with each other.

7. Comparison of the origins of enantioselectivity in allylic substitutions catalyzed by iridium, palladium, and molybdenum complexes.

The origins of enantioselectivity and the changes in configuration that occur during the iridium-catalyzed allylic substitution are distinct from those of catalysts based on complexes of the other metals most commonly used for allylic substitution. Most mechanistic studies have been conducted with palladium and molybdenum catalysts. The step that controls enantioselectivity is distinct from that of palladium systems, and the changes in configuration that occur during the molybdenum-catalyzed reactions are different from those that occur during the iridium-catalyzed reactions.

Many versions of palladium-catalyzed asymmetric allylic substitution have been reported. In general, the configuration of the stereocenter formed at the allyl unit is controlled by the step involving nucleophilic attack on the coordinated ligand. Many palladium-catalyzed reactions involve intermediates containing symmetric allyl groups. In this case, the enantioselectivity is controlled by the relative rates for attack at one terminus of the allyl group over the other. In other cases, palladium-catalyzed reactions of linear or branched, mono-substituted allylic esters that form products from attack at the more substituted position of the allyl group occur with higher enantioselectivity when the rate of $\eta^3-\eta^1-\eta^3$ interconversions are faster than the rate of nucleophilic attack, presumably because the difference in rates of reactions of the diastereomeric allyl complexes is much larger than the equilibrium ratio of diastereomers. The rate of $\eta^3-\eta^1-\eta^3$ interconversions in palladium systems is typically faster than the rate of nucleophilic attack, most likely, because the first step of this interconversion involves association of the counterion with the 16-electron metal center. In contrast to the mode of stereoselection proposed to apply to most palladium-catalyzed asymmetric allylic substitution reactions, the stereoselectivity of iridium-catalyzed allylic substitution originates from the oxidative addition step. The kinetic selectivity for formation of the more stable diastereomer and the relative ratios of the more stable diastereomer over the less stable diastereomer are both sufficiently high to compensate for the faster rate of attack of the nucleophile on the minor diastereomer. In these
iridium-catalyzed allylic substitutions, nucleophilic attack on the minor diastereomeric allyl complex leads to the minor enantiomer of the organic product.

A series of asymmetric allylic substitutions also have been published with molybdenum catalysts,\textsuperscript{39–41} and many reactions with stabilized carbon nucleophiles occur with high enantioselectivity. Like the iridium-catalyzed allylic substitutions, the molybdenum-catalyzed reactions tend to form high ratios of branched to linear substitution products. Thus, one might expect that the origins of stereoselection by the two systems might be similar to each other. However, the studies we report on the changes in configuration during the iridium-catalyzed process show clearly that the iridium and molybdenum systems are distinct. The oxidative addition and reductive elimination steps of the molybdenum-catalyzed reaction occur with retention of configuration,\textsuperscript{25} whereas these steps of the iridium-catalyzed process occur with inversion of configuration.

Finally, the relative rates for reactions of the diastereomeric intermediates in the iridium-catalyzed allylic substitutions are much different from those measured previously for asymmetric hydrogenation. The study by Halpern on the asymmetric hydrogenation of methyl acetamidocinnamate showed that the minor diastereomer formed the major enantiomer because the two diastereomers equilibrate and reaction of the minor diastereomer was several orders of magnitude faster than reaction of the major diastereomer.\textsuperscript{42} In contrast, Bergens has shown that the major diastereomer gives rise to the major enantiomer in ruthenium-catalyzed hydrogenations of ketones, and Curtin–Hammett conditions are not achieved because the formation of the hydrogenation product is faster than the interconversion of the diastereomeric intermediates.\textsuperscript{43} For the iridium system that catalyzes allylic substitution analyzed in the current work, the minor diastereomer reacts faster than the major diastereomer, but the major diastereomer forms the major enantiomer of the product. This scenario can occur in a system that leads to high enantioselectivity because the kinetic and thermodynamic selectivity for formation of the two diastereomers is even higher than the ratio of rate constants for reaction of the diastereomeric intermediates that favors formation of the minor enantiomer.

8. Summary

Studies on the origins of stereoselectivity from iridium-catalyzed allylic substitution reactions showed that the factors controlling enantioselectivity are distinct from those of systems
studied previously. These studies were enabled by the synthesis and characterization of a series of allyliridium complexes generated as both pure diastereomers and as mixtures of diastereomers. The following conclusions were drawn from our data.

1) The more stable diastereomer forms the major enantiomer of the organic product, but reaction of the more stable diastereomer is slower than reaction of the minor diastereomer. Thus, the oxidative addition of the allylic carbonate principally controls the enantioselectivity of the process.

2) Epimerization of the allyl intermediate containing a weakly coordinating anion occurs slowly, even at room temperature. This rate for epimerization is much slower than the rates for epimerization with palladium systems. This difference in rates of epimerization, most likely, results from a difference in coordination sphere. The iridium complex is a pseudo-octahedral, 18-electron $d^6$ system, a class of complex that typically undergoes ligand substitution by dissociative processes, while the palladium complexes are pseudo square-planar, 16-electron $d^8$ systems, which typically undergo ligand substitution by associative processes.

3) The rate for epimerization of individual diastereomeric allyliridium complexes containing weakly coordinating anions is slower than the rate for reaction of the respective diastereomers by attack of typical nucleophiles on the allyl group.

4) Equilibration of the diastereomeric allyliridium complexes likely occurs by reversible oxidative addition. Nucleophilic attack of carboxylate anions on the allyliridium intermediate is fast and thermodynamically downhill, making the oxidative addition process uphill and reversible.  

5) The iridium-catalyzed allylic substitution occurs by an overall retention of configuration that results from two inversions. Oxidative addition of allylic esters occurs by inversion of configuration, and attack of the nucleophile on the allyl intermediate occurs by inversion of configuration. These changes in configuration during the reaction contrast those of the molybdenum system analyzed previously in a similar fashion.

6) The structures of the allyl intermediates containing different substituents on the allyl unit vary by the length of the metal-carbon bond to the substituted terminus, but this
change in distance does not significantly affect the C-C bond distances, and the regioselectivity of the substitution process is high when the difference in M-C bond lengths is only 0.07 Å, as well as when this difference is over 0.27 Å.

Studies that further exploit these features of the catalytic system, studies that alter the relative rates by variations in the coordination sphere of the metal, and studies that reveal the factors that control the site-selectivity of these reactions are in progress.

9. Experimental procedures

9.1. General Procedures. All reactions were conducted in flame or oven-dried round-bottomed flasks fitted with rubber septa under a positive pressure of argon or nitrogen, or in 1 dram vials sealed with a screw cap fitted with PTFE silicon septum under an atmosphere of Argon, unless otherwise stated. Air and moisture-sensitive reagents were transferred via syringe, or were handled in an argon-filled or nitrogen-filled drybox (Innovative Technologies, Newburyport, Massachusetts) equipped with an oxygen sensor (working oxygen level <5 ppm) and low-temperature refrigeration unit (–35 °C). Organic solutions were concentrated by rotary evaporation at 23–35 °C. Flash-column chromatography was performed as described by Still et al.44 employing silica gel (40–63 μm particle size) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm). TLC plates were visualized by exposure to ultraviolet light (UV) or submersion in aqueous potassium permanganate solution (KMnO4), followed by brief heating by a heat gun (175 °C, 3–5 s).

9.2. Instrumentation. Proton nuclear magnetic resonance spectra (1H NMR) were recorded at 500 MHz at 22 °C unless otherwise stated. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl3, δ 7.26; THF, δ 1.73, 3.58; CH2Cl2, δ 5.32). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz. Proton-decoupled carbon nuclear magnetic resonance spectra (13C NMR) were recorded at 125 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl3, δ 77.0; THF, δ 25.5, 67.7; CH2Cl2, δ 53.5) or to an external standard (CFCl3 = 0 for 19F and 85% H3PO4
= 0 for $^{31}$P). Two-dimensional COSY (Correlation Spectroscopy) and Heteronuclear Multiple Quantum Coherence (HMQC) were recorded at 500 MHz at 22 °C. Gas chromatography was performed using an HP 6890 series gas chromatograph equipped with an HP-5 column (25 m, 0.2 mm i.d., 0.33 μm film). GC/MS analyses were performed on an Agilent 6890N GC equipped with a 5973 MS and an HP-5ms column (30 m x 0.25 mm ID x 0.25 μm film). HPLC analyses were carried out on a Waters chromatography system (1525 binary pump, 717+autosampler, 2487 dual wavelength detector). Elemental analyses were obtained at the University of Illinois Microanalysis Laboratory.

9.3. Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran, dichloromethane and benzene were deoxygenated and dried by sparging with argon and passing through columns of activated alumina and supported copper according to the method of Pangborn et al. Aniline, N-methylaniline and octylamine were all dried over KOH, distilled under reduced pressure and freeze pump thawed before transferring into the drybox. Sodium dimethylmalonate was prepared by the reaction of 1 equiv. of the corresponding malonate with 1 equiv NaH in THF or THF-$d_8$ directly before use. Lithium phenolate was prepared by reaction of 1 equiv. phenol with 1 equiv. of a 2.5 molar solution of n-butyllithium in hexane at 0 °C. Triethylamine was dried over CaSO$_4$ and distilled before use. All allylic carbonates ($4b$, $4b$-D-($R$) and $6$) were synthesized by the reaction of the corresponding allylic alcohols with alkyl chloroformate in the presence of pyridine. Monodeuterated enantioenriched alcohols ($\pm$)-(E)-1-[$^2$H$_1$]-3-Phenylprop-2-en-1-ol (corresponding to $4b$-D-($R$)) and (S)-5-phenylpent-1-en-3-ol (corresponding to $5b$-($S$)) were prepared according to the method described previously.$^{25,35}$ Ethylene complex $1a$ was prepared according to an earlier report by our group.$^{46}$ Cinnamyliridium complex $3e$ containing the ligand $1b$ was prepared according to the procedure reported previously by Helmchen and coworkers.$^{21}$

