N–Phenyl Pyrroloimidazolone Derivatives for Stereoselective Birch Reduction-Alkylation and Chiral Imidazolylidene-Iridium Complexation

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Abstract

This thesis describes the synthesis and use of an *N*– based proline–derived directing group towards the Birch reduction, diastereoselective alkylation, and the synthesis of NHC–iridium complexes that are precursors for the study of intramolecular aryl C–H activation. A pair of *ortho*–benzoate esters containing epimeric pyrroloimidazolone chiral auxiliaries underwent sequential Birch reduction and diastereoselective alkylation to provide products ranging from a 50:50 to 95:5 dr for the *anti*– epimer, and 88:12 to >95:5 diastereomeric ratio (dr) for the *syn*– epimer. Single crystal X–ray analysis of key *anti*–epimer–derived products, along with the comparison of the optical rotation measurements of enantiomers that were prepared from the *syn*–or *anti*– starting materials to its known enantiomer confirmed the stereoselectivity of the products. This work includes related Schultz stereoselective Birch reduction alkylation of anisole with a chiral benzamide except that the pyrroloimidazolone replaces the achiral methoxy group and serves as the stereodetermining element. In addition, the synthesis and evaluation of the *N*–phenyl iridium complex derived from the annulated aminal with *syn*–stereochemistry in the backbone was achieved. Exposure of the neutral Ir–complexes to anionic nucleophiles such as MeLi resulted in an increase of electron density at the Ir atom that initiated C–H bond activation. Lastly, a *N*–heterocyclic carbene ligand derived from the *N*–benzyl analogue of the auxiliary was also investigated. Attempts to design a monodentate ligand as well as a bidentate ligand bearing an alcohol side chain were both shown to be unsuccessful at this time.

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Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
Cp	cyclopentadienyl
DBMN	dibenzyl malononitrile
DBDMH	dibromo dimethyl hydantoin
DEAD	diethyl azodicarboxylate
D*o*M	directed *ortho* metalation
dr	diastereomeric ratio
DIBAL–H	diisobutyl aluminum hydride
E^+	electrophile
Et	ethyl
er	enantiomeric ratio
h	hours
HMDS	hexamethyldisilazane
i–	iso
IR	infrared
LDA	lithium diisopropyl amine
Me	methyl
Min	minutes
n–	normal
NBS	*N*–bromosuccinimide

NHC	*N*–heterocyclic carbene
NMR	nuclear magnetic resonance
o	ortho
p	para
PDC	pyridinium dichromate
Ph	phenyl
Pr	propyl
rt	room temperature
RAMP	(R)-1-amino-2-methoxymethylpyrrolidine
SAMP	(S)-1-Amino-2-methoxymethylpyrrolidine
t	tertiary
TBAF	tetrabutyl ammonium fluoride
TES	triethylsilyl
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	*N*, *N*, *N*, *N*–tetramethyl ethylene diamine
Trisyl	2,4,6–triisopropylbenzenesulfonyl

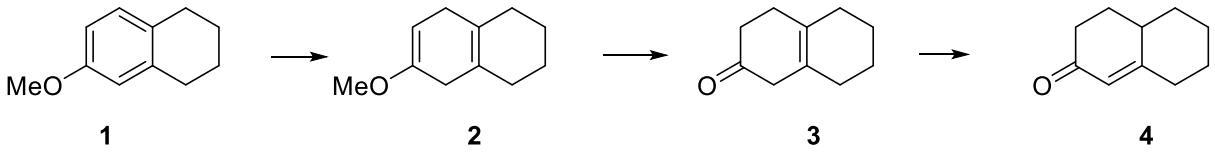
1. Introduction

The synthesis of enantiomerically enriched molecules is of fundamental and practical importance. Since the middle of the 19th century enantiomerically enriched samples have been achieved either by the resolution of a racemic mixture or via asymmetric synthesis.[1] Most of the available chiral auxiliaries employed by synthetic chemists are derived from compounds of natural origin such as proteins, amino acids, and carbohydrates.[2a,b,c] However, because of the difficulty in obtaining optically pure enantiomers on a large scale, synthesizing unnatural chiral molecules is challenging. The focus of the Metallinos group's research involves the design and synthesis of a new type of chiral auxiliary derived from the amino acid *L*–proline. This auxiliary serves the dual purposes of (i) enabling selective introduction of chirality in a position adjacent to nitrogen, and (ii) being easily converted into unique chiral NHC ligands afterwards. As a result, a potentially large number of unusual and previously unknown ligands for asymmetric catalysis can be developed. Overall, the methodology to prepare planar chiral 1, 2–disubstituted amino ferrocenes has been expanded to develop unusual *N*–heterocyclic carbene (NHC) ligands,[3] selective substitution reactions of planar chiral *N*–substituted η^6– arene chromium tricarbonyl complexes,[4] axial chiral allenes, and sp^3 benzyl and propargyl centers.[5]

The first part of this thesis will discuss the application of chiral auxiliaries to the Birch reduction followed by sequential diastereoselective alkylation of the sodium enolate of an *ortho*–ester *N*–phenyl bearing a chiral auxiliary to afford cyclohexadienes possessing a quaternary center. Next the application of the methodology towards the synthesis of nonplanar chiral *N*–substituted phenyl imidazolylidene and imidazolinylidene ligands with the desire to synthesize enantiopure bidentate metal complexes will be mentioned.

1.1 Birch Reduction

In 1921, Kraus first reported sodium metal dissolved in liquid ammonia, and suggested that there was an equilibrium that existed between the metal cations, and anions and neutral substances.[6] Later, the reducing capabilities of alkali metals dissolved in ammonia were observed by Wooster and Godfrey who performed the reduction of toluene with sodium (or potassium) and water in liquid ammonia.[7] Those discoveries ultimately led to the development of the Birch reduction reaction, which is now widely applied in organic synthesis. The Birch reduction was first initiated when a series of reactions to make 19–norsteroid hormones was envisioned.[8] The model reactions were carried out in 1943 using the A–B ring–structure of estrone methyl ether (**1**) converted via the dihydro–enol–ether (**2**) into the 19–nor A–B ring–structure (**4**) containing a cyclohexenone characteristic of most of the sex hormones (Scheme **1**).[8] The success of the first totally synthetic androgenic anabolic sex hormone led on to the synthesis of the 19–norprogestagens, including the first oral contraceptives.

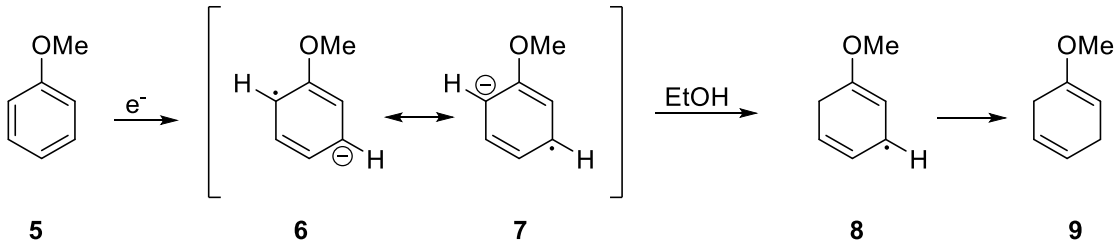


Scheme 1: Preparation of 19–norsteroid hormones.[8]

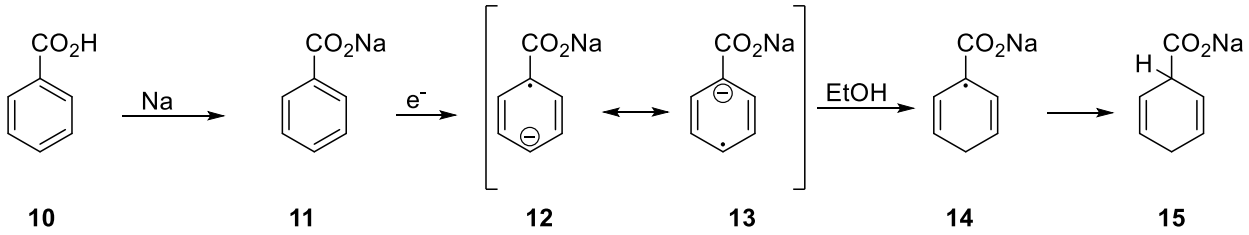
The general procedure for the Birch reduction involves dissolving alkali metals (usually Li, Na, K) in liquid ammonia, with an alcohol (ethanol or *t*–butyl alcohol are common) as a proton source; an inert co–solvent (*e.g.*, diethyl ether, tetrahydrofuran) is usually required.[8] This reaction can employ different alkali metals with different reduction potentials (Li = –2.99 V, K = –2.73 V, Na = –2.59 V, Ca = –2.39 V), which affect the outcome of the reduction, as a source of electrons.[3]

1.1.1 Regioselectivity of the Birch reduction

The functional groups attached to mono–substituted aromatic compounds influence the regioselectivity of the Birch reduction. The resulting arrangement of the diene is dependent on whether the substituent is electron–withdrawing or electron–donating. An electron–donating group (*e.g.*, Alkyl, OMe, NR_2) will appear on an sp^2 hybridised carbon (Scheme **2**), whereas an electron–withdrawing group (*e.g.* C=O) will appear on an sp^3 hybridised carbon in the product (Scheme **3**).[8] Electron–withdrawing groups stabilise the electron density at the *ipso* and *para* positions through conjugation and therefore a negative charge will be found at one of these positions.



Scheme 2: The effect of an electron–donating group on the regioselectivity of the Birch reduction.[8]

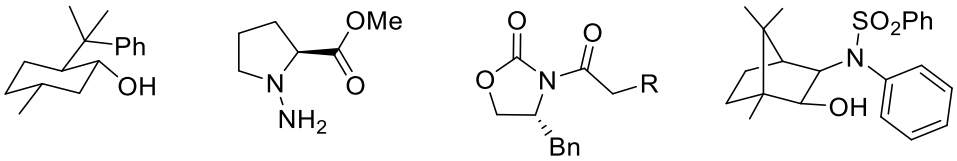


Scheme 3: The effect of an electron–withdrawing group on the regioselectivity of the double bonds.[4]

1.2 Chiral auxiliaries

A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis in order to control the stereochemical outcome of the synthesis.[9a] Chiral auxiliaries have been used in the synthesis of enantiomerically pure compounds and are applicable to a variety of

reactions. There are numerous chiral auxiliaries that have been developed over the past years.[9b,c,d] Some auxiliaries are derived from inexpensive, chiral natural sources and most of the diastereoselective reactions reported proceed with high levels of diastereoselectivity and have profound applications in enolate chemistry (Figure **1).**[9a]



Corey (1975) **Ender (1976)** **Evans (1981)** **Helmchen (1984)**

16 **17** **18** **19**

Figure 1: Selected chiral auxiliaries which have been successfully applied in asymmetric synthesis.[9a]

In enolate chemistry, the ideal chiral auxiliary should (i) be easy to introduce, (ii) provide a strong predisposition for a highly selective enolization process, (iii) provide a strong bias for enolate diastereofacial selection in the new bond construction, (vi) be nondestructive and cleaved under mild condition without racemization of the desired products.[10] The general chiral auxiliary approach to diastereoselection for simple α– alkylation variants can be summarized in Figure **2** which illustrates chiral enolate–derived reactions, wherein the chiral auxiliary (Xc) is both readily available and easily recovered after the desired bond construction has been achieved.

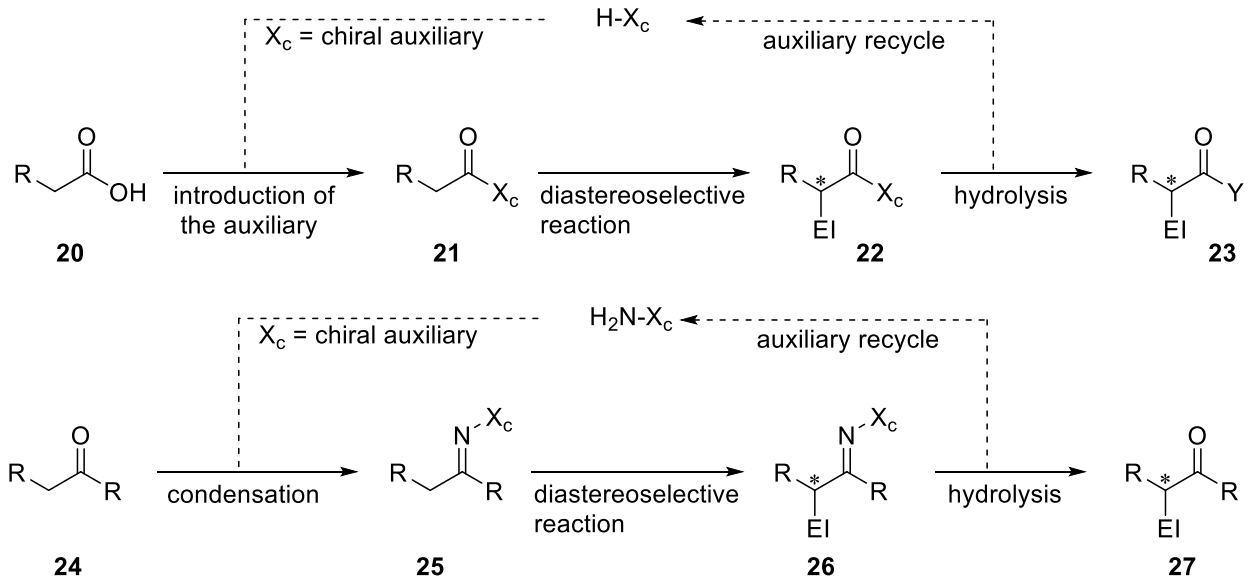
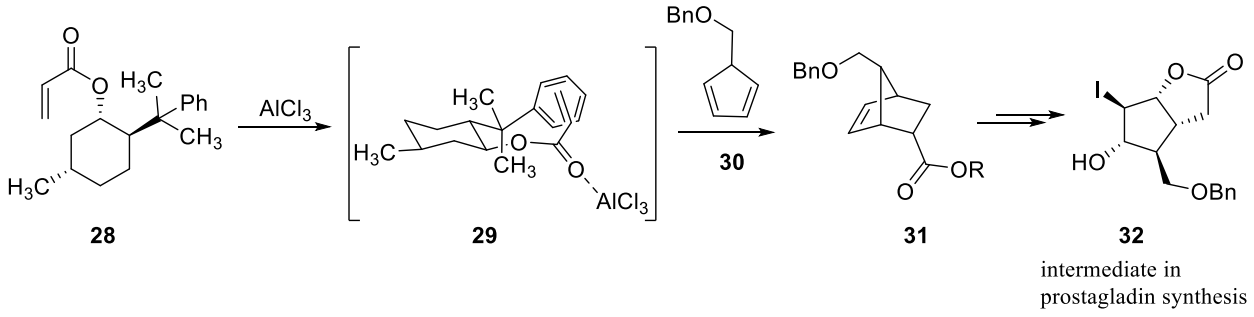


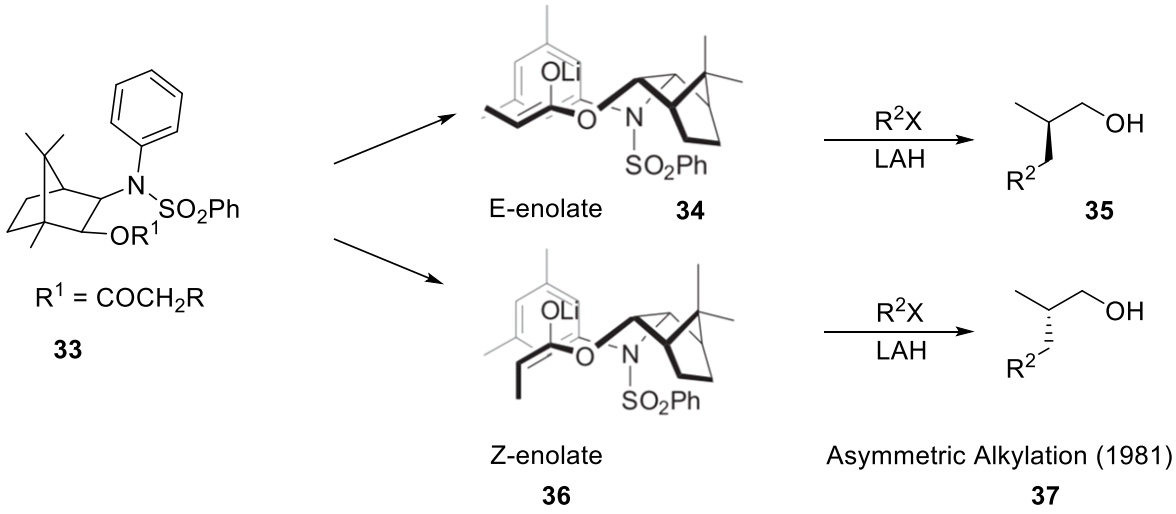
Figure 2: Diastereoselective synthesis with chiral auxiliaries.[10]

The Corey chiral auxiliary, which was synthesized in 1975, is classified as one of the most versatile chiral auxiliaries for asymmetric organic synthesis. Corey introduced (−) −8−phenylmenthol when developing a method for obtaining a chiral intermediate for the synthesis of prostaglandins (PGs) (Scheme **4**).[11a] Along with its enantiomer, (–)−8−phenylmenthol is a useful tool in chiral resolution; stereochemical control in cycloaddition reactions, 1,2– and 1,4–additions, oxidations, reductions, and photochemical reactions.[9a,11b,c]



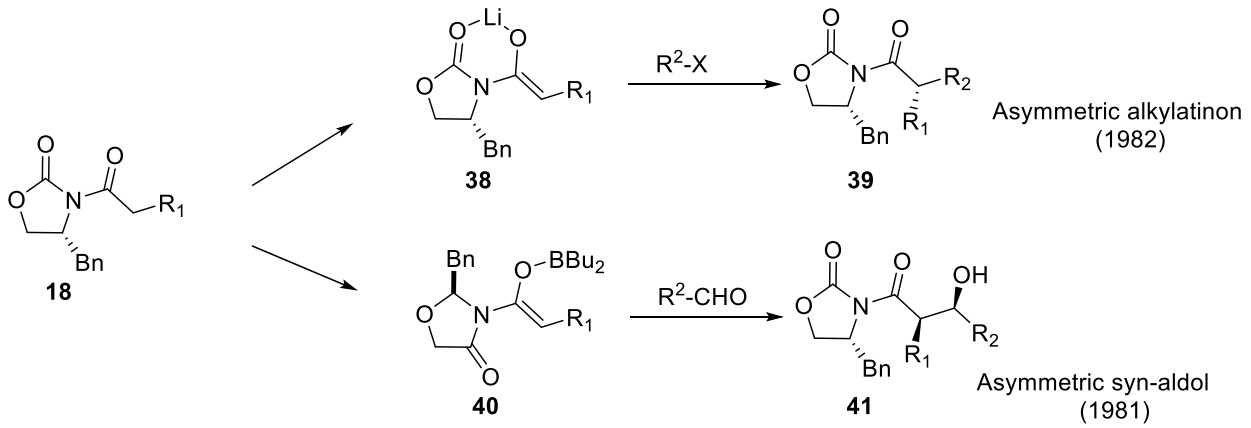
Scheme 4: Diastereoselective Diels–Alder cycloaddition with the chiral auxiliary (–)–8–phenylmenthol in route to the prostaglandins.[11b]

In addition, the widely employed auxiliary controlled reactions are the asymmetric alkylations, aldol reactions, and Diels–Alder reactions.[9a,12a,b] A notable early example of an effective diastereoselective alkylation was developed by the Helmchen group, using concave camphor–derived chiral auxiliaries (Scheme **5**).[12c]

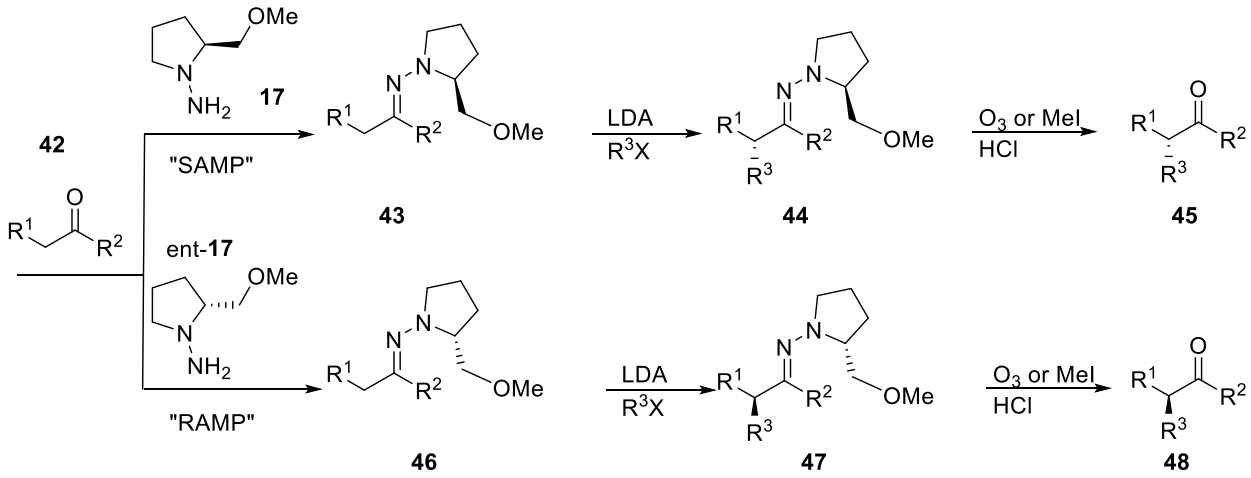


Scheme 5: Asymmetric alkylations reaction using Helmchen's camphor–derived auxiliaries.[12c]

One of the most frequently used chiral auxiliaries in organic synthesis are the chiral oxazolidinones developed by Evans.[14a] Oxazolidinones (**18**) which were initially developed for an efficient asymmetric C–C bond construction in the synthesis of several polyketide–derived natural products, have continually been employed by the Evans group and numerous other groups over the last 20 years.[13,14b,c,d,e,f] The first asymmetric reactions involving these chiral enolate synthons were the aldol and alkylation reactions. In these reactions selective enolization to form the *Z*–enolates was achieved using either lithium and sodium amide bases or dibutylboryl trifluorosulfonate. Subsequent alkylation or aldol reactions of the corresponding metal enolates resulted in the products with the highest levels of asymmetric induction (Scheme **6**).[14b]



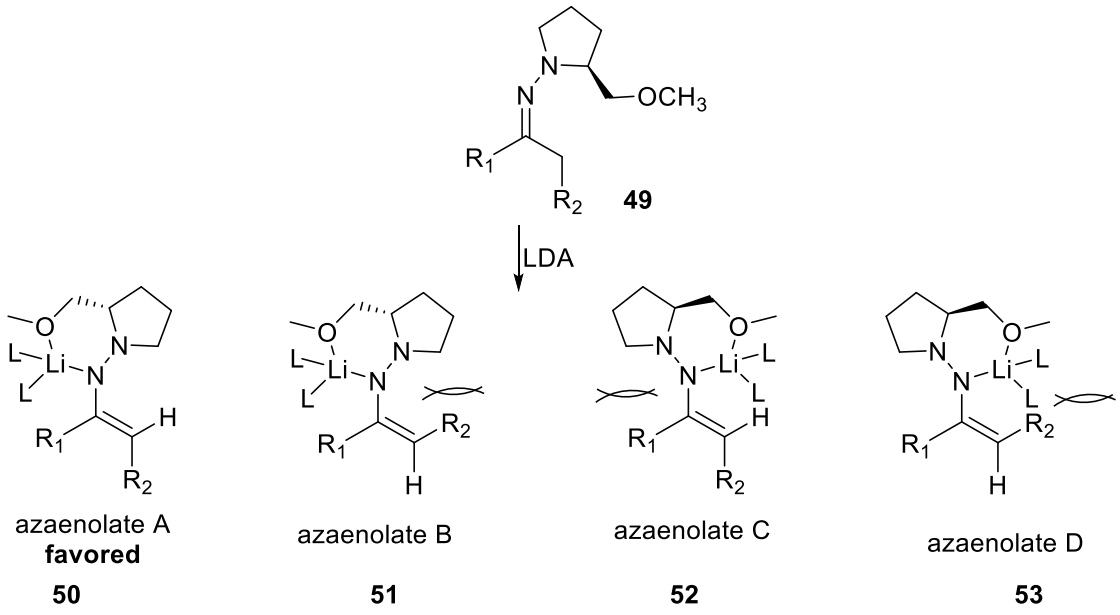
Scheme 6: Alkylation and aldol reaction using Evans oxazolidinones.[14b]



Scheme 7: SAMP/RAMP hydrazone alkylation reaction.[15a]

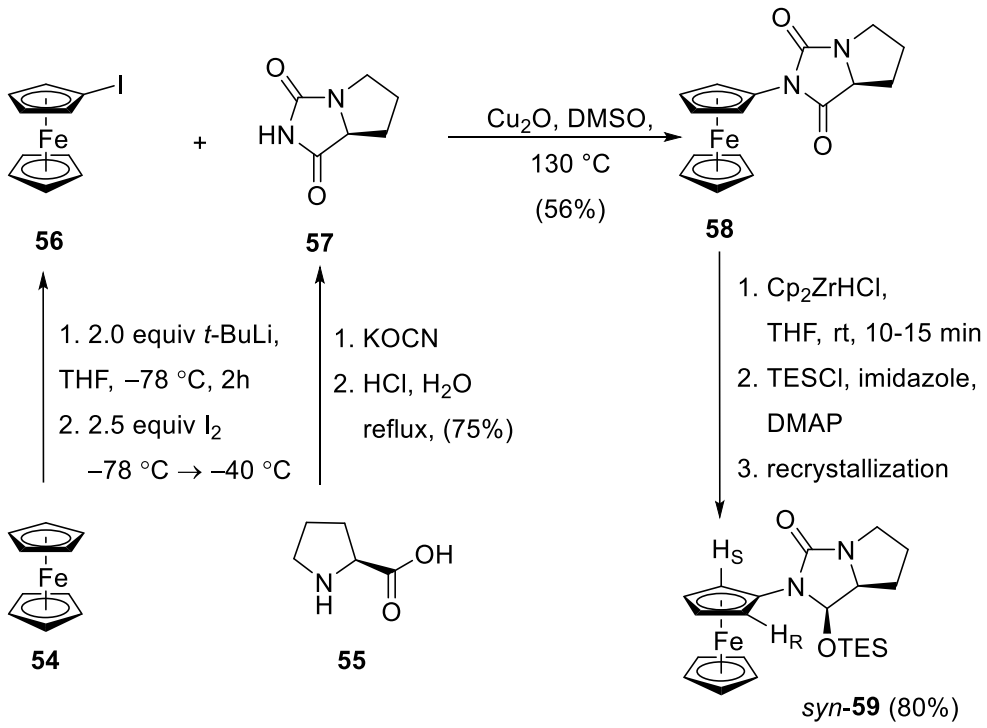
Pyrrolidine chiral auxiliaries were used in the Enders (*S*)–1–amino–2–methoxymethylpyrrolidine (SAMP) and (*R*)–1–amino–2–methoxymethylpyrrolidine (RAMP) hydrazone alkylation reaction (Scheme **7**) which was pioneered by E. J. Corey and D. Enders in 1976 and was further developed by Enders and his group.[15a] The reaction is a useful technique for the asymmetric α–alkylation of ketones and aldehydes. SAMP **17** is synthesized from (*S*)–proline. RAMP (*ent*–**17**)) can be derived from (*R*)–glutamate, and both enantiomers have found widespread use in organic synthesis.[15a,b,c] The mechanism of asymmetric alkylation involves the formation of a hydrazone

intermediate, azaenolate, which is formed after the coordination of lithium to the hydrazone nitrogen, followed by abstraction of a proton by the base. [16] The azaenolate may exist in different conformations and configurations. The most favoured intermediate is the one having low steric repulsion among the olefin groups, chiral auxiliary, and lithium ligands (Scheme **8**). Therefore, when using SAMP as a chiral auxiliary, the addition of the alkyl halide to the azaenolate occurs through the lower face of the olefin because the upper face is sterically hindered by the presence of the auxiliary.



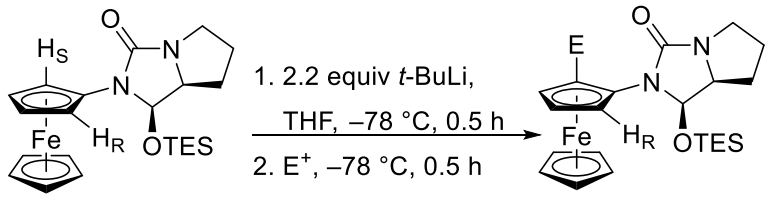
Scheme 8: Structures of the possible azaenolates formed in the asymmetric alkylation reaction.[16]

The Metallinos group has focused extensively on the discovery and development of a chiral auxiliary derived from *L*–proline (Scheme **9**).[3a,b] The auxiliary was initially used for diastereoselective lithiation of planar–chiral ferrocenes.[3a] A copper–mediated coupling between iodoferrocene **56** and *L*−proline hydantoin **57** furnished *N*−ferrocenyl hydantoin **58**. When *syn*–**59** was subjected to lithiation with *t*−BuLi and *in situ* quenching with various carbon and heteroatom–based electrophiles, all products were obtained as a single diastereomer.



Scheme 9: Synthesis of *L*–proline derived pyrroloimidazolidine auxiliary.[3a]

A series of 1,2–disubstituted ferrocenes with ≥95:5 dr (Scheme **10**) were obtained.[3b]

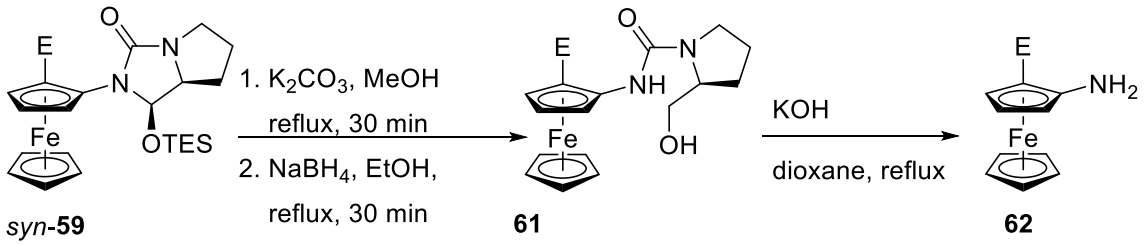


syn-**59** **60a-h** >95:5 dr

60a-j	E^+	E	yield, %
a	MeI	Me	91
b	ICH_2CH_2I	I	91
c	Ph_2CO	$Ph_2C(OH)$	87
d	$SiMe_3Cl$	$SiMe_3$	84
e	$SnBu_3Cl$	$SnBu_3$	87
f	$(MeS)_2$	SMe	94
g	DMF	CHO	70
h	$B(OEt)_3$	$B(OH)_2$	80

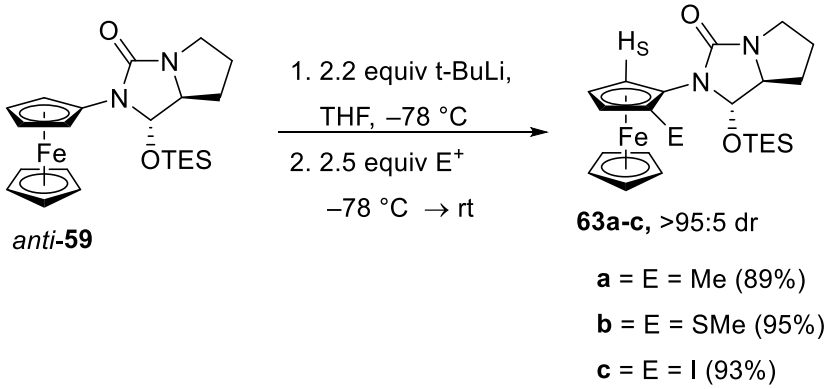
Scheme 10: Substrate scope for lithiation of *syn*–**59**.[3b]

The secondary urea **61** was obtained by reacting *syn*–**59** with potassium carbonate, which mediated desilylation because of the lability of the silyl protecting group in refluxing methanol, followed by reductive ring opening by $NaBH_4$. Hydrolysis of the urea **61** with aqueous base (KOH) led to the formation of planar chiral amino ferrocene **62** (Scheme **11**).[3b]



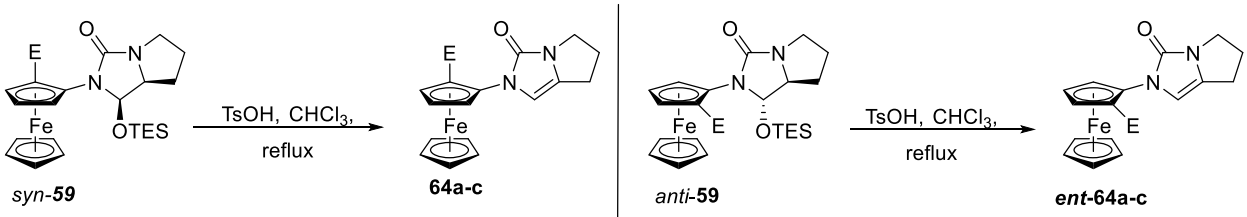
Scheme 11: Hydrolysis of chiral auxiliary.[3b]

Single crystal X–ray analysis of boronic acid **60h,** and comparison of the optical rotation of **60a** to its known enantiomer (*ent*–**60a**) confirmed the stereoselectivity of the lithiation. To demonstrate the opposite selectivity, the configurationally unstable hemiaminal was isolated after hydrozirconation of **58**, followed by deprotonation with base and treatment with chlorotriethylsilane to give a 1:1 mixture of *syn*– and *anti*–**59** that were separated by column chromatography. Treatment of *anti*–**59** with base produced disubstituted ferrocenes **63a–c** as single diastereomers (Scheme **12**). Elimination of the substituted compounds catalysed by TsOH gave a series of solely planar chiral ferrocenes **64a–c** and *ent* **64**–**a–c**.



Scheme 12: Synthesis and lithiation of *anti*–**59.**[3b]

The elimination products were identical spectroscopically, had identical molecular weights, but the optical rotations were equal but opposite in magnitude, indicating that the compounds were enantiomers of each other (Scheme **13**).

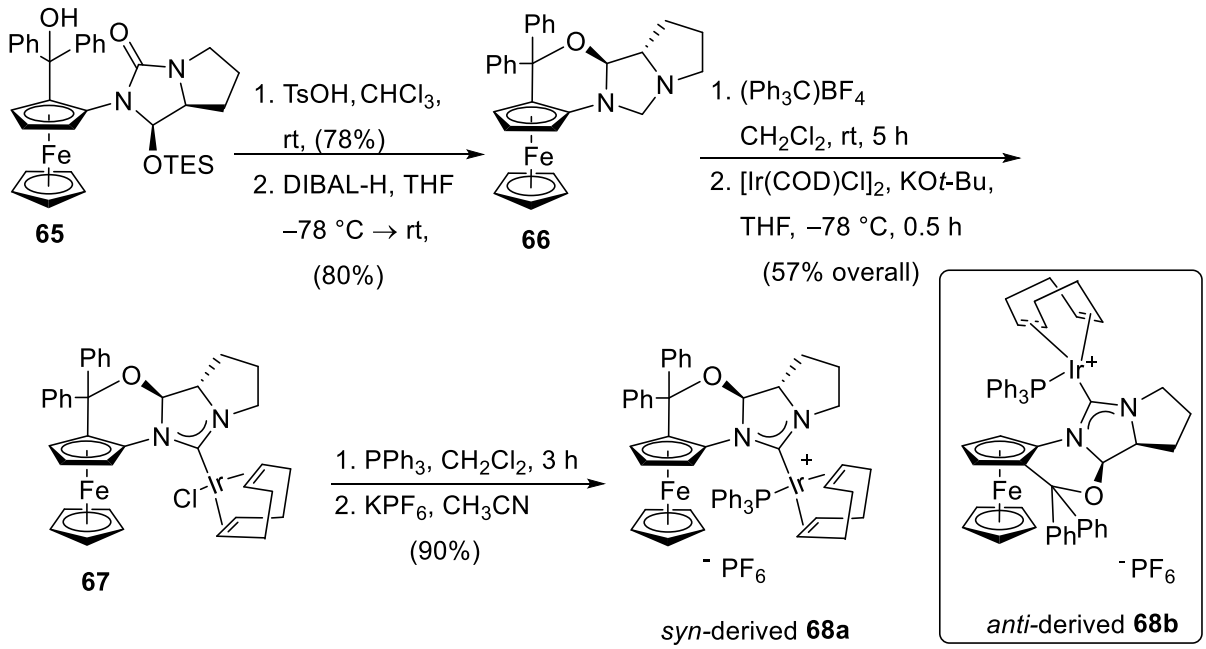


64a-c	E	yield, %	er	$[\alpha]_D^{20}$
a	Me	91	99:1	–29.2
b	SMe	93	98:2	–129
c	I	90	99:1	–38.9

ent-64a-c	E	yield, %	er	$[\alpha]_D^{20}$
a	Me	95	97:3	+31.0
b	SMe	92	95.5:4.5	+136
c	I	85	99:1	+40.3

Scheme 13: Comparison of imidazolone derived from *syn*– and *anti*–epimers.[3b]

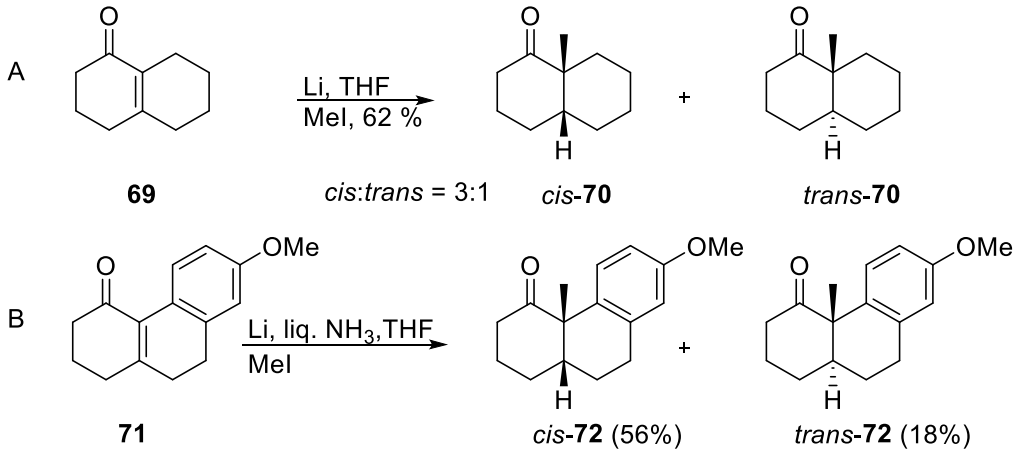
Tetracyclic annulation products which serve as precursors for NHC ligands, were achieved upon treating the diphenylmethanol adduct **65** with acid to induce elimination in which the alcohol group displaced the silyloxy group. The iridium NHC complex was generated when the annulated urea was treated with DIBAL–H and then treated with tritylium tetrafluoroborate, followed by *in–situ* deprotonation of the imidazolinium salt by KO*t*Bu and then trapped with $[Ir(COD)Cl]_2$. The complex was obtained as a mixture of coordination isomers which equilibrated to the major isomer upon further stirring. The identity and stereochemistry of **67** was confirmed by single crystal X–ray diffraction. Treatment of this compound with PPh_3, followed by salt metathesis with KPF_6 afforded cationic Ir–complex **68a**, which was used in the asymmetric hydrogenation of quinolines with up to 90:10 er (Scheme **14**).