9.4. Synthesis of allyliridium complexes

**Cinnamyliridium complex 2c:** 100 mg of Ir(I) ethylene complex $1a$-($R,R,R$) (0.115 mmol) was dissolved in 5 ml THF, and 53.0 mg of cinnamyl trfluoroacetate $4a$ (0.230 mmol, method A) or 44.0 mg of methylcinnamyl carbonate $4b$ (0.230 mmol, method B) was added to the solution. The solution was allowed to stir for 5 min, after which time 22.4 mg AgBF$_4$ (0.115 mmol) was added. Large amounts of dark precipitate formed quickly upon addition of the AgBF$_4$. The
precipitate was removed by syringe filtration through a 25 mm diameter and 0.2 µm pore size filter, and the filtrate was added dropwise to 10 ml of pentane while stirring vigorously. The precipitated product was collected by filtration and dried under vacuum to give 90 mg (75%, Method A) or 96 mg (80%, Method B) of allyliridium complex 2c after drying. Crystals suitable for single-crystal structural analysis were obtained by dissolving 2c in a small amount THF and layering with benzene. Anal. Calc’d for C$_{59}$H$_{56}$BF$_4$IrNO$_2$P: C, 63.21; H, 5.03; N, 1.25. Found: C, 63.45; H, 5.21; N, 1.45. $^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 8.32 (d, $J$ = 8.9 Hz, 1H), 8.25 (d, $J$ = 8.8 Hz, 1H), 7.71 (d, $J$ = 8.8 Hz, 1H), 7.67 – 7.56 (m, 4H), 7.56 – 7.34 (m, 15H), 7.22 – 7.15 (m, 2H), 5.63 (t, $J$ = 12.1 Hz, 1H), 5.26 – 5.14 (m, 1H), 4.93 – 4.78 (m, 1H), 4.24 – 4.14 (m, 1H), 4.02 – 3.88 (m, 2H), 3.56 – 3.47 (m, 1H), 3.02 – 2.89 (m, 2H), 2.89 – 2.71 (m, 2H), 2.55 – 2.38 (m, 2H), 2.27 – 2.16 (m, 1H), 2.15 – 2.04 (m, 2H), 1.93 – 1.79 (m, 1H), 1.69 – 1.54 (m, 2H), 1.24 (t, $J$ = 12.3 Hz, 1H), 0.61 (d, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 148.83, 148.70, 147.50, 147.43, 142.42, 142.32, 140.22, 133.96, 133.91, 133.17, 132.92, 132.24, 132.19, 132.10, 131.95, 129.92, 129.68, 128.97, 128.87, 128.78, 128.67, 128.56, 128.54, 128.49, 128.40, 128.36, 127.61, 127.57, 127.38, 127.17, 126.67, 126.54, 126.24, 124.49, 122.80, 121.93, 121.19, 121.16, 120.97, 101.48, 97.22, 92.84, 91.02, 86.55, 84.15, 66.12, 65.87, 60.62, 39.95, 35.08, 33.32, 28.13, 26.85, 18.66, 17.47. $^{31}$P NMR (202 MHz, THF) δ 118.5.

(2,6-difluoro)cinnamyliridium complex 2d: 100.0 mg of Ir(I) ethylene complex 1a-(R,R,R) (0.115 mmol) was dissolved in 5 ml benzene, and 23.9 mg (2,6-difluoro)cinnamylchloride 4c (0.127 mmol) was added. The resulting solution was added to a solution for 22.4 mg AgBF$_4$ (0.115 mmol) in 2 ml THF, and the resulting mixture was allowed to stir vigorously for 15 min. The precipitate was removed by syringe filtration through a 25 mm diameter and 0.2 µm pore size filter, and the filtrate was left in an argon-filled dry-box with the cap slightly unscrewed for 48 h. Complex 4c (86 mg, 65% yield) crystallized and was collected after drying under vacuum. Anal. Calc. for C$_{59}$H$_{56}$BF$_6$IrNO$_2$P: 61.24; H, 4.70; N, 1.21. Found: C, 61.32; H, 4.81; N, 1.33. $^1$H NMR (500 MHz, THF) δ 8.30 (d, $J$ = 8.9 Hz, 1H), 8.22 (d, $J$ = 8.8 Hz, 1H), 8.08 (dd, $J$ = 8.2, 2.8 Hz, 2H), 7.81 (d, $J$ = 8.8 Hz, 1H), 7.68 (d, $J$ = 8.8 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.51 – 7.44 (m, 3H), 7.42 – 7.30 (m, 10H), 7.17 – 7.11 (m, 2H), 7.06 (dd, $J$ = 10.4, 8.6 Hz, 2H), 5.58 (t, $J$ = 12.3 Hz, 1H), 5.48 – 5.37 (m, 1H), 5.25 (dd, $J$ = 14.6, 6.4 Hz, 1H), 4.44 – 4.25 (m, 1H), 4.01 – 3.81 (m, 2H), 3.49 (dd, $J$ = 20.9, 14.2 Hz, 2H), 3.20 – 3.07 (m, 1H), 2.80 (t, $J$ = 7.1 Hz, 1H), 2.65 –
2.48 (m, 2H), 2.47 – 2.33 (m, 2H), 2.24 (dd, J = 14.6, 7.6 Hz, 1H), 1.99 (d, J = 11.0 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.61 (dddd, J = 18.5, 14.4, 12.0, 6.8 Hz, 2H), 1.17 (t, J = 12.1 Hz, 1H), 0.58 (d, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 147.38, 141.96, 141.85, 140.02, 133.14, 132.90, 132.28, 132.20, 132.14, 132.02, 130.91, 129.63, 128.96, 128.89, 128.77, 128.75, 128.49, 128.35, 128.33, 128.69, 127.65, 127.39, 127.16, 126.76, 126.62, 126.17, 124.60, 120.97, 120.95, 120.89, 120.88, 113.66, 113.47, 110.00, 102.39, 93.98, 93.22, 85.34, 74.30, 74.06, 66.42, 66.18, 60.59, 60.55, 54.09, 53.87, 53.65, 53.44, 53.22, 40.48, 35.21, 35.11, 27.88, 27.64, 18.45. $^{31}$P NMR (202 MHz, THF) δ 115.6.

(2-bromo)cinnamyliridium complex 2e: Ir(I) ethylene complex 1a-(R,R,R) (50.0 mg, 0.058 mmol) was dissolved in 3 ml of either benzene, THF or CH$_2$Cl$_2$. (2-bromo)cinnamylchloride (26.8 mg, 0.115 mmol) (4d) was added to the solution. The resulting solution was added to 11.3 mg of AgBF$_4$ (0.058 mmol) dissolved in 1 ml of THF and allowed to stir vigorously for 15 min. The resulting precipitate was removed by filtration through a 25 mm diameter, 0.2 µm pore size filter, and the filtrate was added dropwise to 10 ml of pentane while stirring vigorously. The precipitated product was collected on a glass frit and dried under vacuum. Yield: 40 mg (60%) from the reaction in benzene, 31 mg (50%) from the reaction in THF, and 36 mg (55%) from the reaction in CH$_2$Cl$_2$. Crystals suitable for solid-state structural analysis were obtained by dissolving the complex in a small amount of THF and layering the resulting solution with benzene. Anal. Calc. for C$_{59}$H$_{55}$BBrF$_4$IrNO$_2$: C, 59.05; H, 4.62; N, 1.17. Found: C, 59.17; H, 4.76; N, 1.39. $^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 8.33 (d, J = 8.9 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.11 (dd, J = 8.2, 2.6 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.76 (dd, J = 7.8, 1.3 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.55 (t, J = 7.6 Hz, 2H), 7.50 – 7.31 (m, 12H), 7.24 – 7.13 (m, 2H), 5.90 (t, J = 12.0 Hz, 1H), 5.40 – 5.27 (m, 1H), 5.02 – 4.87 (m, 1H), 4.35 (d, J = 5.3 Hz, 1H), 4.07 – 3.86 (m, 2H), 3.64 – 3.56 (m, 1H), 3.23 (b, J = 9.3 Hz, 2H), 2.75 (t, J = 6.8 Hz, 1H), 2.56 – 2.39 (m, 3H), 2.35 (dd, J = 12.0, 4.5 Hz, 1H), 2.24 (dd, J = 14.5, 7.8 Hz, 1H), 2.02 (d, J = 10.6 Hz, 1H), 1.95 (b, J = 19.2 Hz, 1H), 1.74 – 1.53 (m, 2H), 1.39 (t, J = 12.4 Hz, 1H), 0.61 (d, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 148.74, 148.62, 147.47, 147.40, 142.12, 142.02, 139.99, 135.21, 134.09, 134.03, 133.17, 132.93, 132.28, 132.20, 132.15, 132.06, 130.48, 129.75, 129.12, 128.96, 128.89, 128.79, 128.70, 128.52, 128.42, 127.67, 127.63, 127.42, 127.16, 126.75, 126.61, 126.35, 122.76, 121.86, 121.08, 120.94, 103.13, 99.14, 94.38, 93.15, 86.13, 85.92, 85.66.
65.88, 65.63, 60.66, 38.22, 37.17, 35.07, 28.82, 27.80, 18.58, 16.19. $^{31}$P NMR (202 MHz, THF) δ 118.5. $^{31}$P NMR (202 MHz, THF) δ 115.4.

**Phenethylallyliridium complex 2f-BF$_4$:** 100.0 mg of [Ir(COD)Cl$_2$] (0.149 mmol) and 160.7 mg phosphoramidite ligand L1a-(R,R,R) (0.298 mmol) were dissolved in 4 ml THF and 58.0 mg AgBF$_4$ (0.298 mmol) dissolved in 1 ml THF was added to the resulting solution followed by 132.0 mg of methyl (5-phenylpent-2-en-1-yl) carbonate. The reaction mixture was allowed to stir for 12 h. The large amount of white precipitate that forms over the course of the reaction was filtered out by syringe filtration through a 25 mm diameter, 0.2 µm pore size filter. The filtrate was added dropwise to 15 ml pentane while stirring vigorously. The precipitated product was collected over a glass frit and dried under vacuum. Yield: 271 mg (85%). $^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 8.32 (d, $J$ = 8.9 Hz, 1H), 8.23 (d, $J$ = 8.8 Hz, 1H), 8.11 (dd, $J$ = 7.6, 6.4 Hz, 2H), 7.84 (d, $J$ = 8.8 Hz, 1H), 7.67 (d, $J$ = 8.8 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.49 (t, $J$ = 7.5 Hz, 2H), 7.46 – 7.27 (m, 15H), 7.08-7.18 (m, 2H), 5.08 (dd, $J$ = 13.9, 7.8 Hz, 1H), 4.45 (dd, $J$ = 19.2, 10.9 Hz, 1H), 4.19 (dd, $J$ = 8.3, 4.0 Hz, 1H), 3.99-3.79 (m, 2H), 3.66 (dd, $J$ = 11.8, 5.6 Hz, 1H), 3.38 – 3.20 (m, 2H), 3.12 (dt, $J$ = 21.0, 13.9, 7.4 Hz, 2H), 3.00 (dd, $J$ = 14.6, 8.2 Hz, 1H), 2.79 (t, $J$ = 7.7 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.55 – 2.40 (m, 2H), 2.39 – 2.26 (m, 1H), 2.20-2.07 (m, 2H), 1.92 (d, $J$ = 11.3 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.71 – 1.50 (m, 3H), 1.10 (t, $J$ = 11.8 Hz, 1H), 0.58 (d, $J$ = 7.4 Hz, 3H). $^{31}$P NMR (202 MHz, CDCl$_3$) δ 120.57. $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 146.81, 145.44, 140.35, 140.26, 138.67, 138.29, 131.21, 130.94, 130.15, 129.89, 127.51, 127.06, 126.91, 126.70, 126.52, 126.28, 125.55, 125.39, 125.15, 124.75, 124.65, 124.50, 124.31, 120.81, 119.94, 119.13, 119.02, 103.71, 100.51, 90.51, 86.70, 80.47, 76.19, 75.94, 64.03, 63.76, 58.47, 42.09, 34.81, 34.62, 32.98, 30.55, 26.09, 23.92, 16.62, 12.47.

**9.5. Assignment of the anti and syn allylic hydrogens:**

The benzylic proton of the allyl (H$_a$ as depicted in Scheme 29) should have the most downfield chemical shift among the allylic hydrogens and couple to only one other proton (H$_b$) in the gCOSY spectrum (Figure 7). Only the signal at 5.61 ppm meets these criteria; this peak was assigned to H$_a$. The proton coupled to H$_a$ should be H$_b$ and the signal at 4.85 ppm was assigned to H$_b$. H$_b$ is coupled to two other protons which should be H$_{anti}$ and H$_{syn}$. The signals at 2.83 and 2.05 are the remaining signals coupled to that of H$_b$. H$_{anti}$ is located closer to the metal...
than H\textsubscript{syn} (2.23 Å vs. 2.77 Å). Because of this structural feature H\textsubscript{anti} will experience a stronger shielding from the metal than H\textsubscript{syn}.\textsuperscript{47-48} The peak at 2.05 ppm was, therefore, assigned to H\textsubscript{anti} and the peak at 2.83 ppm was assigned to H\textsubscript{syn}. This assignment of allylic protons was confirmed by 2D (Figure 8) and 1D-ROESY NMR spectroscopy (Figure 9). The solid-state structure of the allyliridium complex shows that both H\textsubscript{a} and H\textsubscript{anti} should be close enough to the olefin proton (labeled as H\textsubscript{c}) to observe an NOE (The H\textsubscript{a}-H\textsubscript{c} distance is 2.011 Å, and the H\textsubscript{anti}-H\textsubscript{c} distance is 2.383 Å), whereas H\textsubscript{syn} is located too far (The H\textsubscript{syn}-H\textsubscript{c} distance is 4.001 Å) from H\textsubscript{c} to observe an NOE. The 2D-ROESY NMR spectrum of the cinnamyliridium complex shows a strong NOE between H\textsubscript{a} 5.61 ppm and the multiplet at 3.52 ppm. Thus, the multiplet at 3.52 ppm was assigned to H\textsubscript{c}. The 2D-ROESY spectrum also shows that the peak at 3.52 ppm is close in space to the proton with a chemical shift close to 2.05 ppm. Because there are two protons at this chemical shift in \textsuperscript{1}H-NMR spectrum, one corresponding to the allylic proton and the other to a proton from cyclooctadiene, we could not immediately assign the chemical shift at 2.05 ppm to H\textsubscript{syn}. A 1D-ROESY spectrum was obtained with irradiation at the chemical shift of 3.52 ppm (H\textsubscript{c}) to observe the peak shape of the coupled proton at 2.05 ppm. The peak shape of the coupled proton at 2.05 ppm is an apparent doublet, which is the peak shape observed in the \textsuperscript{1}H-NMR spectrum for the allylic proton. No coupling was observed between H\textsubscript{c} and protons with a chemical shift of 2.83. Thus the chemical shift at 2.05 ppm was assigned to H\textsubscript{anti}, and the chemical shift at 2.83 ppm was assigned to H\textsubscript{syn}. The outcome of the ROESY-NMR was in good agreement with our assignment of syn and anti allylic protons based on the \textsuperscript{1}H NMR chemical shifts.

**Scheme 29**
Figure 7. g-COSY spectrum of 2c

Figure 8. 2DROESY spectrum of 2c
9.6. Kinetic studies:

9.6.1. Rate of interconversion of allyliridium diastereomers:

General procedure for the measurement of the rate of interconversion:

1a-(S,S,S) (40 mg, 0.046 mmol) was dissolved in THF (1 ml for the reaction at -40°C and 0.7 ml for the reaction at -30°C) and transferred into a screw capped NMR tube with a sealed capillary tube containing $^{31}$P internal standard. The tube was placed in a dry-ice acetone bath and 5b-(S) was added by syringe (62 µl, 0.28 mmol). The tube was transferred to NMR-probe cooled to -30 or -40°C and decay of 1a-(S,S,S) as well as formation and decay of 2f-CO$_2$CF$_3$-(S,S,S,R) was monitored.

Figure 9. 1DROESY spectrum of 2c obtained by irradiating the peak at 3.52 ppm.
Isomerization at -40°C.

Figure 10. Plots of the change of concentration over time for 1a-(S,S,S), 2f-CO$_2$CF$_3$-(S,S,R) and 2f-CO$_2$CF$_3$-(S,S,S) at -40°C

The 1$^{st}$ order decay of 1a-(S,S,S) corresponds to oxidative addition of 5b-(S) to 1a-(S,S,S). The rate constant for oxidative addition can be determined by plotting ln[1a-(S,S,S)] versus time.

Figure 11. Plot ln[1a-(S,S,S)] versus time for the reaction of 1a-(S,S,S) with 5b-(S) at -40°C.
Isomerization at -30°C.

**Figure 12.** Plots of the change of concentration over time for 1a-(S,S,S), 2f-CO$_2$CF$_3$-(S,S,R) and 2f-CO$_2$CF$_3$-(S,S,S) at -30°C.

**Figure 13.** Plot ln[1a-(S,S,S)] versus time for the reaction of 1a-(S,S,S) with 5b-(S) at -30°C.
Calculation of the rate of isomerization of 2f-CO₂CF₃-(S,S,S,R).²⁷-²⁸

2f-CO₂CF₃-minor is produced by 1a-(S,S,S) and depleted by production of 2f-CO₂CF₃-major. The change in concentration of 2f-CO₂CF₃-minor is governed by the relationship:

$$\frac{d[2f - \text{minor}]}{dt} = k_1[1a - (S,S,S)] - k_2[2f - \text{minor}]$$  (4)

Integrating gives the single transcendental equation:

$$[2f - \text{minor}] = \left((1a - (S,S,S))_o k_1) / (k_2 - k_1)\right) (e^{-k_1t} - e^{-k_2t})$$  (5)

Equation 5 cannot be solved exactly but can be accurately approximated via the mathematical treatment of Emanuel.⁴⁹ Equation 5 can be simplified to

$$\beta_{max} = \kappa[\kappa/(1-\kappa)]$$  (6) (this equation corresponds to the equation 2 in section 4.1)

where $$\beta_{max} = ([2f - \text{minor}]_{max}/[(1a-(S,S,S)]_0)$$ and $$\kappa = k_2/k_1$$

The value of $$\beta_{max}$$ was obtained directly from Figure 5 (for -40°C) or Figure 12 (for -30°C), and $$\kappa$$ can be calculated iteratively so that equation 3 is satisfied. The value of $$k_2$$ is calculated from the product of $$\kappa$$ and $$k_1$$.

9.6.2. Measurements of the rates of nucleophilic attack

The rate of nucleophilic attack on allyliridium complexes was measured by ³¹P NMR spectroscopy on an Unity Inova 400 MHz instrument at -30, -40 or -60°C. The rate constants for nucleophilic attack on allyliridium complexes 2c, 2d, 2f(S,S,S,S) and 3c were determined by conducting reactions of the complexes with 10 equiv of tetrabutyl ammonium acetate or a combination of 25 equiv of primary or a secondary amine nucleophile and 25 equiv of triethylamine as proton acceptor. The rate constants were determined by measuring the decay of the ³¹P-NMR signal of the starting iridium complex. The rate constants for nucleophilic attack were determined by plotting the natural logarithms of concentration vs. time.

**Reaction of 2c with aniline at -30°C in CH₂Cl₂** (Table 4, entry 1)

Complex 2c (20.0 mg, 0.0178 mmol) was dissolved in 0.6 ml CH₂Cl₂ and transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 41 μl of aniline (0.45 mmol) and
62 µl of triethylamine (0.45 mmol) were added to the NMR tube by syrings. The NMR tube was placed into a probe cooled to -30°C and $^{31}$P-NMR spectra were recorded every 3 min.

**Figure 14.** Plot of the change of concentration over time for the reaction of 2c with aniline in CH$_2$Cl$_2$ at -30°C.

**Figure 15.** Graph of ln[2c] vs. time for the reaction of 2c with aniline in CH$_2$Cl$_2$ at -30°C.
Reaction of 2c with aniline at -40°C in THF (Table 4, entry 2)

2c (30 mg, 0.026 mmol) was dissolved in 0.6 ml THF and transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 61 µl aniline (0.65 mmol) and 84 µl triethylamine (0.445 mmol) were injected into the NMR tube. The NMR tube was placed into a probe cooled to -40°C and 31P-NMR spectra were recorded every min.

![Graph](image1)

**Figure 16.** Plot of the change of concentration over time for the reaction of 2c with aniline in THF at -40°C.

![Graph](image2)

**Figure 17.** Graph of ln[2c] vs. time for the reaction of 2c with aniline in THF at -40°C.
Reaction of 2d with aniline at -30°C in CH₂Cl₂ (Table 4, entry 4)
2d (30 mg, 0.026 mmol) was dissolved in 0.6 ml CH₂Cl₂ and transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 61 µl aniline (0.445 mmol) and 84 µl triethylamine (0.445 mmol) were injected into the NMR tube. The NMR tube was placed into a probe cooled to -30°C and ³¹P-NMR spectra were recorded every 4 min.

Figure 18. Plot of the change of concentration over time for the reaction of 2d with aniline in CH₂Cl₂ at -30°C.

Figure 19. Graph of ln[2d] vs. time for the reaction of 2d with aniline in CH₂Cl₂ at -30°C.
Reaction of 2d with N-methyl aniline at -30°C in CH₂Cl₂ (Table 4, entry 5)

2d (40 mg, 0.037 mmol) was dissolved in 0.6 ml CH₂Cl₂ and transferred into a screw-capped NMR tube and cooled in a dry-ice acetone bath. 113 µl of N-methyl aniline (1.05 mmol) and 56 µl of triethylamine (1.05 mmol) were injected into the NMR tube. The NMR tube was placed into a probe cooled to -30°C, and ³¹P-NMR spectra were recorded every 4 min.

Figure 20. Plot of the change of concentration over time for the reaction of 2d with N-methyl aniline in CH₂Cl₂ at -30°C.

Figure 21. Graph of ln[2d] vs. time for the reaction of 2d with N-methyl aniline in CH₂Cl₂ at -30°C.
Reaction of 3c with aniline at -40°C in THF (Table 4, entry 6)

3c (20 mg, 0.018 mmol) was dissolved in 0.6 ml THF and transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 41 µl aniline (0.45 mmol) and 62 µl triethylamine (0.45 mmol) were injected into the NMR tube. The NMR tube was placed into a probe cooled to -40°C and $^3$P-NMR spectra were recorded every 4 min.