Scheme 14: Synthesis of Iridium complexes **67** and **68a,b**.[3b]

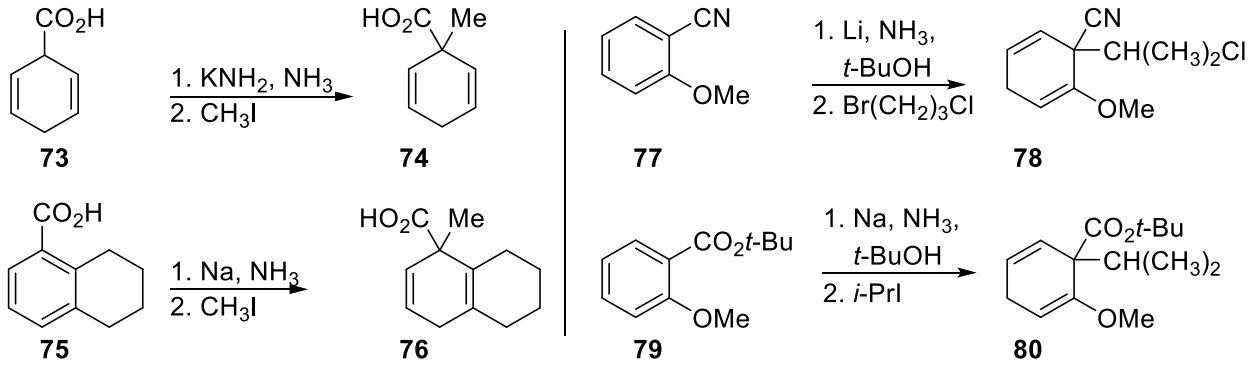
1.3 Chiral auxiliaries in Birch reductive alkylation

The sequential Birch reduction alkylation reaction was originally developed by Stork and coworker in 1961, and it has been applied to synthesize many natural products.[17] Stork reported the isolation of two compounds, *cis*–**70** and *trans*–**70**, in an approximate 3:1 ratio by a Birch reduction alkylation reaction of 3,4,5,6,7,8–hexahydro–2Hnaphthalen–1–one (Scheme **15A**).[17] In 1984, Mukerjee reported a similar result using a tricyclic substrate (Scheme **15B**).[18]



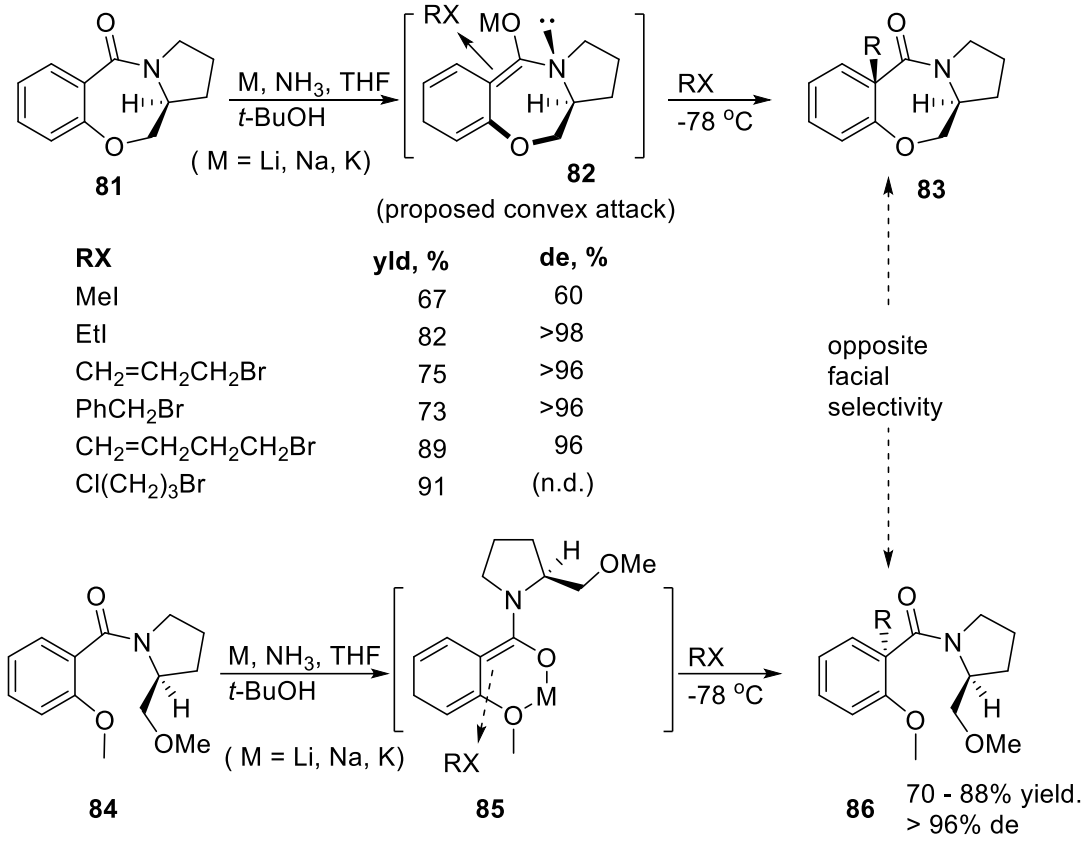
Scheme 15: Previous examples of Birch reduction–alkylation reactions.[17,18]

Most of the related Birch reduction alkylations of substituted aromatic compounds are reported in racemic forms.[18,19,20,21,22] In 1961, Nelson and coworker reported that enolates derived from 1,4–dihydrobenzoic acids are selectively alkylated at the α–carbon.[19] Then Bachi and co–workers first demonstrated reductive alkylation of the aromatic compounds in one step when constructing the ring A system of gibberellin, which contains a cyclohexane ring bearing a methyl group.[20] After that, for anisoles containing *ortho* amides,[21] nitriles[22] or esters[18] (Scheme **16**), Schultz and Wollias demonstrated in the 1980s that it is possible to intercept Birch reduction intermediates by alkylation, leading to 1,4–cyclohexadienes with quaternary chiral centres. [23]



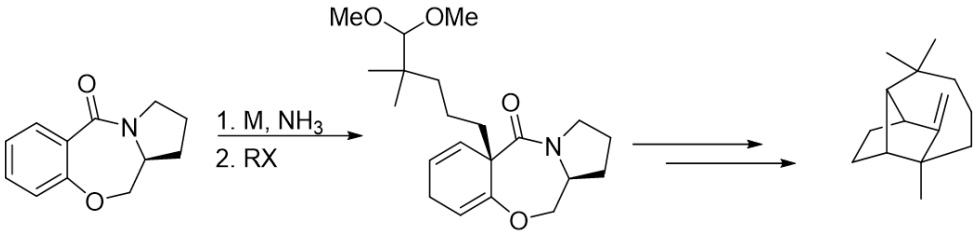
Scheme 16: Racemic preparation of alkylated cyclohexadienes for synthetic intermediates.[18,19,20,21]

Schultz extensively studied and developed chiral benzamide derivatives to synthesize optically pure cyclohexadienes that could be transformed into chiral intermediates that have application in natural products synthesis.[23] Benzoxazepinone **81** was synthesized by the condensation–cyclization of 2–fluorobenzoyl chloride with *L*–prolinol. A diastereomeric series **83**a–f was achieved when the Birch reduction of benzoxazepinone was performed at –78 °C with different alkali metals (Li, Na, or K) in a liquid NH_3–THF solution in the presence of 1 equivalent of *tert*–butyl alcohol, followed by the alkylation of the resulting enolate with alkyl halides at –75 °C (Scheme **17**).[23]



Scheme 17: Birch reduction alkylation of benzoxazepinone.[23]

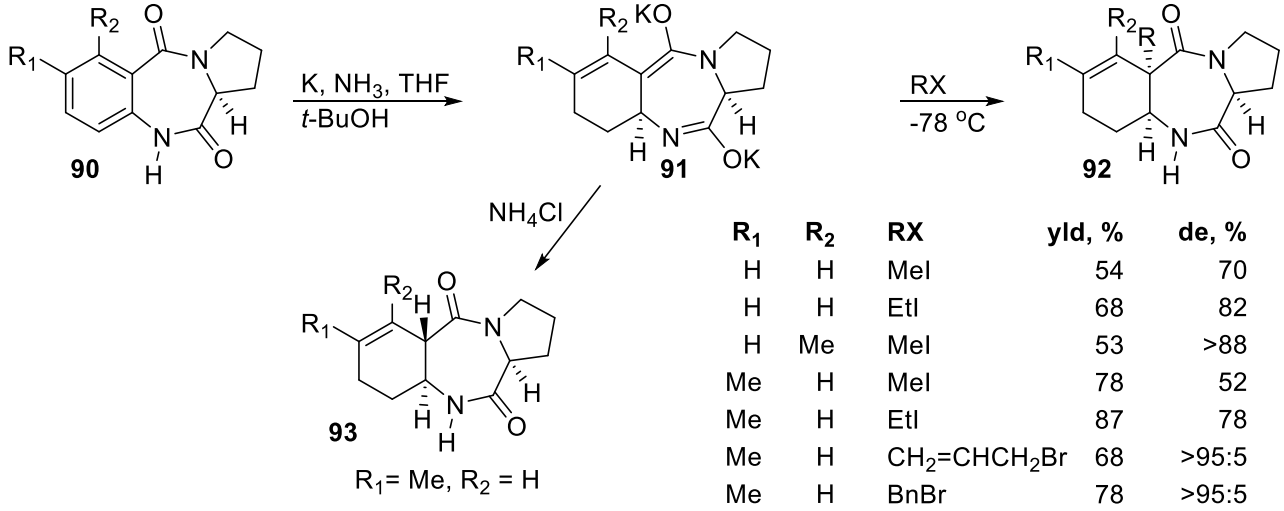
Assignment of configuration for the series was facilitated by conversion of alkylated substrates into a known compound, longifolene (Scheme **18**), and X–ray crystallography of the methylated compound.[23] The chiral auxiliary could be removed by relatively simple hydrolysis.



Scheme 18: Reductive alkylation route to (–)–longifolene.[23]

Schultz proposed that the Birch reduction results in the kinetically controlled formation of a dimeric enolate aggregate wherein the metal is chelated by the aryl ether; the side chain of the

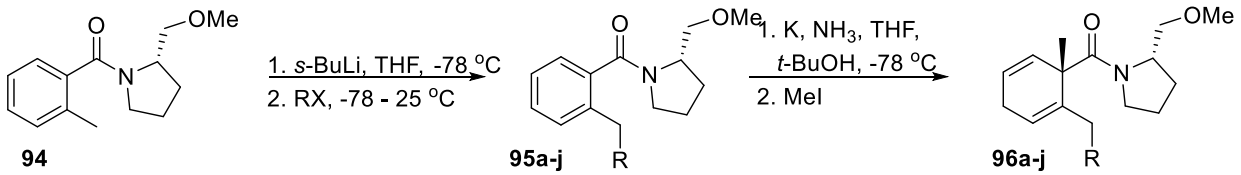
chiral auxiliary was proposed to block the β–face of the enolate.[23] In addition, Schultz demonstrated the viability of Birch reductions of the diazepine dione ring system (Scheme **19**).[24] In this case 4.4 equivalents of potassium were required for the reduction, and ammonium chloride was added to quench the reaction to minimize the alkylation of the secondary amide.[24] Alkylation with iodoethane proceeded with higher diastereoselectivity. The minor diastereoisomer could not be detected when allyl bromide and benzyl bromide were used.



R_1	R_2	RX	yld, %	de, %
H	H	MeI	54	70
H	H	EtI	68	82
H	Me	MeI	53	>88
Me	H	MeI	78	52
Me	H	EtI	87	78
Me	H	CH_2=$CHCH_2$Br	68	>95:5
Me	H	BnBr	78	>95:5

Scheme 19: Birch reductions of the diazepine dione ring system.[24]

In 1991 Schultz conducted another series of experiments to examine the effect of different *ortho*–alkyl groups.[25] Starting with a methyl group *ortho* to the benzamide, directed benzyl lithiation/alkylation with *s*–BuLi, followed by quenching with various electrophiles produced a series of *ortho*–alkyl benzamides **94.** Diastereoselectivities were obtained with more highly functionalized alkylation reagents (Scheme **20**).[25]

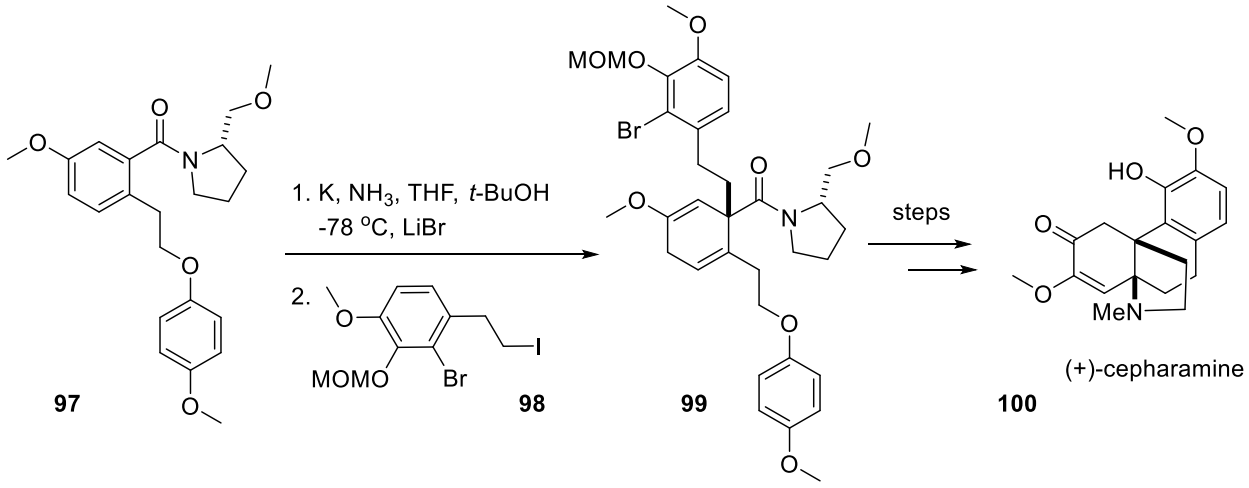


94 **95a-j** **96a-j**

96a-j	R	Yield (%)	dr
a	Me	66	25:1
b	Et	79	19:1
c	allyl	76	29:1
d	homoallyl	69	18:1
e	Bn	62	40:1
f	CH_2Bn	77	26:1
g	$CH_2OCH_2SiMe_3$	71	33:1
h	$CH_2OCH_2SiMe_2t$-Bu	88	53:1
i	CH_2CH_2OH	79	42:1
j	Ph	69	48:1

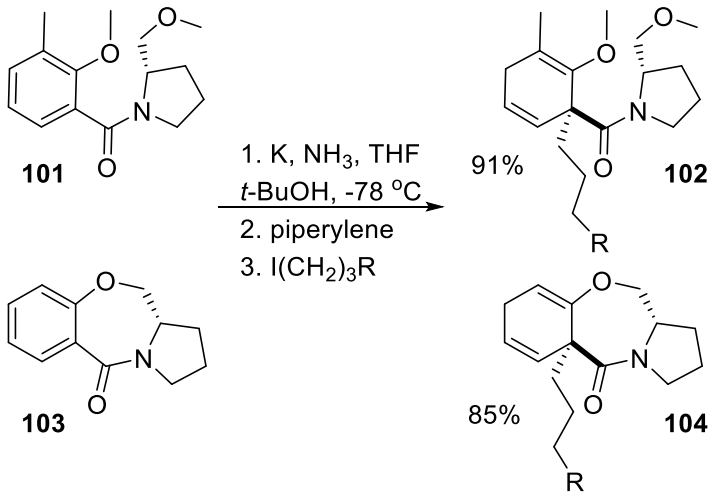
Scheme 20: Synthesis of *ortho*–modified chiral benzamides for reductive alkylation.[25]

The sequential Birch reduction–alkylation reaction, which has been used to synthesize many natural products was originally developed by Stork and coworker in 1961.[17] However, only two kinds of substrates can be found in the literature for the reduction–alkylation reaction of a β–alkoxy–α,β–unsaturated carbonyl compound.[26] The first one is the reaction of *N*,*N*–dialkyl–3–furamide derivatives as substrates, and the latter example is reductive alkylation of chiral 2–alkoxybenzamide derivatives.[26] The first asymmetric synthesis of a hasubanan alkaloid, (+)–cepharamine, has been carried out with complete regio– and stereo–control.[27] The important features of the synthesis are the convergency of the asymmetric Birch reduction alkylation step, which afforded the desired intermediate as a single diastereomer with decent yield (Scheme **21**).



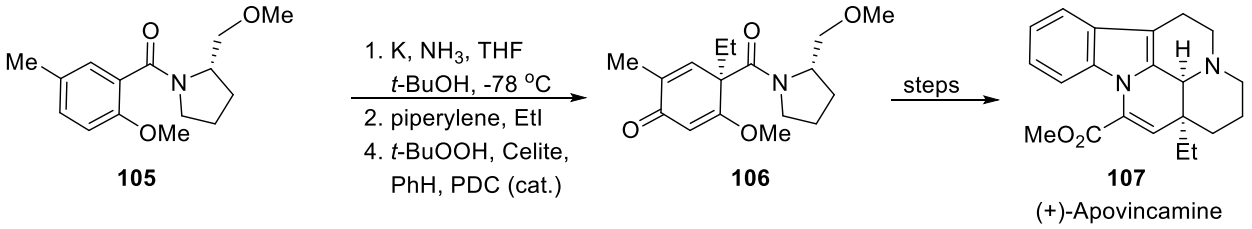
Scheme 21: The asymmetric Birch reduction–alkylation in the synthesis of (+)–cepharamine.[27]

In addition, the asymmetric Birch reductive alkylation has been applied to synthesize gymnodimine A1.[28a] Two types of chiral aromatic substrates, an acyclic benzamide and a benzoxazepinone, were subjected to the Birch reduction under optimized conditions using potassium (3 equivalents) in a 10:1 mixture of liquid ammonia and THF at –78°C, in the presence of *t*–BuOH (1 equivalent). The excess potassium was then quenched with piperylene followed by addition of the electrophile bearing either an azido or a protected alkoxy group. Under these conditions, chiral cyclohexadienes were obtained in decent yields and diastereomeric ratios irrespective of the nature of the aromatic amides and the electrophiles (Scheme **22**).[28a]



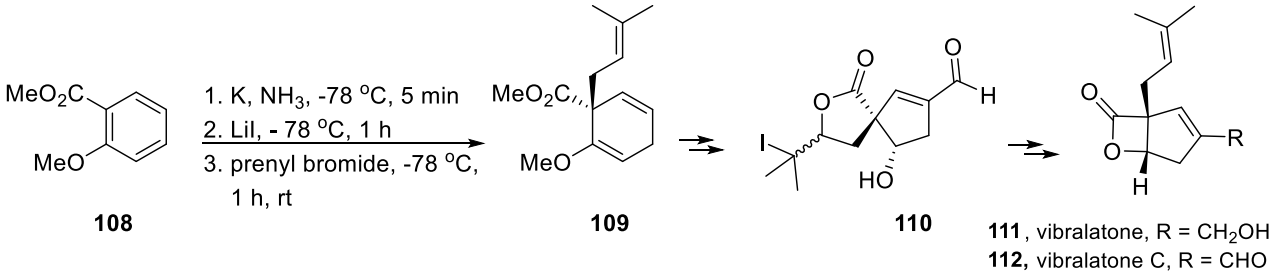
Scheme 22: Asymmetric Birch reductive alkylation of benzamides.[28a]

While constructing the asymmetric total synthesis of two vincane–type alkaloids, (+)–apovincamine and (+)–vincamine, Schultz designed a crucial *cis*–fused pentacyclic diene intermediate.[28b] The synthesis began with the Birch reduction–alkylation of a chiral benzamide to give 6–ethyl–1–methoxy–4–methyl–1,4– cyclohexadiene in a >100:1 diastereomeric purity. This cyclohexadiene was first converted to an enantiopure butyrolactone which, after several steps, was converted to (+)–apovincamine (Scheme **23**).



Scheme 23: Synthesis of (+)–apovincamin.[28b]

In 2008 Snider and Zhou used the Birch reductive alkylation as key step in the synthesis of vibralactone and its derivative.[29] In this synthesis, methyl 2–methoxybenzoate was reduced with K in liquid NH_3 at −78 °C.1,3–Pentadiene was added to consume excess K, and LiI was added to make the lithium dienolate. After that, prenyl bromide was added, followed by slow warming to 25 °C, and the alkylated cyclohexadiene **14** was produced in 77% yield (Scheme **24**).[29]



Scheme 24**:** Synthesis of (±)–vibralactone.[29]

1.4 C–H activation

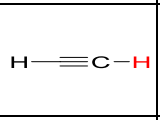
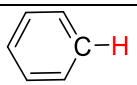
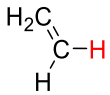
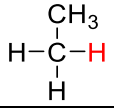
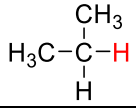
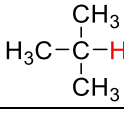
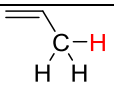
The development of coordination metal–complex catalysis has led to the discovery of different types of molecules, including molecular hydrogen, carbon monoxide, oxygen, nitrogen, olefins, acetylenes, and aromatic compounds, which can take part in catalytic reactions in homogeneous solutions.[30] Under such circumstances, a molecule or its fragment entering the coordination sphere of the metal complex, as a ligand, is chemically activated. This means that a molecule or its fragment possess the capacity to participate in reactions that either do not proceed in the absence of a metal complex or occur at very slow rates. The "C–H activation"[31a] term has been used to emphasize the distinct reactivity pattern of low valent metal complexes from that of classical organic reagents. The main result of "activation" of a C–H bond is the replacement of the strong C–H bond with a weaker, more readily functionalized group.[31b] The activation of an unsaturated species can be induced by coordination of a metal to the unsaturated bond, following which the bond may undergo addition or rupture. [31a, b] For example, olefin and arene π–bonds can be activated by π–complexation. Saturated compounds do not have this advantage, however, coordination between some metals and saturated hydrocarbons have been investigated recently.

1.4.1 The reactivity of the isolated C–H bond

In general, an isolated C–H bond in a molecule has a very low reactivity as a result of the large kinetic barrier associated with C–H bond cleavage, which is in turn related to the non–polar nature of this bond.[32] The bond dissociation energies (BDEs) and acidities of typical C–H bonds in typical simple hydrocarbons are displayed in Table **1**. The BDE decreases along the series C(*sp*)–H→C(sp^2)–H→C(sp^3)–H, and on passing from $1^{\circ} \rightarrow 2^{\circ} \rightarrow 3^{\circ}$ → allylic C(sp^3)–H bonds.[33] This value is inversely proportional to the stability of the radicals obtained from homolytic dissociation

of the bond. The acidity is proportional to the stability of the corresponding deprotonated species. These findings can be summarized by the trend that stronger C–H bonds are in general easier to activate than weaker C–H bonds.[34] To rationalize these trends, Jones and Feher determined that it was the product metal–carbon (M–C, M = Ru, Rh, Pd) bond strengths that dominated in the determination of the position of the hydrocarbon activation equilibria, not the reactant C–H bond strengths.[34] On the basis of the well–known order of C–H bond strengths, H–Ph > H–vinyl > H–CH_3, > H–CH_2R > H–CHR_2> H–CR_3> H–CH_2Ph, the following order of metal–carbon bond strengths was suggested: M–Ph >> M–vinyl>> M–CH_3 >> M–CH_2R >> M–CHR_2>> M–CR_3 >> M–CH_2Ph. These trends of M–C bond strengths were best explained by invoking ionic contributions in the M–C bonding, and repulsive effects, depending on the number and type of ligands on the bonding carbon atom. In particular, the activation of unstrained alkanes is still a challenging problem.[34]

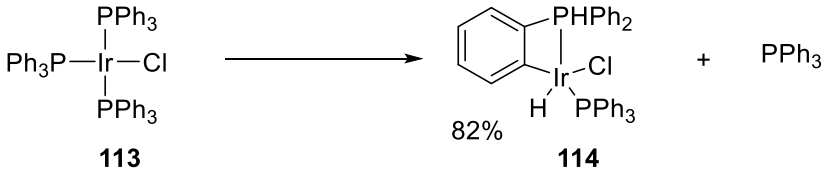
Table 1: Bond dissociation energies and pKa values of selected hydrocarbon C–H bonds.[32]

Type of C–H	C(*sp*)	C(sp^2)$_{ar}$	C(sp^2)$_{vinyl}$	C(sp^3)$_1$^{o}	C(sp^3)$_2$^{o}	C(sp^3)$_3$^{o}	C(sp^3)$_{allylic}$
Structure							
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
pK_a	~25	43	44	~50	~50	~50	43

1.4.2 Aryl C–H Bond Activation

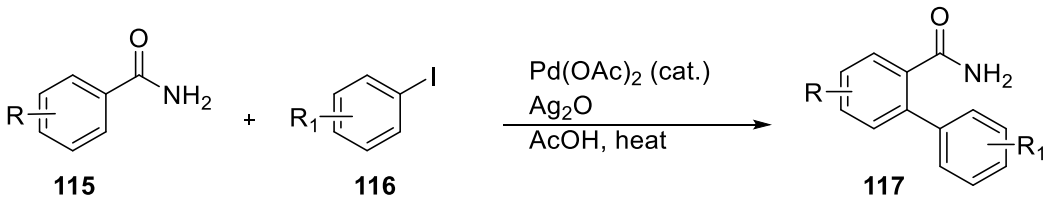
Arylation via the activation of sp^2–hybridized C–H bonds dates back to the preparation of stilbene derivatives from palladium–catalyzed arylation of styrene with benzene and other simple arenes by Moritani and Fujiwara.[35] Later, Itahara and coworker explored the coupling of various heterocycles (thiophene, furan, and pyrrole) with benzene via double C–H activation in the

presence of acetic acid and palladium acetate.[36] These researches later became central to the development of the direct arylation reactions whose mechanism was extensively investigated. For a time, research into transition–metal–catalyzed direct arylation cross–coupling focused on developing optimal reaction conditions primarily for intramolecular reactions or systems with very specific directing groups to control site–selectivity. Cyclometallation of ligand aryl group was developed by Bennett and ultimately found to be quite common (Scheme **25**).[37]



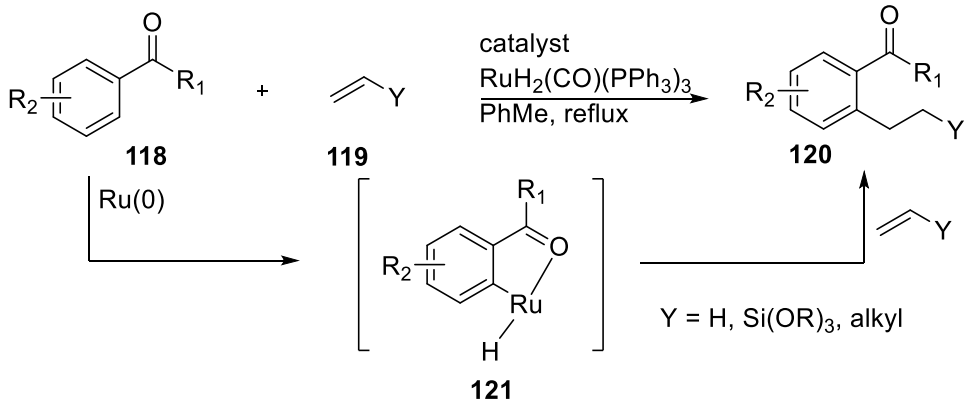
Scheme 25: Cyclometallation of ligand aryl group.[37]

Wang and coworker reported transition–metal–catalyzed direct arylation via the cleavage of sp^2 C–H bond to construct C–C bonds.[38] They performed the Pd–catalyzed regioselective *ortho*–arylation of benzamides by aryl iodides using the simplest amide $CONH_2$ as a directing group. The protocol can be used to synthesize biphenyl–2–carboxamides and applied to a wide range of benzamides and aryl iodides with both electron–donating and electron–withdrawing groups (Scheme **26**).[38]



Scheme 26: Pd–catalyzed direct *ortho*–arylation of benzamides.[38]

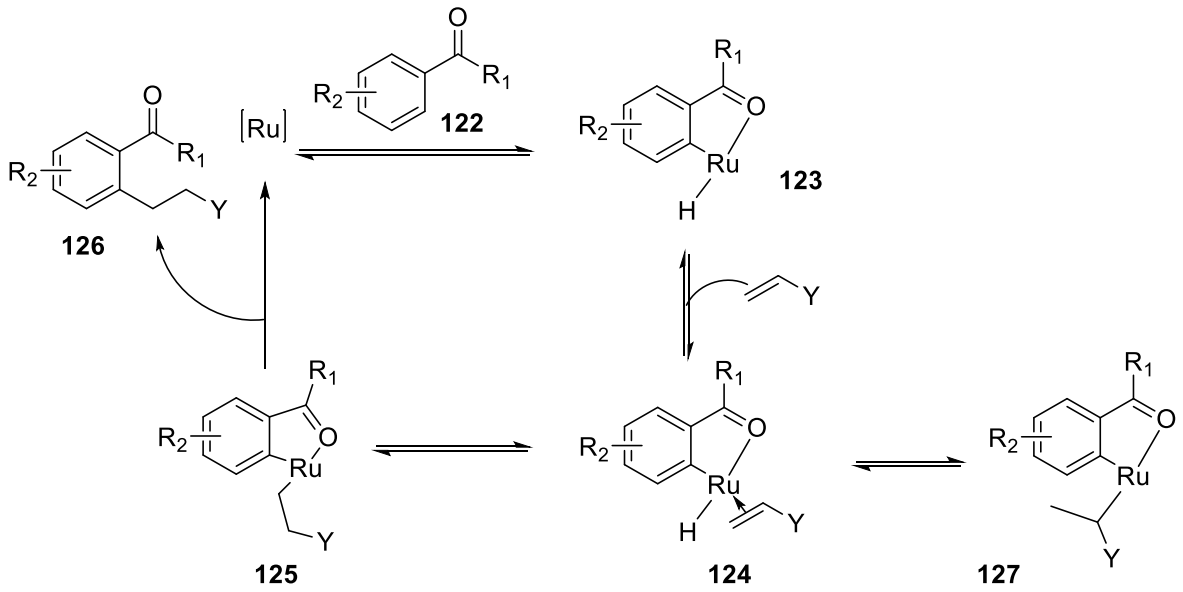
The most significant breakthrough in this field was reported by Murai in 1993.[39] In his report, $Ru(PPh_3)_3(CO)_2$ and $Ru(PPh_3)_3(CO)H_2$ were found to catalyze the insertion of olefins into the *ortho* C–H bonds of aromatic ketones (Scheme **27**). The scope of the system has been extended to include insertion of alkynes as well as olefins and, more importantly, to a very broad range of substrates with a directing group (either N– or O–coordinating) *syn*– to an sp^2 C–H bond.[40]



Scheme 27: $Ru(PPh_3)_3(CO)_2$ or $Ru(PPh_3)_3(CO)H_2$ catalyzed insertion of olefins into the *ortho* C–H bonds of aromatic ketones.[39]

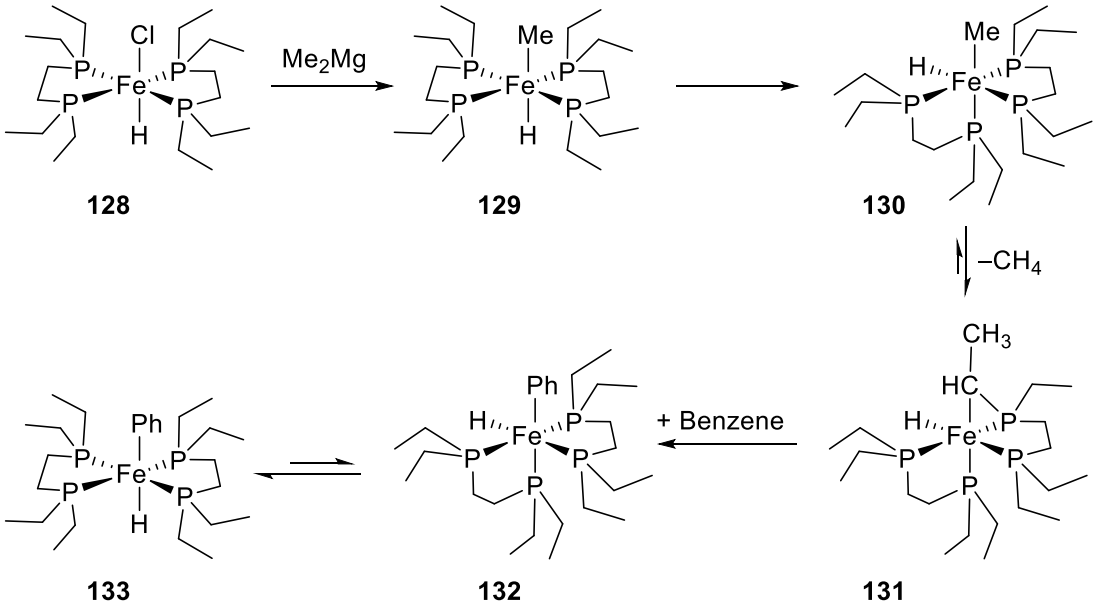
The Ru–catalyzed insertions were found to be very favored by "directing" groups that are conjugated with the π–system of the C–H bond undergoing reaction. Also, $Ru(PPh_3)_3(CO)_2$ and $Ru(PPh_3)_3(CO)H_2$ were found to have a complex role rather than simply bringing the C–H bond into the proximity of the metal center (i.e., minimizing the entropic cost of C–H addition).[39]

The proposed reaction mechanism involved either: (a) initial insertion into the resulting Ru–C bond; or (b) insertion into the resulting Ru–H bond. In each case the appropriate reductive elimination (C–H or C–C respectively) would follow. Murai has presented strong evidence, some of which follows, for the hydrometalation path (b) and the overall reaction pathway was proposed as described in Scheme **28**.[39]



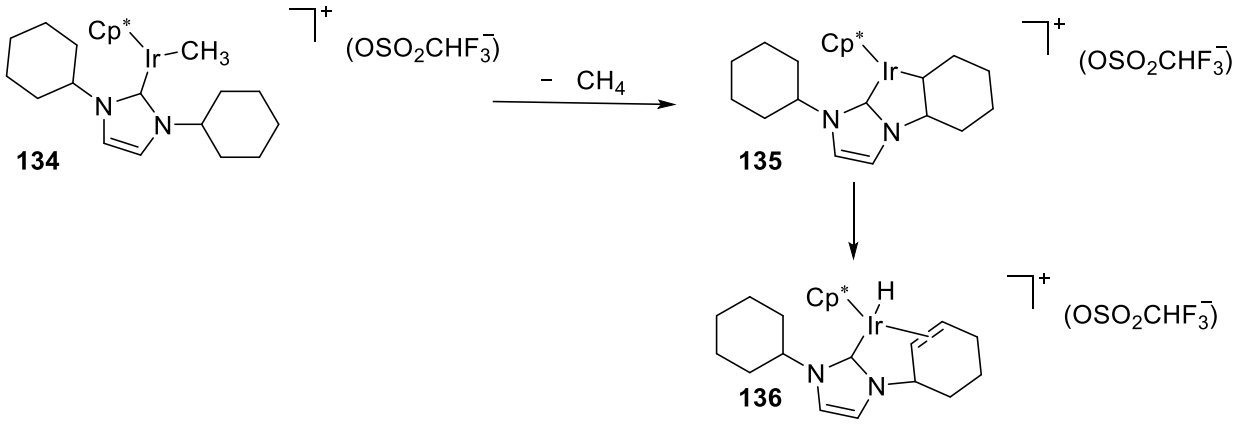
Scheme 28 **:** Proposed mechanism for Ru(0)–catalyzed "site–directed" addition of C–H bonds to olefins.[39]

Baker and Field demonstrated that $Fe(depe)_2$, a coordinatively unsaturated iron (0) complex, readily inserted into the *ortho*–methylene C–H bond to form a ferracycle intramolecularly. After that, the ferracycle cleaved the C–H bond of benzene to generate an organoiron (II) complex (Scheme **29**). The *trans* methyl hydride was generated quantitatively by treating the hydrochloride with excess dimethylmagnesium at low temperature (<230 K). Upon warming, the *trans* isomer isomerized to the *cis* isomer **130**, which rapidly eliminated methane. In inert solvents (THF, pentane) the cyclometalated compound, which was formed by the oxidative addition of the coordinatively unsaturated iron atom into a C–H bond of a methylene group of one of the DEPE ethyl substituents, was achieved. [42]



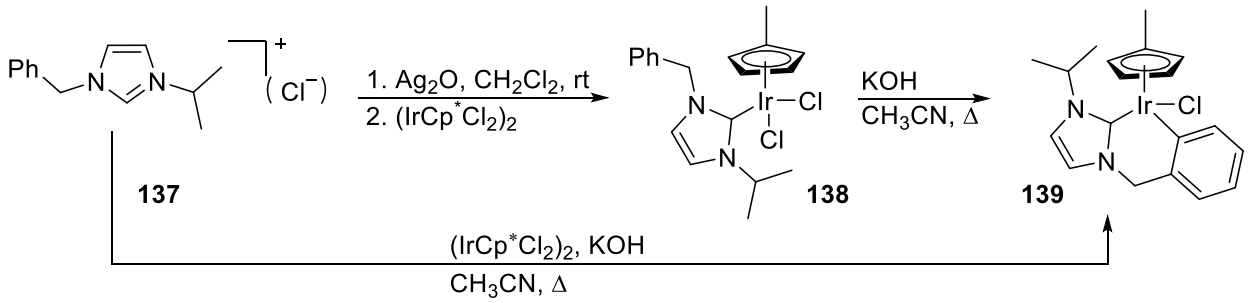
Scheme 29: *Ortho* cyclometalation with methylene C–H bond and reaction with benzene of depe–ligated Iron complex.[42]

The capacity of Cp*Ir(NHC) complexes to undergo intramolecular C–H activation had been reported by Herrmann and colleagues.[43] They described the synthesis of a new type of iridium–carbene complexes, based on the activation and subsequent functionalization of one cyclohexyl substituent at the *N*–heterocyclic carbene by a C–H bond activation/ β–hydrogen migration process at the iridium (III) center (Scheme **30**).[43]



Scheme 30: Intramolecular C–H activation on Iridium–carbene complex complexes.[43]

Bergman and co–workers have extensively studied processes regarding inter– and intramolecular C–H activations using phosphine analogue complexes Cp*Ir(PR_3).[44] Corbera'n and coworker reported a series of Cp*Ir(NHC) complexes that underwent facile intramolecular aromatic C–H activation under mild conditions leading to the corresponding cyclometalated products (Scheme **31**).[45]



Scheme 31: Intramolecular C–H activation on Cp*Ir(NHC) complexes.[45]

1.4.3 Site selectivity

An effective methodology to functionalize C–H bonds requires overcoming the key challenge of differentiating among the multitude of C–H bonds that are present in complex organic molecules.[46] There are two conceptually different pathways of site selection: substrate control (using directing groups, or electronically activated substrate); and reagent control (Figure **3**).[46] The first approach involves substrates that contain coordinating functional groups to direct C–H activation and subsequent functionalization to a proximal site, and the use of heterocyclic substrates that contain highly activated C–H sites. The latter approach involves the design of ligands for the catalyst that exert control over site selectivity in C–H functionalization.