![Graph of ln[3c] vs. time for the reaction of 3c with aniline in THF at -40°C.](image)

**Figure 22.** Plot of the change of concentration over time for the reaction of 3c with aniline in THF at -40°C.

**Figure 23.** Graph of ln[3c] vs. time for the reaction of 3c with aniline in THF at -40°C.
Reaction of 2f(S,S,S,S) with aniline at -40°C in THF (Table 4, entry 8)

1a(R,R,R) (40 mg, 0.046 mmol) was dissolved in 1 ml THF and 5-phenylpent-2-en-1-yl 2,2,2-trifluoroacetate, 5l (12 µl, 51 mmol) was added to the solution and allowed to stir for 15 min. The reaction mixture was transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 93 µl aniline (1 mmol) and 139 µl triethylamine (1 mmol) were injected into the NMR tube. The NMR tube was placed into a probe cooled to -40°C and 31P-NMR spectra were recorded every min.

Figure 24. Plot of the change of concentration over time for the reaction of 2f(S,S,S,S) with aniline in THF at -40°C.

Figure 25. Graph of ln[2f(S,S,S,S)] vs. time for the reaction of 2f(S,S,S,S) with aniline in THF at -40°C.
9.6.3. Measurement of activation parameters of nucleophilic attack

Reaction of 2f(R,R,R,R)-BF₄ with aniline at -40,-30,-20 and -10°C in THF:

2f(R,R,R,R)-BF₄ (40 mg, 0.037 mmol) was dissolved in 0.5 ml THF and transferred into a screw capped NMR tube and cooled in a dry-ice acetone bath. 86 µl aniline (0.94 mmol) and 130 µl triethylamine (0.94 mmol) dissolved in 0.3 ml THF were injected into the NMR tube, making the overall volume of the solution 1 ml. The NMR tube was placed into a probe cooled to -40, -30, -20 or -10°C and ³¹P-NMR spectra were recorded every 3 min.

![Graph](image1)

**Figure 26.** Graph of ln[2f(S,S,S,S)-BF₄] vs. time for the reaction of 2f(S,S,S,S)-BF₄ with aniline in THF at -10°C.

![Graph](image2)

**Figure 27.** Graph of ln[2f(S,S,S,S)-BF₄] vs. time for the reaction of 2f(S,S,S,S)-BF₄ with aniline in THF at -20°C.
Figure 28. Graph of $\ln[2f(S,S,S,S)-BF_4]$ vs. time for the reaction of $2f(S,S,S,S)-BF_4$ with aniline in THF at -30°C.

Figure 29. Graph of $\ln[2f(S,S,S,S)-BF_4]$ vs. time for the reaction of $2f(S,S,S,S)-BF_4$ with aniline in THF at -40°C.
Eyring plot for the reaction of 2f-BF\(_4\) with aniline:
The natural logarithms of the rate constants divided by temperature (\(\ln(k/T)\)) for the reaction of 2f-BF\(_4\) with aniline measured at -10, -20, -30 and -40°C were plotted against the reciprocal of the temperature (1/T) to determine the activation parameters for the nucleophilic attack.

<table>
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<th>T (°C)</th>
<th>(k_{Nu})</th>
<th>T (K)</th>
<th>1/T</th>
<th>ln(k/T)</th>
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<td>-10</td>
<td>1.3 x 10(^{-3})</td>
<td>263</td>
<td>0.03802</td>
</tr>
</tbody>
</table>

Figure 30. Eyring plot for the reaction of 2f-BF\(_4\) with aniline.

From Figure 30:
Slope = -4952 = -\(\Delta H/\)R;
\(\Delta H^\dagger_{nuc} = 4952 \times 8.314 = 41.2\) kJ/mol = 9.8 kcal/mol
Intercept = 6.6 = ln(\(kB/h\)) + \(\Delta S/\)R ;
\(\Delta S^\dagger_{nuc} = [6.6 - \ln(1.38x10-23/6.27x10-34)] \times 8.314 = (6.6-23.8) \times 8.314 = -143\) J/mol•K = -34.2 eu
Thus, the nucleophilic attack on a representative allyliridium complex has a typical entropy of activation for a bimolecular reaction.

For the reaction of aniline with **2f-TFA**

At -40 °C $\Delta G_{\text{nucl}}^{\ddagger} = 75.7 \text{ kJ/mol}$

Estimation of the value of $\Delta \Delta H^{\ddagger}$ for nucleophilic attack versus isomerization at -40°C from $\Delta \Delta G^{\ddagger}$ and $\Delta \Delta S^{\ddagger}$.

$\Delta \Delta G^{\ddagger} = \Delta \Delta H^{\ddagger} - T\Delta \Delta S^{\ddagger};$

Assuming that $\Delta S^{\ddagger}_{\text{nucl}}$ for **2f-TFA** is similar to that for **2f-BF4** and that $\Delta S^{\ddagger}_{\text{epi}}$ is close to zero because it is unimolecular reaction,

$\Delta \Delta S^{\ddagger} = -143 \text{ J/mol\cdot K}$

At $T = 233 \text{ K}$;

$\Delta \Delta H^{\ddagger} = \Delta \Delta G^{\ddagger} + T\Delta \Delta S^{\ddagger}$

$\Delta \Delta G^{\ddagger} = -7.6 \text{ kJ/mol}$ from the ratio of rate constants for nucleophilic attack and epimerization of **2f-TFA**.

$T\Delta \Delta S^{\ddagger} = 143 \times 233 = 33.3 \text{ kJ/mol}$

And $\Delta \Delta H^{\ddagger} = -40.9 \text{ kJ/mol};$

The temperature dependence of the ratio of rate constants of nucleophilic attack and epimerization can be derived as follows:

$$k_{\text{Nu}} = \frac{k_B T}{h} e^{\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R} \quad (7)$$

$$k_{\text{epi}} = \frac{k_B T}{h} e^{\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R} \quad (8)$$

$$\frac{k_{\text{Nu}}}{k_{\text{epi}}} = e^{\Delta \Delta H^{\ddagger}/RT} \times e^{\Delta \Delta S^{\ddagger}/R} \quad (9)$$

$$\left(\frac{k_{\text{Nu}}}{k_{\text{epi}}}\right)_{T_1} = \frac{e^{\Delta \Delta H^{\ddagger}/RT_1} x e^{\Delta \Delta S^{\ddagger}/R}}{e^{\Delta \Delta H^{\ddagger}/RT_2} x e^{\Delta \Delta S^{\ddagger}/R}} \quad (10)$$

$$\left(\frac{k_{\text{Nu}}}{k_{\text{epi}}}\right)_{T_2} = e^{(\Delta \Delta H^{\ddagger}/RT_1) - (\Delta \Delta H^{\ddagger}/RT_2)} \quad (11)$$

$T_1 = -40 \text{ °C}; \ T_2 = 25 \text{ °C}$

$$(k_{\text{Nu}}/k_{\text{epi}})_{T_2}/(k_{\text{Nu}}/k_{\text{epi}})_{T_1} = e^{\Delta(\Delta \Delta H^{\ddagger}/8.314 x 298)} - (-40.9/(8.314 x 233))] = 100.$$
\[ T_1 = -40^\circ \text{C}; \ T_2 = 50^\circ \text{C} \]
\[
\frac{(k_{Nu}/k_{epi})_{T2}}{(k_{Nu}/k_{epi})_{T1}} = e^{[-(40900/(8.314x323)) \cdot (-(40900/(8.314x233))]} = 360.
\]

Thus, a temperature increase from -40°C to 25°C and to 50°C will result in 100 and 360 times increase respectively in the rate constant of epimerization over the rate constant for nucleophilic attack.

9.7. Catalytic reactions of 2-bromocinnamyl carbonate 5:

Ethyl 3-(2-bromophenyl)-2-propen-1-yl carbonate 5 (0.50 mmol, 143 mg) was added to the solution of 1a (0.02 mmol 17.4 mg) in 1 ml THF followed by nucleophile (0.3 mmol). The solution was allowed to stir for the indicated time at indicated temperature. After removing the solvent yields were determined by \(^1\)H-NMR with mesitylene as internal standart. The products were purified by flash column chromatography through silica using with Hex:EtOAc eluent.

N-(1-(2-bromophenyl)allylaniline, 7a: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.58 (dd, \( J = 8.0, \ 1.1 \) Hz, 1H), 7.44 (dd, \( J = 7.8, \ 1.7 \) Hz, 1H), 7.30 – 7.24 (m, 1H), 7.16 – 7.09 (m, 3H), 6.74 – 6.63 (m, 1H), 6.53 (dd, \( J = 8.6, \ 0.9 \) Hz, 2H), 6.04 (ddd, \( J = 17.1, \ 10.3, \ 5.6 \) Hz, 1H), 5.36 (t, \( J = 5.4 \) Hz, 1H), 5.26 (dt, \( J = 10.3, \ 1.2 \) Hz, 1H), 5.24 – 5.19 (m, 1H), 4.13 (b, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 146.89, 140.57, 137.53, 133.33, 129.39, 129.10, 128.58, 128.11, 124.02, 118.04, 117.22, 113.61, 59.48. HRMS-ESI (m/z): [MH\(^+\) calcd. for C\(_{15}\)H\(_{15}\)BrN, 289.1903; found, 289.1901. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99.5/0.5; flow rate = 1 mL/min; detection wave length = 254 nm; TR = 12.1 (R), 14.3 (S) min.

dimethyl 2-(1-(2-bromophenyl)allyl)malonate, 7b: \(^1\)H NMR (499 MHz, CDCl\(_3\)) \( \delta \) 7.58 (dd, \( J = 8.0, \ 1.2 \) Hz, 1H), 7.30 – 7.25 (m, 1H), 7.23 (dd, \( J = 7.8, \ 1.7 \) Hz, 1H), 7.12 – 7.06 (m, 1H), 5.97 (ddd, \( J = 17.1, \ 10.2, \ 8.0 \) Hz, 1H), 5.15 (dd, \( J = 15.0, \ 14.0 \) Hz, 2H), 4.70 (dd, \( J = 10.6, \ 8.1 \) Hz, 1H), 4.02 (d, \( J = 10.6 \) Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 168.20, 167.81, 139.38, 136.43, 133.68, 128.77, 128.66, 127.86, 124.99, 117.92, 56.43, 52.85, 52.77, 48.14. HRMS-ESI (m/z): [MH\(^+\) calcd. for C\(_{15}\)H\(_{15}\)BrN, 328.1784; found, 328.1781. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =95/5; flow rate = 1 mL/min; detection wave length = 254 nm; \( t_R = 32.1 \) (S), 35.3 (R) min.
1-bromo-2-(1-phenoxallyl)benzene, 7c: $^1$H NMR (499 MHz, CDCl$_3$) $\delta$ 7.60 (dd, $J = 19.8$, 7.9 Hz, 2H), 7.40 – 7.23 (m, 3H), 7.23 – 7.09 (m, 1H), 7.01 – 6.82 (m, 3H), 6.25 – 6.03 (m, 2H), 5.48 (d, $J = 16.5$ Hz, 1H), 5.34 (d, $J = 9.9$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 157.51, 139.27, 136.06, 132.87, 129.54, 129.38, 128.36, 128.17, 122.63, 121.17, 117.07, 115.85, 78.67. HRMS-ESI (m/z): [MH]$^+$ calcd. for C$_{15}$H$_{15}$BrN, 290.1751; found, 290.1750. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99.5/0.5; flow rate = 1 mL/min; detection wave length = 254 nm; $t_R = 29.3$ (S), 31.5 (R) min.