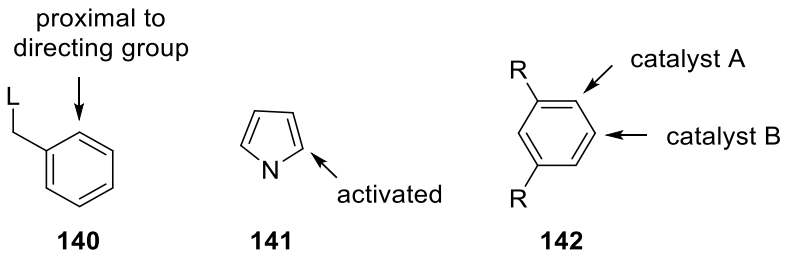
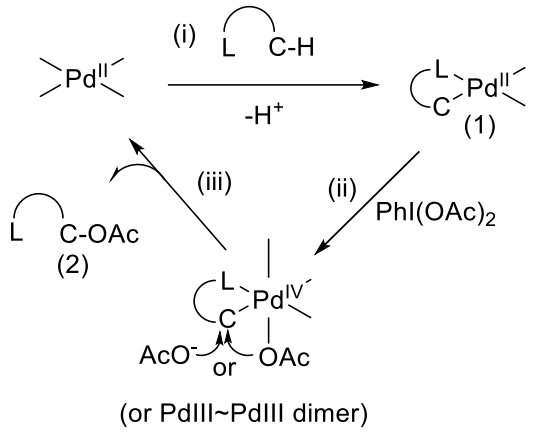


Figure 3: Strategies for controlling site selectivity

Classically, directed C−H functionalization leads to the introduction of groups at the *ortho* position of benzene rings because the transition–metal catalyst first coordinates to the directing group and is therefore in close proximity to the *ortho* C−H bond. In recent years, there has been considerable interest in the extension of C−H functionalization to sp^3 C−H bonds.[47]

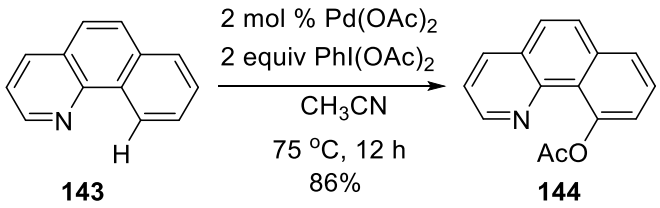
1.4.3.1 Substrate–based control of selectivity through the use of directing groups

Sanford's group has focused on developing a ligand–directed version of Crabtree's $Pd(OAc)_2$–catalyzed arene acetoxylation with $PhI(OAc)_2$.[48] They aimed to exploit the well–known cyclopalladation reaction (stoichiometric ligand–directed C–H bond activation at Pd(II) to achieve site–selective C–H cleavage (Scheme **32**, step i). A subsequent reaction between the cyclopalladated intermediate (1) and $PhI(OAc)_2$ could then release the desired acetoxylated product (2) (Scheme **32,** steps ii, iii).[48]



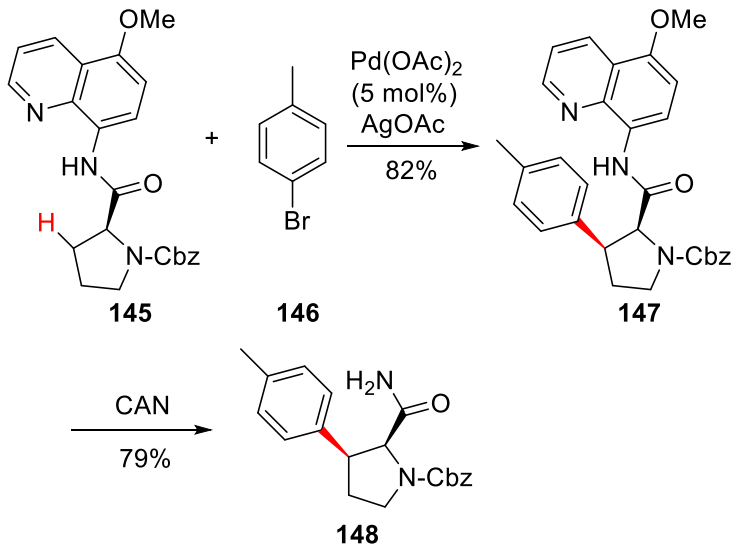
Scheme 32: Catalytic cycle for ligand–directed C–H acetoxylation.[48]

They first performed the $Pd(OAc)_2$–catalyzed C–H acetoxylation of benzo[h]quinoline. The C–H oxygenation occurred in high yield and produced the acetoxylated product as a single isomer (Scheme **33**).[48]



Scheme 33: Ligand–directed C–H acetoxylation.[48]

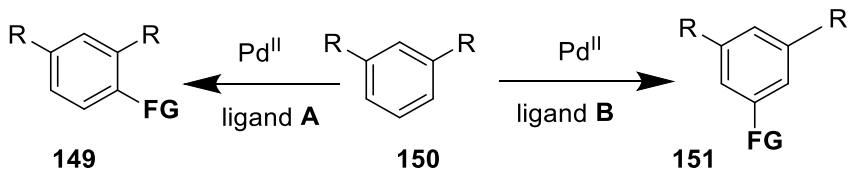
In 2014 Bull and co–workers described the palladium–catalyzed arylation of the proline derivative **145** with the aryl bromide **146** to generate the 3–arylated pyrrolidine **147** in 82% yield (Scheme **34**). The directing group not only controlled the site selectivity of the reaction but also, through predefined stereochemistry in the substrate, ensured that the *cis* product **148** was formed exclusively.[49]



Scheme 34: The palladium–catalyzed arylation.[49]

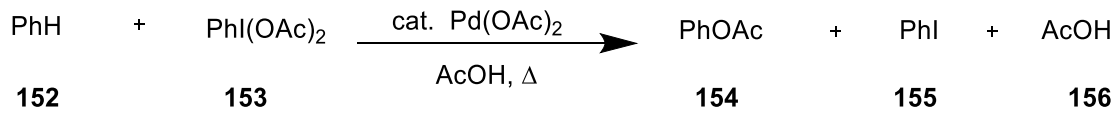
1.4.3.2 Catalyst–based control of selectivity

The site selectivity of C–H functionalization can also be controlled by modifying the catalyst structure. This method aims to obtain predictable site selectivity without biasing the substrate. This approach targets C–H substrates that lack directing or activating groups, with the ultimate goal of achieving selective formation of different isomeric products by simply changing the ligands at the metal center (Scheme **35**).[50] This method has historically proven difficult because the huge majority of metal–catalyzed C–H functionalization reactions proceed most efficiently under "ligandless conditions" (involving simple Pd salts like $Pd(OAc)_2$ as catalysts). As such, a key challenge has been to identify ligands that both accelerate these reactions and modulate their site selectivity.[52]



Scheme 35: Catalyst control of selectivity with ancilliary ligands.[50]

In 1996 Crabtree proved $PhI(OAc)_2$ was an effective oxidant in the acetoxylation of arenes with $Pd(OAc)_2$ as the catalyst (Scheme **36**).[51]

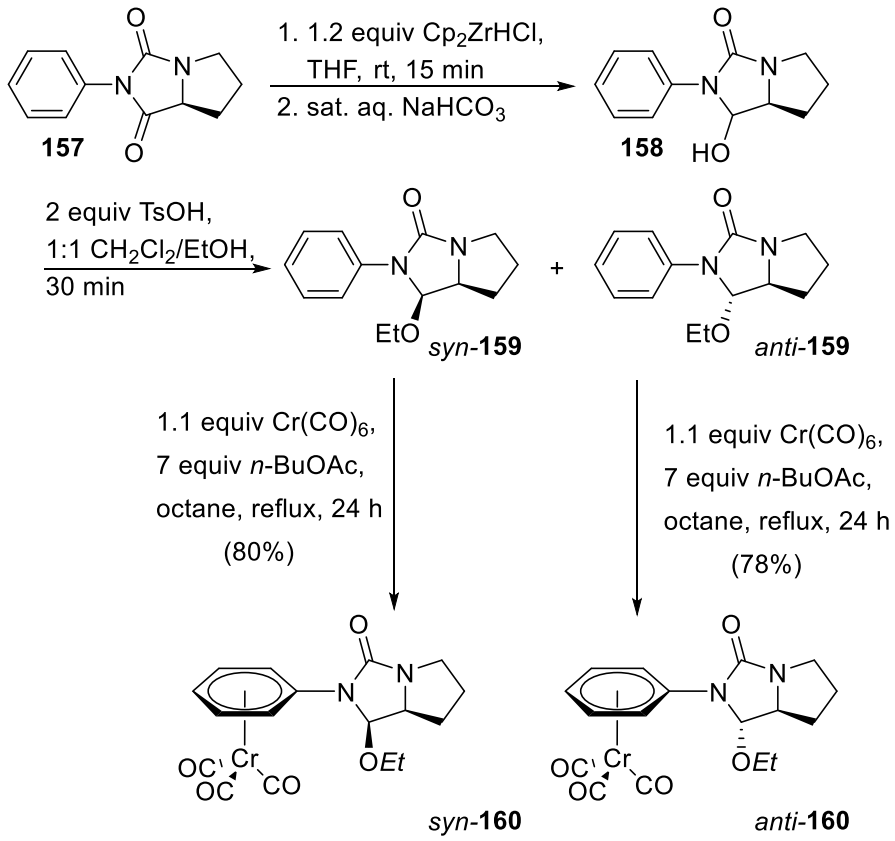


Scheme 36: Acetoxylation of benzene.[51]

The reaction, which was believed to proceed via reductive elimination from a $Pd(II)Ar_2$ intermediate, is favored by the presence of a Lewis acid (silver ion). The reaction produced good yield and selectivity, however, the turnover number was high and the presence of undesired aryl coupling product.[53]

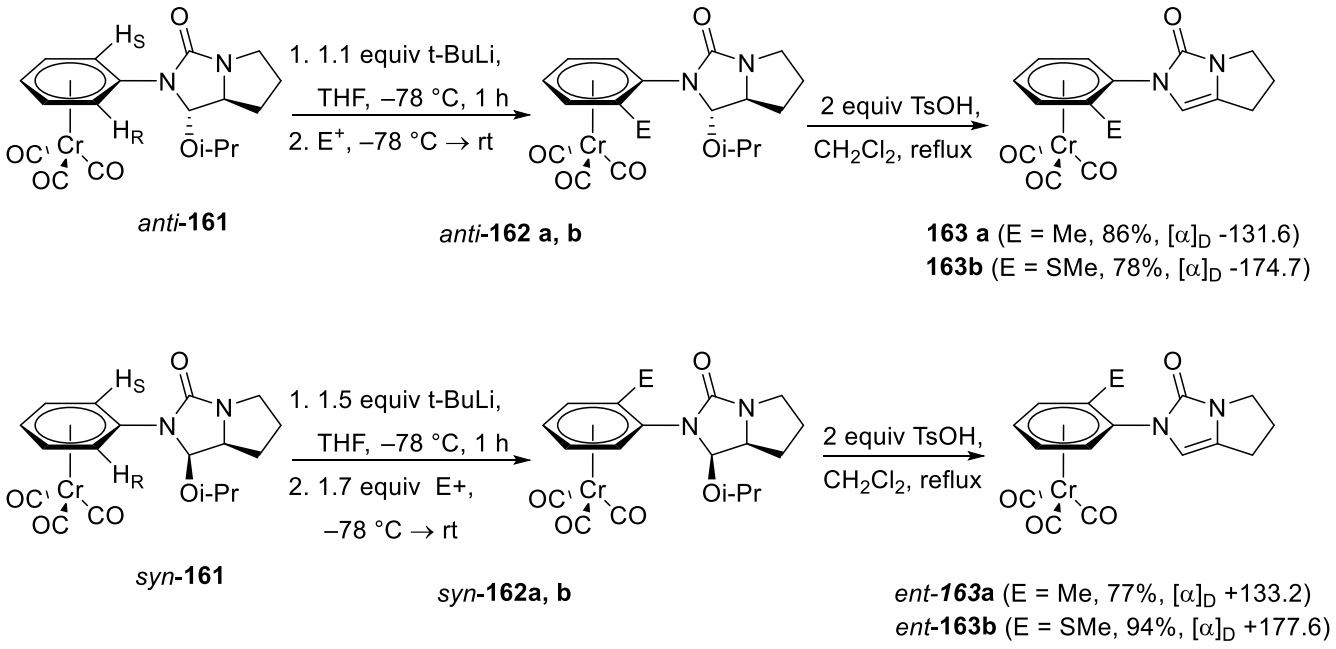
1.5 The utility of the epimeric imidazolone directing group

Recent work in the Metallinos group has focused on investigating planar chirality and expanding the utility of the epimeric imidazolone directing group towards the diastereoselective lithiation–substitution of η^6–arene chromium tricarbonyl complexes ($ArCr(CO)_3$).[4a,b] The reversal of lithiation selectivity was also observed as in the case of ferrocene when the β–stereocentre was epimerized. A modified *N*–phenyl version of the auxiliary was used to screen the lithiation of chromium complexes. From hydrozirconation of **157**, hemiaminal **158** was isolated and alkylated using TsOH in the presence of excess alcohol (ethanol, or iso propanol) yielding a mixture of *syn*– and *anti*–**159**. Epimeric chromium complexes *syn*– and *anti*– **160** were obtained by heating each epimer with hexacarbonyl chromium (Scheme **37**).



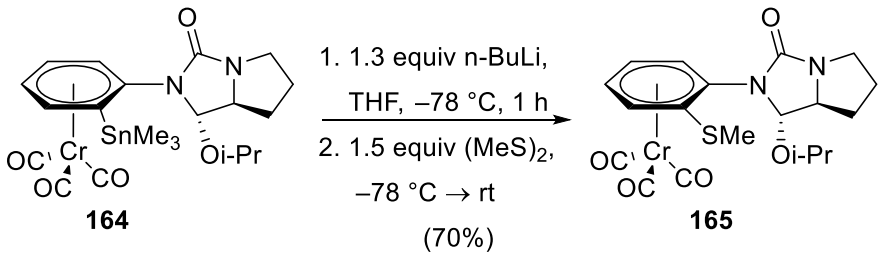
Scheme 37: Synthesis of epimeric η6–arene chromium tricarbonyl complexes.[4a]

Both epimers were treated with *t*–BuLi following a series of electrophile quenches to afford substituted substrates **162** as single diastereomers. Acid–mediated elimination yielded planar chiral imidazolones (Scheme **38**), which was analogous to the ferrocene series. The obtained optical rotations of elimination products **163a–b** were nearly equal and opposite to those of *ent*–**163a–b**, indicating that the substituted *syn*–**162** and *anti*–**162** epimers were enantiomer of each other.[4]



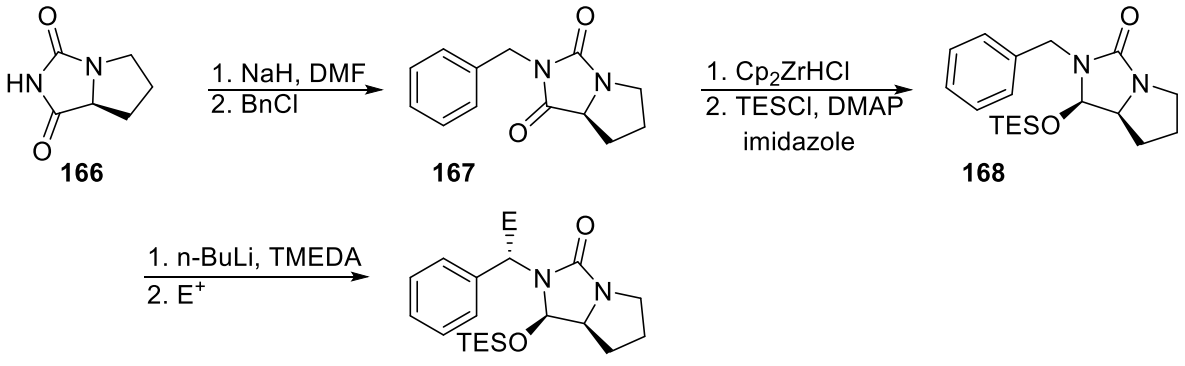
Scheme 38: Lithiation of chromium carbonyl complexes and planar chiral imidazolones.[4a]

A transmetalation experiment with stannane **164,** which involved lithiation followed by electrophile quenched, was carried out to prove that the anion of the *anti*– compound had configurational stability, and that all of the products obtained from the lithiation of the *anti*–compounds have the same relative stereochemistry (Scheme **39**). The obtained product from the transmetalation was physically (melting point and R_f) and spectroscopically (^1H and ^{13}C NMR, specific rotation) identical to the substrate obtained by direct lithiation of the *anti*–compound. Absolute stereochemistry was confirmed by X–ray crystallography of sulfide **165**, showing that, as for the ferrocene cases, the hemiaminal ether group pointed away from the metal centre, with the urea carbonyl directing the lithiation reaction.[4a]



Scheme 39: Transmetalation of stannane **164.**[4b]

In addition, the scope of the *L*−proline derived chiral auxiliary was expanded to diastereoselective lithiation of an *N*–benzyl substrate.[5] Benzyl lithiation of the substrates was the first example of stereoselective functionalization of an sp^3 centre using these types of auxiliaries. *N*–Benzyl proline hydantoin **167** was prepared by deprotonation of **166** with sodium hydride followed by treatment with benzyl chloride (Scheme **40**). Compound **168** was obtained by hydrozirconation followed by sequential silylation. Diastero–substituted products were collected through deprotonation using *n*–BuLi and an electrophile quench. The *N*–benzyl substituted products **169** were obtained as a mixture of diastereomers in up to a 91:9 dr.



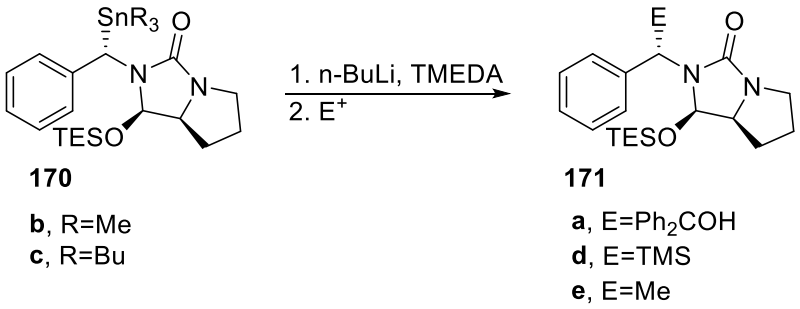
166 **167** **168**

169

a, E=Ph_2COH, 91:9 dr
b, E=$SnMe_3$, 89:11 dr
c, E=$SnBu_3$, 91:9 dr
d, E=TMS, 82:18 dr
e, E=Me, 82:18 dr

Scheme 40: Synthesis of *N*–benzyl substrates and their stereoselective lithiation.[5]

Single major diastereomer **169a** was purified and isolated for characterization. From X–ray crystallography, **169a** was assigned the *R* configuration at the benzylic carbon, *anti*–relative to the other two stereocentres. Analogous to the chromium complexes, transmetalation experiments with stannane**,** which involved lithiation followed by electrophile quenched were carried out to prove that all of the products obtained from the lithiation of *anti*–compounds had the same relative stereochemistry (Scheme **41**).



170

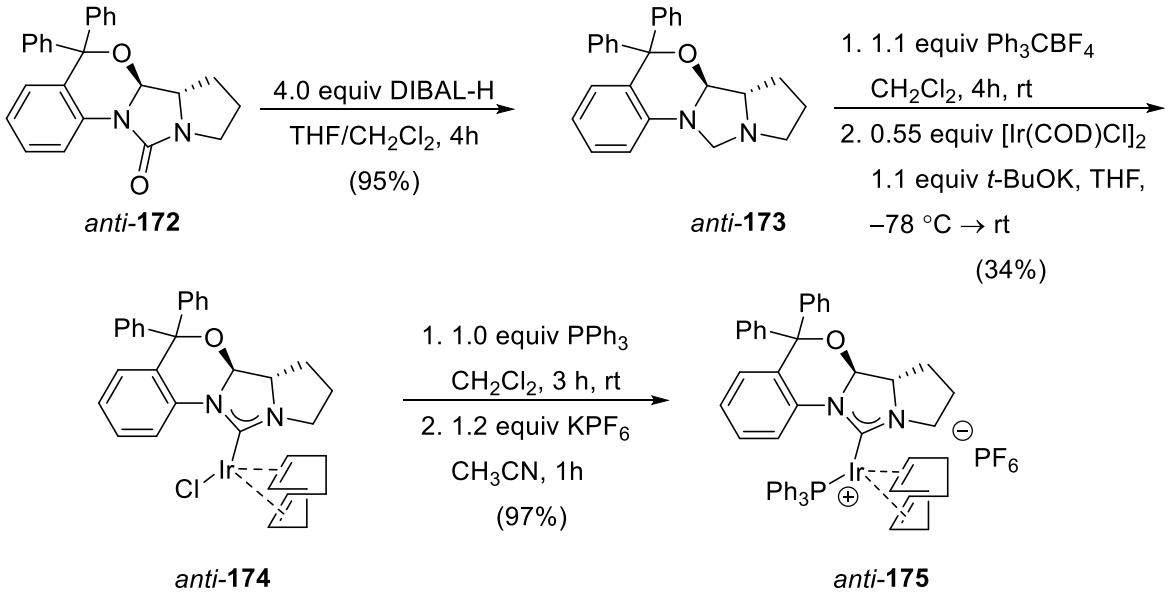
b, R=Me
c, R=Bu

171

a, E=Ph_2COH
d, E=TMS
e, E=Me

Scheme 41: Transmetallation studies of stannanes.[5]

An analogous complex of ferrocenyl fused NHC–Ir complex was also synthesized starting from *N*–phenyl hydantoin aminal **173** (Scheme **42**).[4b]



anti-**172**

anti-**173**

anti-**174**

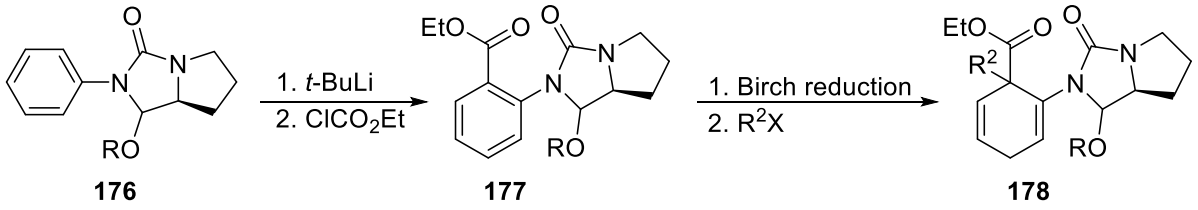
anti-**175**

Scheme 42: Synthesis of chiral iridium complexes derived from ferrocenyl and phenyl auxiliaries, respectively.[4b]

2. Research Objectives

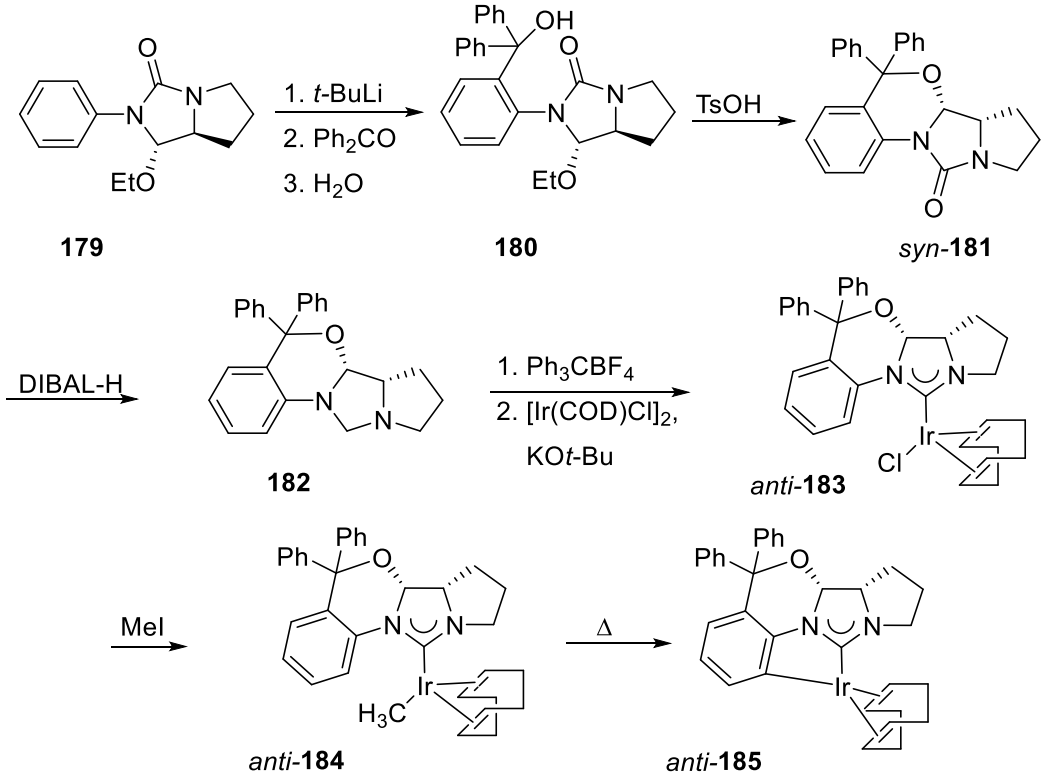
Based on previous work and observations in the Metallinos group, the objective of this thesis is to expand the application of *N*–aryl pyrroloimidazoles derivatives, first used to prepare pi–arene chromium complexes to investigate:

1./ Asymmetric alkylative Birch reduction (Scheme **43**).



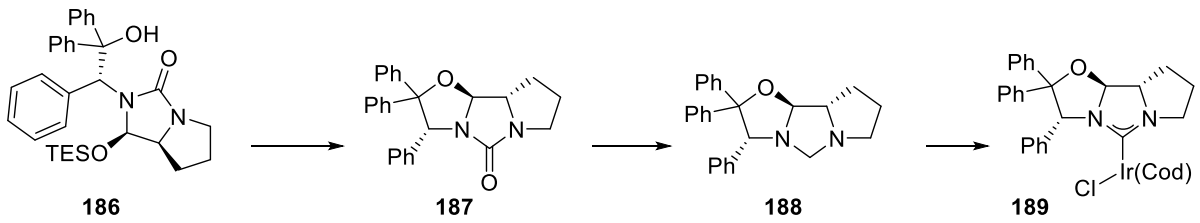
Scheme 43: Synthesis and stereoselective reductive alkylation of benzoester **177.**

2./ The propensity of *N*–aryl analogues of the ferrocenyl fused NHC–Ir complexes to undergo intramolecular C–H activation, which is based on the observation of a downfield shift of the ferrocene complexes and the *N*–aryl analogues in ^{1}H NMR (Scheme **44**).



Scheme 44: Proposed synthesis of iridacycle *anti*–**185**.

3./ An *N*–benzyl pyrroloimidazolone derived from L–proline hydantoin undergoes asymmetric lithiation with *n*–BuLi/TMEDA in toluene to give products of electrophile quench (E^{+}) with ideal diastereomeric ratio (dr).[5] Therefore, the final goal is to investigate the utility of the alkylated product was explored as a potential ligand precursor (Scheme **45**).

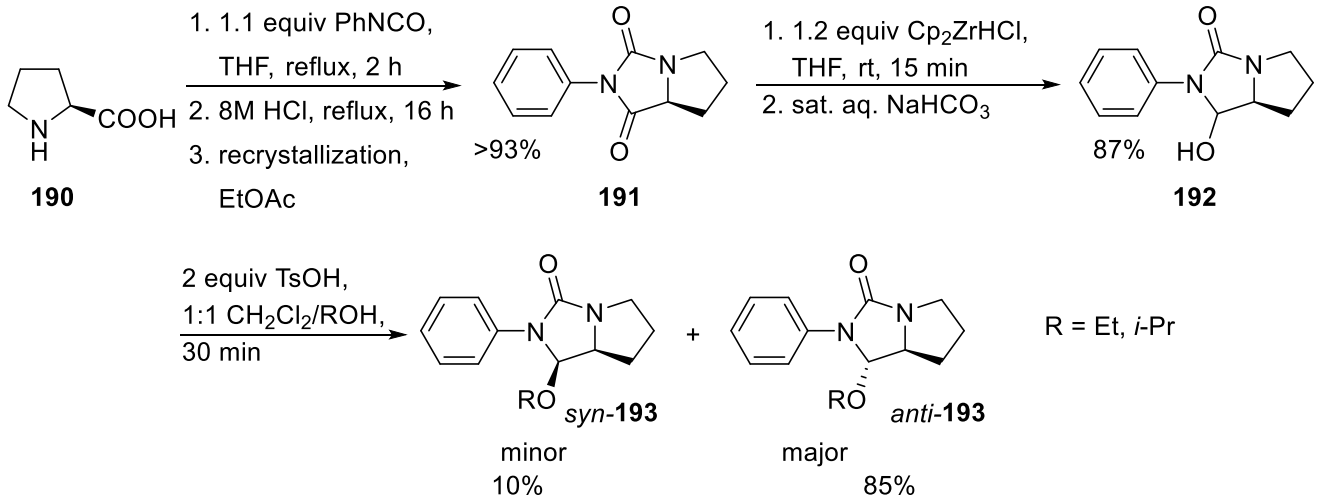


Scheme 45: Proposed synthesis of iridium–carbene complex **189**.

3. Results and Discussion

3.1 Synthesis of novel chiral auxiliaries derived from N–phenyl hydantoin

The synthesis of the *N*–phenyl derivative was carried out by acid–catalyzed condensation of phenylisocyanate with L–proline. Crystallization of the product from the reaction mixture using EtOAc produce **191** in quantitative yield with high enantiomeric purity (>95:5 er). Treatment of **191** with Schwartz reagent gave hemiaminal **192**. Treatment of hemiaminal **192** with alcohol (ethanol, or isopropanol) under acidic conditions gave epimeric *N*–phenyl imidazolones *syn*– and *anti*–**193** (Scheme **46**).

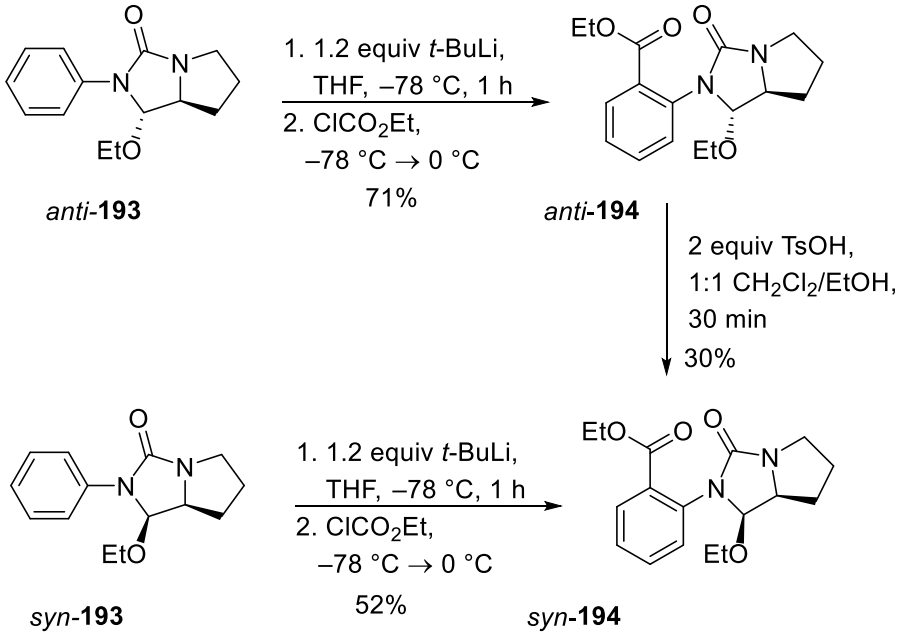


Scheme 46: Preparation of *N*–phenyl auxiliary *anti*–**193**.

Minor epimer *syn*–**193** could be obtained by equilibrating the *anti*–**193** and both epimers were used as precursors toward alkylative Birch reductions and Ir–NHC ligand synthesis.

3.2 Attempted alkylative Birch reduction

The utility of epimeric pyrroloimidazolone auxiliaries in the asymmetric Birch reduction–alkylation of benzoate esters compounds was investigated. In this case, the pyrroloimidazolones served as replacements for the methoxy group, and the derivatives place the chiral auxiliary *ortho* to the expected site of alkylation. Also, the extent of diastereoselectivity provided by sequential Birch reduction and alkylation of these substrates, the stereochemistry of the products, and determining if the epimeric starting materials can afford products with opposite configuration at the newly generated quaternary chiral centers alpha to the ester were studied (Scheme **47**).

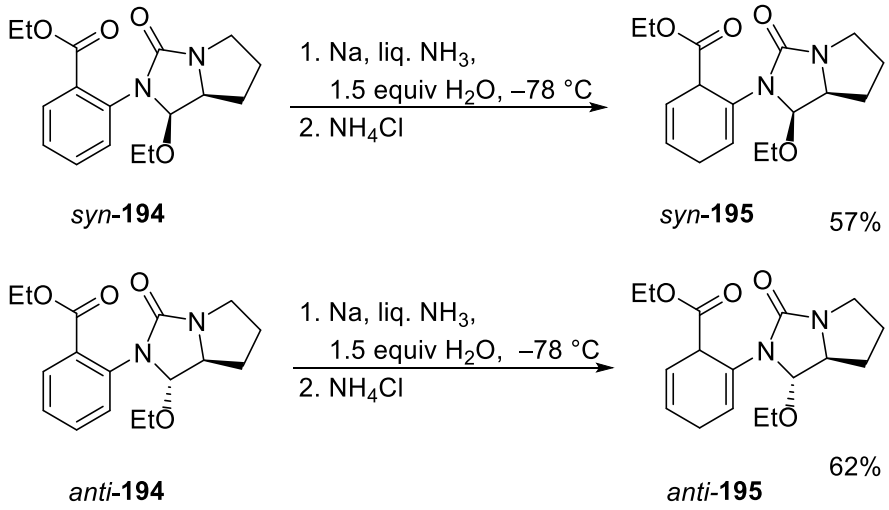


Scheme 47: Synthesis of benzoate esters *syn*– and *anti*–**194**.

The epimeric ethoxy protected *N*–phenyl proline hydantoins, *syn*– and *anti*–**193** were subjected to directed *ortho* metalation with *t*–BuLi and quenched with ethyl chloroformate to obtain aromatic

esters *syn*– and *anti*–**194** with 45% – 92 % yield. Lithiation of the *syn*– substrate was difficult because the substrate solidified when cooled to –78 °C prior to the addition of base. This issue was solved by equilibrating *anti*–**194** to *syn*–**194.** The remaining mass balance from this epimerization reaction was recovered *anti*–1**94** that could be recycled to give *syn*–1**94** that was used for reductive alkylation of the *syn*–substrate.

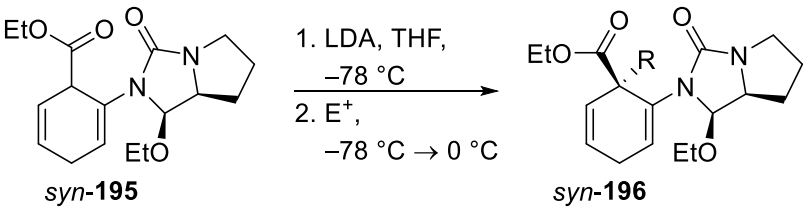
Birch reduction of pyrroloimidazolone esters *syn*– and *anti*–**194** (Scheme **48**) was conducted with sodium metal in ammonia at –78 °C using THF as a co–solvent, and either water or *t*–BuOH as proton sources. Products, which were stable at – 15 °C, were achieved by the addition of 2.5 equivalents of sodium and 1.5 equivalents of water. To ensure consistency of conditions for the subsequent alkylation reactions, cylcohexa–1,4–diene esters *syn*– and *anti*–**195** were chromatographically isolated and purified with 47–85% yields. Recovered aromatic esters *syn*– and *anti*–**194** were accounted for the remaining mass balance.



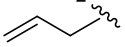
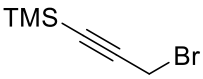
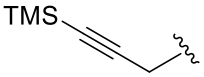
Scheme 48: Birch reduction of *syn*– and *anti*–**194** epimers

Firstly, asymmetric alkylation experiments focused on deprotonation–substitution of *syn*–**195** (Scheme **49**). Secondly, treatment of *syn*–**195** with LDA in THF at –78 °C followed by the addition of alkyl halides gave diene *syn*–**196a–g** in 47–85% yields and ranging from 88:12 to >95:5 dr

according to NMR spectroscopy. According to Schultz and co–workers, alkylation failed with less reactive alkyl halides.[21a] High diastereoselectivities were also observed for electrophiles such as benzyl bromide, allyl bromide, and iodomethane (**196 a–d**). No alkylation product was obtained in the case of **196e**. Lower diastereoselectivities were observed with electrophiles such as chloroacetonitrile (**196f**, 88:12 dr) and TMS–propargyl bromide (**14g**, 90:10 dr), which may have resulted from their lower reactivity.



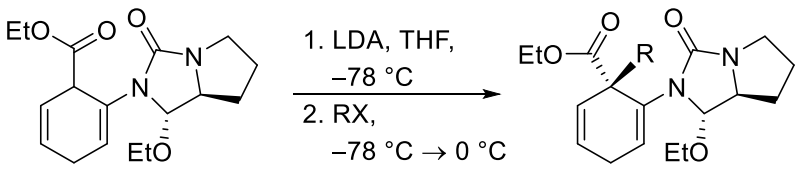
syn-**195** *syn*-**196**

syn-**196a-g**	E^+	E	yld, %	Dr
a	EtI	Et	85	95:5
b	$PhCH_2Br$	$PhCH_2$	74	95:5
c			93	95:5
d	MeI	Me	47	95:5
e	$Br\text{-}CH_2CH_2Br$	CH_2CH_2	SM	N/A
f	$ClCH_2CN$	CH_2CN	54	88:12
g			63	90:10

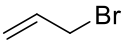
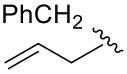
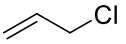
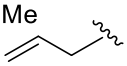
Scheme 49: Diastereoselective alkylation of *syn*–**195**

Lithiation–alkylation of *anti*–**195** (Scheme **50**) was more variable. While alkylation with more sterically demanding and reactive alkyl halides such as iodoethane and benzyl bromide proceeded well (91:9 to 95:5 dr), lower selectivity was observed for alkylation with ally bromide (80:20 dr), and no product was formed for the alkylation with allyl chloride. The use of iodomethane as the electrophile gave almost equal amounts of both diastereomers (49:51 dr). As observed in Schultz's case, MeI only gave moderate stereoselectivity in the enolate alkylation step, and more sterically demanding alkyl halides afforded better stereocontrol.[21b] The diastereomers formed from the

reactions were chromatographically inseparable. The remaining mass balance of these reaction were recovered starting material and corresponding aromatic esters.

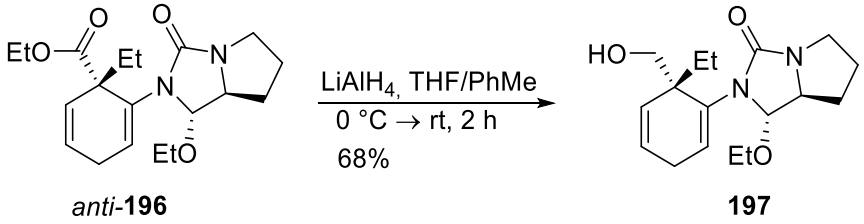


anti-**195** *anti*-**196**

anti-**196 a-e**	RX	R	yld, %	dr
a	EtI	Et	72	>95:5
b	$PhCH_2Br$	$PhCH_2$	78	91:9
c			43	80:20
d	MeI	Me	75	49:51
e			SM	N/A

Scheme 50: Diastereoselective alkylation of *anti*–**195**.

Alkylated products appeared to be colourless oils. Therefore, in order to determine the stereochemistry of the new quaternary chiral centres, *anti*–**196b** was reduced with $LiAlH_4$ to give alcohol **197** as a highly crystalline material (Scheme **51**).



anti-**196** **197**

Scheme 51: Reduction of ester **196b** to alcohol **197**

Single–crystal X–ray diffraction of substrate **197** showed that this compound had the *S* configuration at the quaternary chiral center (Figure **4**), which suggested that alkylation of the enolate had occurred on the face opposite to the alkoxy group in the pyrroloimidazolone.

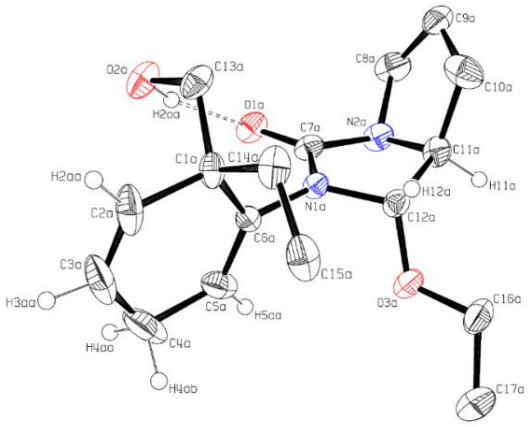
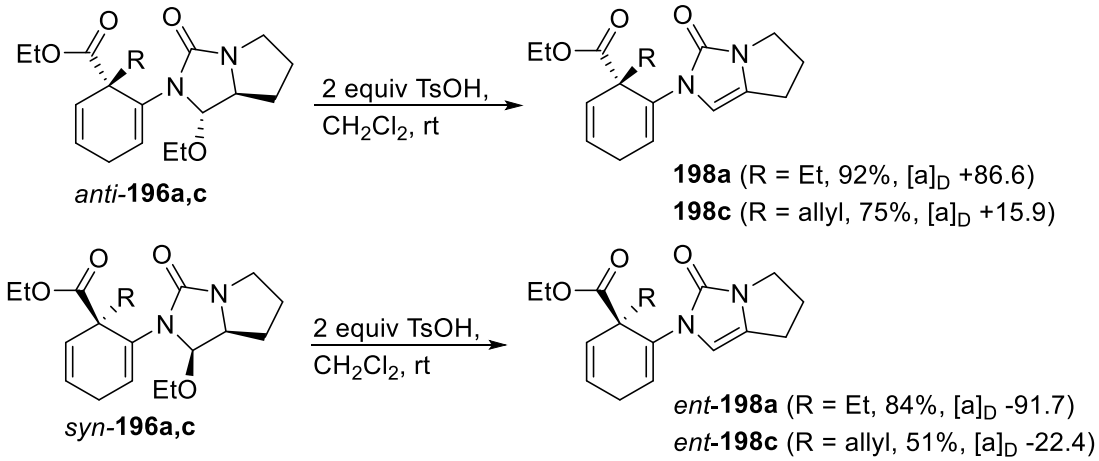


Figure 4: ORTEP plot of **197**. Most hydrogen atoms omitted for clarity.[54]

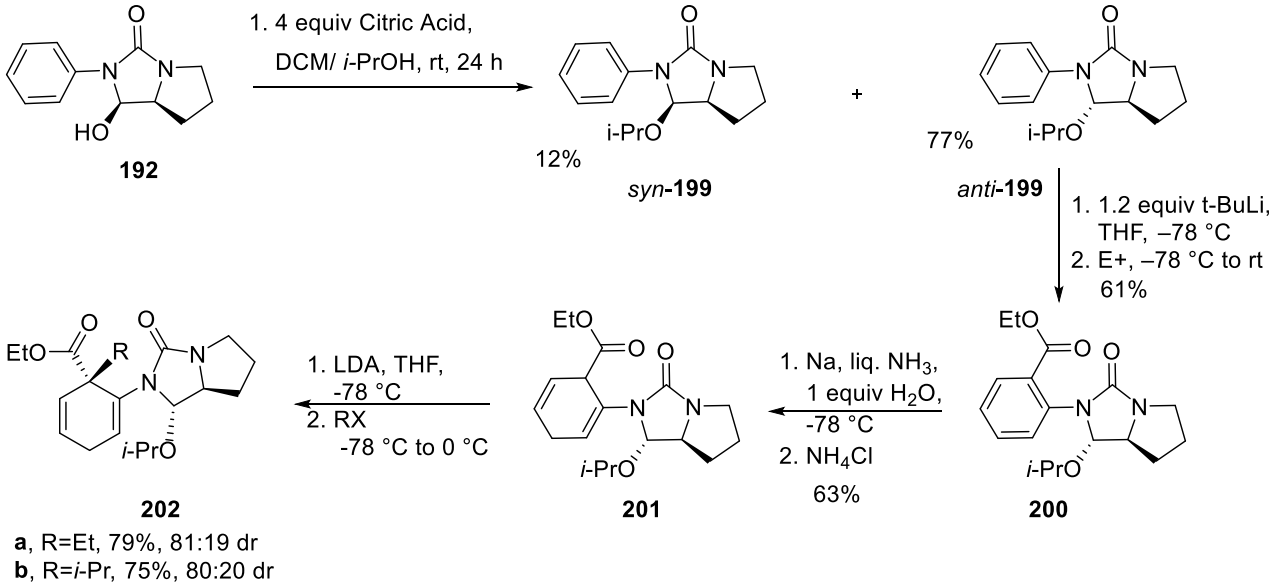
Verification that the alkylated products derived from *syn*– and *anti*–**196** had opposite stereochemistry *alpha* to the ester was provided by acid–induced elimination of products *anti*– and *syn*–**196a,c** with TsOH (Scheme **52**). Comparison of spectroscopic data and the specific rotations of **198a,c** and *ent*–**198a,c**, which retained only the quaternary chiral center, showed that they were in fact enantiomers of each other. The lower optical rotation of *ent*–**198c** was expected based on the lower stereoselectivity in allylation of *anti*–**196**.



Scheme 52: Synthesis of enantiomeric imidazolones **198a,b** and *ent*–**198a,b**

3.3 Effect of alkoxy protecting group on stereoselectivity of enolate alkylation

Different alkyl groups of the hemiaminal ether were studied to solve the issue of low selectivity related to the alkylation of *anti*–**196** (Scheme **53**).



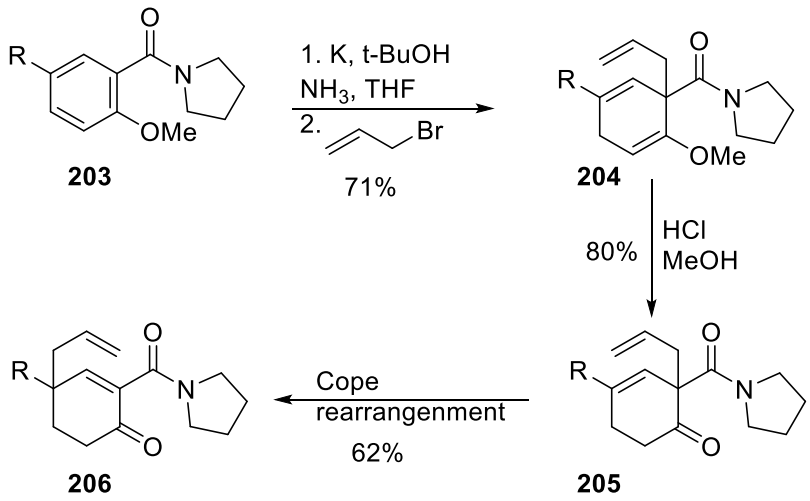
Scheme 53: Synthesis of isopropyl hemiaminal ethers as Birch reduction substrates

Isopropyl substituted hemiaminal were also investigated. Hemiaminal **192** was treated with citric acid and excess isopropyl alcohol dissolved in dichloromethane to give *anti*– and *syn*–**199** as colourless solids. Directed *ortho* lithiation yielded aromatic ester *anti*–**200**, which was converted into diene *anti*–**201** via a Birch reduction. The key alkylation step was carried out under the same conditions as the ethyl substituted case. In this case, the diastereomers formed from the reaction were chromatographically separable, allowing for access to single compounds. However, this modification did not lead to an increase in diastereomeric ratio.

3.4 Expansion of alkylated Birch reduction products

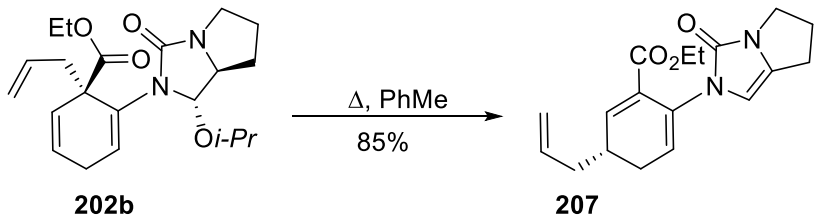
The alkylated products obtained from the Birch reduction alkylation served as useful intermediates for further synthesis. The Birch reduction–allylation was combined with the Cope rearrangement

to create a powerful tool for the construction of substituted 2–cyclohexenones, a potentially versatile synthetic intermediate.[53] Banerji and Malachowski subjected *N*–pyrrolidinyl 2–methoxy–5–methylbenzamide to a Birch reduction–allylation.[53] The resulting alkylated product was treated under thermal conditions to afford an excellent yield of the rearranged product (Scheme **54**).



Scheme 54: Birch reduction–allylation and Cope rearrangement of *N*–pyrrolidinyl 2–methoxy–5–methylbenzamide.[53]

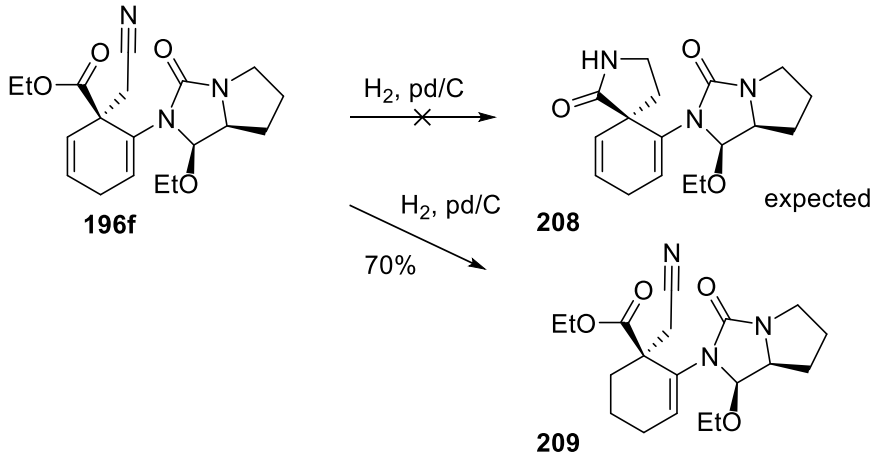
One of the allyl alkylated product was heated (200 ^{o}C) in toluene. The Cope rearrangement product was formed in up to 85% yield. The isopropoxy group was eliminated during the process.



Scheme 55: Cope rearrangement of alkylated product **202b**

In addition, the alkylated product was also tested to produce a spiro lactam through reductive cyclization (Scheme **56**). However, a vinyl *N*–phenyl compound was produced instead. A different

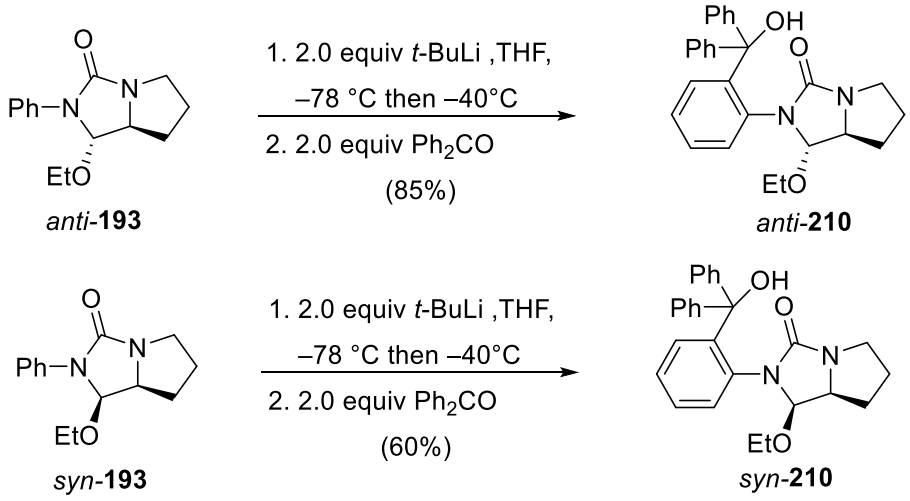
reduction procedure to convert **196f** to **208**, using Adam's catalyst, will be pursued by another member of the group.



Scheme 56: Cope rearrangement of alkylated product **196f**.

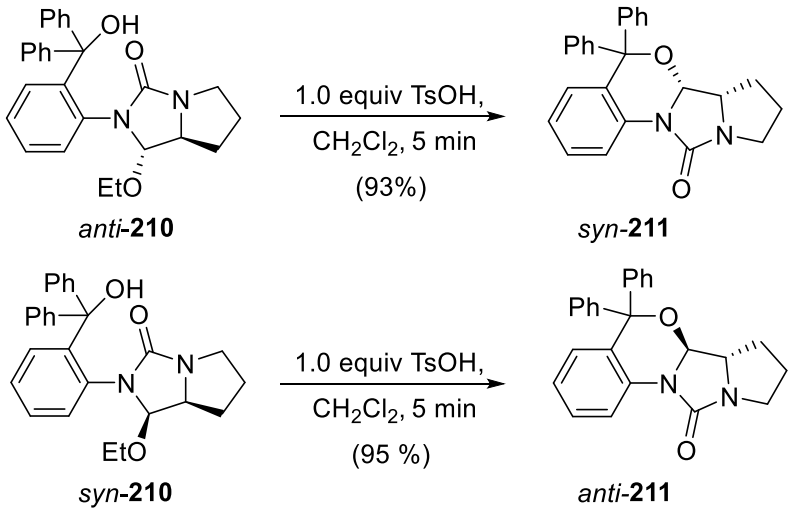
3.5 Attempt toward Ir–NHC ligand synthesis

Both *syn*– and *anti*– **193**, which were viable lithiation substrates, were individually subjected to lithiation with *t*–BuLi and again quenched with benzophenone providing both *syn*– and *anti*–**210** (Scheme **57**).



Scheme 57: *ortho*–Lithiation of ethoxy–modified imidazolones.

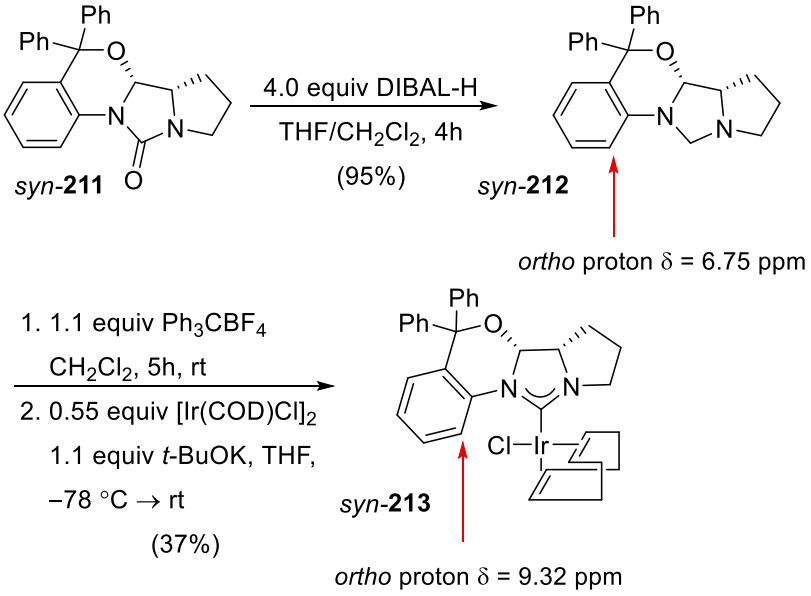
Following the same methodology used to prepare the ferrocenyl NHC Ir–catalysts,[4] *syn*– and *anti*–**210** were then subjected to acid–induced annulation with TsOH (Scheme **58**). In both cases, a single product was isolated within 10 minutes, which by ^{1}H and ^{13}C NMR appeared to be a single diastereomer. The reaction proceeded through an iminium intermediate and cyclized through the addition of the alcohol to the iminium with inversion of stereochemistry, which was determined by the coupling constants of the methine hydrogen atom located on heminal–acetal carbon.



Scheme 58: Acid–catalyzed annulation of diphenylmethanol adducts.

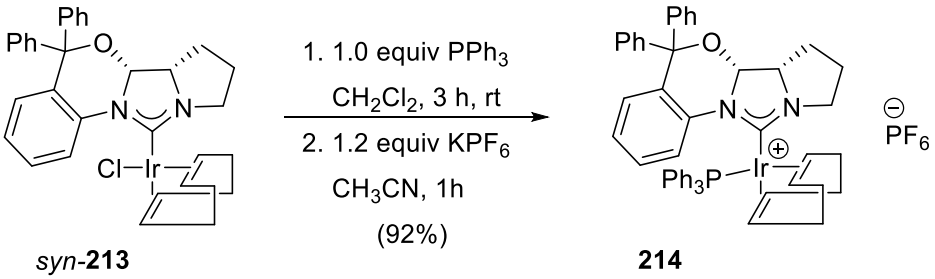
Compound **211** possessing *syn*–stereochemistry at the methine showed a doublet with a coupling constant of 6.8 Hz, while compounds possessing *anti*–stereochemistry displayed a doublet with a coupling constant of 1.6 Hz. *Syn*–**211** was then treated with DIBAL–H using PhMe as the solvent, followed by a Fraiser workup to give *syn*–**212** with up to 93% yield. The Ir–NHC ligand was prepared in situ. *Syn*–**212** was treated with triphenylcarbenium tetrafluoroborate in degassed THF and stirred for 5 hours at room temperature to generate the imidazolinium intermediate. KO*t*Bu was then added to the mixture at –78 ^{o}C to produce the imidazolylidene, which was immediately

trapped with $[Ir(COD)Cl]_2$, providing *syn*–**213,** which was isolated by column chromatography in 37% over two steps (Scheme **59**).



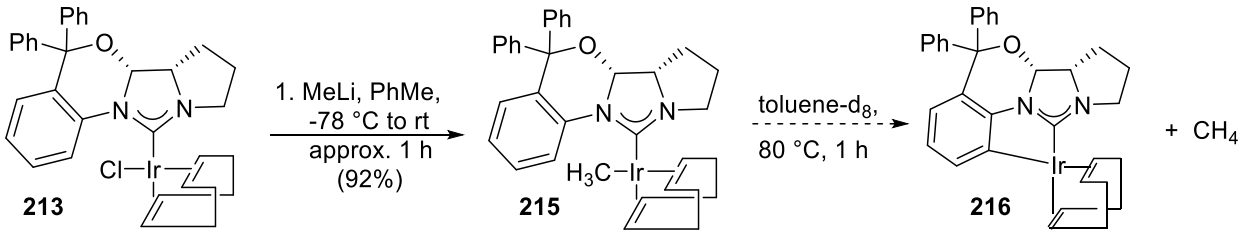
Scheme 59: Conversion of annulated urea to Ir–complex *syn*–**213**.

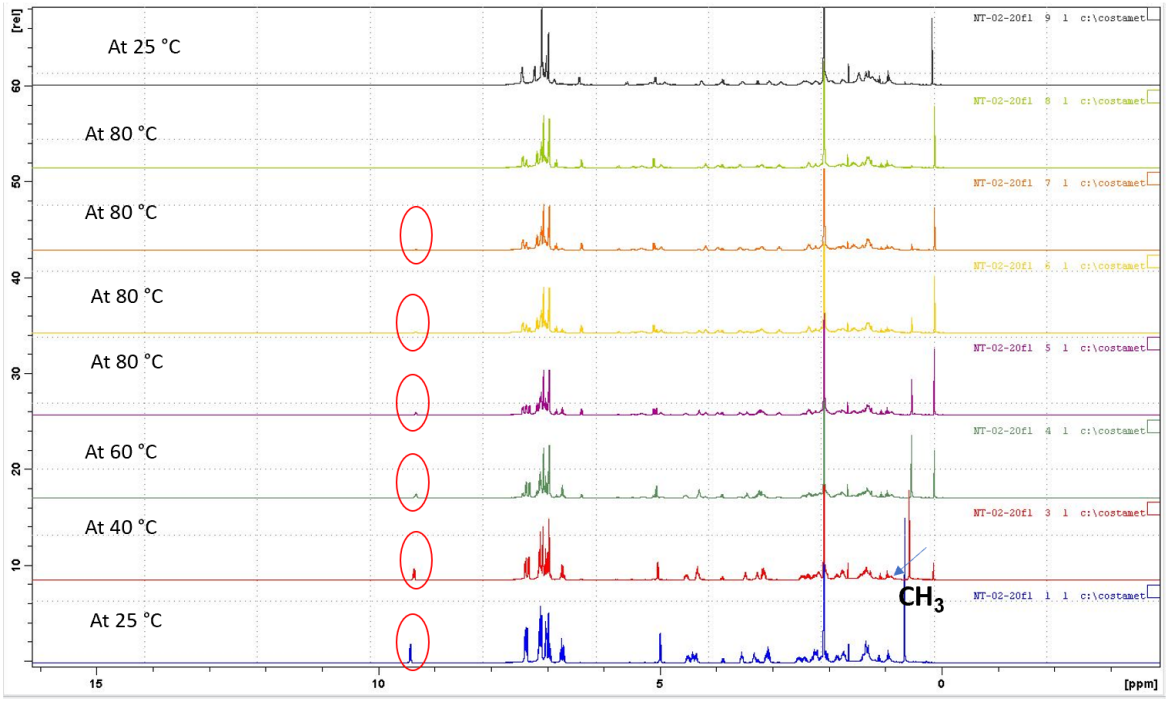
This downfield shift of the *orthro* proton in Ir–complex *syn*–**213** appeared at δ = 9.32 ppm compared to the *ortho* proton signal of aminal **212** (δ = 6.75 ppm). This proton was assumed to be deshielded by the electron cloud of the iridium atom. Experiments were performed to test whether the electron cloud of the metal would affect the *ortho* proton signal. Compound **213** was treated with triphenyl phosphine, and a downfield shift from 9.32 ppm to 8.42 ppm was observed for the *ortho* proton (Scheme **60**).



Scheme 60: Synthesis of Ir cationic **214**

This data proved that there was an interaction between the *ortho* proton and the metal. Based on these observations, the aryl sp^2 C–H bond could be activated and generated a functional C–M bond. Exposure of **213** to MeLi gave complex **215** in quantitative yield. Compound **215** was air unstable and decomposed upon interaction with silica gel. Upon heating, **215** underwent C–H activation of the phenyl ring with concomitant loss of methane. The loss of the signals corresponded to the *ortho*–phenyl hydrogen, and the iridium methyl group was monitored by ^{1}H NMR, along with simultaneous formation of free methane (Scheme **61**, Figure **3**).

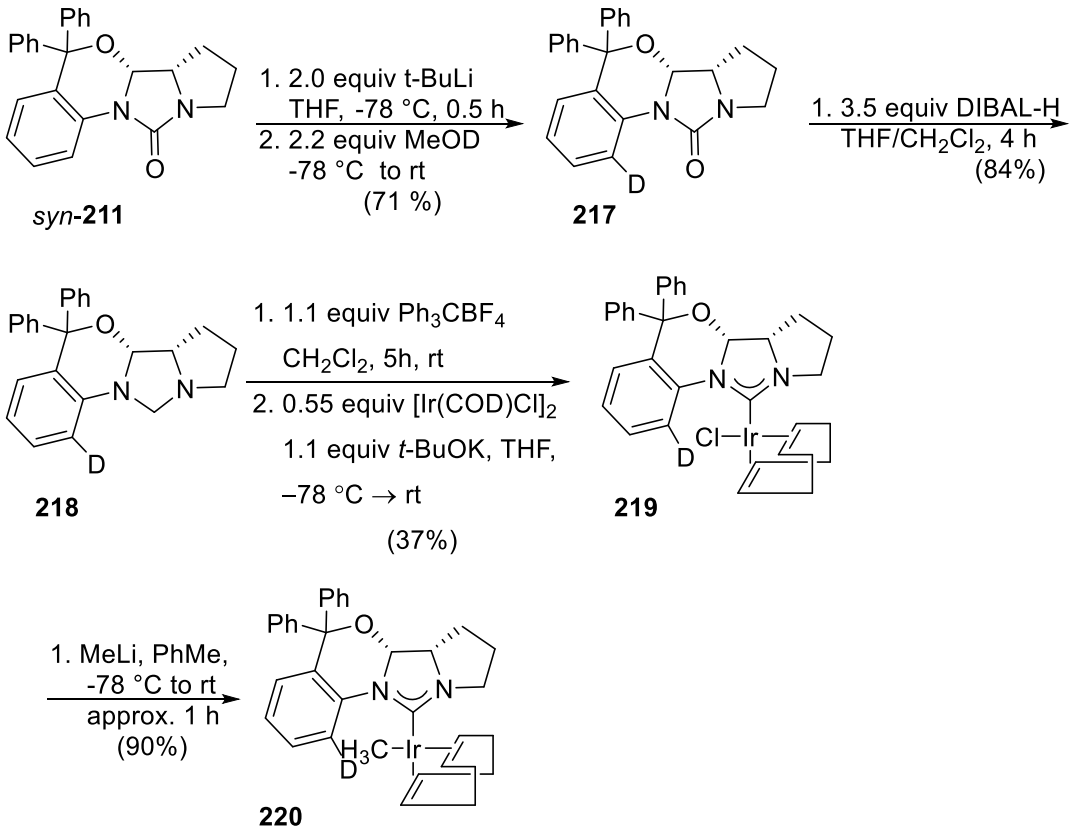




Scheme 61: NMR study of Iridacycle **216**

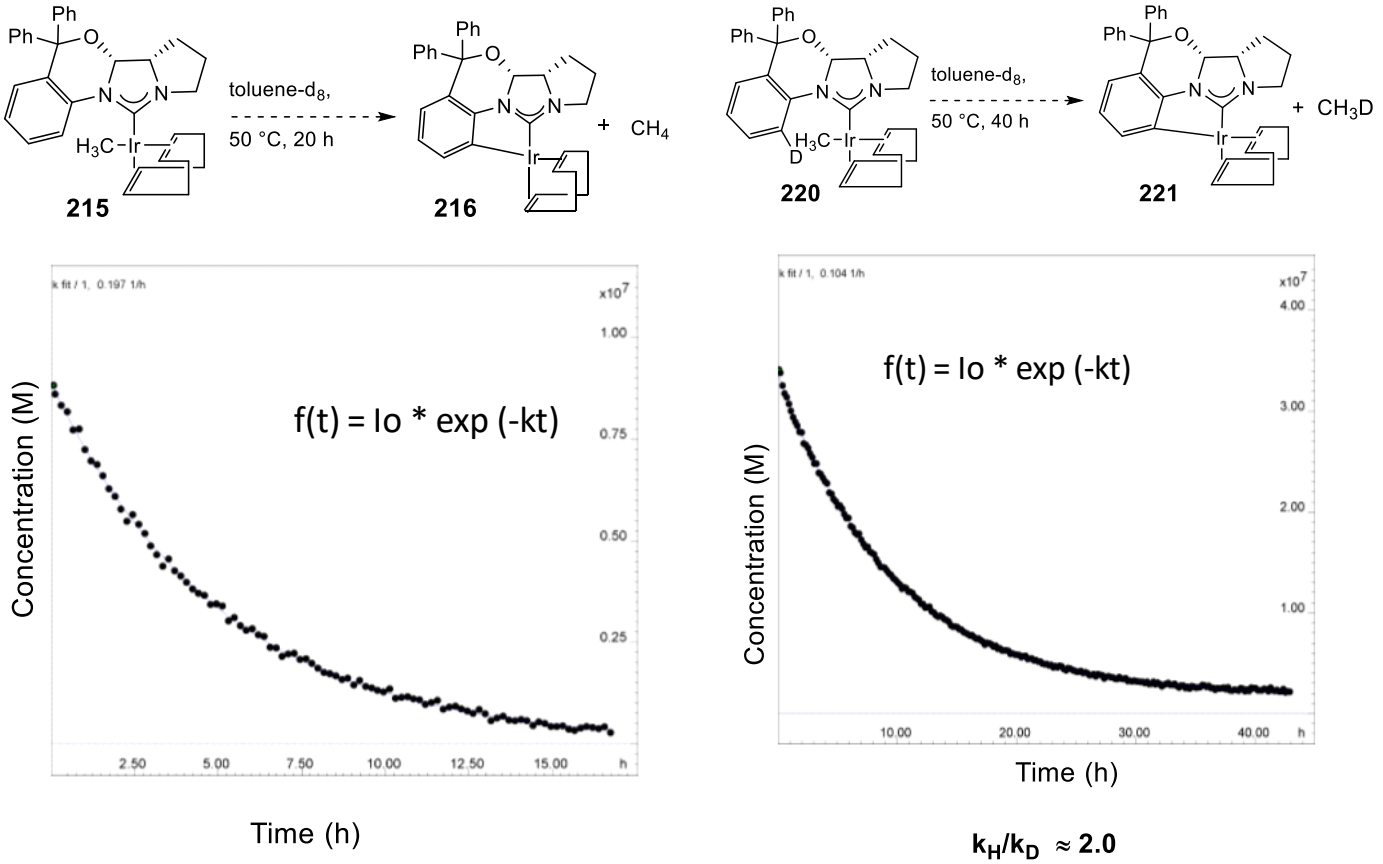
3.6 Experiment of kinetic isotope effect

The kinetic isotope effect, which was defined as the ratio of the rate constants corresponding to the unlabelled and labelled species at a given internal energy, was further investigated.[56] These experiments have been repeated with an *ortho*–deuterated analogue of complex **216** (Scheme **62**).



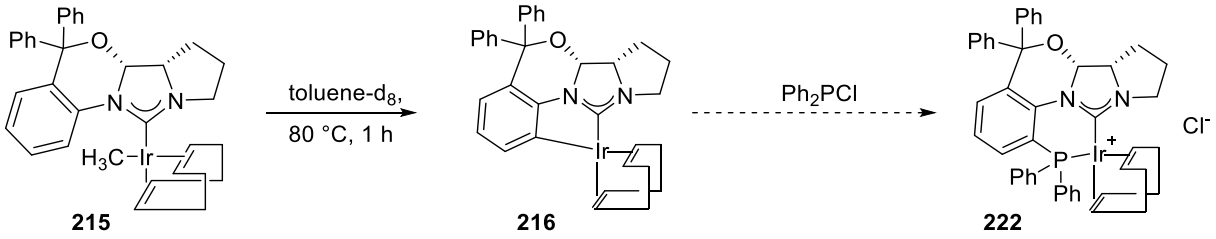
Scheme 62: Synthesis of deuterated N–Phenyl Imidazolone

In the deuterated case, a slower reaction rate was observed, along with production of deuterated methane. This result was strongly indicative of a primary kinetic isotope effect (k_H/k_D = 2) (Scheme **63**).



Scheme 62: Kinetic isotope effects study of *N*–phenyl imidazolone

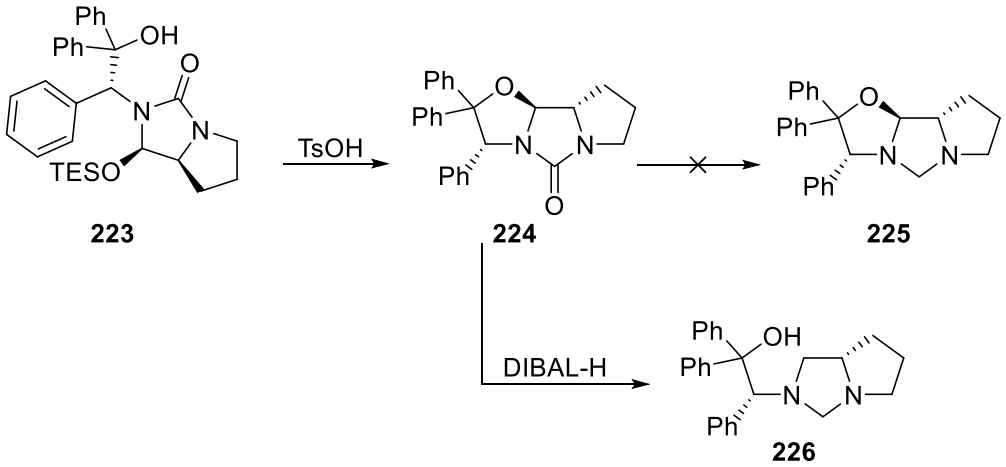
Compound **221** was very unstable, leading to challenges in structural determination. However, with the success in synthesizing of the compound **221** will supply a new way to produce bidentate ligand **222**.



Scheme 63: Proposed pathway to synthesize bidentate ligand **222**.

3.7 Attempt towards an NHC ligand derived from *N*–benzyl hydantoin

An *N*–benzyl pyrroloimidazolone derived from *L*–proline hydantoin underwent asymmetric lithiation with *n*–BuLi/TMEDA in toluene to give products of electrophile quench (E^+) with an ideal diastereomeric ratio (dr). The alkylated compound **223** was treated with TsOH acid to produce urea **224.** There were many attempts to reduce tetracyclic urea **224** to produce the desired compound **225**. However, only the alcohol **226** was collected (Scheme **65**).



Scheme 64: Cyclization and reductive ring opening of N–benzyl derived substrate

4. Conclusion and Future Work

Ortho–substituted benzoates *syn*– and *anti*–**194** were shown to undergo smooth Birch reduction to produce isolable 1,4–cyclohexadienes *syn*– and *anti*–**195**. Asymmetric lithiation–alkylation of these dienes gave substituted products with quaternary chiral centers in generally good diastereomeric ratios (from 80:20 to >95:5 dr). The selectivity obtained by alkylation of *anti*–**195** was more varied, ranging from a low of 53:46 dr to 95:5 dr using iodomethane or iodoethane electrophiles, respectively. Treating the purified minor allyl–substituted diastereomer **202b** with high temperatures in a sealed tube apparatus induced the Cope rearrangement reaction, which

transfered chirality to a remote position of the cyclohexadiene without racemization. The stereochemistry of the *anti*– and *syn*–derived products was determined by X–ray crystallography of key alcohol **197**, in combination with specific rotation measurements of the *syn*– and *anti*–derived elimination products **198a,b** and *ent*–**198a,b**. Further work to explore applications of this methodology will be carried on in our laboratories.

The synthesis and partial evaluation of the *N*–phenyl iridium complex derived from the annulated aminal with *syn*–stereochemistry in the backbone was achieved. In addition to this, treatment of the neutral Ir–complexes with anionic nucleophiles such as MeLi resulted in an increase of electron density at the Ir atom and initiated C–H bond activation.

Aminal **226** was treated with triphenylcarbenium tetrafluoroborate and did not lead to the formation of an iminium as with the ferrocenyl and phenyl series. Several oxidation methods were explored by another member of the research group in attempts to achieve the NHC precursor. However, all attempts did not result in the desired products. It is likely that the alcohol moiety of **226** interferes with the oxidation process and oxidation of protected analogs could be explored in the future.

5. Experiment and Procedures

General. All reagents were purchased from Aldrich, Fisher Scientific, Acros, Strem or Oakwood chemicals and used as received unless otherwise indicated. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone ketyl under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. All alkyllithiums were titrated against *N*–benzylbenzamide to a blue endpoint. All reactions were performed under nitrogen or argon in flame– or oven–dried glassware using syringe–septum cap techniques unless otherwise indicated. TLC was performed on silica gel 60 F_{254}. Column chromatography was performed on silica gel 60 (70–230 mesh). Schwartz's reagent was prepared according to a literature procedure.[54] NMR spectra were obtained on a Bruker Avance 300, 400 or 600 MHz instrument and are referenced to the residual proton signal of the deuterated solvent for ^{1}H spectra, and to the carbon multiplet of the deuterated solvent for ^{13}C spectra according to published values.[55] FT–IR spectra were obtained on Bruker ALPHA platinum ATR spectrometer as neat materials. Specific rotations of diastereomerically and enantiomerically pure materials were measured on a Rudolph Research Autopol III automatic polarimeter. Mass spectra were obtained on a **Micromass GCT** spectrometer. The same mass spectrometer machine was used for LR–MS and HR–MS. Combustion analyses of the most stable compounds were performed by Atlantic Microlab Inc., Norcross, GA, USA. Melting points were determined on a Kofler hot–stage apparatus and are uncorrected.

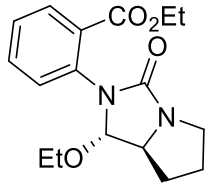
Method a

Ethyl2-[(1R,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]benzoate (*syn*–194).** A solution of *syn*–**193** (240 mg, 0.98 mmol) in THF (5.0 mL) at −78 °C was treated with *t*–BuLi (6.13 mL, 0.40 M, 2.14 mmol). The solution turned deep yellow. After 30 minutes, ethylchloroformate (0.21 ml, 2.14 mmol) was added. The solution mixture turned brownish green upon addition of the electrophile, and the reaction was then stirred at –78 ºC for additional 30 minutes, and then allowed to stir to room temperature (30 mins). Water (0.25 mL) was added and the reaction mixture which was then extracted with EtOAc (3x 3 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2) gave *syn*–**194** (165 mg, 52 %) as a clear oil; $[\propto]_D^{20} = -35.3$ (c =1.03, acetone); IR (ATR, solid) ν_{max} 2975, 2932, 2880, 1707, 1621, 1600, 1577, 1489.6,1454, 1403, 1367, 1327, 1289, 1251, 1158, 1087, 854, 796, 758, 709 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 7.85 (d, 1H, *J* = 7.7 Hz), 7.59 (t, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 7.9 Hz), 7.39 (t, 1H, *J* = 7.6 Hz), 5.32 (d, 1H, *J* = 6.8 Hz), 4.31 – 4.23 (m, 2H), 4.15 (q, 1H, *J* = 6.6 Hz) 3.50 (q, 3H, *J* = 6.2 Hz), 3.09 – 3.04 (m, 1H), 2.07 – 1.99 (m, 2H), 1.96 – 1.87 (m, 2H), 1.34 (t, 3H, *J* = 7.2 Hz), 1.12 (t, 3H, *J* = 7.2 Hz), ^{13}C NMR (100 MHz, acetone–d_6) δ 166.1, 159.2, 138.04, 131.9, 130.5, 129.5, 128.8, 126.4, 88.7, 64.6, 61.3, 60.6, 45.4, 26.01, 24.6, 14.6, 13.6 ; LR–MS (EI) [m/z (%)] 318 (M^+, 2), 289 (55), 272 (43), 243 (100), 227 (40), 218 (74), 215 (31), 146 (50); HR–MS (EI) calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found 318.1574.

Method b

To a solution of *anti*–**194** (500 mg, 1.57 mmol) in DCM (10.0 mL) and excess ethanol (50ml), pTSOH (597 mg, 3.14 mmol) was added. The mixture was stirred for 30 minutes at room

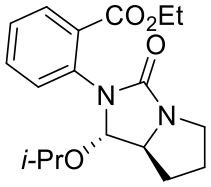
temperature, and the acid was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (25 ml). The reaction mixture was extracted with EtOAc (3 x 15 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2) gave *syn*–**194** (150 mg, 30 %) as a clear oil.

Ethyl2-[(1S,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]benzoate (*anti*–**194).** 

A solution of *anti*–**193** (1.00 g, 4.06 mmol) in THF (15.0 mL) at −78 °C was treated with *t*–BuLi (6.25 mL, 1.30 M, 8.12 mmol). The solution turned orange upon addition and progressively darkened to red. After 30 minutes, ethylchloroformate (0.78 ml, 8.12 mmol) was added. The solution mixture turned brownish green upon addition of the electrophile, and the reaction was then stirred at –78 ^oC for additional 30 minutes, and then allowed to stir to room temperature (30 mins). Water (1.00 mL) was added and the reaction mixture which was then extracted with EtOAc (3x15 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.3) gave *anti*–**194** (0.91g, 71 %) as a clear oil that crystallized upon standing; mp 99–101 °C (EtOAc/hexane); $[\propto]_D^{20} = -12.8$ (c =1, acetone); IR (ATR, solid) ν_{max} 2974, 2935, 2897, 1710, 1600, 1578, 1491,1453, 1399, 1367, 1325, 1291, 1252, 1222, 1078, 802, 762, 706 cm^{-1}; ^1H NMR (600 MHz, acetone–d_6) : δ 7.83 (d, 1H, *J* = 7.7 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 5.40 (s, 1H), 4.33 – 4.21 (m, 2H), 3.68 (dd, 1H, *J* = 9.72 Hz, 6.48 Hz) 3.64 – 3.50 (m, 2H), 3.53 – 3.51 (m, 1H), 3.05 (ddd, 1H, *J* = 13.26 Hz, 9.06 Hz, 4.44 Hz), 2.12 – 2.09 (m, 1H), 2.04 – 1.98 (m, 1H), 1.92 – 1.85 (m, 1H), 1.76 – 1.69 (m, 1H), 1.34 (t, 3H, *J* = 7.12 Hz), 1.13 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 166.1, 161.3, 137.7, 131.97, 130.22, 129.2, 127.5, 126.2, 90.4,

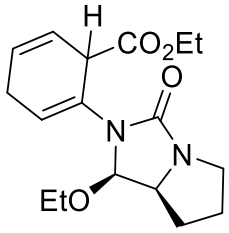
63.8, 61.1, 60.6, 45.3, 28.3, 24.7, 14.8, 13.7 ; LR–MS (EI) [m/z (%)] 318 (M^+, 1), 289 (31), 272 (42), 243 (51), 218 (30), 146 (31), 83 (100), 71 (64), 52 (73); HR–MS (EI) calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found 318.1574.