9.8. Stereochemical route of the reaction:

9.8.1. Stereochemistry of oxidative addition:

Reaction between 1a and monodeuterated cinnamyl trifluoroacetate, 4a-D: 1a-(R,R,R) (30 mg, 0.035 mmol) was dissolved in 1 ml C$_6$H$_6$, and 4a-D (10.2 mg, 0.042 mmol) was added to it. AgBF$_4$ (6.8 mg, 0.035 mmol) was dissolved in 0.5 ml THF and added to the first solution. The mixture was allowed to stir for 5 min. Precipitated AgCl was removed by filtration, and the solution was left in the drybox overnight with the cap slightly unscrewed. Crystals formed overnight and were washed with C$_6$H$_6$ and dried under vacuum. The obtained crystals were dissolved in CD$_2$Cl$_2$, and the ratio between the syn and anti deuterated complexes was determined by $^1$H-NMR spectroscopy (Figure 31).

9.8.2. Stereochemistry of nucleophilic attack.

Cinnamyliridium complex 2c monodeuterated at anti allylic hydrogen (40 mg 0.038 mmol) was dissolved in 0.5 ml CH$_2$Cl$_2$. Aniline (7 µl, 0.076 mmol) and triethylamine (11 µl 0.076 mmol) was added to the solution. The reaction mixture was allowed to stir for 15 min. Triphenylphosphine (20 mg, 0.076 mmol) was added to the solution to free the olefin. The product was purified by preparatory TLC plate chromatography over silicagel with 9:1 Hexane : Ethylacetate eluent. The ratio between the cis and trans deuterated product was determined through $^1$H-NMR of the CDCl$_3$ solution of the product. Ee was determined by chiral HLPC. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99/1; flow rate= 1 mL/min; detection wave length = 254 nm; TR = 29 (R), 31 (S) min.
Figure 31. NMR spectra of fully proteated 2c and 2c obtained after reaction with 4a-D.
9.8.3. Catalytic reactions to determine the stereochemical route.

Reactions of 4b-D-(R) with aniline catalyzed by 1a-(R,R,R), 1a-(S,S,S) or 1b-(S,S,S):

In a small, vial linear allylic carbonate 4b-D-(R) (39 mg, 0.2 mmol) was combined with the catalyst (either one of 1a-(R,R,R) 7 mg, 0.08 mmol; 1a-(S,S,S) 7mg, 0.08 mmol or 1b-(S,S,S) 7.5 mg, 0.08 mmol) in 1ml THF. Aniline (22 µl, 0.24 mmol) was added to each of the vials. The reaction mixture was allowed to stir for 1h. Solvents were removed under reduced pressure. Yields and branched to linear ratios were determined by $^1$H-NMR with mesitylene standard. The crude reaction product was purified by flash column chromatography with 9:1 hexane:ethylacetate eluent phase. Ees were determined by chiral HPLC. HPLC conditions: Daicel CHIRALCEL OJ-H (0.46 cm x 25 cm); hexane/2-propanol =99/1; flow rate= 1 mL/min; detection wave length = 254 nm; TR = 29 (R), 31 (S) min.
10. References

The bond angles in the structures of allyliridium complexes 2a-e involving C47 and C45 also change with substitution at the allyl terminus. The bond angle between cent1-Ir-C47 (centroid of the alkene unit cis to the allyl-Ir-branched allylic terminus) is 101-103° for 2a, 2b and 3a and 105-106° for 2c-e. The C47-Ir-C45 angle which corresponds to the bite angle of the allyl unit is ~66° for 2a,b and 3a and 62-63° for 2c-e. The angle between the Cent2 (centroid of the alkene unit in the axial position of the complex) and C45 (the unsubstituted terminus of the allyl unit) increases with increasing substitution on the allyl: the Cent2-Ir-C45 bond angle is 89-91° for 2a,b and 3a and 93-94° for 2c-e. As a consequence, the angle between C21 (cyclometallated carbon) and C45 decreases in the series: C21-Ir-C45 bond angle is ~103° for 2a,b, 105° for 3a and ~100° for 2c-e. The opposite can be observed for the branched allylic terminus, where the bond angle between Cent2 (axial centroid) and C47 (branched allylic terminus) decreases with the size of substitution on the allyl: Cent2-Ir-C47 bond angle is 96-97° for 2a,b, 3a and ~92° for 2c-e. As a consequence, the angle between C21 (cyclometallated carbon) and C47 (branched allylic terminus) increases in the series: C21-Ir-C47 bond angle is 90-91° for 2a,b, 92° for 3a and 95-96° for 2c-e.

These differences between the structures can also be seen in Figure 3. And finally, the angle between the allylic carbons C45-C46-C47 is 121°-122° for 2a,c-e, 3a and 127.5(3) for 2b.


(26) The bond angles in the structures of allyliridium complexes 2a-e involving C47 and C45 also change with substitution at the allyl terminus. The bond angle between cent1-Ir-C47 (centroid of the alkene unit cis to the allyl-Ir-branched allylic terminus) is 101-103° for 2a, 2b and 3a and 105-106° for 2c-e. The C47-Ir-C45 angle which corresponds to the bite angle of the allyl unit is ~66° for 2a,b and 3a and 62-63° for 2c-e. The angle between the Cent2 (centroid of the alkene unit in the axial position of the complex) and C45 (the unsubstituted terminus of the allyl unit) increases with increasing substitution on the allyl: the Cent2-Ir-C45 bond angle is 89-91° for 2a,b and 3a and 93-94° for 2c-e. As a consequence, the angle between C21 (cyclometallated carbon) and C45 decreases in the series: C21-Ir-C45 bond angle is ~103° for 2a,b, 105° for 3a and ~100° for 2c-e. The opposite can be observed for the branched allylic terminus, where the bond angle between Cent2 (axial centroid) and C47 (branched allylic terminus) decreases with the size of substitution on the allyl: Cent2-Ir-C47 bond angle is 96-97° for 2a,b, 3a and ~92° for 2c-e. As a consequence, the angle between C21 (cyclometallated carbon) and C47 (branched allylic terminus) increases in the series: C21-Ir-C47 bond angle is 90-91° for 2a,b, 92° for 3a and 95-96° for 2c-e. These differences between the structures can also be seen in Figure 3. And finally, the angle between the allylic carbons C45-C46-C47 is 121°-122° for 2a,c-e, 3a and 127.5(3) for 2b.


(29) The initial concentration of amine in a typical iridium-catalyzed allylic substitution is 2 to 2.4 M.


(31) Look at the reference 29


(34) As a side note, the yields of these reactions depended on the strength of the nucleophile. The reaction of aniline with 6 gave 26% yield of product 7a, whereas the reaction of
lithium phenoxide gave the substitution product 7c in 53% yield, and that of sodium dimethylmalonate gave the analogous product 7b in 90% yield.


(36) This trifluoroacetate was prepared from the known labeled alcohol


(47) Ogasawara, M.; Takizawa, K.-i.; Hayashi, T. Organometallics 2002, 21, 4853.


Chapter 4: Origins of Regioselectivity in Iridium Catalyzed Allylic Substitution

1. Introduction

Allylic substitutions catalyzed by iridium phosphoramidite complexes have been studied extensively during the last few years. Complexes of Iridium containing cyclometalated phosphoramidite ligands catalyze allylic substitution reaction with high selectivity for the formation of branched allylic substitution products.\textsuperscript{1-2} Mechanistic studies on reaction catalyzed by these iridium complexes have revealed the resting state of the catalyst, the origins of enantioselection, and activation of the catalyst by cyclometalation of the chiral phosphoramidite ligand.\textsuperscript{3-6} However, mechanistic studies of reactions catalyzed by iridium complexes of triphenylphosphite, the first system shown to give branched products from linear allylic carbonates, are limited. A cyclometalated species was proposed to be the active catalyst, but this species was never observed directly and characterized.\textsuperscript{7} Most important, the origin of the high selectivity for the formation of the branched product was not investigated for either system.

Palladium catalyzed allylic substitution reactions typically give products from allylic substitution in which the nucleophile adds to the least hindered terminus.\textsuperscript{8-10} Thus, palladium catalyzed allylic substitution with mono-substituted allylic electrophiles gives linear allylic substitution products. However, a study done by Yudin and co-workers on the origin of regioselectivity of palladium catalyzed allylic substitution showed that the branched substitution product was kinetically favored for reactions of amines.\textsuperscript{11} The initially formed branched product undergoes isomerization to the thermodynamically more stable linear product during the course of the reaction. The isomerization was thought to proceed by protonation of the amine, followed by oxidative addition of the resulting ammonium salt to palladium. A process that is selective for the formation of the branched substitution product was developed by conducting reactions with a strong, non-nucleophilic base.\textsuperscript{12}

Here we describe the preparation of Ir(I) and Ir(III) complexes containing cyclometalated triphenylphosphite ligands. The kinetic competence of the corresponding allyliridium complexes to be intermediates in allylic substitution reactions catalyzed by iridium-triphenylphosphite complexes was assessed by subjecting them to stoichiometric reactions with stabilized carbon and heteroatom nucleophiles. The isolated Ir(I) and Ir(III) complexes serve as a tool to reveal the origins of regioselectivity of iridium catalyzed allylic substitution reactions. These studies show
that the major factor favoring the formation of the branched product is not the presence of the phosphorus ligand trans to the substituted allylic terminus. Instead, the branched selectivity is more likely to result from the more favorable binding affinities of terminal olefins over branched olefins to the iridium center and the irreversibility of nucleophilic attack.

2. Preparation and characterization of iridium complexes

To reveal the differences in allylic substitution catalyzed by iridium and palladium complexes, we prepared iridium complexes of the achiral triphenylphosphite ligand. As will be seen from the structures of these complexes, these two types of complexes allowed us to assess the importance of the donor group trans to the two ends of the allyl unit and the relative metal-carbon bond lengths in the ground-state structure.

2.1 Preparation of Ir(III) and Ir(I) complexes containing cyclometalated triphenylphosphite ligand

Allyliridium complexes containing a cyclometalated triphenylphosphite ligand formed from the reaction of [Ir(COD)Cl]$_2$ ((1,5-Cyclooctadiene)(chloro)iridium(I) dimer), triphenylphosphite, AgBF$_4$ and an allylic carbonate (Scheme 30). This procedure is similar to that developed by Helmchen and co-workers for the preparation of allyliridium complexes containing cyclometalated phosphoramidite ligands. As adapted for the synthesis of triphenylphosphite complexes, [Ir(COD)Cl]$_2$ was combined with P(OPh)$_3$ in THF to form P(OPh)$_3$Ir(COD)Cl. A solution of AgBF$_4$ in THF was added to the solution of P(OPh)$_3$Ir(COD)Cl, followed by an allylic carbonate. Allyliridium complexes 3a and 3b were formed in 80% and 85% isolated yields, respectively, in one hour. Carbon dioxide, ethanol or methanol and AgCl were the byproducts of this reaction.