Isopropoxy–2-[(1S,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]benzoate



(*anti*–**200).** A solution of *anti*–**199** (300 mg, 1.15 mmol) in THF (6.0 mL) at −78 °C was treated with *t*–BuLi (1.82 mL, 1.27 M, 2.31 mmol). The solution turned deep orange upon addition. After 30 minutes, ethylchloroformate (0.22 ml, 2.31 mmol) was added. The solution mixture turned brownish blue upon addition of the electrophile, and the reaction was then stirred at –78 °C for additional 30 minutes, and then allowed to stir to room temperature (30 mins). Water (0.5 mL) was added and the reaction mixture which was then extracted with EtOAc (3x10 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2) gave *anti*–**200** (195 mg, 52%) as a clear oil $[\propto]_D^{20} = -36.4$ (c =1, acetone); IR (ATR, solid) ν_{max} 2972, 1716, 1599, 1493,1454, 1409, 1293, 1254, 1083, 765 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 7.85 (dd, 1H, *J* = 7.76 Hz, *J* = 1.52 Hz), 7.60 (td, 1H, *J* = 7.40 Hz, *J* = 1.60 Hz), 7.51 (dd, 1H, *J* = 8.0 Hz, *J* = 1.16 Hz), 7.39 (td, 1H, *J* = 7.60 Hz, *J* = 1.30 Hz), 5.37 (d, 1H, *J* = 0.88 Hz), 4.35 – 4.23 (m, 2H), 3.70 (q, 1H, *J* = 6.12 Hz), 3.64 – 3.59 (m, 1H), 3.56 (dt, 1H, *J* = 11.04 Hz, 7.80 Hz), 3.04 (ddd, 1H, *J* = 13.32 Hz, 8.76 Hz, 4.52 Hz), 2.15 – 2.09 (m, 1H), 2.04 – 1.97 (m, 1H), 1.94 – 1.83 (m, 1H), 1.79 – 1.69 (m, 1H), 1.34 (t, 3H, *J* = 7.12 Hz), 1.12 (d, 3H, *J* = 6.08 Hz), 1.02 (d, 3H, *J* = 6.12 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 166.0, 161.2, 137.7, 131.9, 130.2, 129.6, 128.8, 126.4, 89.9, 70.0, 65.7, 60.6, 45.3, 28.1, 24.8, 22.3, 21.9, 13.6 ; LR–MS (EI) [m/z (%)] 332 (M^+, 1), 272 (100), 243 (36), 218 (38), 200 (48), 171 (20); HR–MS (EI) calcd. for $C_{18}H_{24}N_2O_4$: 332.1736; found 332.1728.

Ethyl 2-[(1R,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]cyclohexa-2,4-diene-1-carboxylate (*syn*–195). To a solution of *syn*–**194** (230 mg, 0.723 mmol) in THF (5.0 mL),



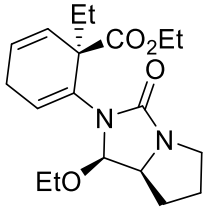
and water (0.02 ml, 1.08 mmol) at –78 ^{o}C, liquid ammonia was condensed. Na (41.57 mg, 1.81 mmol) metal was then added slowly in small pieces. After the blue color persists, and the reaction mixture was left stirring at that temperature for additional 2 hours. Aqueous NH_4Cl was added slowly until decolourization obtained. Cold bath was removed, and liquid ammonia was evaporated with backflow of Nitrogen. The reaction mixture was then extracted with Et_2O (3x 5mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f =0.3) gave *syn*–**195** (168 mg, 72%) as a clear oil; $[\propto]_D^{20} = -41.9$ (c = 0.25, acetone); IR (ATR, solid) ν_{max} 3038, 2975, 2933, 2879, 2821, 1730, 1699, 1403, 1374, 1347, 1329, 1274, 1238, 1178, 1082, 1031, 996, 803, 758, 686 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 5.84 – 5.82 (m, 2H), 5.75 – 5.72 (m, 1H), 5.01 (d, 1H, *J* = 7.2 Hz), 4.59 – 4.56 (m, 1H), 4.14 – 4.099 (m, 1H), 4.09 – 4.03 (m, 1H) 3.97 (q, 1H, *J* = 7.2 Hz), 3.68 – 3.63 (m, 1H), 3.58 – 2.53 (m, 1H), 3.36 – 3.32 (m, 1H), 2.97 – 2.93 (m, 1H), 2.82 – 2.80 (m, 2H), 1.99 – 1.93 (m, 1H), 1.92 – 1.81 (m, 3H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.19 (t, 3H, *J*= 7.0 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 170.91, 158.1, 131.98, 125.5, 122.5, 115.4, 88.95, 63.6, 61.03, 60.3, 44.9, 42.99, 26.3, 26.2, 24.6, 14.6, 13.6 ; LR–MS (EI) [m/z (%)] 320 (M^+, 1), 274 (56), 227 (100), 201 (24); HR–MS (EI) calcd. for $C_{17}H_{24}N_2O_4$: 320.1736; found 320.1730.

Ethyl2-[(1S,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]cyclohexa-2,4-diene-1-carboxylate (*anti*–*195*). To a solution of *anti*–**194** (500 mg, 1.57 mmol) in THF (10.0 mL), and water (0.04 ml, 2.36 mmol) at –78 ^{o}C, liquid ammonia was condensed. Na (90.28 mg, 2.93 mmol) metal was then added slowly in small pieces. The brownish blue colour persists, and the reaction mixture was left stirring at that temperature for additional 2 hours. Aqueous NH_4Cl was added slowly until decolourization obtained. Cold bath was removed, and liquid ammonia was evaporated with backflow of Nitrogen. The reaction mixture was then extracted with Et_2O (3x15 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.5) gave *anti*–**195** (264 mg, 52 %) as a clear oil; $[\propto]_D^{20} = -89.6$ (c =1, acetone); IR (ATR, solid) ν_{max} 3038, 2974, 2936, 2898, 2879, 2822, 1729, 1704, 1648, 1398, 1179,1071, 1032, 804, 765, 680 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.91 – 5.896 (m, 1H), 5.86 – 5.82 (m, 1H), 5.77 – 5.73 (m, 1H), 5.01 (s, 1H), 4.82 – 4.77 (m, 1H), 4.12 – 4.04 (m, 2H) 3.56 (q, 2H, *J* = 6.8 Hz), 3.52 – 3.48 (m, 2H), 2.9 7(ddd, 1H, *J* = 13.76 Hz, 8.52Hz, 5.24 Hz), 2.86 – 2.82 (m, 2H), 2.04 – 1.98 (m, 1H), 1.87–1.78 (m, 2H), 1.397 – 1.295 (m, 1H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.21(t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 170.99, 161.2, 125.4, 122.4, 115.0, 90.2, 63.4, 60.4, 58.9, 45.5, 43.3, 26.1, 24.3, 14.7, 13.6 ; LR–MS (EI) [m/z (%) 320 (M^+, 9), 273 (31), 227 (100), 201 (15); HR–MS (EI) calcd. for $C_{17}H_{24}N_2O_4$: 320.1736; found 320.1730.

[(1S,7aS)-1-Isopropoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-yl]cyclohexa-2,4-diene-1-carboxylate (*anti*–201).** To a solution of *anti*–**199** (400 mg, 1.20 mmol) in THF (8.0 mL), and water (0.03 ml, 1.80 mmol) at –78 ^{o}C, liquid ammonia was condensed. Na (69 mg, 3.0 mmol) metal was then added slowly

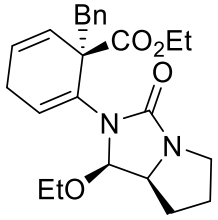
in small pieces. The blue colour persists, and the reaction mixture was left stirring at that temperature for additional 4 hours. Aqueous NH_4Cl was added slowly until decolourization obtained. Cold bath was removed, and liquid ammonia was evaporated with backflow of Nitrogen. The reaction mixture was then extracted with Et_2O (3x10 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.4) gave *anti*–**201** (203 mg, 57 %) as a clear oil; $[\propto]_D^{20} = -89.8$ (c = 0.75, acetone); IR (ATR, solid) ν_{max} 3038, 2971, 2935, 2898, 2877, 2822, 1704, 1649, 1461, 1346, 1179,1061, 1022, 997, 837, 791, 682 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 5.99 (tt, 1H, *J* = 3.7 Hz, *J* = 0.96 Hz), 5.87 – 5.82 (m, 1H), 5.77 – 5.73 (m, 1H), 4.99 (s, 1H), 4.73 – 4.67 (m, 1H), 4.13 – 4.04 (m, 2H), 3.94 (quint, 2H, *J* = 6.12 Hz), 3.57 – 3.45 (m, 2H), 2.95 (ddd, 1H, *J* = 13.72 Hz, 8.48 Hz, 5.28Hz), 2.87 – 2.82 (m, 2H), 2.04 – 1.99 (m, 1H), 1.88 – 1.76 (m, 2H), 1.39 – 1.28 (m, 1H), 1.24 – 1.19 (m, 9H, 3 methyl groups overlapped); ^{13}C NMR (100 MHz, acetone–d_6) δ 171.1, 161.1, 131.9, 125.4, 122.5, 116.9, 89.8, 68.9, 65.3, 60.4, 45.4, 43.6, 27.8, 26.1, 24.4, 22.8, 22.1, 13.6 ; LR–MS (EI) [m/z (%)] 334 (M^+, 1), 273 (58), 272 (100), 227 (68), 200 (52), 171 (30); HR–MS (EI) calcd. for $C_{18}H_{26}N_2O_4$: 334.1893; found 334.1889.

Ethyl(1S)–2–[(1R,7aS)–1–ethoxy–3–oxo–hexahydro–1H–yrrolo[1,2–c]imidazole–2–yl]–1–ethylcyclohexa–2,4–diene–1–carboxylate (*syn*–**196a**) To a solution of *syn*–**195** (20 mg, 0.0625 mmol) in THF (1.0 mL) at –78 °C, LDA (0.097 ml, 1.29 M, 0.125 mmol) was added. The reaction mixture was left stirring at that temperature for 1 hour. Ethyl Iodide (0.01 ml, 0.125 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f =



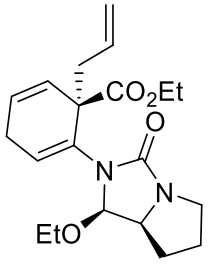
0.17 gaves *syn*–**196a** (13 mg, 62%) as a clear and colourless oil; $[\propto]_D^{20} = -97.9$ (c =0.195, acetone); IR (ATR, solid) ν_{max} 3027, 2973, 2933, 2878, 2815, 1714, 1643, 1455, 1400, 1329, 1232, 1175, 1156, 1081, 977, 879, 787, 653 cm^{-1}; ^1H NMR (600 MHz, acetone–d_6) : δ 5.93 5.92 (m, 1H), 5.90 – 5.89 (m, 1H), 5.44 (m, 1H), 4.93 (d, 1H, *J* = 6.30 Hz), 4.05 – 4.00 (m, 3H), 3.55 – 3.48 (m, 2H), 3.34 (dt, 1H, *J* = 10.62 Hz, 7.50 Hz), 2.97 (ddd, 1H, *J* = 11.04 Hz, 7.26 Hz, 4.62 Hz), 2.85 – 2.82 (m, 2H), 2.03 – 1.96 (m, 1H), 1.98 – 1.94 (m, 1H), 1.93 – 1.89 (m, 1H), 1.86 (q, 2H, *J* = 7.2 Hz), 1.78 – 1.74 (m, 1H), 1.18 (t, 6H, *J* = 7.08 Hz), 2 triplets overlapped, 0.80 (t, 3H, *J* = 7.50 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.3, 158.97, 132.9, 128.97, 124.9, 123.2, 89.2, 63.2, 60.8, 60.2, 52.3, 44.8, 27.03, 26.98, 26.4, 24.5, 14.4, 13.4, 8.1 ; LR–MS (EI) [m/z (%)] 348 (M^+, 17), 302 (48), 275 (100) 229 (86), 211 (22), 125(25), 111 (52); HR–MS (EI) calcd. for $C_{19}H_{28}N_2O_4$: 348.2049; found 348.2044.

Ethyl(1S)–2–[(1R,7aS)–1–ethoxy–3–oxo–hexahydro–1H–pyrrolo[1,2–c]imidazol–2–yl]–1–Benzylcyclohexa–2,4–diene–1–carboxylate (*syn*–196b). To a solution of *syn*–**195** (20 mg, 0.0625 mmol) in THF (1.0 mL) at –78 °C, LDA (0.097 ml, 1.29 M, 0.125 mmol) was added. The reaction mixture was left stirring at that temperature for 1 hour. Benzyl bromide (0.01 mL, 0.125 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2 gave *syn*–**196b** (17 mg, 74%) as a clear oil; $[\propto]_D^{20} = -85.6$ (c =0.195, acetone); IR (ATR, solid) ν_{max} 3028, 2973, 2928, 2878, 2813, 1708, 1643, 1454, 1401, 1330, 1218, 1039, 981, 878, 756, 709, 633 cm^{-1}; ^1H NMR (600 MHz, acetone–d_6) : δ 7.27 (d, 2 H, *J* = 7.4 Hz), 7.23 (t, 1H, *J* = 7.3 Hz), 7.18 (t, 1H, *J* = 7.1 Hz), 5.85 – 5.83 (m, 1H), 5.81 (m, 1H), 5.63 – 5.61 (m, 1H), 4.32 (d,



1H, *J* = 6.4 Hz), 4.13 – 4.04 (m, 2H), 3.97 (q, 1H, *J* = 7.1 Hz), 3.43 – 3.38 (m, 2H), 3.35 (d, 1H, *J* = 10.3 Hz), 3.32 (d, 1H, *J* = 14.8 Hz), 3.13 (d, 1H, *J* = 14.5 Hz), 3.06 – 3.02 (m, 1H), 2.81 – 2.77 (m, 1H), 2.61 – 2.57 (m, 1H), 2.00 – 1.94 (m, 2H), 1.88 – 1.83 (m, 2H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.14 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 171.8, 158.7, 138.4, 133.9, 130.2, 130.0 127.6, 126.01, 124.56, 118.5, 89.4, 63.1, 60.8, 60.3, 52.3, 44.9, 41.5, 40.96, 26.6, 26.5, 24.5, 14.4, 13.5, ; LR–MS (EI) [m/z (%)] 410 (M^+, 5), 364 (6), 125 (61), 111 (96), 97 (100), 84 (84), 71 (82); HR–MS (EI) calcd. for $C_{24}H_{30}N_2O_4$: 410.2206; found 410.2205

Ethyl(1S)–2–[(1R,7aS)–1–ethoxy–3–oxo–hexahydro–1H–pyrrolo[1,2–c]imidazol–2–yl]–1–allylcyclohexa–2,4–diene–1–carboxylate (*Syn*–196c). To a solution of *syn*–**195** (20 mg, 0.0625

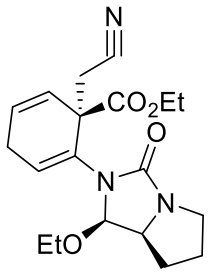


mmol) in THF (1.0 mL) at –78 °C, LDA (0.097 ml, 0.125 mmol, 1.29 M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Allyl bromide (0.01 ml, 0.125 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.1 gave *syn*–**196c** (21 mg, 93 %) as a clear oil; $[\propto]_D^{20} = -96.6$ (c =0.50, acetone); IR (ATR, solid) ν_{max} 3072, 3030, 2975, 2931, 2881, 2815, 1712, 1641, 1402, 1222, 1081, 1041, 916, 814, 759 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 5.94 (broad m, 1H), 5.88 – 5.87 (broad m, 1H), 5.80 – 5.73 (m, 1H), 5.48 (d, 1H, *J* = 9.7 Hz), 5.06 (d, 1H, J = 17.0 Hz), 5.00 (d, 1H, J = 10.1 Hz), 4.86 (d, 1H, J = 6.2 Hz), 4.09 – 4.01 (m, 4H), 3.57 – 3.52 (m, 1H), 3.51 – 3.43 (m, 2H), 3.35 – 3.31 (m, 1H), 3.01 – 2.97 (m, 1H), 2.84 – 2.77 (m, 2H), 2.70 (dd, 1H, *J* = 14.7 Hz, J = 7.7 Hz), 2.59 (dd, 1H, J = 14.6 Hz, J = 6.4 Hz), 1.89 – 1.86 (m, 2H), 1.19 (t, 6H, *J* = 6.7 Hz, 2 triplets overlapped); ^{13}C NMR (100 MHz, acetone–d_6) δ 171.7, 158.9, 135.2, 133.9, 129.2, 124.9, 120.8,

116.4, 89.7, 63.2, 60.8, 60.3, 51.3, 44.8, 39.2, 26.8, 24.6, 14.4, 13.4. LR–MS (EI) [m/z (%)] 360 (M^+, 7), 313 (24), 287 (19), 241 (24), 227 (100), 218 (6), 172 (7), 128 (26); HR–MS (EI) calcd. for $C_{20}H_{28}N_2O_4$: 360.2049; found 360.2040.

Ethyl(1S)–2–[(1R,7aS)–1–ethoxy–3–oxo–hexahydro–1H–pyrrolo[1,2–c]imidazol–2–yl]–1–methylcyclohexa–2,4–diene–1–carboxylate (*syn*–196d). To a solution of *syn*–***195*** (20 mg, 0.0625 mmol) in THF (1.0 mL) at –78 °C, LDA (0.099 ml, 1.26 M, 0.125 mmol) was added. The reaction mixture was left stirring at that temperature for 1 hour. Iodomethane (0.008 ml, 0.125 mmol) was added, and the reaction mixture was stirred to 0 ° C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.1) gave *syn*–**196d** (9.8 mg, 47%) as a clear oil; $[\propto]_D^{20} = -151.1$ (c =0.275, acetone); IR (ATR, solid) ν_{max} 3029, 2976, 2931, 2879, 2815, 1712, 1645, 1445, 1402, 1375, 1354, 1331, 1267, 1225, 1175, 1096, 1041, 978, 864, 759, 605 cm^{-1}; ^1H NMR (600 MHz, acetone–d_6) : δ 5.87 – 5.85 (m, 1H), 5.81 – 5.78 (m, 1H), 5.54 – 5.52 (m, 1H), 4.92 (d, 1H, *J* = 6.5 Hz), 4.09 – 4.00 (m, 3H), 3.56 – 3.45 (m, 2H), 3.38 – 3.33 (m, 1H), 2.99 – 2.86 (m, 1H), 2.83 – 2.78 (m, 2H), 1.97 – 1.83 (m, 4H), 1.38 (s, 3H), 1.18 (t, 6H, *J* = 7.1 Hz) two triplets overlapped; ^{13}C NMR (100 MHz, acetone–d_6) δ 172.5, 159.2, 135.2, 131.0, 123.8, 122.7, 89.3, 63.5, 60.9, 60.3, 48.0, 45.0, 27.0, 26.3, 24.6, 22.4, 14.4, 13.4 ; LR–MS (EI) [m/z (%)] 334 (M^+, 3), 288 (27), 261 (70), 215 (100), 197 (7), 97 (36); HR–MS (EI) calcd. for $C_{18}H_{26}N_2O_4$: 334.1893; found 334.1882.

Ethyl(R)–1–(cyanomethyl)–2–((1R,7aS)–1–ethoxy–3–oxotetrahydro–1H–pyrrolo[1,2–c]imidazol–2(3H)–yl)cyclohexa–2,5–diene–1–carboxylate (*syn*—196f). To a solution of *syn*–**195** (35 mg, 0.110 mmol) in THF (1.0 mL) at –78 °C, LDA (0.18 ml, 0.22mmol, 1.16 M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Chloroacetonitrile (0.014 ml, 0.22 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.1 gave *syn*–**196f** (21 mg, 53 %), a clear and colorless oil ratio of inseparable diastereomers 88:12; $[\propto]_D^{20} = -49.2$ (c =0.55, acetone); IR (ATR, solid) ν_{max} 3035, 2976, 2939, 2882, 2813, 2253, 1703, 1406, 1229, 1092, 1052 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 6.14 – 6.12 (broad m, 1H), 6.08 (broad m, 1H), 5.76 – 5.74 (broad m, 1H), 4.99 (d, 1H, *J* = 6.42 Hz), 4.26 – 4.12 (m, 2H), 4.01 (q, 1H, *J* = 6.32 Hz), 3.72 – 3.56 (m, 2H), 3.44 – 3.37 (m, 1H), 3.05 – 2.99 (m, 2H), 2.98 – 2.93 (m, 3H), 1.98 – 1.85 (m, 4H), 1.26 (t, 3H, *J* = 7.12 Hz), 1.18 (t, 3H, *J* = 7.0 Hz), ^{13}C NMR (100 MHz, acetone–d_6) δ 170.6, 159.9, 131.1, 127.5, 126.8, 126.1, 117.5, 88.6, 65.4, 61.5, 60.9, 49.9, 45.3, 27.2, 26.3, 25.6, 24.7, 14.6, 13.5. LR–MS (EI) [m/z (%)] 359 (M^+, 4), 330 (11), 313 (42), 289 (5), 272 (27), 240 (100), 227 (72), 200 (26), 171 (25), 70 (25), 57 (26); HR–MS (EI) calcd. for $C_{19}H_{25}N_3O_4$: 359.1845; found 359.1839.

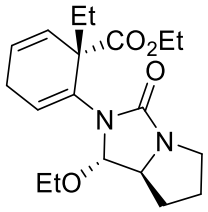


Minor isomer: Characteristic signals: ^1H NMR (400 MHz, acetone−d_6) δ 5.68 (dt, 1H, *J* = 9.72 Hz, 1.96 Hz).

Ethyl (R)–2–((1R,7aS)–1–ethoxy–3–oxotetrahydro–1H–pyrrolo[1,2–c]imidazol–2(3H)–yl)–1–(3–(trimethylsilyl)prop–2–yn–1–yl)cyclohexa–2,5–diene–1–carboxylate (*syn*–196g). To a solution of *syn*–**195** (30 mg, 0.094 mmol) in THF (1.0 mL) at –78 °C, LDA (0.16 ml, 0.19mmol, 1.16 M) was added. The reaction mixture was left stirring at that temperature for 1 hour. (3–bromoprop–1–yn–1–yl) trimethylsilane (0.03 ml, 0.19 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2 gave *syn*–**196g** (25 mg, 64 %), a clear oil as a 90:10 ratio of inseparable diastereomers determined by ^{1}H NMR; **Major isomer** : IR (ATR, solid) ν_{max} 3033, 2960, 2896, 2812, 2176, 1714, 1646, 1404, 1227, 1084, 1033, 841, 759, 639 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 6.11 (broad t, 1H), 5.95 (broad dt, 1H), 5.56 (broad dt, 1H), 4.98 (d, 1H, *J* = 6.30 Hz), 4.09 – 4.05 (m, 2H), 4.03 – 4.00 (m, 1H), 3.69 (dt, 1H, *J*= 9.18 Hz, *J* = 7.08 Hz), 3.61 – 3.56 (m, 1H), 3.32 (dt, 1H, *J* = 10.4 Hz, *J* = 7.38 Hz), 2.99 – 2.95 (m, 1H), 2.89 – 2.86 (m, 2H), 2.74 (q, 2H, *J* = 20.8 Hz), 1.97 – 1.90 (m, 3H), 1.89 – 1.85 (m, 1H), 1.22 (t, 3H, *J* = 6.99 Hz), 1.19 (t, 3H, *J* = 7.12 Hz), 0.12(s, 9H); ^{13}C NMR (100 MHz, acetone–d_6) δ 171.0, 158.9, 132.9, 128.3, 125.5, 122.8, 104.5, 90.3, 85.95, 64.2, 61.0, 60.6, 51.6, 44.9, 27.1, 26.8, 26.7, 24.6, 14.6, 13.4, 0.67; LR–MS (EI) [m/z (%)] 430 (M^+, 9), 311 (100), 273 (15), 243 (7), 227 (58), 200 (14), 171 (6), 73 (12); HR–MS (EI) calcd. for $C_{23}H_{34}N_2O_4Si$: 430.2288; found 430.2277.

Minor isomer: Characteristic signals: ^{1}H NMR (600 MHz, acetone−d_6) δ 4.91 (d, 1H, *J* = 6.48 Hz).

Ethyl(1S)-2-[(1S,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-2-yl]-1 ethylcyclohexa-1,4-diene-1-carboxylate (*anti*–196a). To a solution of *anti*–**195** (16 mg, 0.05

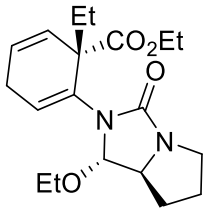


mmol) in THF (1.0 mL) at –78 ºC, LDA (0.12 ml, 0.11 mmol, 0.94M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Then ethyl iodide (0.008 ml, 0.10 mmol) was added, and the reaction mixture was stirred to 0 ºC. DI water was added, and the reaction mixture was then extracted with Et_2O (3 x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.3 gave *anti*–**196a** (13 mg, 75 %), a clear colourless oil, as ratio of inseparable diastereomers 95:5 by ^{1}H NMR; IR (ATR, solid) ν_{max} 3029, 2971, 2932, 2899, 2877, 2816, 1716, 1644, 1456, 1395, 1323, 1256, 1221, 1156, 1072, 978, 857, 805, 787, 649 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.98 (td, 1H, *J* = 3.6, 1.1 Hz), 5.89 (dtd, 1H, *J* = 9.8, 3.3, 1.2 Hz), 5.41 (dt, 1H, *J* = 9.8, 1.9 Hz), 4.94 (s, 1H), 4.05 (q, 2H, *J* = 7.12 Hz), 3.59 – 3.44 (m, 4H), 2.96 (ddd, 1H, *J* = 13.72, 9.0 Hz, 4.72 Hz), 2.85 – 2.82 (m, 2H), 2.04 – 2.02 (m, 2H), 1.93 – 1.81 (m, 2H), 1.79 – 1.69 (m, 1H), 1.32 – 1.29 (m, 1H), 1.184 (t, 3H, *J* = 6.9 Hz), 1.182 (t, 3H, *J* = 7.1 Hz), 2 triplets almost overlapped, 0.77 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.3, 161.8, 132.4, 131.9, 128.9, 124.8, 123.1, 89.7, 63.0, 60.2, 59.4, 52.6, 45.6, 27.3, 26.9, 24.4, 14.6, 13.5, 8.1 ; LR–MS (EI) [m/z (%)] 348 (M^+, 6), 302 (23), 292 (34), 268 (52), 229 (100), 227 (42); HR–MS (EI) calcd. for $C_{19}H_{28}N_2O_4$: 348.2049; found 348.2044.

Minor isomer: Characteristic signals: ^{1}H NMR (400 MHz, acetone−d_6) δ 4.89 (s, 1H)

Alternative method:

Ethyl(1S)-2-[(1S,7aS)-1-ethoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-2-yl]-1 ethylcyclohexa-1,4-diene-1-carboxylate (196a). To a –78 ^{o}C solution of *anti*–**195** (200 mg, 0.63



mmol) and DI water (0.02 ml, 0.94 mmol) in THF and liquid NH_3 was added sodium metal (36.2 mg, 1.57 mmol) in small pieces causing a colour change to deep blue. After 2 hours of stirring at this temperature the reaction was treated with ethyl iodide (0.1 mL, 1.26 mmol) and stirred for another hour. The reaction was quenched with aqueous NH_4Cl (saturated) and then warmed to room temperature to allow evaporation of NH_3. The reaction mixture was then treated with brine and extracted with Et_2O (3 x 3 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.3 gave *anti*–**196a** (124 mg, 62 %), a clear colourless oil, as ratio of inseparable diastereomers 95:5 by ^{1}H NMR; IR (ATR, solid) ν_{max} 3029, 2971, 2932, 2899, 2877, 2816, 1716, 1644, 1456, 1395, 1323, 1256, 1221, 1156, 1072, 978, 857, 805, 787, 649 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.98 (td, 1H, *J* = 3.6, 1.1 Hz), 5.89 (dtd, 1H, *J* = 9.8, 3.3, 1.2 Hz), 5.41 (dt, 1H, *J* = 9.8, 1.9 Hz), 4.94 (s, 1H), 4.05 (q, 2H, *J* = 7.12 Hz), 3.59 – 3.44 (m, 4H), 2.96 (ddd, 1H, *J* = 13.72, 9.0 Hz, 4.72 Hz), 2.85 – 2.82 (m, 2H), 2.04 – 2.02 (m, 2H), 1.93 – 1.81 (m, 2H), 1.79 – 1.69 (m, 1H), 1.32 – 1.29 (m, 1H), 1.184 (t, 3H, *J* = 6.9 Hz), 1.182 (t, 3H, *J* = 7.1 Hz), 2 triplets almost overlapped, 0.77 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.3, 161.8, 132.4, 131.9, 128.9, 124.8, 123.1, 89.7, 63.0, 60.2, 59.4, 52.6, 45.6, 27.3, 26.9, 24.4, 14.6, 13.5, 8.1 ; LR–MS (EI) [m/z (%) 348 (M^+, 5), 302 (25), 275 (66), 229 (100); HR–MS (EI) calcd. for $C_{19}H_{28}N_2O_4$: 348.2049; found 348.2044.

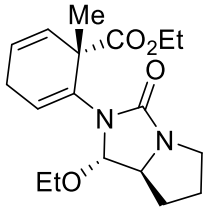
Ethyl (S)–1–benzyl–2–((1S,7aS)–1–ethoxy–3–oxotetrahydro–1H–pyrrolo[1,2–c]imidazol–2(3H)–yl)cyclohexa–2,5–diene–1–carboxylate (196b). To a solution of *anti*–**195** (23 mg, 0.072 mmol) in THF (1.0 mL) at –78 ^{o}C, LDA (0.19 ml, 0.158 mmol, 0.83M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Then benzyl bromide (0.019 ml, 0.158 mmol) was added, and the reaction mixture was stirred to 0 ^{o} C. DI water was added, and the reaction mixture was then extracted with Et_2O (3 x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2 gave *anti*–***196b*** (23.1 mg, 78%); a clear colourless oil, as ratio of inseparable diastereomers 90:10 determined by ^{1}H NMR; IR (ATR, solid) ν_{max} 3028, 2973, 2928, 2878, 2813, 1708, 1643, 1454, 1401, 1330, 1218, 1039, 981, 878, 756, 709, 633 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 7.21–7.18 (m, 5H), 5.86 – 5.84 (m, 1H), 5.73 –5.69 (m, 1H), 5.52 – 5.48 (m, 1H), 5.10 (s, 1H), 4.09 (q, 2H, *J* = 7.08 Hz), 3.63 – 3.51 (m, 4H), 3.28 (q, 2H, *J* = 14.12 Hz), 3.03 (ddd, 1H, *J* = 13.72 Hz, 9.00 Hz, 4.72 Hz), 2.66 – 2.64 (m, 1H), 2.35 – 2.29 (m, 1H), 1.94 – 1.88 (m, 2H), 1.87 – 1.82 (m, 1H), 1.42 – 1.35 (m, 1H), 1.21 (t, 3H, *J* = 6.96 Hz), 1.20 (t, 3H, *J* = 7.16 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.0, 161.4, 137.8, 132.4, 130.6, 128.9 127.4, 127.3, 125.9, 124.2, 120.9, 88.99, 62.9, 60.5, 59.1, 52.5, 45.7, 41.8, 26.5, 24.4, 14.6, 13.5; LR–MS (EI) [m/z (%)] 410 (M^+, 1), 365 (30), 273 (100), 227 (32), 107 (61), 91 (41), 79 (22), 57 (27); HR–MS (EI) calcd. for $C_{24}H_{30}N_2O_4$: 410.2206; found $[M+H]^+$ 411.2277.

Minor isomer: Characteristic signals: ^{1}H NMR (400 MHz, acetone−d_6) δ 4.98 (s, 1H).

Ethyl (S)–1–allyl–2–((1S,7aS)–1–ethoxy–3–oxotetrahydro–1H–pyrrolo[1,2–c]imidazol–2(3H)–yl)cyclohexa–2,5–diene–1–carboxylate (196c). To a solution of *anti*–**195** (20 mg, 0.0625 mmol) in THF (1.0 mL) at –78 °C, LDA (0.15 ml, 0.125 mmol, 0.83M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Then allyl bromide (0.17 ml, 0.125 mmol) was added, and the reaction mixture was stirred to 0 ° C. DI water was added, and the reaction mixture was then extracted with Et_2O (3 x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.3 gave *anti*–**196c** (13 mg, 58 %) a clear and colorless oil as a 91:9 ratio of inseparable diastereomer determined by ^{1}H NMR; IR (ATR, solid) ν_{max} 3074, 3031, 2975, 2932, 2899, 2816, 1713, 1639, 1395, 1324, 1218, 1071, 1038, 913, 802, 765, 683 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.99 – 5.98 (broad m, 1H), 5.87 – 5.84 (broad m, 1H), 5.49 – 5.39 (m, 1H), 5.04 – 4.96 (m, 2H), 4.95 (s, 1H), 4.06 (q, 2H, *J* = 7.04 Hz), 3.59 – 3.47 (m, 5H), 3.01 – 2.95 (m, 1H), 2.85 –2.81 (m, 2H), 2.76 (dd, 1H, *J* = 14.84 Hz, 6.60 Hz), 2.54 (dd, 1H, *J* = 22.48 Hz, 7.56 Hz), 2.04 – 1.99 (m, 1H), 1.94 –1.79 (m, 2H), 1.40 – 1.31 (m, 1H), 1.19 (t, 3H, *J* = 7.12 Hz), 1.18 (t, 3H, *J* = 7.00 Hz);^{13}C NMR (100 MHz, acetone–d_6) δ 171.7, 161.6, 134.9, 132.9, 128.9, 124.5, 121.9, 116.6, 89.7, 63.2, 60.3, 59.4, 51.5, 45.7, 39.4, 28.0, 26.8, 24.4, 14.6, 13.5; LR–MS (EI) [m/z (%)] 360 (M^+, 6), 313 (47), 272 (68), 267 (56), 227 (100), 200 (75), 171 (45), 97 (20); HR–MS (EI) calcd. for $C_{20}H_{28}N_2O_4$: 360.2049; found 360.2049.

Minor isomer: Characteristic signals: ^{1}H NMR (400 MHz, acetone−d_6) δ 4.92 (s, 1H); ^{13}C NMR (100 MHz, acetone–d_6) δ 87.97.

Methyl(1S)–2–[(1S,7aS)–1–ethoxy–3–oxo–hexahydro–1H–pyrrolo[1,2–c]imidazol–2–yl]–1–methylcyclohexa–2,4–diene–1–carboxylate (196d). To a solution of *anti*–**195** (30 mg, 0.094 mmol) in THF (1.0 mL) at –78 °C, LDA (0.2 ml, 0.188 mmol, 0.94M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Iodomethane (0.01 ml, 0.188 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3x 3 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.1 gave *anti*–**196d** (24 mg, 76%) a clear oil as a 51:49 mixture of inseparable diastereomers ; IR (ATR, solid) ν_{max} 3030, 2975, 2935, 2899, 2816, 1713, 1445, 1396, 1372, 1325, 1217, 1172, 1072, 1034, 959, 859, 801, 766, 645 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 5.89 – 5.87 (broad m, 1H), 5.85 – 5.84 (broad m, 1H), 5.58 – 5.51 (m, 1H), 4.89 (s, 1H), 4.06 (q, 2H, *J* = 7.20 Hz), 3.62 – 3.46 (m, 4H), 2.97 (ddd, 1H, *J* = 13.68 Hz, 8.96 Hz, 4.80 Hz), 2.89 –2.83 (m, 3H), 2.00 –1.95 (m, 1H), 1.94 – 1.78 (m, 2H), 1.33 (s, 3H), 1.19 (t, 3H, *J* = 7.12 Hz), 1.18 (t, 3H, *J* = 7.00 Hz);^{13}C NMR (100 MHz, acetone–d_6) δ 173.4, 162.1, 135.1, 130.9, 123.6, 122.0, 90.3, 63.7, 63.3, 61.8, 59.7, 45.6, 28.2, 27.1, 24.5, 22.9, 14.9, 13.5; ; LR–MS (EI) [m/z (%)] 334 (M^+, 3), 288 (26), 261 (35), 215 (81), 97 (25) 57 (100); HR–MS (EI) calcd. for $C_{18}H_{26}N_2O_4$: 334.1893; found 334.1881

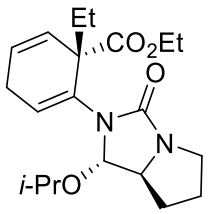


Minor isomer: Characteristic signals: ^1H NMR (400 MHz, acetone−d_6) *δ* 4.95 (s, 1H); ^{13}C NMR (100 MHz, acetone–d_6) δ 88.3.

Ethyl(1S)-2-[(1S,7aS)-1-isopropoxy-3-oxo-hexahydro-1H-pyrrolo[1,2-c]imidazol-2-yl]-1 ethylcyclohexa-1,4-diene-1-carboxylate (202a). To a solution of *anti*–**201** (30 mg, 0.09 mmol) in THF (1.0 mL) at –78 °C, LDA (0.15 ml, 0.18 mmol, 1.24 M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Ethyl iodide (0.01 ml, 0.18 mmol) was added, and

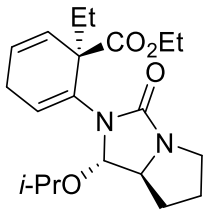
the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3 x 3 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane) gave *anti*–**202a** a clear and colourless oil as an 81:19 ratio of separable diastereomer determined by ^{1}H NMR. Minor diastereomer (5 mg, 15 %, R_f = 0.4, 35:65 EtOAc/hexane), and major diastereomer (20 mg, 63%, R_f = 0.23, 35:65 EtOAc/hexane).

Major Diastereomer



IR (ATR, solid) ν_{max} 3029, 2970, 2934, 2899, 2876, 2816, 1716, 1643, 1406, 1381, 1224, 1120, 1062, 1023, 766, 706 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 6.09 (td, 1H, *J* = 1.3, 3.7 Hz), 5.89 (dtd, 1H, *J* = 9.9, 3.4, 1.3 Hz), 5.45 (dt, 1H, *J* = 9.9, 1.98 Hz), 4.97 (s, 1H), 4.03 (q, 2H, *J* = 7.2 Hz), 3.91 (sep, 1H, *J* = 6.1 Hz), 3.55 – 3.51 (m, 1H), 3.47 (dd, 1H, *J* = 6.4 Hz, *J* = 10.1 Hz), 2.95 (ddd, 1H, *J* = 13.80 Hz, 9.06 Hz, 4.74 Hz), 2.86 (td, 1H, *J* = 2.2 Hz, *J* = 3.5 Hz), 2.83 (td, 1H, *J* = 3.7 Hz, *J* = 1.9 Hz), 1.94 – 1.87 (m, 3H), 1.85 – 1.81 (m, 1H), 1.80 – 1.74 (m, 1H), 1.41 – 1.33 (m, 1H), 1.20 (d, 3H, *J* = 6.1 Hz), 1.19 (d, 3H, *J* = 6.4 Hz), 1.18 (t, 3H, *J* = 7.1 Hz), 0.78 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.1, 161.7, 132.4, 128.8, 124.4, 123.9, 89.4, 69.02, 65.2, 60.2, 52.4, 45.7, 27.7, 27.6, 26.9, 24.5, 22.8, 22.1, 13.5, 8.3 ; LR–MS (EI) [m/z (%)] 362 (M^+, 11), 289 (64), 229 (74), 85 (60), 71 (86), 57 (100); HR–MS (EI) calcd. for $C_{20}H_{30}N_2O_4$: 362.2201; found 362.2200.

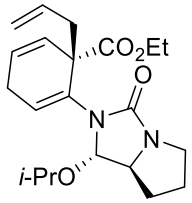
Minor Diastereomer



IR (ATR, solid) ν_{max} 3029, 2970, 2936, 2898, 2878, 2815, 1716, 1683, 1460, 1390, 1222, 1119, 1064, 1024, 786, 706 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.93 (td, 1H, *J* = 1.3, 3.7 Hz), 5.91 (dtd, 1H, *J* = 9.3, 3.7, 1.3 Hz), 5.49 (dt, 1H, *J* = 9.9, 1.96 Hz), 4.86 (s, 1H), 4.23 – 4.16 (m, 1H), 4.096 – 4.02 (m, 1H),

3.84 (sep, 1H, *J* = 6.1 Hz), 3.58 – 3.52 (m, 1H), 3.42 (dd, 1H, *J* = 6.4 Hz, *J* = 10.9 Hz), 2.93 (ddd, 1H, *J* = 13.88 Hz, 8.84 Hz, 5.08 Hz), 2.88 – 2.86 (m, 2H), 2.04 – 1.98 (m, 1H), 1.96 – 1.69 (m, 4H), 1.38 – 1.28 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.14 (d, 3H, *J* = 6.1 Hz), 1.13 (d, 3H, *J* = 6.1 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 173.2, 162.3, 131.1, 128.2, 127.7, 124.3, 87.6, 70.1, 65.3, 60.6, 52.4, 45.7, 27.8, 27.6, 27.2, 24.6, 22.6, 22.2, 13.5, 8.0 ; LR–MS (EI) [m/z (%) 362 (M^+, 6), 302 (34), 289 (62), 229 (100), 85 (62), 71 (54), 57 (32); HR–MS (EI) calcd. for $C_{20}H_{30}N_2O_4$: 362.2201; found 362.2200.

Ethyl 1–allyl–2–((1S,7aS)–1–isopropoxy–3–oxotetrahydro–1H–pyrrolo[1,2–c]imidazol–2(3H)–yl)cyclohexa–2,5–diene–1–carboxylate (202b). To a solution of *anti*–**201** (70 mg, 0.21 mmol) in THF (1.0 mL) at –78 °C, LDA (0.42 ml, 0.42 mmol, 1.00 M) was added. The reaction mixture was left stirring at that temperature for 1 hour. Allyl bromide (0.036 ml, 0.42 mmol) was added, and the reaction mixture was stirred to 0 °C. DI water was added, and the reaction mixture was then extracted with Et_2O (3 x 3 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane) gave *anti*–**202b** (59 mg, 75 %) a clear colourless oil as an 80:20 ratio of diastereomer determined by ^{1}H NMR.

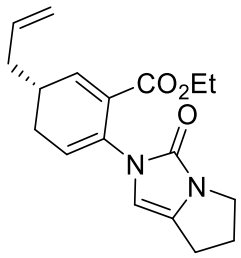


Minor diastereomer: (11.8 mg, 15%); clear and colorless oil (R_f = 0.*6* (80:20 EtOAc/hexane); $[\propto]_D^{20} = -34.9$ (c = 0.45, acetone);; IR (ATR, solid) ν_{max} 3072, 3032, 2934, 2899, 2876, 2814, 1715, 1407, 1219, 1119, 1061, 1022, 765, 740 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 6.02–5.92 (m, 2H), 5.84 (dtd, 1H, *J* = 9.9, 3.4, 1.3 Hz), 5.51 (dt, 1H, *J* = 9.9, 1.96 Hz), 5.02 – 4.94 (m, 1H), 4.98 – 4.96 (m, 1H), 4.89 (s, 1H), 4.21 (dq, 1H, *J* = 10.8, 7.1 Hz), 4.08 (dq, 1H, *J* = 10.9 Hz, *J* = 7.12 Hz), 3.83 (hep, 1H, *J* = 6.12 Hz), 3.54 (ddd, 1H, *J* = 11.20 Hz, 8.40 Hz, 6.80 Hz), 3.44 (dd, 1H, *J* = 9.96 Hz, 6.36 Hz), 2.96 (ddd, 1H, *J* = 11.44 Hz, 8.91 Hz, 4.92 Hz), 2.86 – 2.84 (m,

2H), 2.67 – 2.61 (m, 1H), 2.58 – 2.52 (m, 1H), 2.04 – 1.99 (m, 1H), 1.96 – 1.77 (m, 2H), 1.41 – 1.32 (m, 1H), 1.25 (t, 3H, *J* = 7.12 Hz), 1.14 (t, 6H, *J* = 5.86 Hz). ^{13}C NMR (100 MHz, acetone–d_6) δ 172.7, 162.4, 135.4, 131.4, 128.3, 127.9, 123.8, 116.4, 87.8, 70.6, 65.5, 60.8, 51.4, 45.7, 40.3, 27.6, 27.1, 24.6, 22.5, 22.2, 13.5 ; LR–MS (EI) [m/z (%)] 374 (M^+, 22), 313 (60), 301 (16), 285 (17), 272 (37), 268 (45), 241 (47), 227 (100), 200 (40), 157 (36), 99 (57), 85 (56), 83 (44), 57 (44); HR–MS (EI) calcd. for $C_{21}H_{30}N_2O_4$: 374.2206; found 374.2194.

Major Diastereomer (inseparable with rearomatized substrate); Characteristic signals: ^{1}H NMR (400 MHz, acetone−d_6) δ 6.09 (td, 1H, *J* = 3.76, 1.28 Hz), 5.87 (dtd, 1H, *J* = 11.88, 3.4, 1.32 Hz), 5.73 – 5.63 (m, 1H), 5.49 (dt, 1H, *J* = 9.92, 2.00 Hz), 5.08 – 5.02 (m, 2H), 4.97 (s, 1H), 4.04 (q, 2H, *J* = 7.12 Hz), 3.89 (quintet, 1H, *J* = 6.12 Hz), 3.56 – 3.44 (m, 2H), 2.94 (ddd, 1H, *J* = 13.84 Hz, 9.00 Hz, 4.88 Hz), 2.86 – 2.81 (m, 2H), 2.63 – 2.60 (m, 2H), 1.95 – 1.78 (m, 3H), 1.45 – 1.34 (m, 1H), 1.19 – 1.13 (m, 9H).

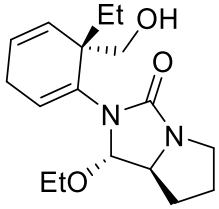
Ethyl (R)–3–allyl–6–(3–oxo–6,7–dihydro–3H–pyrrolo[1,2–c]imidazol–2(5H)–yl)cyclohexa–1,5–diene–1–carboxylate (207). Minor diastereomer **202b** (5mg) was dissolved in toluene (0.25 ml) in a sealed tube and heated to 200 °C. Upon cooling, the solvent was removed, and the residue purified by silica gel column chromatography (eluted with 20:80 hexanes/EtOAc) to provide white crystalline product (EtOAc/hexane) (3.3 mg, 81 %, R_f = 0.1, mp = 89 – 91 °C (EtOAc/hexane)).



$[\propto]_D^{20} = 124.5$ (c = 0.105, acetone); IR (ATR, solid) ν_{max} 3112, 3049, 2954, 2922, 2898, 2853, 1718, 1686, 1407, 1239, 1084, 1055, 709 cm^{-1}; ^{1}H NMR (600 MHz, acetone–d_6) : δ 6.31 (dd, 1H, *J* = 9.64, 2.74 Hz), 6.28 (broad m, 1H), 5.73 – 5.66 (m, 2H), 5.02 – 4.99 (m, 2H), 4.13 – 4.09 (m, 1H), 4.05 – 3.99 (m, 1H), 3.59 (td, 2H, *J* = 7.4, 1.9 Hz), 2.77 – 2.75 (m, 2H), 2.45 – 2.37 (m, 4H), 2.17 – 2.12 (m, 1H), 2.09 – 2.01 (m, 2H), 1.13 (t, 3H, *J* = 7.02 Hz). ^{13}C NMR (100 MHz, acetone–

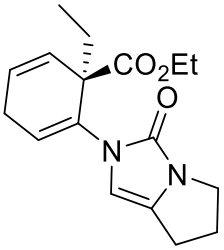
d_6) δ 165.7, 140.9, 127.4, 123.3, 122.5, 120.3, 116.5, 102.0, 59.8, 41.9, 41.5, 36.98, 32.9.4, 27.7, 25.96, 22., 13.5; LR–MS (EI) [m/z (%)] 314 (M^+, 16), 268 (16), 267 (53), 127 (30), 113 (39), 99 (50), 85 (98), 71 (100), 57 (98); HR–MS (EI) calcd. for $C_{18}H_{22}N_2O_3$: 314.1630; found 314.1626.

Ethyl(1S,7aS)–1–ethoxy–2–((S)–6–ethyl–6–(hydroxymethyl)cyclohexa–1,4–dien–1–yl)hexahydro–3H–pyrrolo[1,2–c]imidazol–3–one (197). To a solution of *anti*–**196a** (35 mg, 0.1

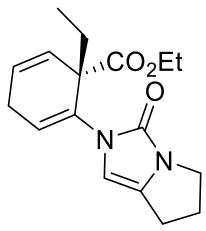


mmol) in THF (1.0 mL) at 0 ºC, $LiAlH_4$ (3.8 mg, 0.1 mmol) in PhMe (1.0 ml) was cannulated. The reaction mixture was left stirring at that temperature for 30 minutes, then room temperature for additional 2 hours. Saturated NH_4Cl solution was added slowly until solid gel was formed. The organic layer was decanted, solid gel was washed with EtOAc (2 x 3ml). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.2 gave *anti*–**197** (20 mg, 65 %) as a white solid; m.p 103–105.5 °C (Et_2O/hexane) ; $[\propto]_D^{20} = -$ 96.4 (c = 0.25, acetone); IR (ATR, solid) ν_{max} 3390, 3019, 2972, 2936, 2882, 2821, 1688, 1673, 1412, 1065, 960, 739, 606 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 6.07 (broad m, 1H), 5.85 – 5.82 (broad m, 1H), 5.30 – 5.27 (broad m, 1H), 4.88 (s, 1H), 4.57(dd, 1H, *J* = 7.8 Hz, *J* = 3.8 Hz), 3.68 – 3.56 (m, 4H), 3.35 (dd, 1H, *J* = 7.7 Hz, *J* = 3.8 Hz), 3.07 – 2.97 (m, 2H), 2.00 – 1.95 (m, 1H), 1.93 – 1.89 (m, 1H), 1.47 – 1.39 (m, 2H), 1.37 – 1.27 (m, 2H), 1.20 (t, 3H, *J* = 7.0 Hz), 1.09 (sextet, 2H, *J* = 7.4 Hz), 0.85 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 164.9, 134.3, 132.2, 131.7, 124.1, 89.7, 68.3, 64.2, 61.9, 49.3, 45.7, 27.9, 26.4, 24.7, 14.7, 8.3; LR–MS (CI) [m/z (%)] 307($M+H]^+$, 8), 275 (20), 261 (50), 229 (18), 85 (16), 59 (37), 57 (100); HR–MS (CI) calcd. for $C_{17}H_{26}N_2O_3$: 306.1943; found $[M+H]^+$: 307.2019.

Ethyl (R)–1–ethyl–2–(3–oxo–6,7–dihydro–3H–pyrrolo[1,2–c]imidazol–2(5H)–yl)cyclohexa–2,5–diene–1–carboxylate (20a). To a solution of *syn*–**198a** (17 mg, 0.049 mmol) in DCM (1.0 mL), pTSOH (10.2 mg, 0.054 mmol) was added. The solution turned pale yellow upon addition of the acid. The mixture was stirred for 10 minutes at room temperature, and the acid was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (3.5 ml). The reaction mixture was extracted with EtOAc (3 x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (80:20 EtOAc/hexane R_f = 0.2) gave **198a** (13 mg, 87 %) as a clear oil; $[\propto]_D^{20} = -91.8$ (c = 0.115, acetone); IR (ATR, solid) ν_{max} 3028, 2968, 2936, 2817, 1723, 1694, 1673,1633, 1412, 1363, 1217, 1027, 707 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 5.98 – 5.96 (m, 1H), 5.95 – 5.92 (m, 2H), 5.43 (dt, 1H, *J* =9.82 Hz, 1.99 Hz), 4.14 – 4.06 (m, 2H), 3.56 (t, 2H, *J* = 6.84 Hz), 2.89 – 2.87 (m, 2H), 2.71 (td, 2H, *J* = 7.12Hz, 1.44 Hz), 2.37 (quin, 2H, *J* = 7.12 Hz), 1.89 – 1.72 (m, 2H), 1.21 (t, 3H, *J* = 7.08), 0.76 (t, 3H, *J* = 7.52 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.6, 149.1, 132.2, 128.5, 126.6, 125.6, 122.6, 102.0, 60.5, 52.3, 41.8, 27.6, 26.8, 26.4, 22.3, 13.5, 7.9; LR–MS (EI) [m/z (%)] 302 (M^+, 40), 229 (100), 84 (62), 69.06 (58), 57 (37); HR–MS (EI) calcd. for $C_{17}H_{22}N_2O_3$: 302.1630; found 302.1625.

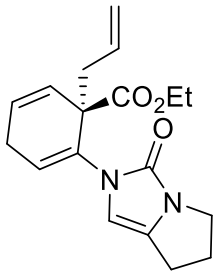


Ethyl (S)–1–ethyl–2–(3–oxo–6,7–dihydro–3H–pyrrolo[1,2–c]imidazol–2(5H)–yl)cyclohexa–2,5–diene–1–carboxylate (*ent*–198a). To a solution of *anti*–**196a** (57 mg, 0.16 mmol) in DCM (2.0 mL), pTSOH (34.2 mg, 0.18 mmol) was added. The solution turned pale yellow upon addition of the acid. The mixture was stirred for 10 minutes at room temperature, and the acid was then quenched by the addition of saturated



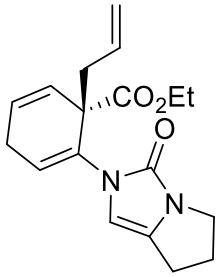
aqueous $NaHCO_3$ solution (3.5 ml). The reaction mixture was extracted with EtOAc (3 x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (80:20 EtOAc/hexane R_f = 0.20) gave *ent*–**198a** (41.7 mg, 84%) as a clear oil; $[\propto]_D^{20} = 86.6$ (c = 0.265, acetone); IR (ATR, solid) ν_{max} 3028, 2968, 2936, 2817, 1723, 1694, 1673,1633, 1412, 1363, 1217, 1027, 707 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 5.98 – 5.96 (m, 1H), 5.95 – 5.92 (m, 2H), 5.43 (dt, 1H, *J* = 9.78Hz, 1.98 Hz), 4.14 – 4.06 (m, 2H), 3.56 (t, 2H, *J* = 6.84 Hz), 2.89 – 2.87 (m, 2H), 2.71 (td, 2H, *J* =7.12Hz, 1.44 Hz), 2.41 (quin, 2H, *J* = 7.12 Hz), 1.89 – 1.72 (m, 2H), 1.21 (t, 3H, *J* = 7.08), 0.76 (t, 3H, *J* = 7.52 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.6, 149.1, 132.2, 128.5, 126.6, 125.6, 122.6, 102.0, 60.5, 52.3, 41.8, 27.6, 26.8, 26.4, 22.3, 13.5, 7.9; LR–MS (EI)[m/z (%)] 302 (M^+, 40), 229 (100), 84 (62), 69 (58); HR–MS (EI) calcd. for $C_{17}H_{22}N_2O_3$: 302.1630; found 302.1625.

Ethyl (R)–1–allyl–2–(3–oxo–6,7–dihydro–3H–pyrrolo[1,2–c]imidazol–2(5H)–yl)cyclohexa–2,5–diene–1–carboxylate (198c). To a solution of *Syn*–**196c** (40 mg, 0.11 mmol) in DCM (1.0 mL), pTSOH (23 mg, 0.12 mmol) was added. The solution turned pale yellow upon addition of the acid. The mixture was stirred for 10 minutes at room temperature, and the acid was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2.5 ml). The reaction mixture was extracted with EtOAc (3 x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (80:20 EtOAc/hexane R_f = 0.2) gave **198c** (18 mg, 52%) as a clear oil; $[\propto]_D^{20} = -22.5$ (c = 0.77, acetone); IR (ATR, solid) ν_{max} 3029, 2976, 2928, 2813, 1724, 1691, 1677, 1637, 1412, 1218, 1037 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 5.97 (t, 1H, *J* = 1.55 Hz), 5.94 (td, 1H, *J* = 3.92 Hz,



1.22 Hz), 5.89 (dtd, 1H, *J* = 9.77 Hz, 3.42 Hz, 1.28Hz), 5.76 – 5.65 (m, 1H), 5.48 (dt, 1H, *J* = 9.80 Hz, 2.0 Hz), 4.98 – 4.91 (m, 2H), 4.17 – 4.08 (m, 2H), 3.56 (t, 2H, *J* = 6.96 Hz), 2.88 –2.86 (m, 2H), 2.73 –2.69 (m, 2H), 2.67 –2.63 (m, 1H), 2.59 –2.53 (m, 1H), 2.40 (quint, 2H, *J* = 7.28 Hz), 1.21 (t, 3H, *J* = 7.12 Hz);^{13}C NMR (100 MHz, acetone–d_6) δ 171.9, 149.1, 134.4, 132.9, 128.7, 126.8, 125.1, 122.1, 116.8, 102.3, 60.6, 51.3, 41.8, 38.9, 27.6, 26.7, 22.3, 13.5; LR–MS (EI) [m/z (%)] 314 (M^+, 52), 313 (54), 272 (66), 267 (56), 241 (52), 227 (100), 200 (72), 171 (68), 144 (44), 130 (22), 97 (16) ; HR–MS (EI) calcd. for $C_{18}H_{22}N_2O_3$: 314.1630; found 314.1621.

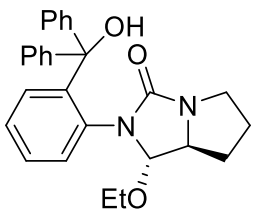
Ethyl (S)–1–allyl–2–(3–oxo–6,7–dihydro–3H–pyrrolo[1,2–c]imidazol–2(5H)–yl)cyclohexa–2,5–diene–1–carboxylate (*ent***–198c).** To a solution of *anti*–**196c** (68 mg, 0.19 mmol) in DCM



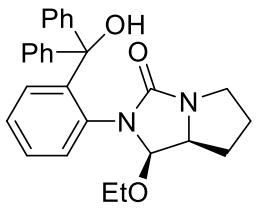
(2.0 mL), pTSOH (39.5 mg, 0.21 mmol) was added. The solution turned pale yellow upon addition of the acid. The mixture was stirred for 10 minutes at room temperature, and the acid was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2.5 ml). The reaction mixture was extracted with EtOAc (3 x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (80:20 EtOAc/hexane R_f = 0.2) gave *ent*–**198c** (45.3 mg, 76 %) as a clear oil; $[\propto]_D^{20} = 15.9$ (c = 0.5, acetone); IR (ATR, solid) ν_{max} 3029, 2976, 2928, 2813, 1724, 1691, 1677, 1637, 1412, 1218, 1037 cm^{-1}; ^{1}H NMR (400 MHz, acetone–d_6) : δ 5.97 (t, 1H, *J* = 1.52 Hz), 5.94 (td, 1H, *J* = 3.88 Hz. 1.22 Hz), 5.89 (dtd, 1H, *J* = 9.77 Hz, 3.48 Hz, 1.28Hz), 5.76 – 5.65 (m, 1H), 5.48 (dt, 1H, *J* = 9.77 Hz, 1.96 Hz), 4.98 – 4.91 (m, 2H), 4.17– 4.08 (m, 2H), 3.56 (t, 2H, *J* = 6.96 Hz), 2.88 –2.86 (m, 2H), 2.73 –2.69 (m, 2H), 2.67 –2.63 (m, 1H), 2.59 –2.53 (m, 1H), 2.40 (quint, 2H, *J* = 7.28 Hz), 1.21 (t, 3H, *J* = 7.12 Hz);^{13}C NMR (100 MHz, acetone–d_6) δ 171.9, 149.1, 134.4, 132.9, 128.7, 126.8, 125.1, 122.1, 116.8, 102.3, 60.6, 51.3, 41.8, 38.9, 27.6, 26.7, 22.3, 13.5; LR–MS (EI) [m/z

(%)] 314 (M^+, 52), 313 (40), 272 (28), 267 (36), 241 (32), 227 (46), 85 (84), 71 (94), 57 (100); (HR–MS (EI) calcd. for $C_{18}H_{22}N_2O_3$: 314.1630; found 314.1620.

(–)–(1*S*,7a*S*)–2–(2–(hydroxydiphenylmethyl)phenyl)–1–isopropoxytetrahydro–1*H*–pyrrolo[1,2–*c*]imidazol–3(2*H*)–one (*anti*–210). A solution of *anti*–**209** (361 mg, 1.47 mmol) in

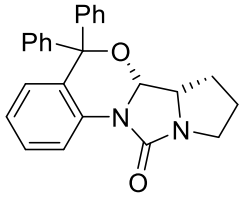


PhMe (3.0 mL) at −78 °C was treated with *t*–BuLi (1.73 mL, 1.7 M, 2.94 mmol). The solution turned yellow upon addition and progressively darkened to red. After 15 minutes, the reaction mixture was warmed to −40 ° C by switching cold baths, and stirred at that temperature for an additional 15 min. A solution of benzophenone (589 mg, 3.23 mmol) in THF (2.00 mL) was added by cannula. The solution turned green upon addition of the electrophile, and the reaction was then allowed to warm to room temperature (*ca.* 25 min). Water (1.00 mL) was added and the reaction mixture was extracted with EtOAc (3x10 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (35:65 EtOAc/hexane R_f = 0.4) gave *anti*–**210** (757 mg, 89%) as a colorless oil that crystallized upon standing; mp 149–152 °C (EtOAc/hexane); $[\propto]_D^{20} = -10.2$ (c , acetone); IR (ATR, solid) ν_{max} 3414, 3055, 3031, 2971, 2928, 2892, 1696, 1487, 1446, 1399, 1265, 1221, 1160, 1074, 1045, 809, 759, 702, 640 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) : δ 7.49 (d, 1H, *J* = 8.0 Hz), 7.47–7.36 (m, 7H), 7.31–7.23 (m, 5H), 6.79 (d, 1H, *J* = 8.0 Hz), 5.97 (s, 1H), 3.91 (s, 1H), 3.47–3.39 (m, 2H) 3.33–3.26 (m, 2H), 2.95–2.88 (m, 1H), 1.79–1.69 (m, 2H), 1.64–1.56 (m, 1H), 1.07 (t, 3H), 0.58– 0.52 (m, 1H); ^{13}C NMR (100 MHz, acetone–d_6) δ 164.2, 148.9, 147.0, 146.9, 146.8, 135.7, 134.2, 130.7, 128.5, 128.1, 127.8, 127.5, 126.9, 126.8, 126.6, 90.36, 80.6, 80.5, 64.9, 64.2, 45.4, 27.4, 24.7, 14.5 ; LR–MS (EI) [m/z (%)] 428 (M^+, 11), 382 (100), 364 (16), 335 (45), 305 (37), 285 (22), 256 (13), 159 (27), 104 (24); HR–MS (EI) calcd. for $C_{27}H_{28}N_2O_3$: 428.2100; found 428.2098. Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59. Found: C, 75.75; H, 6.48.

(–)–(1*R*,7a*S*)–2–(2–(hydroxydiphenylmethyl)phenyl)–1–ethoxytetrahydro–1*H*–pyrrolo[1,2–*c*]imidazol–3(2*H*)–one (*syn*–210). 

A solution of *syn*–**209** (500 mg, 2.03 mmol) in PhMe (5 mL) at −78 ° C was treated with *t*–BuLi (0.90 mL, 1.70 M, 4.06 mmol). The solution turned yellow initially and progressively darkened to reddish orange. After 15 minutes the reaction mixture was warmed to −40 ° C bath by switching cold baths, and stirred at that temperature for an additional 15 min. A solution of benzophenone (739.8 mg, 4.06 mmol) in THF (5 mL) was added by cannula. The solution turned green upon addition of the electrophile, and the reaction mixture was allowed to warm to room temperature (*ca.* 30 min). Water (5 mL) was then added and the mixture was extracted with EtOAc (3x 10 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (50:50 EtOAc/hexanes R_f = 0.5) gave *syn*–**210** (660 mg, 76%) as a light clear orange oil that was solidified from acetone/hexane to cuboidal crystals; mp 151–153 °C (acetone/hexane); $[\propto]_D^{20}$ −114.3 (c 1.0, acetone); IR (ATR, solid) ν_{max} 3303, 3089, 3067, 3028, 2968, 2930, 2909, 2875, 1958, 1945, 1882, 1848, 1666, 1450, 1084 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 7.55−7.24 (m, 13H), 6.94 (d, 1H, *J* = 8.0 Hz), 5.59 (s, 1H), 3.78 (d, 1H, *J* = 6.8 Hz), 3.38−3.35 (m, 1H), 3.28−3.20 (m, 2H), 2.95 (quin, 1H, *J* = 4.4 Hz), 1.88−1.81 (m, 3H), 1.63−1.60 (m, 1H), 0.96 (t, 6H, 6.4 Hz); ^{13}C NMR (100 MHz, acetone–d_6) δ 161.4, 148.8, 146.7, 146.3, 136.2, 133.0, 130.5, 128.3, 127.9, 127.8, 127.5, 127.4, 126.6, 126.5, 126.4, 89.0, 80.3, 75.2, 61.3, 59.6, 44.8, 26.4, 24.3, 19.9, 14.4, 13.6; LR–MS (EI) [m/z (%)] 428 (M^+, 16), 382 (100), 335 (98), 305 (44) 285 (82), 256 (72), 254 (26), 208 (28), 165 (44), 104 (68); HR–MS (EI) calcd for $C_{27}H_{28}N_2O_3$: 428.2100; found: 428.2092.

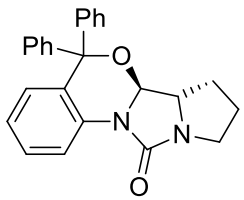
(+)–(6aR,6bS)–5,5–diphenyl–6b,7,8,9–tetrahydro–5H–



benzo[d]pyrrolo[1',2':3,4]imidazo[5,1–b] [1,3]oxazin–11(6aH)–one (*syn*––**211)** To a solution of *anti*–**147** (3.0 g, 7.0 mmol) in CH_2Cl_2 (50 mL) was added *p*–toluenesulfonic acid (2.67 g, 14.0 mmol) and stirred for 5 min. The acid was neutralized by addition of a sat. aq. $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with EtOAc (2x 25 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (50:50 hexanes/EtOAc, R_f = 0.5) gave *syn*–**118** (2.3 g, 86%) as a white solid which was recrystallized from Et_2O providing needle shaped crystals; mp 187–189 °C (Et_2O); $[\propto]_D^{20}$ + 391.3 (c 1.0, acetone); IR (ATR, solid) ν_{max} 3059, 3033, 2947, 2931, 2894, 1710, 1601, 1490, 1403 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 7.90 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.46 – 7.41 (m, 3H), 7.32 –7.26 (m, 6H), 7.22 – 7.19 (m, 2H), 6.99 (td, 1H, *J* = 8.4, 1.2 Hz), 6.89 (dd, 1H, *J* = 6.4, 1.2 Hz), 5.23 (d, 1H, *J* = 6.8 Hz), 4.01 (q, 1H, *J* = 6.8 Hz), 3.73 (dt, 1H, *J* = 5.6, 1.6 Hz), 3.09 (dt, 1H, *J* = 5.6, 1.2 Hz), 2.29 – 2.24 (m, 1H), 2.04 – 1.98 (m, 1H), 1.97–1.93 (m, 2H); ^{13}C NMR (100 MHz, acetone–d_6) δ 159.1, 146.5, 143.8, 134.9, 129.6, 129.2, 128.3, 128.2, 127.8, 127.5, 127.4, 127.3, 122.0, 120.7, 85.1, 78.5, 59.3, 45.5, 25.8, 24.2; LR–MS (EI) [*m/z* (%)] 382 (M^+, 100), 305 (41), 285 (32), 284 (21), 256 (35), 254 (17), 165 (22), 105 (44), 77 (12), 70 (36); HR–MS (EI) calcd for: $C_{25}H_{22}N_2O_2$: 382.1676; found: 382.1692. Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80. Found: C, 78.35; H, 5.83.

(−)–(6aS,6bS)–5,5–diphenyl–6b,7,8,9–tetrahydro–5H–

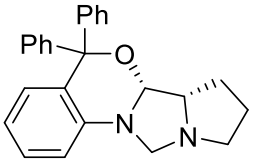
benzo[d]pyrrolo[1',2':3,4]imidazo[5,1–b][1,3]oxazin–11(6aH)–one (*anti*–**211).** To a solution



of *syn*–**210** (275 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) was added *p*–toluenesulfonic acid (235 mg, 1.24 mmol) and stirred for 2 min. The acid was neutralized by addition of a sat. aq. $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (15 mL). The organic extracts were washed with water, brine, dried over anhydrous. Na_2SO_4, filtered and concentrated under reduced pressure. Flash column

chromatography (50:50 hexanes/EtOAc, R_f = 0.7) gave *anti*–**211** (123 mg, 96%) as a white solid which was recrystallized from EtOAc/CH_2Cl_2/hexanes providing needle shaped crystals; mp >230 °C (EtOAc/CH_2Cl_2/hexanes); $[\propto]_D^{20}$ −467.4 ° (c 1.0, CH_2Cl_2); IR (ATR, solid) ν_{max} 3057, 3033, 2971, 2898, 1716, 1601, 1489, 1307 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 8.07 (dd, 1H, *J* = 8.0, 0.8 Hz), 7.44 –7.41 (3H, m), 7.34 –7.25 (m, 6H), 7.20 –7.18 (m, 2H), 7.03 (t, 1H, *J* = 6.8 Hz), 6.89 (dd, 1H, *J* = 6.8, 1.2 Hz), 5.04 (d, 1H, *J* = 1.6 Hz), 3.84 – 3.80 (m, 1H), 3.62 – 3.56 (m, 1H), 3.18 – 3.11 (m, 1H), 2.02 – 1.90 (m, 3H)m 1.43 – 1.38 (m, 1H); ^{13}C NMR (100 MHz, acetone–d_6) δ 159.1, 146.4, 143.7, 134.6, 129.8, 129.2, 128.3, 128.25, 128.2, 128.14, 127.8, 127.54, 127.5, 122.4, 120.3, 85.4, 81.7, 62.5, 45.5, 28.1, 25.18; LR–MS (EI)[*m/z* (%)] 382 (M^+, 100), 313 (12), 285 (68), 256 (49), 132 (43), 85 (64), 83 (94), 69 (30); HR–MS (EI) calcd for: $C_{25}H_{22}N_2O_2$: 382.1676; found: 382.1672.

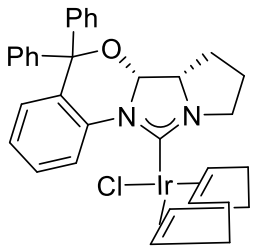
(−)–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–5H–benzo[d]pyrrolo[1',2':3,4] imidazo[5,1–b][1,3]oxazine (*syn*–119). To a solution of (*syn*–**212**) (1.0 g, 2.62 mmol) in PhMe



(15 ml) at −78 °C was added dropwise a solution of DIBAL–H in hexane (9.65 mL, 9.17 mmol, 0.95 M). The cold bath was removed, and the solution was allowed to warm to room temperature (*ca.* 25 min) and stirred for an additional 3 hours. The reaction was quenched applying Fieser method (0.4mL of water was added slowly at 0 °C followed by adding 0.4 mL of 10 % aqueous sodium hydroxide, then 0.1 mL of water was added. The reaction was allowed to warm to room temperature and stirred for 30 mins after that anhydrous magnesium sulfate was added into the reaction flask which then was stirred for additional 15 minutes before being filtered over Celite and concentrated under reduced pressure. Flash column chromatography (49:49:2 hexanes/ EtOAc/ Et_3N , R_f = 0.2) gave *syn*–**212** (964 mg, 95%) as a white solid which was recrystallized from acetone to give colourless needle shaped crystals; mp 190 –

192 °C (acetone); $[\propto]_D^{20}$ + 308.0° (c 1.0, CH_2Cl_2); IR (ATR, solid) ν_{max} 3062, 3029, 2931, 2871, 2854, 1601, 1573, 1483, 1447, 1330, 752, 696 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 7.45 – 7.37 (m, 3H), 7.32 – 7.25 (m, 5H), 7.17 – 7.15 (m, 3H), 6.75 (d, 1H, *J* = 8.0 Hz), 6.71 – 6.66 (m, 2H), 4.59 (d, 1H, *J* = 5.2 Hz), 4.53 (d, 1H, *J* = 7.9 Hz), 4.34 (d, 1H, *J* = 8.0 Hz), 3.69 – 3.66 (m, 1H), 3.16 – 3.12 (m, 1H), 2.96 –2.90 (m, 1H), 2.40 – 2.34 (m, 1H), 1.96 – 1.88 (m, 3H); ^{13}C NMR (100 MHz, acetone–d_6) δ 147.2, 144.4, 141.8, 129.2, 128.2, 127.9, 127.8, 127.7, 117.5, 116.3, 84.9, 82.2, 73.5, 67.8, 53.7, 25,1 23.1; LR–MS (EI)[*m/z* (%)] 368 (M^+, 8), 270 (6), 256 (8), 194 (4), 165 (10), 84 (17), 83 (100), 82 (8), 55 (22); HR–MS (EI) calcd for: $C_{25}H_{24}N_2O$: 368.1833; found: 368.1876. Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57. Found: C, 81.48.75; H, 6.70.

(–)–Chloro[η⁴–1,5–cyclooctadiene]2–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–



5H– benzo[d]pyrrolo[1',2':3,4]imidazo–2–ylidene]iridium (213a). A solution of *syn*–**212** (106 mg, 0.29 mmol) and tritylium tetrafluoroborate (104.5 mg, 0.32 mmol) in degassed CH_2Cl_2 (2 mL) was stirred in a Schlenk flask at room temperature covered from light. After 5 hours, solvent was removed in vacuo and the crude solid was washed with dry diethyl ether (3 x 5 mL) and dried in vacuo. To this was added Ir(μ–Cl)(COD)]$_2$ (100.7 mg, 0.15 mmol) and degassed THF (6 mL) in glovebox. The solution was cooled to –78 °C and with increased flow of argon, KOtBu (34.8 mg, 0.31 mmol) was added at –78 °C. After 1 hour, the cold bath was removed, and the volatiles were removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2:8 EtOAc/hexanes, R_f = 0.57 and 0.3) afforded **213a** (56 mg, 28%) and **213b** (50 mg, 25%).

Major (213a); mp >230 °C (acetone); $[\propto]_D^{20}$ +81.2 ° (c =1.0, $CHCl_3$); IR (ATR, solid) ν_{max} 2955, 2925, 2878, 2831, 1603, 1579, 1447, 1402, 1367, 752, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 9.32

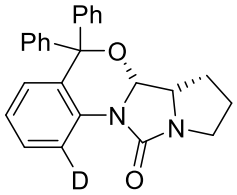
(d, 1H, *J* = 8.8 Hz), 7.50 –7.42 (m, 3H), 7.39 – 7.35 (m, 5H), 7.25 (t, 3H, *J* = 4.0 Hz), 7.07 (t, 1H, *J* = 7.2 Hz), 6.83 (d, 1H, *J* = 8.0Hz), 5.32 (d, 1H, *J* = 8.0 Hz), 4.70 – 4.64 (m, 1H), 4.59 – 4.56 (m, 1H), 4.49 – 4.44 (m, 1H), 4.30 – 4.26 (m, 1H), 3.77 – 3.69 (m, 1H), 5.45 (t, 1H, J = 6.0 Hz), 3.03 – 2.98 (m, 1H), 2.49 – 2.33 (m, 2H), 2.23 –2.19 (m, 4H), 1.92 – 1.87 (m, 2H), 1.66 –1.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 146.5, 143.1, 137.1, 129.9, 129.3, 128.9, 128.6, 128.3, 128.2, 127.6, 127.4, 126.7, 123.3, 122.6, 85.7, 85.6, 84.5, 83.1, 66.4, 54.96, 48.8, 48.3, 34.9, 31.3, 30.8, 27.5, 26.1, 23.3, LR–MS (EI)[*m/z* (%)] 667 (M^+– Cl, 100), 665 (83), 663 (25); HR–MS (FAB) calcd for $C_{33}H_{30}ON_2Ir$: 663.1982; found : 663.2003 NOTE: compound unstable, easily loses Cl and 4H atoms. ESI at two different voltages: 128.5 V and 241.0 V shows this compound loses 4 additional H atoms. Anal. Calcd for $C_{33}H_{30}ON_2Ir$: C, 56.44; H, 4.88. Found: C, 57.08; H, 5.06. Compound likely failed CH analysis because it was unstable.

Minor (213b): $[\propto]_D^{20}$ +251.8 ° (c 1.0, $CHCl_3$); IR (ATR, solid) ν_{max} 2982, 2937, 2878, 2830, 1600, 1573, 1487, 1402, 1361, 1239, 1227, 758, 705 cm^{-1}; ^{1}H NMR (400 MHz, Acetone) δ 8.92 (d, 1H, *J* = 8.0 Hz), 7.44 –7.38 (m, 4H), 7.33 – 7.25 (m, 5H), 7.17 – 7.13 (m, 3H), 6.95 (t, 1H, *J* = 8.0 Hz), 5.28 (d, 1H, *J* = 7.6Hz), 4.59 – 4.58 (m, 2H), 4.49 – 4.42 (m, 1H), 4.34 – 4.28 (m, 1H), 3.67 – 3.60 (m, 1H), 2.96 – 2.93 (m, 1H), 2.41 – 2.32 (m, 2H), 2.28 –2.18 (m, 3H), 2.16 –2.10 (m, 1H), 1.96 –1.89 (m, 1H), 1.81–1.74 (m, 1H), 1.60 –1.52 (m, 3H), 1.32 – 1.25 (m, 2H); ^{13}C NMR (100 MHz, Acetone) δ 207.3, 146.4, 143.6, 137.4, 129.29, 129.26, 128.5, 128.4, 128.2, 127.9, 127.6, 126.8, 123.9, 123.7, 85.6, 85.5, 84.1, 82.6, 67.0, 52.7, 50.8, 47.2, 32.9, 32.7, 26.9, 22.6; LR–MS (EI)[*m/z* (%)] 667 (M^+–Cl, 100), 665 (83), 663 (25); HR–MS (FAB) calcd for $C_{33}H_{30}ON_2Ir$: 663.1982; found : 663.2003 NOTE: compound unstable, easily loses Cl and 4H atoms. ESI at two different voltages: 128.5 V and 241.0 V shows this compound loses 4 additional H atoms. Anal. Calcd for

$C_{33}H_{30}ON_2Ir$: C, 56.44; H, 4.88. Found: C, 57.29; H, 5.65. Compound likely failed CH analysis because it was unstable.

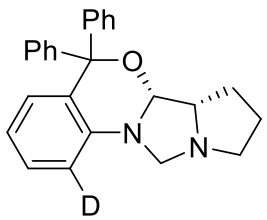
(–)–[η⁴–1,5–cyclooctadiene][triphenylphosphine]2–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–5H– benzo[d]pyrrolo[1',2':3,4]imidazo–2–ylidene]iridium hexafluorophosphate (213). To a solution of **213** (50 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was added a solution of triphenylphosphine (18.7 mg, 0.07 mmol) in CH_2Cl_2 (1 mL). The resulting red solution was stirred for 3 hours at room temperature and then evaporated. The residue was dissolved in small amount of CH_3CN. After that KPF_6 (16.3 mg, 0.09 mmol) in CH_3CN was added and stirred at room temperature for another hour. The mixture was then passed through Celite and washed with CH_2Cl_2. Solvents were removed under reduced pressure and the resulting red solid was triturated with pentane to afford **213** as red crystalline solid (56 mg, 73 %). mp 190–191 °C (pentane); IR (ATR, solid) ν_{max} 3056, 3025, 2925, 2879, 2855, 1739, 1601, 1574, 1230, 1093, 832, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 7.9 Hz), 7.59 – 7.49 (m, 14H), 7.43 – 7.36 (m, 5H), 7.33 – 7.28 (m, 3H), 7.20 – 7.16 (m, 3H), 7.10 – 7.08 (m, 2H), 6.96 (dd, 1H, *J* = 7.92 Hz, 1.04 Hz), 4.83 (d, 1H, *J* = 7.72 Hz), 4.62 (quint, 1H, *J* = 3.64 Hz), 4.15 – 3.99 (m, 3H), 3.80 – 3.74 (m, 1H), 3.36 (q, 1H, *J* = 9.57 Hz), 3.15 – 3.09 (m, 1H), 2.59 – 2.51 (m, 1H), 2.45 – 2.34 (m, 2H), 2.22 – 1.96 (m, 6H), 1.88 –1.84 (m, 1H), 1.79 –1.73 (m, 1H), 1.67 – 1.59 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (d, 1C, $^1J\ ^{13}C–^{31}P$ = 9.0 Hz), 145.2, 142.8, 136.2, 133.9, 133.8, 131.5, 131.4, 130.4, 130.3, 129.9, 129.3, 129.0, 128.9, 128.8. 128.4, 128.2, 127.9, 127.8, 127.3, 124.8, 121.5, 86.7, 86.6, 85.9, 85.0, 84.9, 83.2, 81.9, 81.1, 77.2, 67.5, 47.6, 31.1, 30.7, 30.4, 26.7, 22.4; ESI–MS[*m/z* (%)] 929 (M^+, 100), 523 (10), 288 (4); HR–MS (FAB) calcd for $C_{51}H_{49}ON_2IrP$: 929.3206; found: 929.3174.