Scheme 30. Preparation of allyliridium complexes 3a and 3b

Preparation of Ir(I) complexes containing a cyclometalated triphenylphosphite ligand proved to be a more challenging than the preparation of allyliridium(III) complexes containing
the same cyclometallated ligand. Initially we attempted to prepare Ir(I) complexes by base-assisted cyclometalation of coordinated triphenylphosphite, followed by trapping of the formed cyclometalated complex with an alkene ligand. This procedure was developed by our own group to prepare Ir(I) complexes containing cyclometalated phosphoramidite ligands, and is summarized in Scheme 31a. However, this procedure did not form cyclometalated Ir(I) complexes. The $^{31}\text{P}$-NMR spectrum of the major product of the reaction consisted of three doublets of doublets, and the $^1\text{H}$-NMR spectrum contained a doublet of triplets at δ -8.9 ppm. We proposed that the hydrido complex 4 in Scheme 31a containing three phosphite ligands is the product of this reaction. The same complex forms quantitatively in the reaction of [Ir(COD)Cl] with 6 equiv of triphenylphosphite in the presence of an amine base (Scheme 31b).

![Scheme 31. Attempts to prepare cyclometalated Ir(I) complex through base assisted cyclometalation.](image)

**Scheme 31.** Attempts to prepare cyclometalated Ir(I) complex through base assisted cyclometalation.

![Scheme 32. Preparation of the ethylene-ligated cyclometalated Ir(I) complex through nucleophilic attack followed by a ligand exchange.](image)

**Scheme 32.** Preparation of the ethylene-ligated cyclometalated Ir(I) complex through nucleophilic attack followed by a ligand exchange.

Instead, we prepared the Ir(I) complex containing a cyclometalated triphenylphosphite 5 by nucleophilic attack on allyliridium complexes containing cyclometalated triphenylphosphite 3a or 3b. Complex 3b was chosen as the most suitable allyliridium complex for this procedure because the addition of propylamine would form of a volatile allylic substitution product.
According to this procedure, crotyliridium complex 3b was allowed to react with an excess of propylamine. After nucleophilic attack the reaction vessel was exposed to 1 atm of ethylene in a Schlenck vessel, for several hours. Ethylene-ligated complex 5 was isolated in 85% yield from this procedure (Scheme 32).

2.2 Characterization of the prepared Ir(III), Ir(I) complexes.

Cinnamyliridium complex 3a and crotyliridium complex 3b both form as a mixture of 2 isomers in solution, as determined by 31P-NMR spectroscopy. The two isomers of cinnamyliridium complex 3a resonated in the 31P-NMR spectrum at δ 97.0 ppm and 95.7 ppm in CH2Cl2 and formed in a 70:30 ratio respectively. The two isomers of crotyliridium complex 3b formed in a 43:57 ratio and resonated in the 31P-NMR spectrum at δ 99.4 ppm and 97.1 ppm in CH2Cl2 respectively. Both complexes are sparingly soluble in THF and were crystallized by slow diffusion of THF into the solution of 3a or 3b in CH2Cl2 at -35°C. Crystals of complex 3a suitable for solid state structural analysis were obtained by this slow diffusion procedure. Both cinnamyl and crotyl complexes 3a and 3b crystallize predominantly in the form of the major isomer. However, dissolution of the crystals in CH2Cl2 at room temperature led to the rapid establishment of the original thermodynamic ratio. The isomerization was sufficiently slow at -78°C to obtain NMR spectra of the single isomers. Thus solutions of complexes 3a and 3b prepared at -78°C containing predominantly one isomer were characterized by 1H, 31P, and 2D-gCOSY spectroscopies at low temperature. The 31P-NMR shift of the isolated isomer of the cinnamyliridium complex 3a appears at δ 97.3 ppm at -60°C. The allylic protons of the isolated isomer of 3a resonate at δ 4.90, 4.63, 4.34 and 3.98 ppm in the 1H-NMR and 2D-gCOSY spectra. A solution of complex 3b containing a single isomer was also characterized by 31P-NMR, 1H-NMR and 2D-gCOSY-NMR spectroscopies. The 31P-NMR spectrum of 3b containing a single isomer consisted of a single peak at δ 99.7 ppm at -30°C. In addition, allyliridium complexes 3a and 3b were characterized by high resolution ESI-MS. M⁺ values of 3a and 3b obtained by ESI-MS matched well with the calculated values. Crystals of complex 3a suitable for solid state structural analysis were obtained by slow diffusion of THF into the solution of 3a in dichloromethane at -35°C. The solid-state structure of 3a is shown in Figure 32.
Complex 3a crystallizes as the isomer in Figure 32. The complex adopts a structure that is close to a six-coordinate octahedron with the allyl group, phosphorus, and an olefin coordinated in the equatorial plane. The covalently bound carbon atom and one of the pi-bound olefins occupy the axial positions of the structure. One of the features of the structure that provides a means to analyze the origins of regioselectivity is the similarity of the Ir-C_1 and Ir-C_3 bond lengths. These bond lengths are both 2.28 Å. The similarities of these bond lengths could result from the binding of the unsubstituted allylic terminus trans to the phosphorus and binding of the substituted allylic terminus trans to the equatorial olefin. The influence of the trans ligand on the Ir-C distance, then, would be similar to the influence of the phenyl substituent on the iridium-carbon length.

The ethylene-ligated iridium (I) complex 5 forms by the displacement of the olefinic unit of the allylic substitution product generated by nucleophilic attack on the allyliridium complex 3b. This complex was characterized by ^1H, ^31P and ^13C-NMR spectroscopies. The ^31P-NMR spectrum of ethylene-ligated Ir(I) complex 5 consists of a singlet at δ 128.4 ppm in THF.

3. Stoichiometric reactions of allyliridium complexes with nucleophiles and reactions catalyzed by cyclometalated allyliridium triphenylphosphite complexes

Cyclometalated allyliridium triphenylphosphite complexes have been proposed as intermediates in allylic substitution reactions catalyzed by iridium triphenylphosphite complexes. However, cyclometalated iridium triphenylphosphite complexes were never isolated and explicitly shown to be intermediates in iridium catalyzed allylic substitution reactions. We
performed a series of catalytic and stoichiometric reactions to assess the competence of allyliridium complexes 3a and 3b to be intermediates in iridium catalyzed allylic substitution reactions.

3.1 Stoichiometric reactions of allyliridium complexes 3a and 3b with nucleophiles

Allyliridium complexes 3a and 3b were allowed to react with stabilized enolate, alkoxide and amine nucleophiles to assess the competence of 3a and 3b to be intermediates in iridium catalyzed allylic substitution reactions catalyzed by complexes of iridium containing triphenylphosphite ligands. Suspensions of allyliridium complexes 3a or 3b in d8-THF were allowed to react with the nucleophiles. A slight excess of triphenylphosphine was added to the reaction solutions after full conversion to displace the coordinated organic product from the iridium. The yield of the reaction was determined by 1H-NMR spectroscopy by integrating the peak corresponding to the product vs the internal standard (Si₂Me₆ or mesitylene). The outcome of these stoichiometric reactions is summarized in Table 8.

The yields of the reactions of cinnamyliridium complex 3b depended on the strength of the nucleophile. Anionic nucleophiles (Table 8, entries 1, 2, 5) or alkylamine nucleophiles (Table 8, entry 3) formed the products of nucleophilic attack in quantitative yields. However, the reaction of aniline with triethylamine as proton acceptor (Table 8, entry 3) gave a significantly lower yield of the organic product (60%). In this reaction a small amount of double allylation product of aniline was also formed. Very high regioselectivities for the formation of the branched products were observed for all of the reactions (9:10 > 94:6). Both secondary and tertiary stabilized carbon nucleophiles formed the branched products with high yield and selectivity (Table 8, entries 1 and 5).

The yields of organic products from the reactions of crotyliridium complex 3b with potassium phenoxide and octylamine were slightly lower than the yields of the reactions of cinnamyliridium complex 3a with the same nucleophiles (Table 8, entries 8 and 9). However, the selectivities for the formation of branched organic products were universally high (9:10 = 99:1). The yields of the reactions of crotyliridium complex 3b with stabilized carbon nucleophiles were similar to the yields of the reactions of cinnamyliridium complex 3a with the same nucleophiles (Table 8, entries 6 and 7).
Table 8. Reactions of allyliridium complexes with nucleophiles

![Chemical structure]

<table>
<thead>
<tr>
<th>Allyliridium complex</th>
<th>Nucleophile</th>
<th>6:7</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 3a</td>
<td>NaCH(COOME)$_2$</td>
<td>99:1</td>
<td>100</td>
</tr>
<tr>
<td>2 3a</td>
<td>KOPh</td>
<td>94:6</td>
<td>100</td>
</tr>
<tr>
<td>3 3a</td>
<td>PhNH$_2$/TEA</td>
<td>97:3</td>
<td>60</td>
</tr>
<tr>
<td>4 3a</td>
<td>OctylNH$_2$</td>
<td>97:3</td>
<td>100</td>
</tr>
<tr>
<td>5 3a</td>
<td>NaCMe(COOME)$_2$</td>
<td>97:3</td>
<td>96</td>
</tr>
<tr>
<td>6 3b</td>
<td>NaCMe(COOME)$_2$</td>
<td>99:1</td>
<td>96</td>
</tr>
<tr>
<td>7 3b</td>
<td>NaCH(COOME)$_2$</td>
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<td>80</td>
</tr>
<tr>
<td>8 3b</td>
<td>KOPh</td>
<td>99:1</td>
<td>70</td>
</tr>
<tr>
<td>9 3b</td>
<td>OctylNH$_2$</td>
<td>99:1</td>
<td>70</td>
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</tbody>
</table>

These stoichiometric reactions showed that the isolated allyliridium complexes containing a cyclometalated triphenylphosphite ligand 3a and 3b are chemically and kinetically competent to be intermediates in allylic substitution reactions catalyzed by iridium triphenylphosphite complexes. In the solid-state structure, the substituted allylic terminus is located trans to an olefin, and the unsubstituted terminus is located trans to a phosphorus ligand. The iridium-carbon distance for both allylic termini is the same 2.28 Å. The observed high selectivity of nucleophilic attack for the formation of branched allylic substitution product shows that neither the iridium-carbon bond length nor the trans phosphorus are responsible for the high selectivity of nucleophilic attack at the substituted carbon.

4. Kinetic studies on oxidative addition of branched and linear allylic acetates to ethylene-ligated iridium (I) complex 5 containing a cyclometalated triphenylphosphite ligand.