(+)–(6aR,6bS)–5,5–diphenyl–6b,7,8,9–tetrahydro–5H–benzo[d]pyrrolo[1',2':3,4]imidazo[5,1–b] [1,3]oxazin–11(6aH)–one (*syn*–217). A solution of



syn–**211** (200 mg, 0.52 mmol) in THF (4 mL) at –78 °C was treate with *t*–BuLi (0.61 ml, 1.7 M, 1.04 mmol). After 30 mins, methanol–d_4 (0.13 ml, 1.3mmol) was added by syringe. The reaction was stirred at the same temperature for additional 30 minutes, then the reaction was allowed to warm to room temperature (*ca*. 25 mins). Water (0.5 mL) was then added and the mixture was extracted with Et_2O (2x 3.0 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (80:20 hexanes/EtOAc, R_f = 0.4) gave *syn*–**217** (140 mg, 70%) as a white solid which was recrystallized from EtOAc providing needle shaped crystals; mp 201–202.5 °C (EtOAc); $[\propto]_D^{20}$ + 360.6 (c 1.0, acetone); IR (ATR, solid) ν_{max} 3059, 3033, 2959, 2929, 2875, 1707, 1597, 1489, 1403, 760, 699 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 7.43 –7.30 (m, 3H), 7.29–7.25 (m, 6H), 7.20 –7.19 (m, 2H), 6.99 (td, 1H, *J* = 7.6, 7.6 Hz), 6.89 (dd, 1H, *J* = 6.4, 1.2 Hz), 5.22 (d, 1H, *J* = 6.8 Hz), 4.02 (q, 1H, *J* = 7.2 Hz), 3.73 (m, 1H), 3.10 (dt, 1H, *J* = 5.6, 1.2 Hz), 2.22–2.20 (m, 1H), 2.02–1.98 (m, 1H), 1.97–1.93 (m, 2H); ^{13}C NMR (100 MHz, acetone–d_6) δ 159.1, 146.5, 143.8, 134.8, 129.6, 129.2, 128.3, 128.2, 128.1, 127.8, 127.5, 127.3, 122.0, 85.1, 78.5, 59.3, 45.5, 25.8, 24.2; LR–MS (EI)[*m/z* (%)] 383 (M^+, 100), 306 (42), 286 (32), 257 (36), 105 (28); HR–MS (EI) calcd for: $C_{25}H_{21}DN_2O_2$: 383.1739; found: 383.1756. Anal. Calcd for $C_{25}H_{21}DN_2O_2$: C, 78.51; D as H, 5.78. Found: C, 78.30; D as H, 5.93.

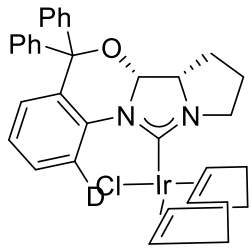
(−)–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–5H–benzo[d]pyrrolo[1',2':3,4] imidazo[5,1–b][1,3]oxazine (*syn*–218). To a solution of (*syn*–**217**) (1.0 g, 2.61 mmol) in PhMe



(20 ml) at −78 °C was added dropwise a solution of DIBAL–H in hexane (9.62 mL, 9.14 mmol, 0.95 M). The cold bath was removed, and the solution was allowed to warm to room temperature (*ca.* 25 min) and stirred for an additional 3 hours. The reaction was quenched applying Fieser

method (0.4 mL of water was added slowly at 0 °C followed by adding 0.4 mL of 10 % aqueous sodium hydroxide, then 0.1 mL of water was added. The reaction was allowed to warm to room temperature and stirred for 30 minutes after that anhydrous magnesium sulfate was added into the reaction flask which then was stirred for additional 15 mins before being filtered over Celite and concentrated under reduced pressure. Flash column chromatography (49:49:2 hexanes/ EtOAc/ Et_3N , R_f = 0.4) gave *syn*–**218** (734 mg, 76%) as a white solid which was recrystallized from EtOAc to give white crystals; mp 193–194.5 °C (EtOAc); $[\propto]_D^{20}$ + 397.6 ° (c 1.0, CH_2Cl_2); IR (ATR, solid) ν_{max} 3063, 3024, 2979, 2953, 2929, 2870, 2853, 1601, 1595, 1569, 1488, 1445, 1385, 758, 752, 697 cm^{-1}; ^1H NMR (400 MHz, acetone–d_6) δ 7.40 –7.32 (m, 5H), 7.28 –7.26 (m, 3H), 7.18 –7.14 (m, 3H), 6.73 – 6.67 (m, 2H), 4.67 (d, 1H, *J* = 5.2 Hz), 4.64 (d, 1H, *J* = 7.6 Hz), 4.37 (d, 1H, *J* = 7.6 Hz), 3.76 – 3.74 (m, 1H), 3.25 – 3.21 (m, 1H), 3.02 – 2.96 (m, 1H), 2.44 – 2.37 (m, 1H), 2.11–1.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 144.2, 143.4, 129.7, 129.5, 128.4, 128.2, 127.9, 127.8, 127.7,127.2, 125.5, 117.9, 85.0, 82.1, 73.8, 68.1, 54.3, 25,4, 23.4; LR–MS (EI)[*m/z* (%)] 369 (M^+, 6), 281 (4), 221 (6), 153 (24), 136 (24), 107 (68), 89 (40), 83 (80), 77 (100); HR–MS (EI) calcd for: $C_{25}H_{23}DN_2O$: 369.1951; found: 369.1940. Anal. Calcd for $C_{25}H_{23}DN_2O$: C, 81.27; D as H, 6.55. Found: C, 81.17; D as H, 6.69.

(–)–Chloro[η⁴–1,5–cyclooctadiene]2–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–



5H– benzo[d]pyrrolo[1',2':3,4]imidazo–2–ylidene]iridium (219). A solution of *syn*–**218** (300 mg, 0.81 mmol) and tritylium tetrafluoroborate (295 mg, 0.89 mmol) in degassed CH_2Cl_2 (5 mL) was stirred in a Schlenk flask at room temperature covered from light. After 5 hours, solvent was removed in vacuo and the crude solid was washed with dry diethyl ether (3 x 5 mL) and dried in vacuo. To this was added Ir(μ–Cl)(COD)]$_2$ (272 mg, 0.41 mmol) and degassed THF (7 mL) in glovebox. The solution was cooled to –78 °C and with increased flow of argon, KOtBu (99.98 mg, 0.89 mmol) was added at –78 °C. After 1 hour, the cold bath was removed, and the volatiles were

removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2:8 EtOAc/hexanes, R_f = 0.5 and 0.20) afforded **219a** (157 mg, 28%) and **219b** (80 mg, 14%).

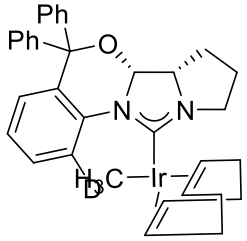
Major (219a) ; mp >230 °C (acetone); $[\propto]_D^{20}$ +69.7 ° (c =0.5, $CHCl_3$); IR (ATR, solid) ν_{max} 3060, 3023, 2955, 2922, 2877, 2831, 1598, 1574, 1488, 1467, 1447, 1425, 1400, 1265, 1235, 1204, 814, 799,773, 758, 746, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 –7.31 (m, 8H), 7.28–7.22 (m, 3H), 7.06 (t, 1H, J = 8Hz), 6.79 (dd, 1H, *J* = 8.0 Hz, J = 1.6 Hz), 5.28 (d, 1H, J = 8.0 Hz), 4.82–4.73(m, 2H), 4.64 (q, 1H, *J* = 8.0 Hz), 3.67–3.61 (m, 1H), 3.40 – 3.37 (m, 1H), 3.02 (s, 1H), 2.50 –2.39 (m, 2H), 2.35 – 2.23 (m, 3H), 2.21–2.12 (m, 1H), 2.08 – 1.99 (m, 2H), 1.94 –1.82 (m, 2H), 1.70–1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 145.9, 143.1, 136.5, 130.1, 129.6, 128.9, 128.4, 128.2, 128.1, 127.9, 126.8, 123.8, 86.9, 85.9, 83.0, 66.6, 55.5, 49.3, 48.8, 35.2, 31.6, 31.1, 27.8, 26.3, 23.7; ESI–MS[*m/z* (%)] 668 (M^+–Cl, 100), 704 (35), 703 (100), 702 (10), 701 (30); HR–MS (FAB) calcd for $C_{33}H_{33}DClIrN_2O$: 703.2046; found: 703.2037. NOTE: There may have deuterium–hydrogen exchanged on the sample (could have come from the FAB matrix); The dissociated ion $[M–Cl]^+$ shown in ESI has the mass matching with the Deuterated structure.

Minor (219b); mp >230 °C (acetone); $[\propto]_D^{20}$ = 249.2 (c =0.5, acetone); IR (ATR, solid) ν_{max} 3064, 3022, 2983, 2936, 2916, 2879, 2831, 1615, 1597, 1569, 1487, 1445, 1401, 1281, 1255, 1202, 805, 761,751, 700, 676, 654; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 –7.35 (m, 4H), 7.29–7.26 (m, 5H), 7.12 –7.07(m, 3H), 6.86 (dd, 1H, *J* = 7.6 Hz, J = 1.2 Hz), 5.22 (d, 1H, J = 7.2 Hz), 4.82–4.73(m, 2H), 4.52 – 4.45 (m, 1H), 4.17 – 4.12 (m, 1H), 3.80 – 3.74 (m, 1H), 2.93–2.89 (m, 1H), 2.44 – 2.40 (m, 1H), 2.36 – 2.06 (m, 6H), 1.89 – 1.77 (m, 2H), 1.69 –1.60 (m, 2H), 1.36 –1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 146.1, 143.4, 136.9, 129.6, 129.1, 128.4, 128.2, 128.0, 127.6, 126.97, 123.9, 86.9, 85.84, 85.81, 82.6, 66.96, 53.5, 51.5, 47.6, 33.2, 32.9, 29.6, 28.7, 27.1, 22.9; ESI–MS[*m/z* (%)] 668 (M^+– Cl, 100), 704 (55), 703 (100), 702 (45), 701 (30); HR–MS

(FAB) calcd for $C_{33}H_{33}DClIrN_2O$: 703.2046; found: 703.2053. NOTE: There may have deuterium–hydrogen exchanged on the sample (could have come from the FAB matrix); The dissociated ion $[M–Cl]^+$ shown in ESI has the mass matching with the deuterated structure.

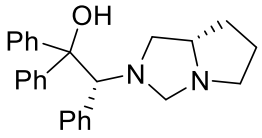
(–)–Chloro[η^4–1,5–cyclooctadiene]2–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–5H– benzo[d]pyrrolo[1',2':3,4]imidazo–2–ylidene]iridium (215). A solution of **213a** (20 mg, 0.03 mmol) and toluene (1 ml) at –78 ^oC was treated with MeLi (0.04 ml, 0.82M, 0.033 mmol). The yellow solution slowly turned to reddish orange. After 30 min the cold bath was removed, and the reaction mixture was allowed to warm to room temperature (*ca.* 30 min). Water was then added, and the mixture was extracted with EtOAc (3x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered through Celite and concentrated under reduced pressure to afford **215** (17 mg, 85%), as an orange red powder which was air unstable. IR (ATR, solid) ν_{max} 3023, 2910, 2872, 2827, 1601, 1576, 1400, 815, 752, 697; ^1H NMR (400 MHz, acetone–d_6) δ 9.10 (d, 1H, *J* = 7.88 Hz), 7.44 –7.41 (m, 3H), 7.36 – 7.34 (m, 2H), 7.26 –7.23 (m, 6H), 7.00 –6.97 (m, 1H), 6.80 (dd, 1H, *J* = 7.84 Hz, 1.12 Hz), 5.33 (d, 1H, *J* = 7.69 Hz),4.47 (dt, 1H, *J* = 11.28 Hz, 7.12 Hz), 4.16 (q, 1H, *J* = 7.83 Hz), 3.96 – 3.88 (m, 2H), 3.62 – 3.56 (m, 1H), 3.38 – 3.35 (m, 1H), 3.59 (ddd, 1H, *J* = 15.4 Hz, 8.68 Hz, 5.20 Hz), 3.37 – 3.35 (m, 1H), 3.01 (sextet, 1H, *J* = 4.28 Hz), 2.39 – 2.22 (m, 3H), 2.17 – 2.09 (m, 4H), 1.93 –1.89 (m, 2H), 1.73 – 1.69 (m, 1H), 1.61– 1.56 (m, 2H), 0.12 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.7, 143.5, 129.3, 129.2, 128.3, 128.24, 128.20, 127.7, 127.4, 126.3, 122.7, 85.6, 82.8, 76.8, 76.7, 66.4, 64.8, 57.4, 48.9, 33.7, 32.8, 30.3, 29.6, 25.8, 23.8, 1.1; LR–MS (EI)[*m/z* (%)] 667 (M^+– CH_3, 6), 665 (30), 663 (100); HR–MS (FAB) calcd for $C_{33}H_{30}ON_2Ir$: 663.1982; found : 663.1931 NOTE: compound unstable, easily loses CH_3 and 4H atoms. ESI at two different voltages: 128.5 V and 241.0 V shows this compound loses 4 additional H atoms.

(–)–Chloro[η^4–1,5–cyclooctadiene]2–(6aS,6bS)–5,5–diphenyl–6a,6b,7,8,9,11–hexahydro–5H– benzo[d]pyrrolo[1',2':3,4]imidazo–2–ylidene]iridium (220).



A solution of **219** (20 mg, 0.03 mmol) and toluene (1 ml) at –78 ^{o}C was treated with MeLi (0.038 ml, 0.82M, 0.0312 mmol). The yellow solution slowly turned to reddish orange. After 30 minutes the cold bath was removed, and the reaction mixture was allowed to warm to room temperature (*ca.* 30 min). Water was then added, and the mixture was extracted with EtOAc (3x 2 mL). The organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered through celite and concentrated under reduced pressure to afford **220** (16.7 mg, 82%) as an orange red powder which was air unstable. (R_f = 0.4 (80 hexane:20 EtOAc)), mp >230 °C (acetone); $[\propto]_D^{20}$ +240.2 (c =0.5, acetone); IR (ATR, solid) ν_{max} 2954, 2922, 2878, 1633, 1615, 1599, 1417, 1373, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 –7.38 (m, 4H), 7.36 – 7.34 (m, 2H), 7.18 –7.13 (m, 4H), 6.99 (br m, 4H), 6.76(m, 2H), 5.02 (d, 1H, *J* = 7.72 Hz), 4.51 (ddd, 1H, *J* = 11.00 Hz, 7.80 Hz, 6.6 Hz), 4.47 – 4.43 (m, 1H), 4.39 (dt, 1H, *J* = 7.64 Hz, 4.72 Hz), 3.59 – 3.56 (m, 1H), 3.37 – 3.33 (m, 1H), 3.16 – 3.06 (m, 2H), 2.60 – 2.41 (m, 2H), 2.35 – 2.23 (m, 3H), 1.91 –1.85 (m, 1H), 1.83 – 1.71 (m, 3H), 0.69 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.4, 136.8, 129.6, 129.2, 128.9, 128.00, 127.9, 127.4, 127.0, 126.4, 122.9, 82.7, 78.2, 78.1, 66.1, 65.8, 64.9, 57.5, 48.9, 34.3, 33.4, 30.8, 28.9, 25.7, 23.9, 2.1; LR–MS (EI)[*m/z* (%)] 668 (M^+– CH_3, 6), 665 (30), 663 (100); HR–MS (FAB) calcd for $C_{33}H_{29}DON_2Ir$: 664.2050; found : 664.1931 NOTE: compound unstable, easily loses CH_3 and 4H atoms. ESI shows this compound loses 4 additional H atoms.

(+)–(*R*)–1,1,2–triphenyl–2–[(*S*)–tetrahydro–1*H*–pyrrolo[1,2–*c*]imidazol–2(3*H*)–yl]ethanol



(**226**). A solution of **225** (200 mg, 0.51 mmol) in PhMe (4 mL) at −78 °C was treated dropwise with a solution of DIBAL–H in hexane (2.06 mL, 2.02 mmol, 0.98 M). The solution was stirred at −78 °C for 1 hour, and after removal of the cold bath, left to stir at room temperature for an additional 3 hours. After cooling to 0 °C, the reaction mixture was worked up by sequential addition of 0.1 mL of water, 0.1 mL of 10 % aqueous sodium hydroxide, and 0.2 mL of water. The crude mixture was left to stand for 30 minutes, dried over anhydrous magnesium sulfate for 15 minutes, filtered through Celite using EtOAc, and concentrated under reduced pressure. Flash column chromatography (49:49:2 hexanes/EtOAc/Et3N, R_f = 0.3) gave **226** (100 mg, 51%) as a colorless solid; mp 150–152 °C (EtOAc/hexane); $[\propto]_{\mathrm{D}}^{20} = +305$ (*c* 0.5, acetone); IR (ATR, solid) νmax 3297, 3060, 3028, 2958, 2918, 2866, 2815, 1597 cm–1; 1H NMR (400 MHz, acetone–d6) δ 7.99 (d, 2H, J = 8.0 Hz) , 7.53 (d, 2H, J = 7.2 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.36 (t, 2H), 7.22 (t, 1H), 7.11– 7.02 (m, 3H), 6.97 (t, 2H), 6.83 (t, 1H), 5.68 (s, 1H), 4.79 (s, 1H), 3.32–3.30 (m, 1H), 3.10–3.07 (ABq, 2H, *J* = 8.0 Hz), 2.91–2.87 (m, 1H), 2.60–2.54 (m, 1H), 2.22–2.16 (m, 2H), 1.86–1.76 (m, 1H), 1.75–1.73 (m, 1H), 1.52–1.49 (m, 1H), 1.36–1.28 (m, 1H); 13C NMR (100 MHz, acetone–d6) δ 149.9, 146.4, 139.4, 130.2, 127.8, 127.3, 127.0, 126.9, 126.2, 125.9, 125.5, 125.2, 78.8, 76.5, 72.7, 63.1, 59.5, 55.6, 33.1, 26.0; CIMS [m/z (%)] 385 [M+H, 5], 183 (100); HRMS (CI) calcd for C26H29N2O: 385.2280; found 385.2268

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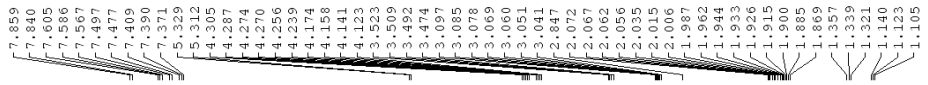
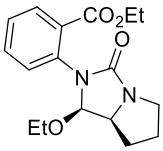
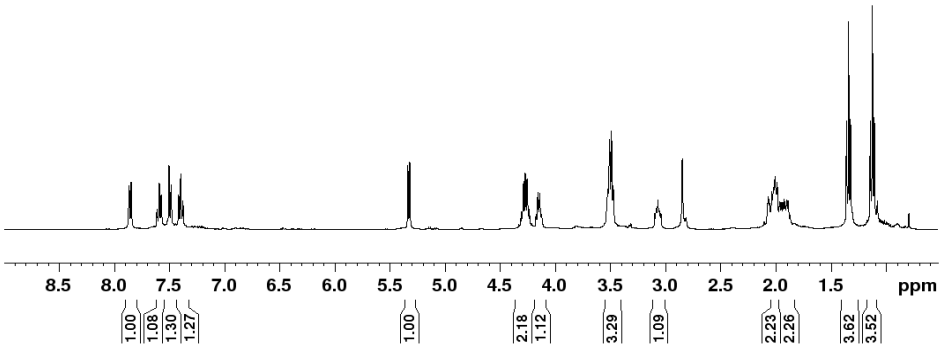
7. **Appendix**

^{1}H NMR (400 MHz, acetone–d_6)

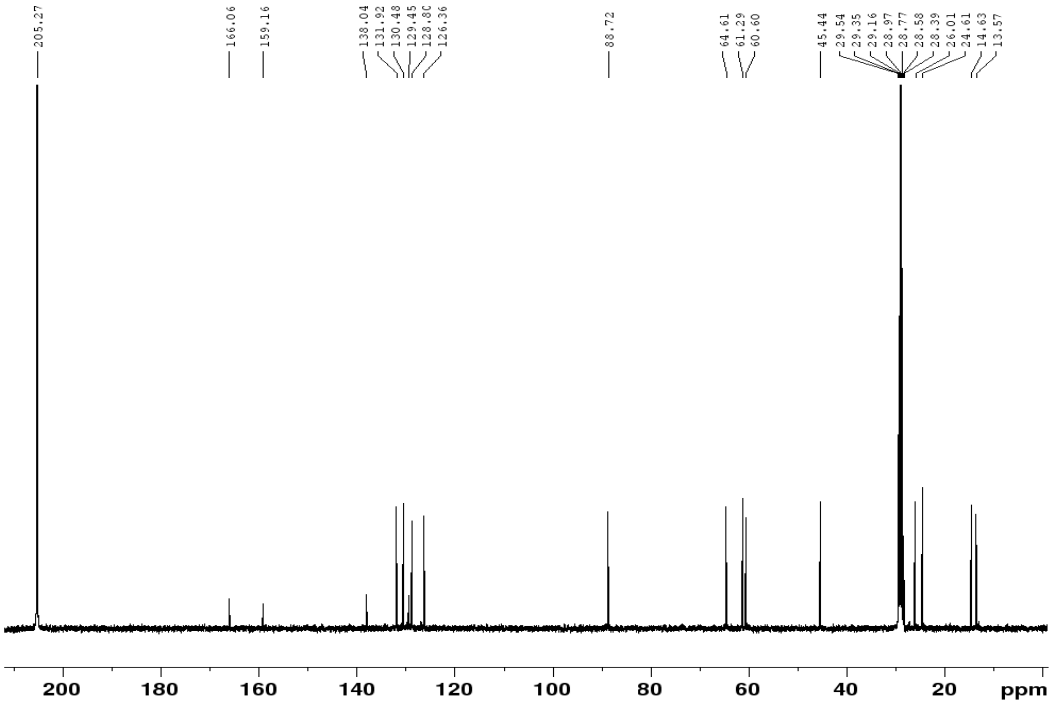


Syn-1**94**

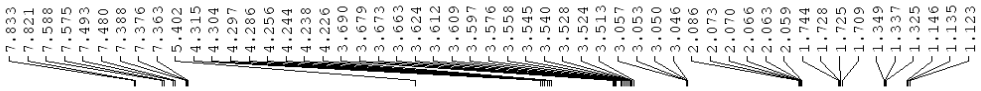




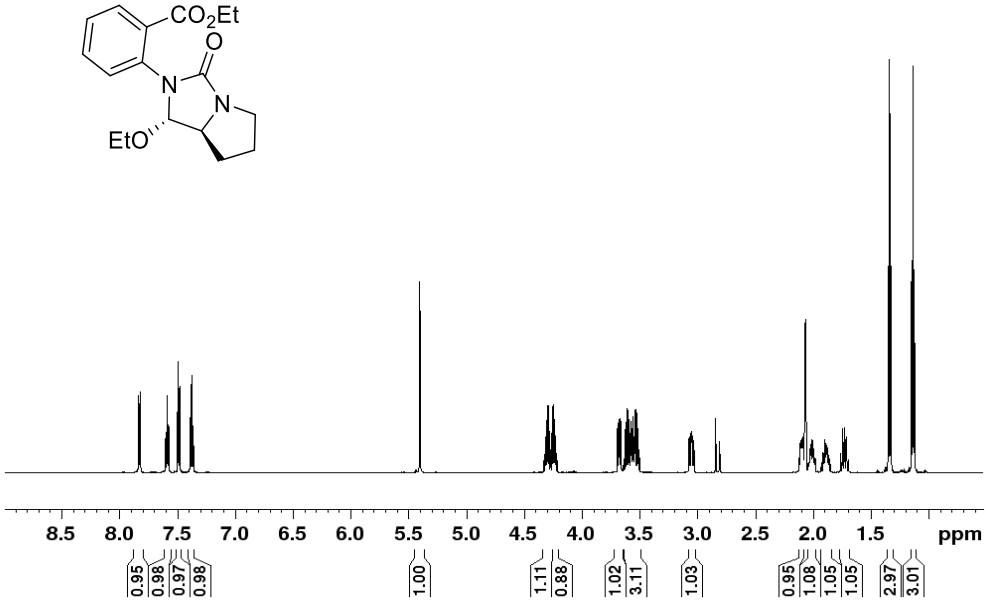
^{13}C NMR (100.7 MHz, acetone–d_6)



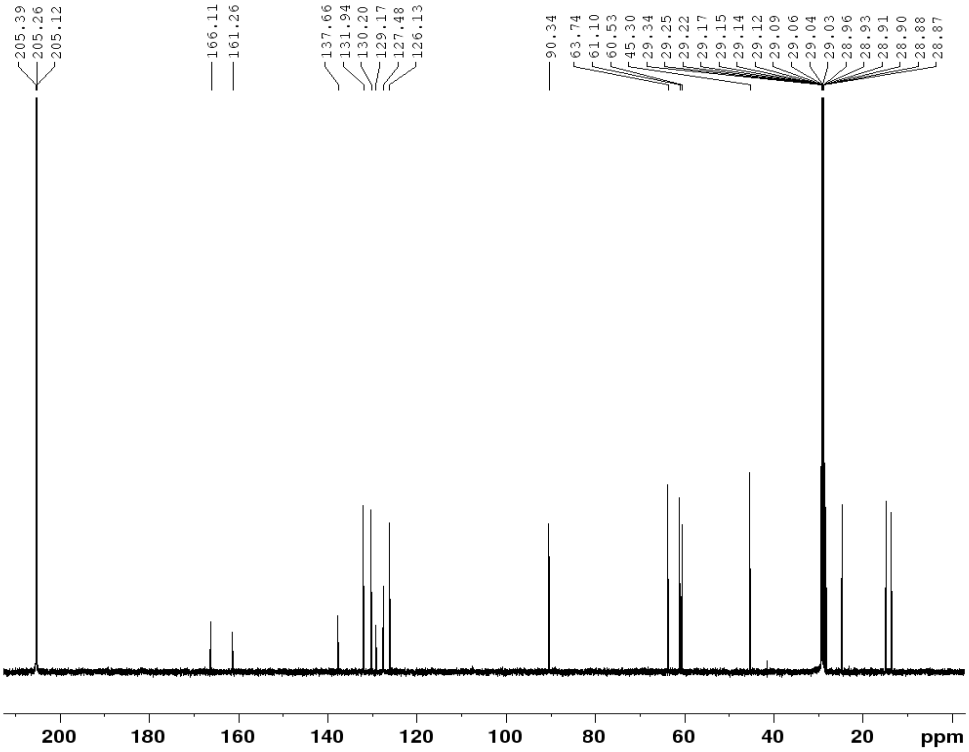
^{1}H NMR (600 MHz, acetone–d_6)



Anti-**194**

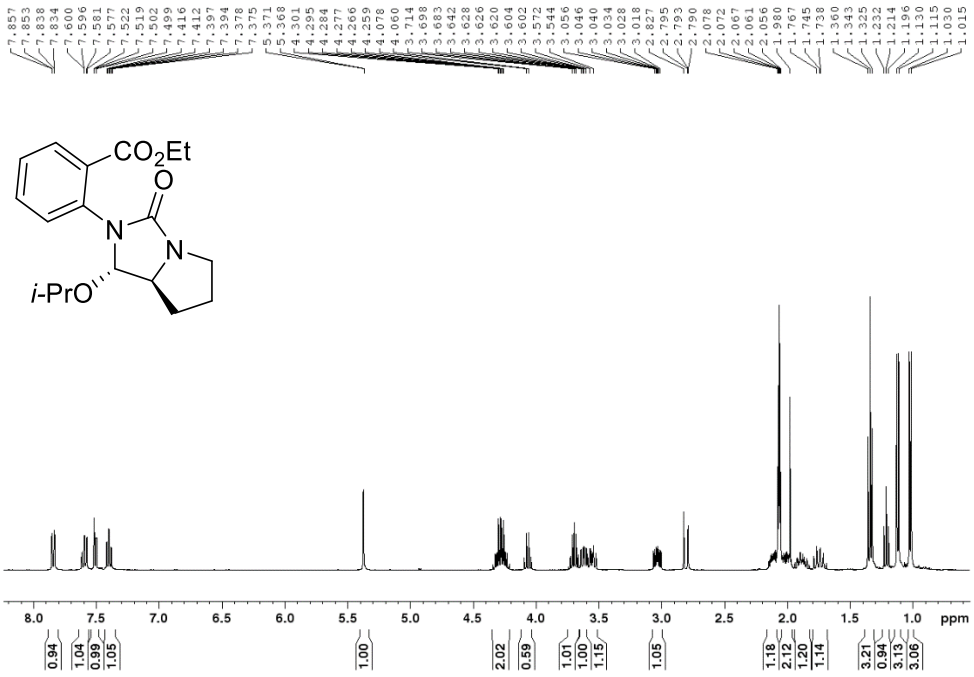


^{13}C NMR (100.7 MHz, acetone–d_6)

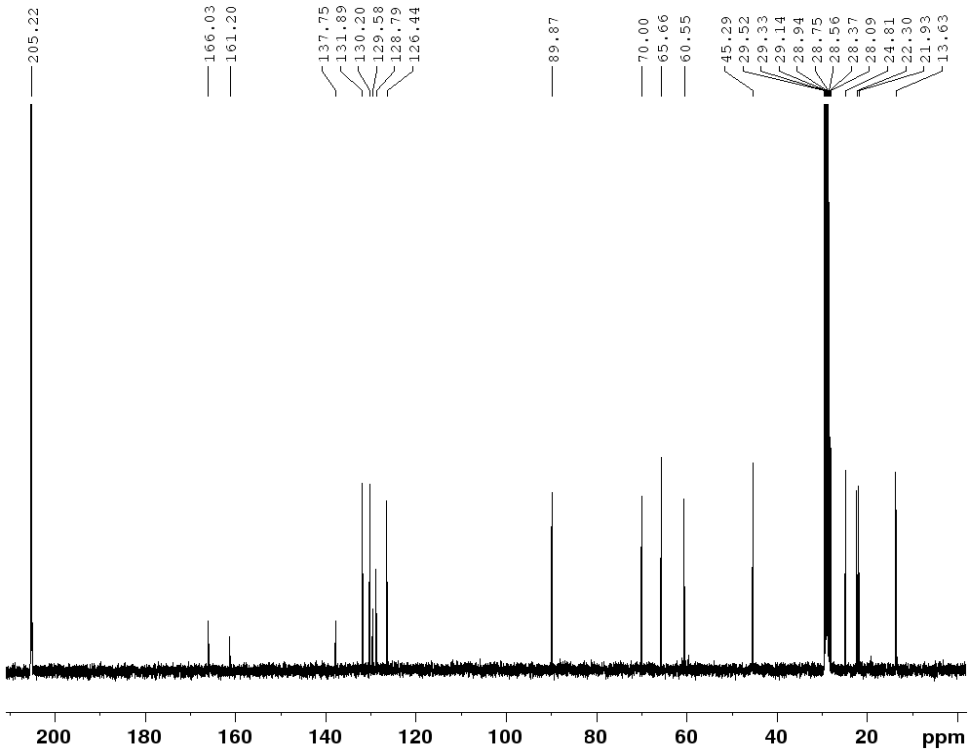


^{1}H NMR (400 MHz, acetone–d_6)

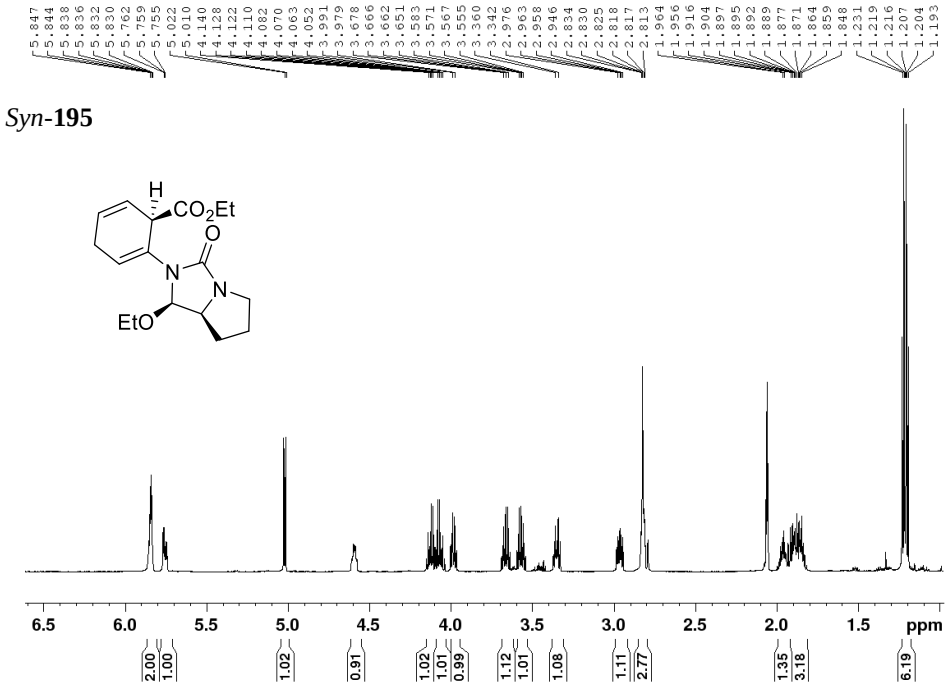
Anti-**200**



^{13}C NMR (100.7 MHz, acetone–d_6)

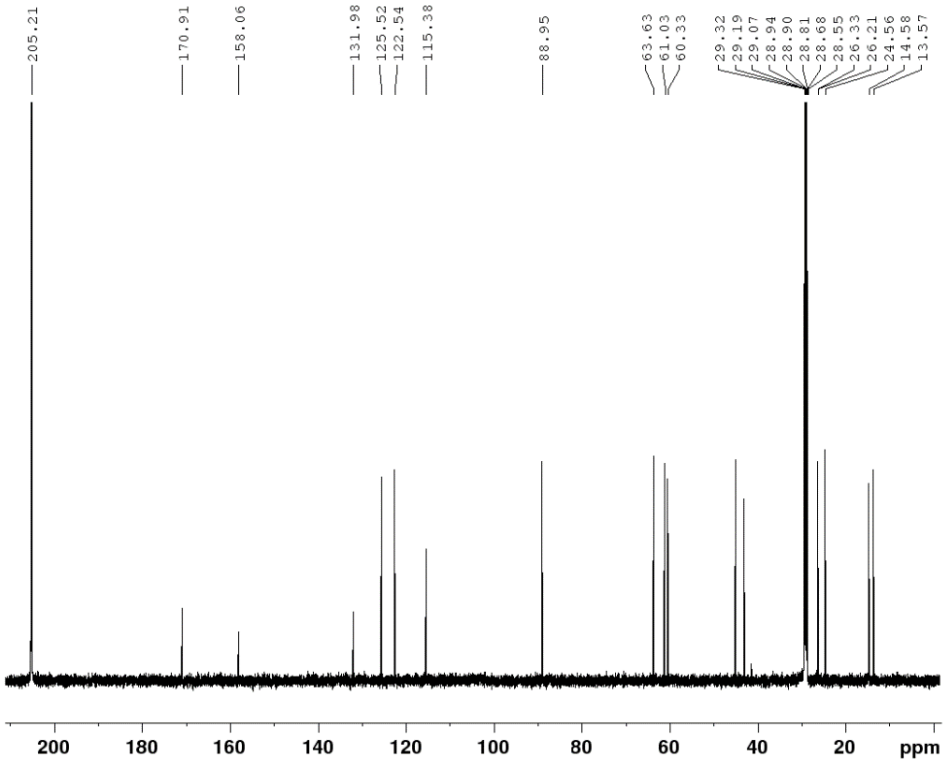


^{1}H NMR (600 MHz, acetone–d_6)



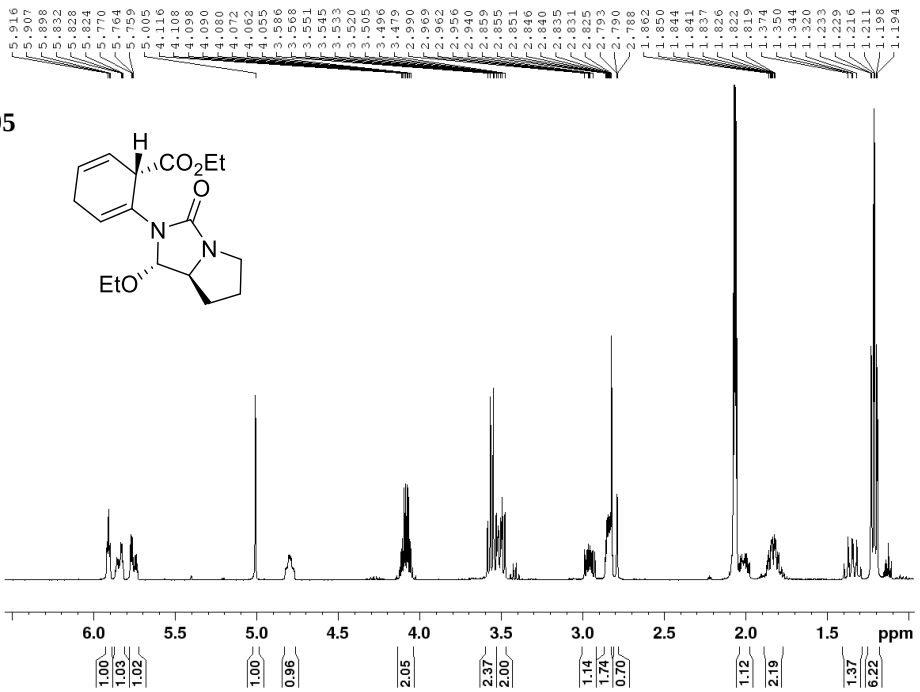
Syn-**195**

^{13}C NMR (100.7 MHz, acetone–d_6)

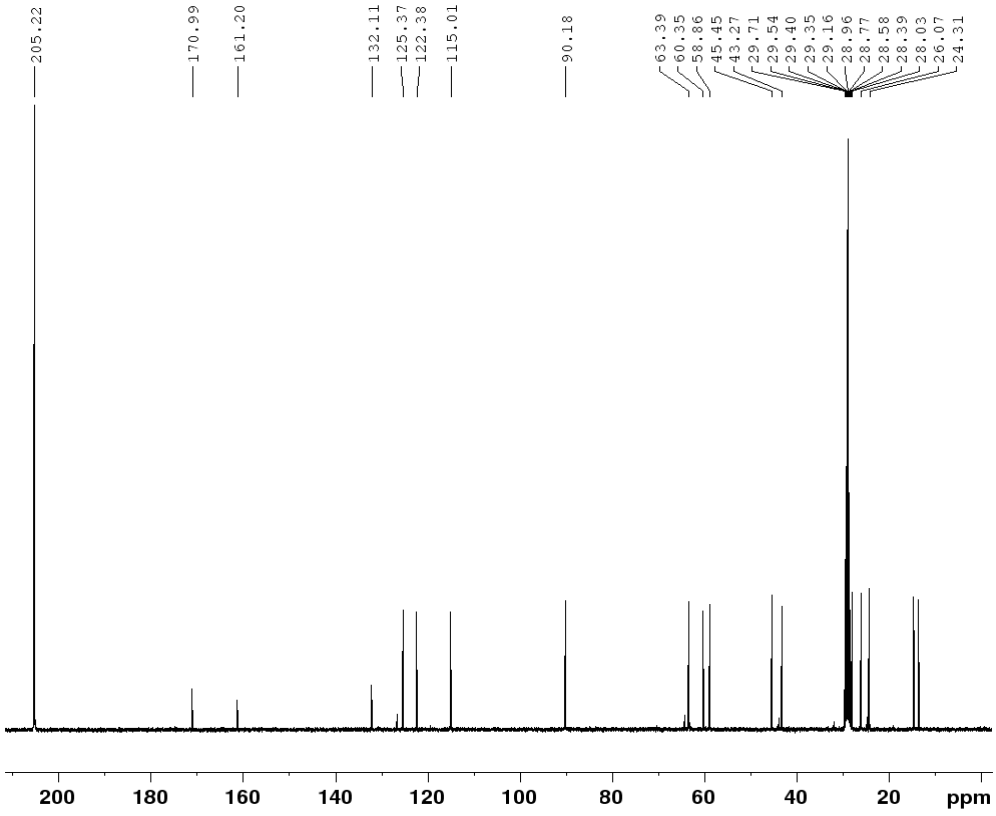


^{1}H NMR (400 MHz, acetone–d_6)