The selectivity of nucleophilic attack on allyliridium complexes is generally high for the formation of the branched substitution product regardless of the type of substituent on the allylic
unit. Thus, the kinetics of nucleophilic attack at the substituted allylic terminus (to form the branched product) and at the unsubstituted allylic terminus (to form the linear product) of allyliridium complexes cannot be measured directly. However, insight into the kinetics of nucleophilic attack can be gained by studying the kinetics of oxidative addition of branched and linear allylic electrophiles to the cyclometalated Ir(I) triphenylphosphite complex 5 because oxidative addition is the reverse of reductive elimination by nucleophilic attack in allylic substitution.

![Graph](image)

**Figure 33.** Change of concentration over time graph for the reaction of branched allylic electrophile 9 with ethylene-ligated complex 5.

We were unable to measure directly the rate constant for oxidative addition of allylic electrophiles 8 and 9 to cyclometalated Ir(I) triphenylphosphite complex 5 under pseudo-first order conditions in the concentration of 5 due to the reversibility of the oxidative addition and the establishment of equilibrium between the Ir(III) allyl and Ir(I) ethylene complexes in the presence of the added ethylene needed to maintain a constant concentration of this reaction component. Excess amounts of both allylic electrophile (25 equiv) and ethylene (20 equiv) are needed to render the reaction pseudo-first order in the concentration of ethylene-ligated Ir(I) complex 5. Thus, we conducted kinetic measurements with excess of both ethylene and allylic electrophile 8 or 9 and measured the first order rate constant of approach to equilibrium.
The oxidative addition forms complex 3c-TFA as a mixture of two isomers by $^{31}$P-NMR spectroscopy. These isomers form in 65:35 ratio and display $^{31}$P-NMR chemical shifts at $\delta$ 100.2 ppm and 98.6 ppm respectively. The reaction was monitored by $^{31}$P-NMR spectroscopy and a plot of concentration vs time for the reaction of branched allylic electrophile 9 with ethylene-ligated complex 5 is provided in Figure 33. The rate constants for oxidative addition were derived from the rate constant of approach to equilibrium and equilibrium constant of the reaction. The rate constants for oxidative addition of linear and branched allylic electrophiles are provided in Table 9, and details of calculation of rate constants are provided in the experimental section.

**Table 9.** Rate constants for oxidative addition of linear and branched allylic electrophiles 8 and 9 ethylene ligated Ir(I) complex 5

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>T (°C)</th>
<th>$k_1$ or $k_2$ (s$^{-1}$)</th>
</tr>
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<tbody>
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<td>1</td>
<td>12</td>
<td>-10</td>
<td>8.2·10^{-4}</td>
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<tr>
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<td>7.5·10^{-5}</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>20</td>
<td>2.7·10^{-4}</td>
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</tbody>
</table>

The rate constants of oxidative addition of branched electrophile 9 to ethylene-ligated complex 5 $k_1$ were measured at -10, -15, -20 and -25°C. The rate constant of oxidative addition of linear electrophile 8, $k_2$ was measured at 20°C. To make a direct comparison between the rate constants $k_1$ and $k_2$ for addition of the linear and branched allylic esters, respectively, at the same temperature we extrapolated the rate constants for oxidative addition of branched electrophile 9 to ethylene-ligated complex 5 $k_2$ at the lower temperatures to 20°C. Activation parameters were
derived from an Eyring plot for the rate constants $k_2$ at -10 to -25 °C (Figure 34). The enthalpy of activation for the reaction of branched electrophile 9 with ethylene ligated complex 5 was 20.2 kcal/mol and entropy of activation for the same reaction was 4.4 eu. The rate constant for oxidative addition of 9 to 5 at 20°C was 0.09 s$^{-1}$ based on the measured activation parameters. Thus, rate constant of oxidative addition of branched electrophile 9 to ethylene-ligated complex 5 is more than 300 times faster than the rate constant of oxidative addition of linear electrophile 8 to 5.

![Eyring plot for oxidative addition of branched electrophile 12 to ethylene-ligated complex 5.](image)

**Figure 34.** Eyring plot for the oxidative addition of the branched electrophile 12 to ethylene-ligated complex 5.

These kinetic studies showed that the rate constant for oxidative addition of the branched electrophile to ethylene-ligated complex 5 is more than 300 times faster than the rate constant of oxidative addition of a linear electrophile to 5. This difference corresponds to a difference in the free energy of activation of at least 3.3 kcal. This selectivity is similar to the observed selectivity for nucleophilic attack to form the branched substitution product over attack to form the linear product.

The difference of 3.3 kcal/mol between the activation energies for oxidative addition of linear and branched electrophiles likely arises from the combination of two factors. The first factor is the difference between the ground state energies of linear allylic trifluoroacetate 8 and branched allylic trifluoroacetate 9. When an excess of linear allylic trifluoroacetate 8 is allowed
to equilibrate in the presence of ethylene ligated complex 5 and excess ethylene, a 3:1 mixture of linear 8 and branched 9 forms. This equilibrium ratio shows that ground state of linear 8 is 0.65 kcal/mol more stable than the ground state of branched 9. The second, more important factor influencing the difference between the two activation energies is the difference between the binding energies of the branched and linear alkenes to the cyclometalated iridium center. The branched alkene is a monosubstituted alkene and will likely have a much greater bonding affinity than the linear disubstituted alkene. Thus, the binding affinity of the branched 9 to cyclometalated iridium is more than 2.6 kcal/mol (difference between free energies of activation and ground state energies of linear 8 and branched 9) favored over binding of linear 8 to the cyclometalated iridium. This difference in binding affinity of branched and linear olefins is probably the most important factor controlling the selectivity of nucleophilic attack in iridium catalyzed allylic substitution. The contributions from the ground state energy difference and from binding affinity of the two olefins are summarized in Figure 35.

**Figure 35.** Energy diagram for the reaction of linear and branched allylic electrophiles 8 and 9 with ethylene-ligated complex 5.

In palladium catalyzed allylic substitution reactions, the products of substitution at the least hindered allylic terminus are usually formed. The different selectivity in palladium catalyzed allylic substitution likely stems from similar binding affinities of branched and linear olefins for to palladium. Also, nucleophilic attack is usually reversible in palladium catalyzed allylic substitution, for amine and alkoxide nucleophiles, which allows for the formation of thermodynamically more stable linear products, despite favorable kinetics for the formation of branched products.
5. Conclusions

Allyliridium complexes 3a and 3b with cyclometalated triphenylphosphite were prepared. Through a series of stoichiometric reactions these allyliridium complexes were found to be competent to be intermediates in allylic substitution reactions catalyzed by a combination of iridium and triphenylphosphite. The selectivity of nucleophilic attack along with solid state structural data showed that iridium-carbon bond lengths or presence of a trans-phosphorus do not influence the position of nucleophilic attack. Ethylene-ligated Ir(I) complex 5 containing a cyclometalated triphenylphosphite ligand was prepared from allyliridium complexes 3a and 3b. Kinetic measurements on oxidative addition of branched and linear allylic electrophiles to ethylene-ligated complex 5 showed that branched electrophiles have significantly favorable kinetics for oxidative addition over the linear electrophiles. Thus, the major factor influencing this selectivity is proposed to be the greater binding affinity of terminal olefins over internal olefins. Thus, the difference in binding affinity of the organic products to cyclometalated iridium is proposed to be the most important factor controlling the regioselectivity of iridium catalyzed allylic substitution.

6. Future work

The future work will concentrate on computational and experimental studies directed at determining origins of regioselectivity in iridium catalyzed allylic substitution reactions using the prepared complexes. A similar study will be performed on palladium systems which are known to be selective for allylic substitution at the least hindered allylic terminus.

7. Experimental section

7.1 General Procedures.

All reactions were conducted in flame or oven-dried round-bottomed flasks fitted with rubber septa under a positive pressure of argon or nitrogen, or in 1-dram vials sealed with a screw cap fitted with PTFE silicon septum under an atmosphere of Argon, unless otherwise stated. Air and moisture-sensitive reagents were transferred via syringe, or were handled in an argon-filled or nitrogen-filled drybox (Innovative Technologies, Newburyport, Massachusetts) equipped with an oxygen sensor (working oxygen level <5 ppm) and low-temperature refrigeration unit (−35 °C). Organic solutions were concentrated by rotary evaporation at 23–35 °C. Flash-column chromatography was performed as described by Still et. al.\textsuperscript{16} employing silica
gel (40–63 μm particle size) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm). TLC plates were visualized by exposure to ultraviolet light (UV) or submersion in aqueous potassium permanganate solution (KMnO₄), followed by brief heating by a heat gun (175 °C, 3–5 s).

7.2 Instrumentation.

Proton nuclear magnetic resonance spectra (¹H NMR) were recorded at 500 MHz at 22 °C unless otherwise stated. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl₃, δ 7.26; THF, δ 1.73, 3.58; CH₂Cl₂, δ 5.32). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz. Proton-decoupled carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 125 MHz at 22 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃, δ 77.0; THF, δ 25.5, 67.7; CH₂Cl₂, δ 53.5) or to an external standard (CFCl₃ = 0 for ¹⁹F and 85% H₃PO₄ = 0 for 31P). Two-dimensional COSY (Correlation Spectroscopy) and Heteronuclear Multiple Quantum Coherence (HMQC) were recorded at 500 MHz at 22 °C. Gas chromatography was performed using an HP 6890 series gas chromatograph equipped with an HP-5 column (25 m, 0.2 mm I.D., 0.33 μm film). GC/MS analyses were performed on an Agilent 6890N GC equipped with a 5973 MS and an HP-5ms column (30 m x 0.25 mm ID x 0.25 μm film). HPLC analyses were carried out on a Waters chromatography system (1525 binary pump, 717+autosampler, 2487 dual wavelength detector). ESI-MS analyses were performed in University of Illinois Mass Spectrometry Center.

7.3 Materials

Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran, dichloromethane and benzene were deoxygenated and dried by sparging with argon and passing through columns of activated alumina and supported copper according to the method of Pangborn et al.¹⁷ Aniline and octylamine were dried over KOH, distilled under reduced pressure and freeze pump thawed before transferring into the drybox. Sodium dimethylmalonate and Sodium dimethyl methylmalonate were prepared by the reaction of 1 equiv. of the corresponding malonate with 1 equiv NaH in THF or THF-d₈ directly before use.
Lithium phenolate was prepared by reaction of 1 equiv. phenol with 1 equiv. of a 2.5 molar solution of n-butyllithium in hexane at 0°C. Triethylamine was dried over CaSO₄ and distilled before use. All allylic trifluoroacetates (8 and 9) were synthesized by the reaction of the corresponding allylic alcohols with trifluoroacetic anhydride in the presence of pyridine.

7.4 Preparation of iridium complexes

Cinnamyliridium complex 3a: Allyliridium complexes were prepared according to a general scheme described by Helmchen and coworkers. According to this procedure [IrCODCl]₂ (200 mg, 0.298 mmol) was combined with triphenylphosphite (156 µl, 0.596 mmol) in 10 ml THF in a 20 ml vial. AgBF₄ (116 mg, 0.596 mmol) was dissolved in 5 ml THF and added to the solution of [IrCODCl]₂ and triphenylphosphite. Upon addition of AgBF₄ the large amount of AgCl precipitates and the solution turns dark. After this Ethylcinnamyl carbonate (253 µl, 1.192 mmol) was added to the reaction vessel. Solution becomes pale after the addition of allylic carbonate and a large amount of precipitate forms. After stirring for 1 hour in the vial the solution was transferred into a 50 ml round bottom flask and 15 ml of CH₂Cl₂ was added. The solution was allowed to stir for another 5 minutes. Precipitate was removed by syringe filtration through a 25 mm diameter and 0.2 µm pore size filter. The clear mother liquor was added dropwise to 50 ml pentane in a 100 ml round bottom flask while stirring vigorously. The precipitated product was collected over a glass frit and washed twice with 10 ml portions of diethyl ether. Yield: 390 mg, 80%. Crystals suitable for solid state structural analysis were obtained by slow diffusion of THF into the solution of 3a in CH₂Cl₂ at -35°C. ³¹P NMR (202 MHz, CD₂Cl₂) δ 97.04, 95.74 (ratio: 70:30). ¹H NMR of the single isomer isolated after recrystallization (500 MHz, CD₂Cl₂, -60°C) δ 7.25 – 6.96 (m, 14H), 6.86 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 7.9 Hz, 2H), 6.40 – 6.33 (m, 2H), 5.82 (dd, J = 14.8, 8.1 Hz, 1H), 4.99 – 4.80 (m, 2H), 4.63 (t, J = 6.5 Hz, 1H), 4.34 (d, J = 12.3 Hz, 1H), 4.21 (dd, J = 15.5, 8.0 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.98 (t, J = 10.7 Hz, 1H), 3.65 – 3.26 (m, 4H), 2.83 – 2.69 (m, 2H), 2.08 – 1.98 (m, 1H), 1.95 – 1.86 (m, 1H). ESI-MS C₃₅H₃₅IrO₃P: calc. 727.1953, obs: 727.1955.

Crotyliridium complex 3b: Complex 3b was prepared similarly to complex 3a using methyl crotylcarbonate instead of ethylcinnamyl carbonate. ³¹P NMR (202 MHz, CDCl₃) δ 99.36, 97.13 ratio (43:57). ¹H NMR (500 MHz, CD₂Cl₂) δ 7.54 – 7.28 (m, 5H), 7.22 – 6.82 (m, 7H), 6.48 (d, J = 7.1 Hz, 2H), 5.73 (dd, J = 15.3, 8.2 Hz, 1H), 4.89 – 4.84 (m, 1H), 4.51 (t, J = 7.4 Hz, 1H), 4.18
– 4.01 (m, 2H), 3.89 – 3.75 (m, 2H), 3.65 – 3.24 (m, 5H), 2.87 – 2.72 (m, 1H), 2.72 – 2.60 (m, 1H), 2.08 – 1.96 (m, 1H), 1.94 – 1.75 (m, 4H). ESI-MS, C$_{30}$H$_{33}$IrO$_{3}$P: calc. 665.1797, obs: 665.1798.

**Ethylene ligated Ir(I) complex 5:** In a drybox crotyliridium complex 3b (100 mg, 0.133 mmol) was suspended in 10ml THF in a 25 ml schlenk bomb. Propylamine (44 µl, 0.532 mmol) was added to the suspension. Upon addition of propylamine the solution becomes homogenous and bright yellow. The bomb was closed and taken outside of the drybox. The bomb was connected to a schlenck line and pressurized with 1 atmosphere of ethylene. The solution in the bomb under ethylene atmosphere was allowed to stand for 3 hours without stirring. After 3 hours, the bomb was brought into the drybox and volatiles were removed under reduced pressure. The remaining solid was dissolved in 2ml CH$_2$Cl$_2$ and remaining precipitate was removed by syringe filtration through a 25 mm diameter and 0.2 µm pore size filter. The dissolution in CH$_2$Cl$_2$ and filtration was repeated 2 times. 72 mg of product (85%) was isolated after removing CH$_2$Cl$_2$ under reduced pressure. $^{31}$P NMR (202 MHz, THF) 128.4 ppm.

![Figure 36. $^1$H-NMR spectrum of cinnamyliridium, complex 3a.](image-url)
Figure 37. 2D-gCOSY spectrum of allyliridium complex 3a.

7.5 Kinetic measurements.

General procedures for the measurements of the rate constants of approach to equilibrium:

A 0.025 M stock solution was prepared by dissolving 5 (64 mg, 0.1 mmol) in 4 ml THF. In the drybox, 0.5 ml amount of this stock solution was transferred into a screw capped NMR-tube with a PTFE septum. A capillary tube containing 31P-NMR internal standard was also placed into the tube. The NMR-tube was tightly closed and taken out of the drybox. The NMR tube was placed into a dry-ice acetone bath and connected to a vacuum line through a needle. The screw capped NMR-tube was evacuated and filled with 1 atmosphere of ethylene (1 atm, 4 ml, ~20 equiv). 67 mg of linear allylic trifluoroacetate 8 or branched allylic trifluoroacetate 12 dissolved in 0.1 ml THF was added with a syringe to the NMR tube. The NMR tube was shaken to mix the solutions and placed into the NMR probe set to the necessary temperature. Kinetic data was collected by monitoring the disappearance of the $^{31}$P-NMR signal at $\delta$ 128.4 ppm corresponding to 5 and appearance of the two $^{31}$P-NMR shifts corresponding to 3c-TFA.

Calculation of the rate constants for oxidative addition:
The rate constants for oxidative addition were calculated based on the two experimentally determined parameters: 1) rate constant of approach to equilibrium and 2) equilibrium constant of the reaction at the temperature of measurement.

Rate constant of oxidative addition of branched electrophile 9 to ethylene ligated complex 5 at -10°C, $k_2$:

$T_1 = 436 \text{ s}$; Rate constant of approach: $k_a = 1/T_1 = 2.3\cdot10^{-3} \text{ s}^{-1} = k_2 + k_{-2}$; $K = k_{-2}/k_2 = 11/6 = 1.8$

(determined from the graph)

$k_{-2} = 1.8k_2$ and $2.3\cdot10^{-3} \text{ s}^{-1} = 2.8k_2$; $k_2 = 8.2\cdot10^{-4} \text{ s}^{-1}$

Rate constant of oxidative addition of branched electrophile 9 to ethylene ligated complex 5 at -15°C, $k_2$:

$T_1 = 720 \text{ s}$; Rate constant of approach: $k_a = 1/T_1 = 1.4\cdot10^{-3} \text{ s}^{-1} = k_2 + k_{-2}$; $K = k_{-2}/k_2 = 21/7 = 3$

(determined from the graph)

$k_{-2} = 3k_2$ and $1.4\cdot10^{-3} \text{ s}^{-1} = 4k_2$; $k_2 = 3.5\cdot10^{-4} \text{ s}^{-1}$

Rate constant of oxidative addition of branched electrophile 9 to ethylene ligated complex 5 at -20°C, $k_2$:

$T_1 = 2700 \text{ s}$; Rate constant of approach: $k_a = 1/T_1 = 3.7\cdot10^{-4} \text{ s}^{-1} = k_2 + k_{-2}$; $K = k_{-2}/k_2 = 8/4 = 2$

(determined from the graph)

$k_{-2} = 2k_2$ and $3.7\cdot10^{-4} \text{ s}^{-1} = 3k_2$; $k_2 = 1.3\cdot10^{-4} \text{ s}^{-1}$

Rate constant of oxidative addition of branched electrophile 9 to ethylene ligated complex 5 at -25°C, $k_2$:

$T_1 = 2800 \text{ s}$; Rate constant of approach: $k_a = 1/T_1 = 3.6\cdot10^{-4} \text{ s}^{-1} = k_2 + k_{-2}$; $K = k_{-2}/k_2 = 15/4 = 3.8$

(determined from the graph)

$k_{-2} = 3.8k_2$ and $3.7\cdot10^{-4} \text{ s}^{-1} = 4.8k_2$; $k_2 = 7.5\cdot10^{-5} \text{ s}^{-1}$

Rate constant of oxidative addition of branched electrophile 8 to ethylene ligated complex 5 at 20°C, $k_1$:

$T_1 = 2400 \text{ s}$; Rate constant of approach: $k_a = 1/T_1 = 4.2\cdot10^{-4} \text{ s}^{-1} = k_1 + k_{-1}$; $K = k_{-1}/k_1 = 11/7 = 1.6$

(determined from the graph)

$k_{-1} = 1.6k_1$ and $3.7\cdot10^{-4} \text{ s}^{-1} = 2.6k_1$; $k_1 = 2.7\cdot10^{-4} \text{ s}^{-1}$
Figure 38. Graph for the approach to the equilibrium of the reaction between 5 and branched electrophile 9 at -10°C.

Figure 39. Graph with exponential decay of ethylene-ligated complex 5, for the reaction of 5 with branched electrophile 9 at -10°C.
**Figure 40.** Graph for the approach to the equilibrium of the reaction between 5 and branched electrophile 9 at -15°C.

**Figure 41.** Graph with exponential decay of ethylene-ligated complex 5, for the reaction of 5 with branched electrophile 9 at -15°C.
Figure 42. Graph for the approach to the equilibrium of the reaction between 5 and branched electrophile 9 at -20°C.

Figure 43. Graph with exponential decay of ethylene-ligated complex 5, for the reaction of 5 with branched electrophile 9 at -20°C.
Figure 44. Graph for the approach to the equilibrium of the reaction between 5 and branched electrophile 9 at -25°C.

Figure 45. Graph with exponential decay of ethylene-ligated complex 5, for the reaction of 5 with branched electrophile 9 at -25°C
Figure 46. Graph for the approach to the equilibrium of the reaction between 5 and linear electrophile 8 at 20°C.

Figure 47. Graph with exponential decay of ethylene-ligated complex 5, for the reaction of 5 with linear electrophile 8 at 20°C.
## Calculation of activation parameters

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Slope of the Eyring plot $m = \Delta H^\prime/R$; $\Delta H^\prime = 10180 \cdot 8.314 = 84.6 \text{ kJ/mol} = 20.2 \text{ kcal/mol}$;

Intercept of the Eyring plot $26 = \ln(k_B/h) + \Delta S^\prime/R = \ln(1.38 \cdot 10^{-23}/6.63 \cdot 10^{-34}) + \Delta S^\prime/R$;

$\Delta S^\prime = 8.314 \cdot (26 - 23.8) = 8.314 \cdot 2.2 = 18.3 \text{ J/mol} = 4.4 \text{ eu}$

Rate of oxidative addition of the branched electrophile at 20°C:

$$k = (k_B \cdot T/h) \cdot e^{(-\Delta H^\prime/RT)} \cdot e^{(\Delta S^\prime/R)} = 1.2 \cdot 10^{-13} \cdot 8.3 \cdot 10^{-16} = 0.09 \text{ s}^{-1}$$

### References