Anti-**195**

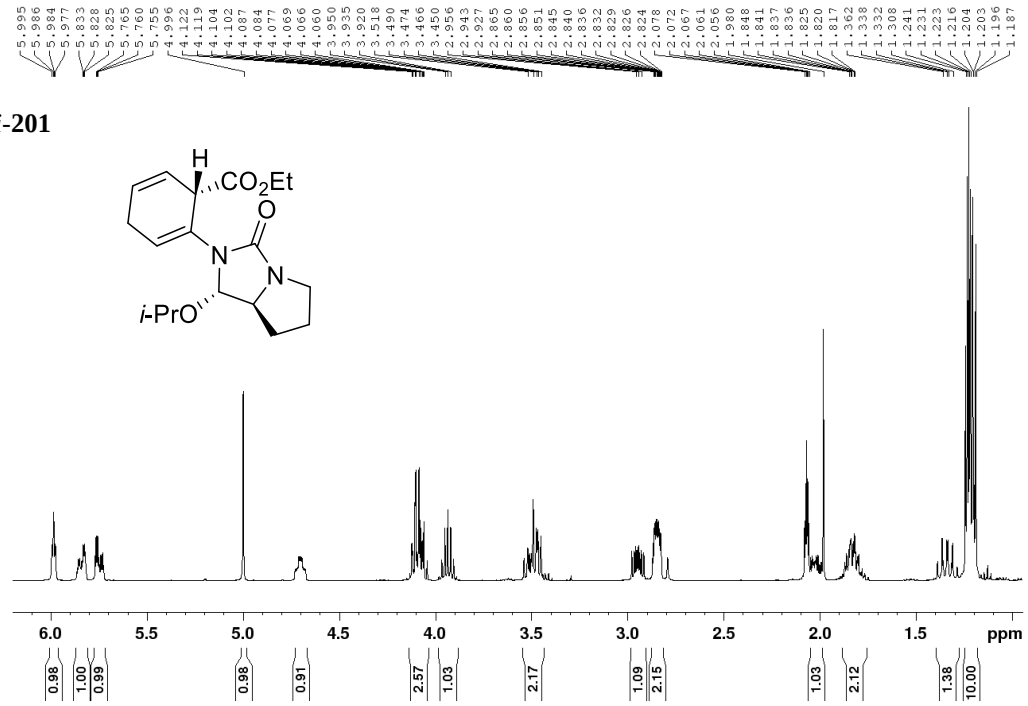


^{13}C NMR (100.7 MHz, acetone–d_6)

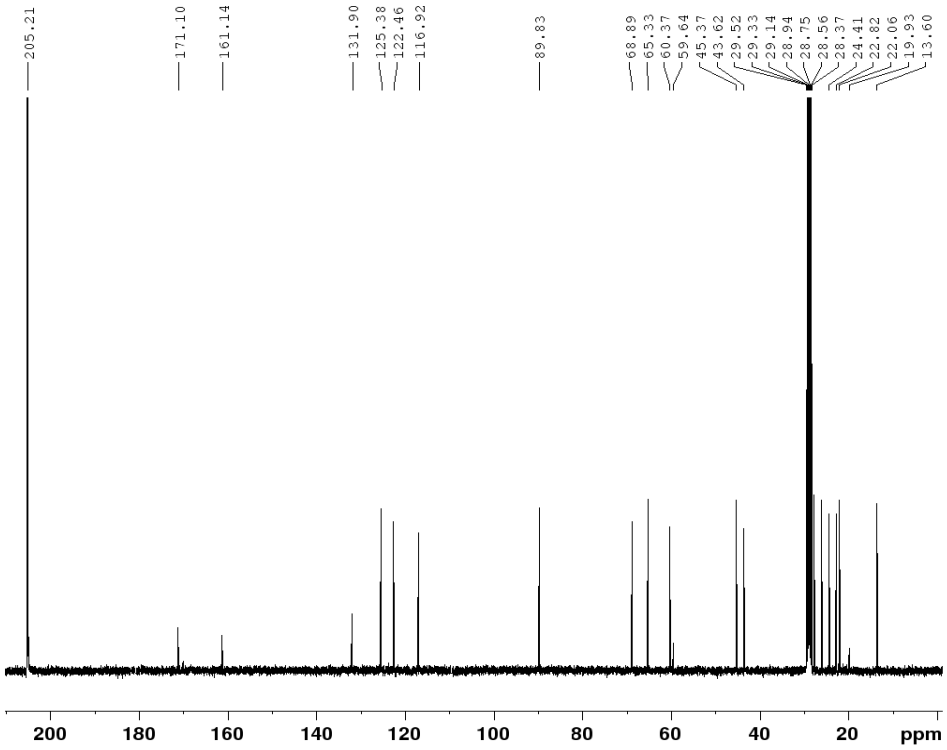


^{1}H NMR (400 MHz, acetone–d_6)

Anti-**201**

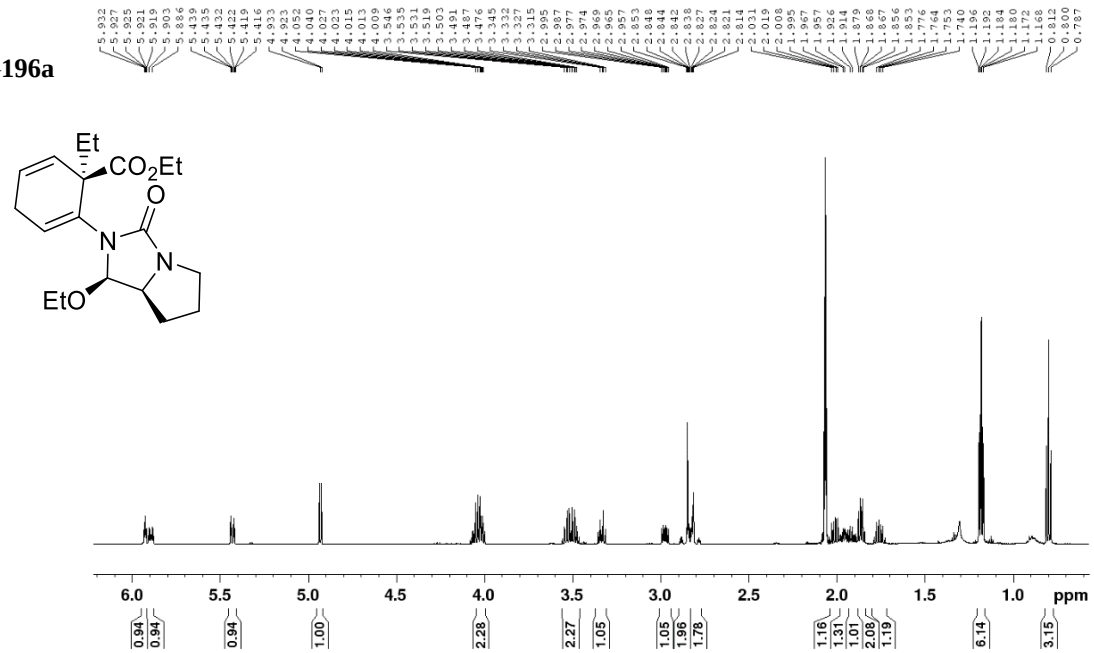


^{13}C NMR (100.7 MHz, acetone–d_6)

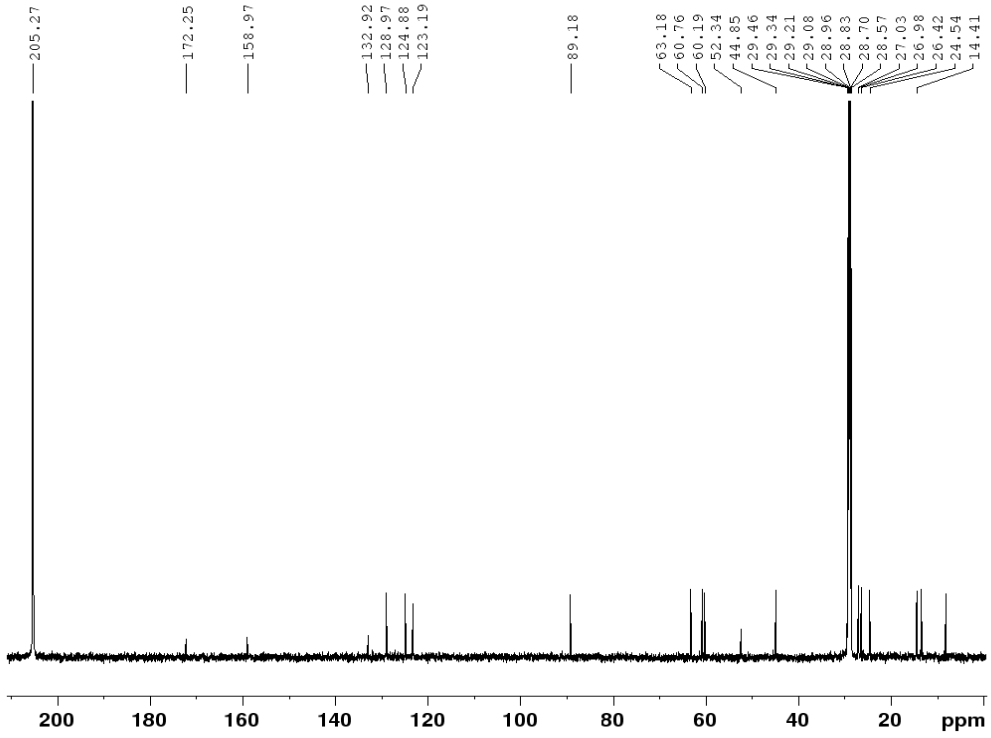


[1] H NMR (600 MHz, acetone–d_6)

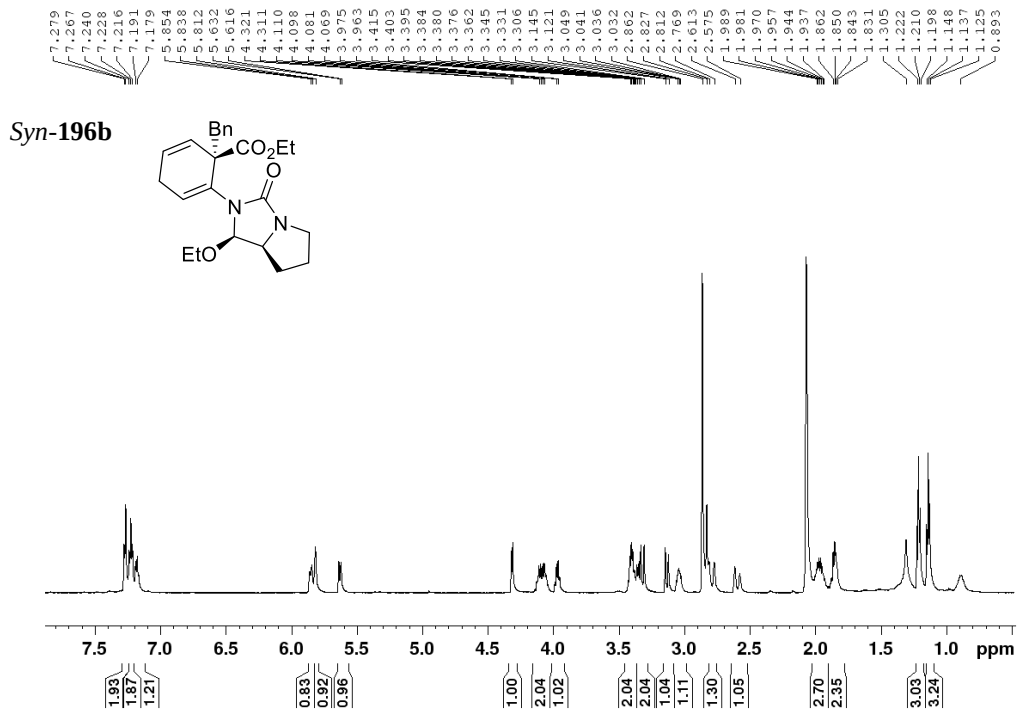
Syn–**196a**



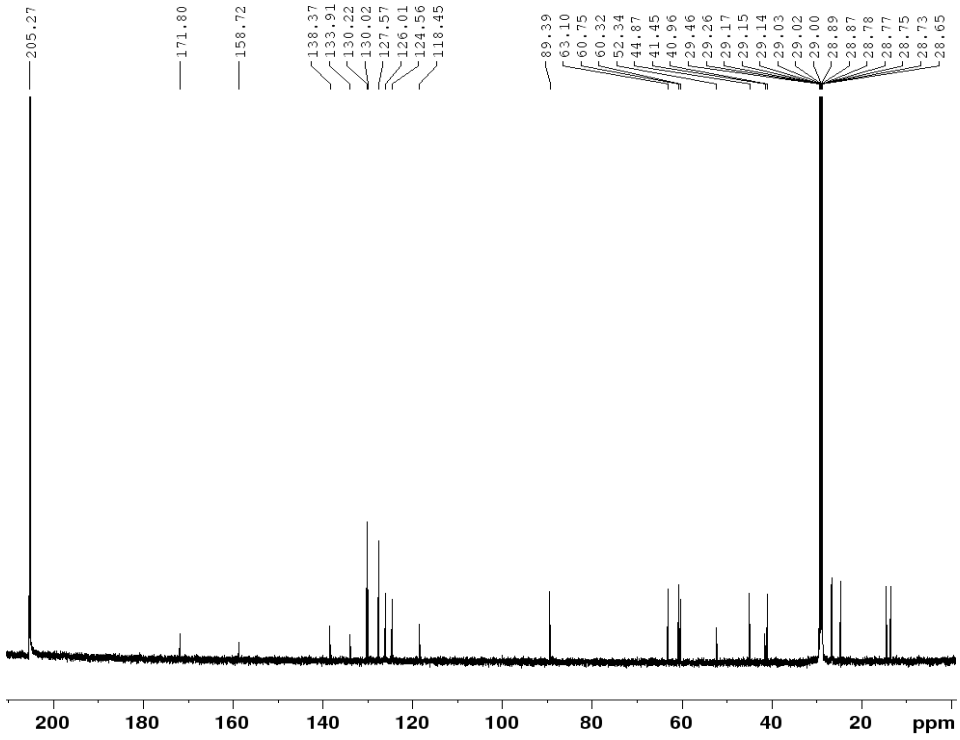
^{13}C NMR (100.7 MHz, acetone–d_6)



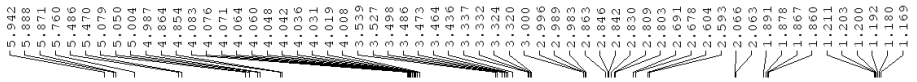
^{1}H NMR (600 MHz, acetone–d_6)



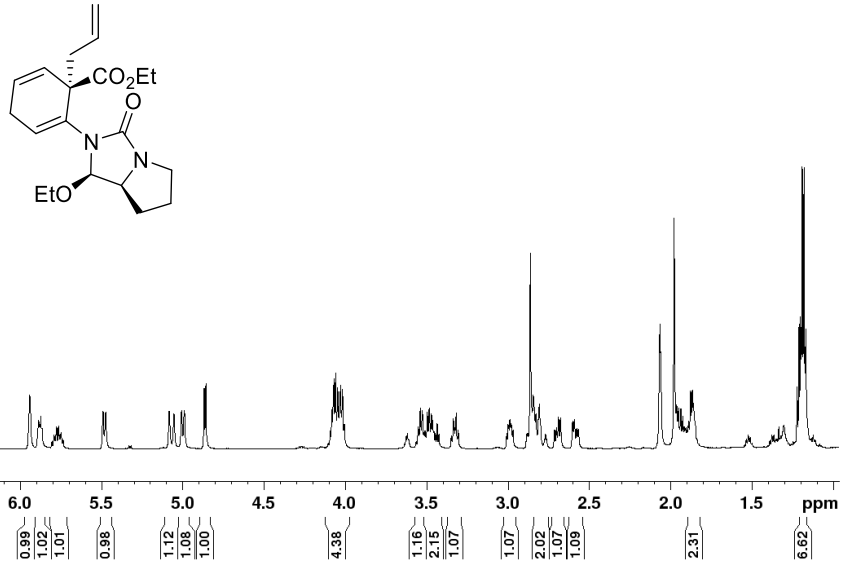
^{13}C NMR (100.7 MHz, acetone–d_6)



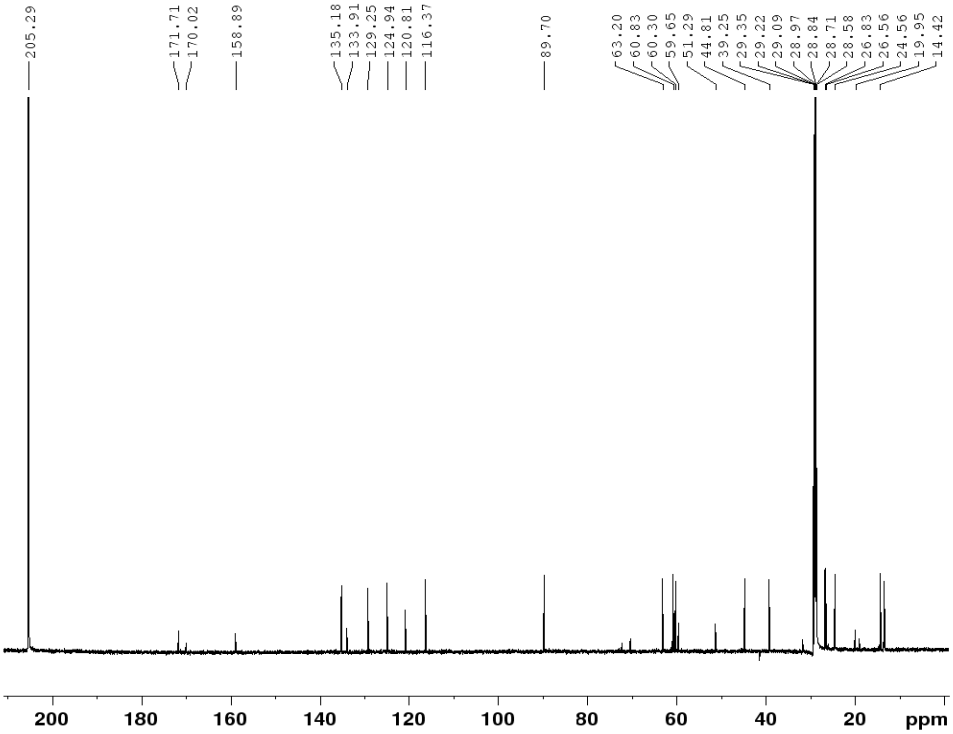
^{1}H NMR (600 MHz, acetone–d_6)



Syn-**196c**

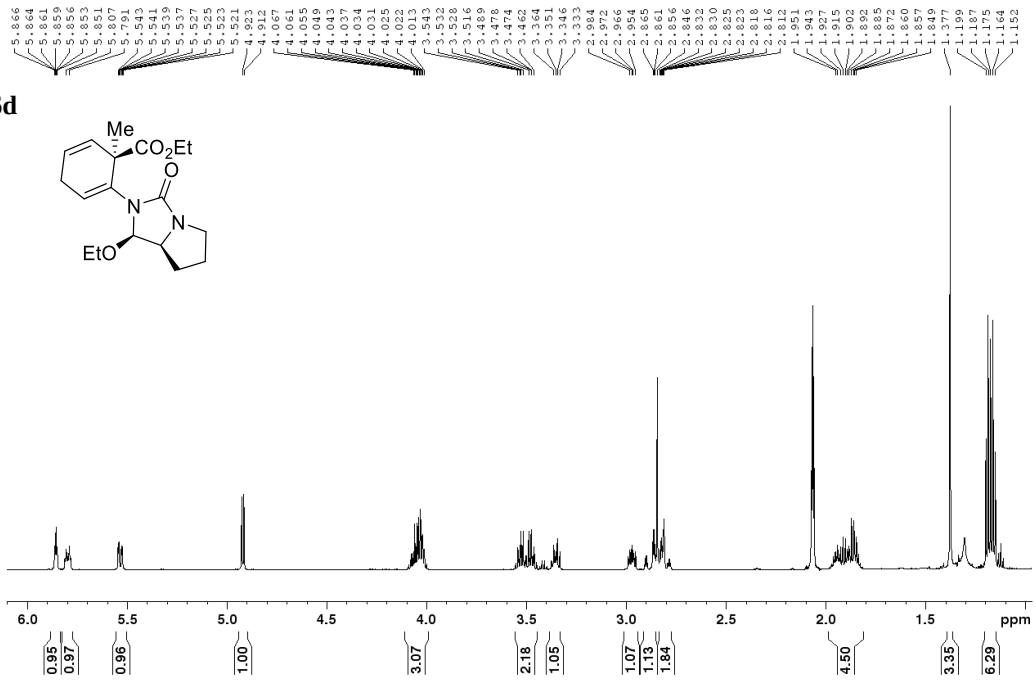


^{13}C NMR (100.7 MHz, acetone–d_6)

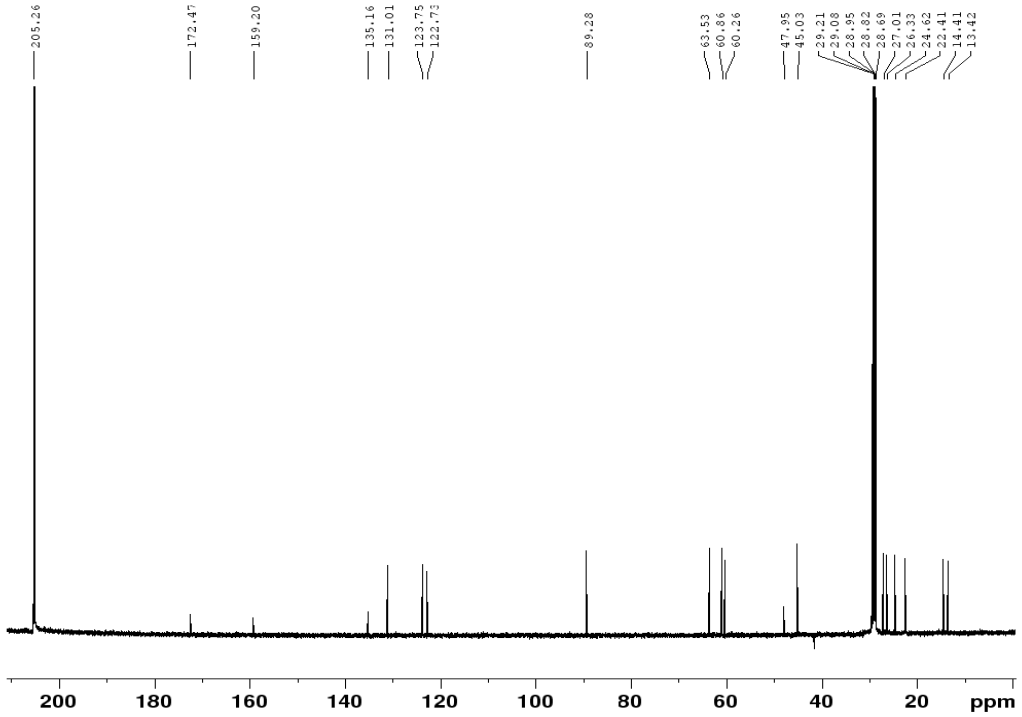


^{1}H NMR (600 MHz, acetone–d_6)

Syn-**196d**

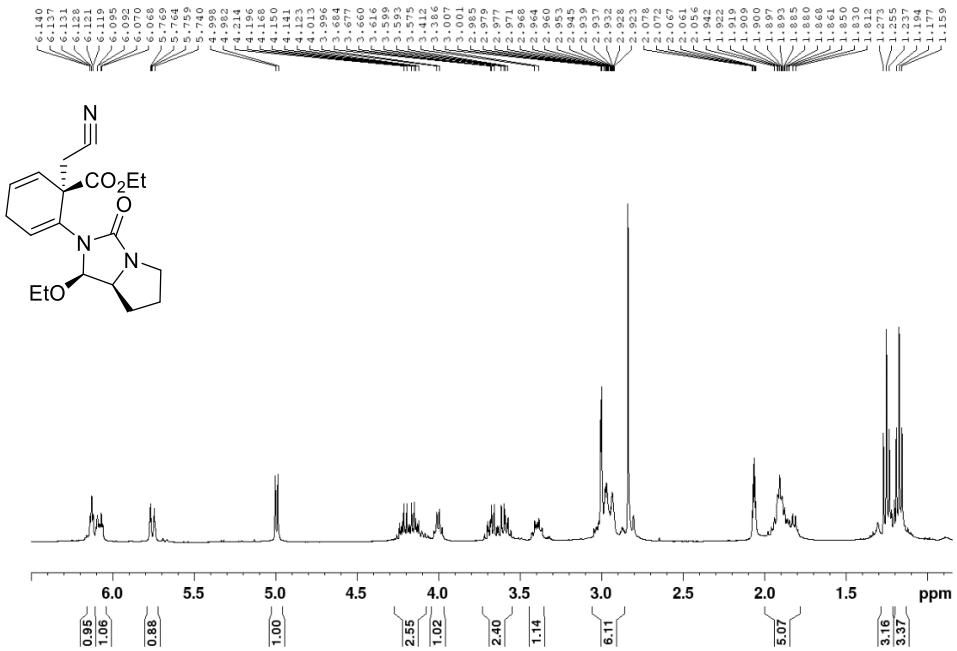


^{13}C NMR (100.7 MHz, acetone–d_6)

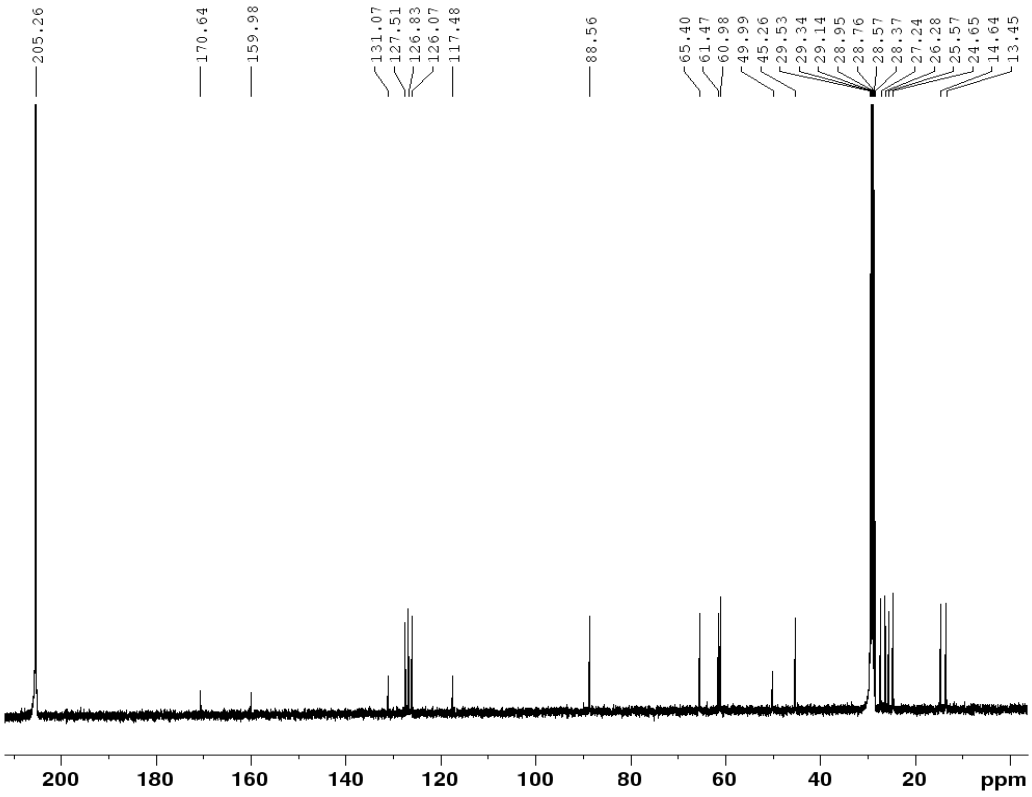


^{1}H NMR (400 MHz, acetone–d_6)

Syn-**196f**

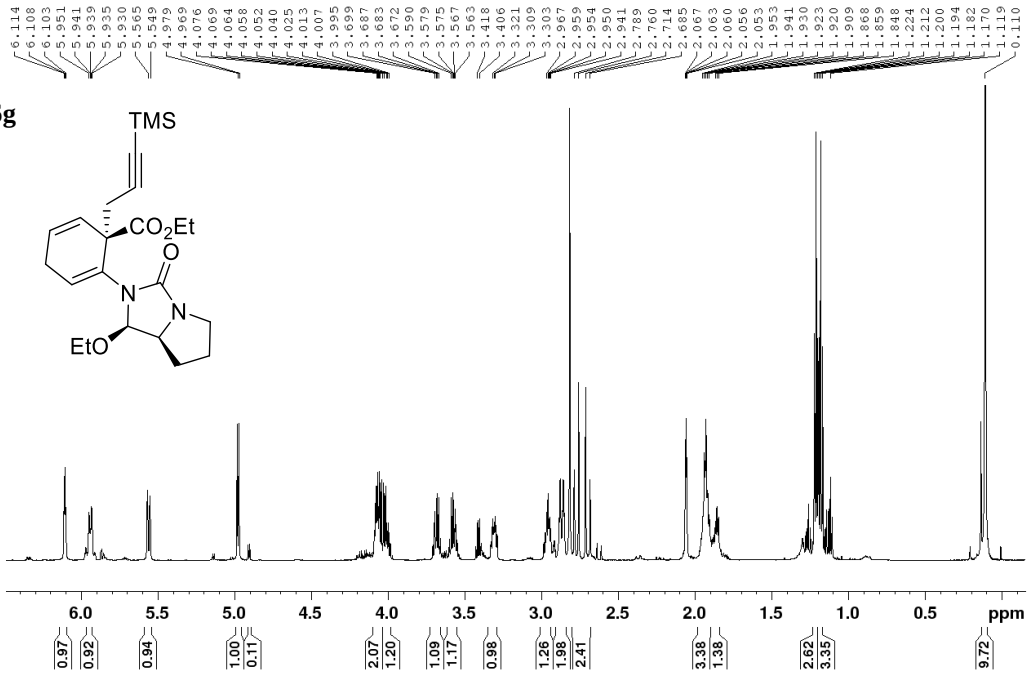


^{13}C NMR (100.7 MHz, acetone–d_6)

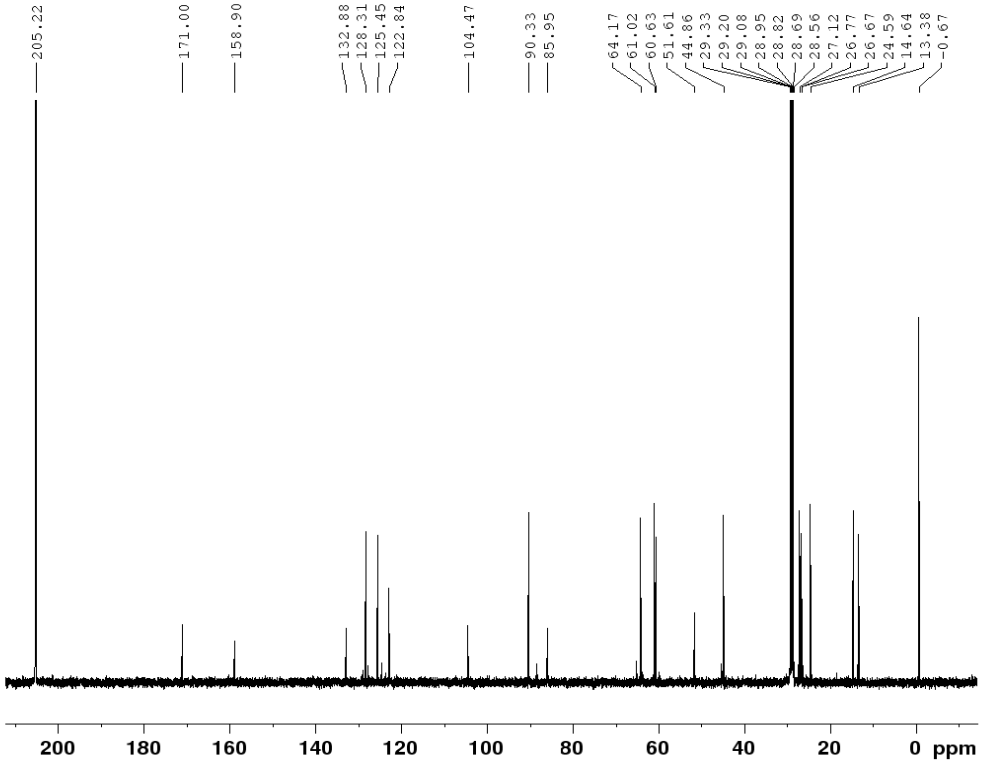


^{1}H NMR (600 MHz, acetone–d_6)

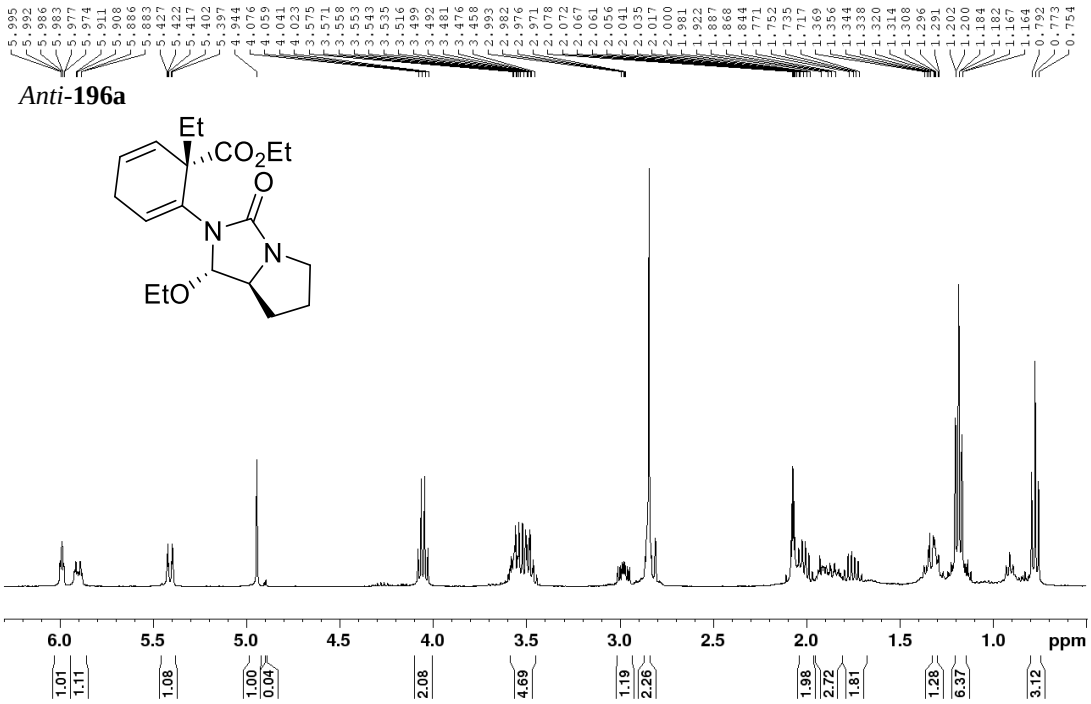
Syn-**196g**



^{13}C NMR (100.7 MHz, acetone–d_6)

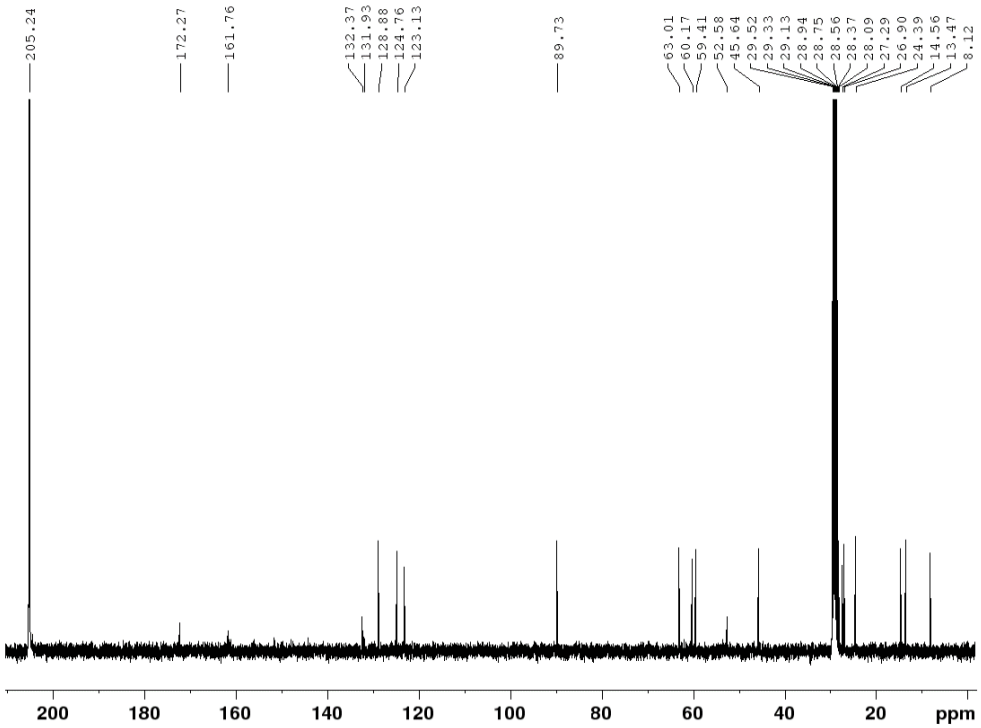


[1] H NMR (400 MHz, acetone–d_6)

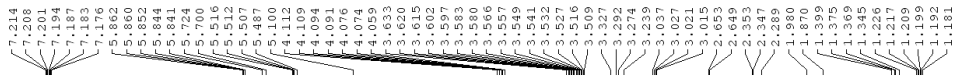


Anti-**196a**

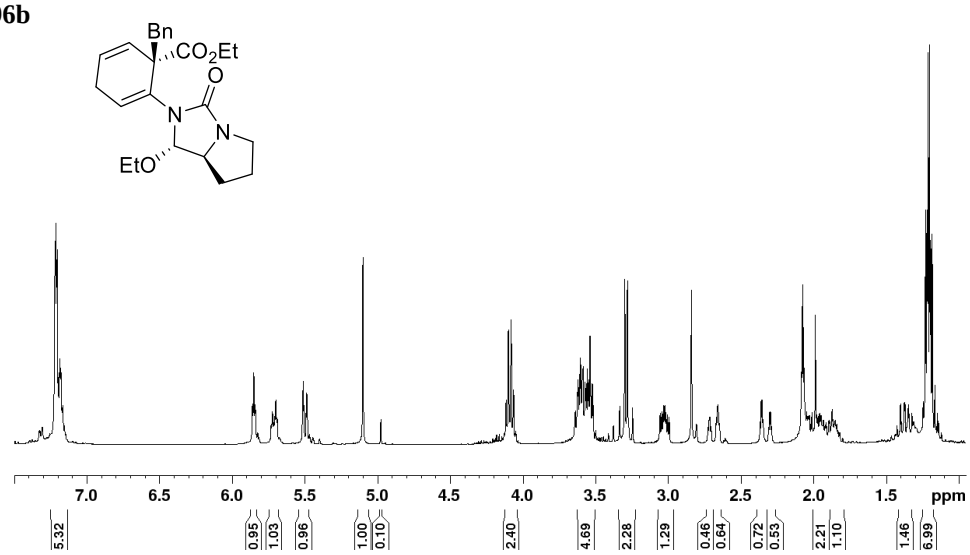
[13]C NMR (100.7 MHz, acetone–d_6)



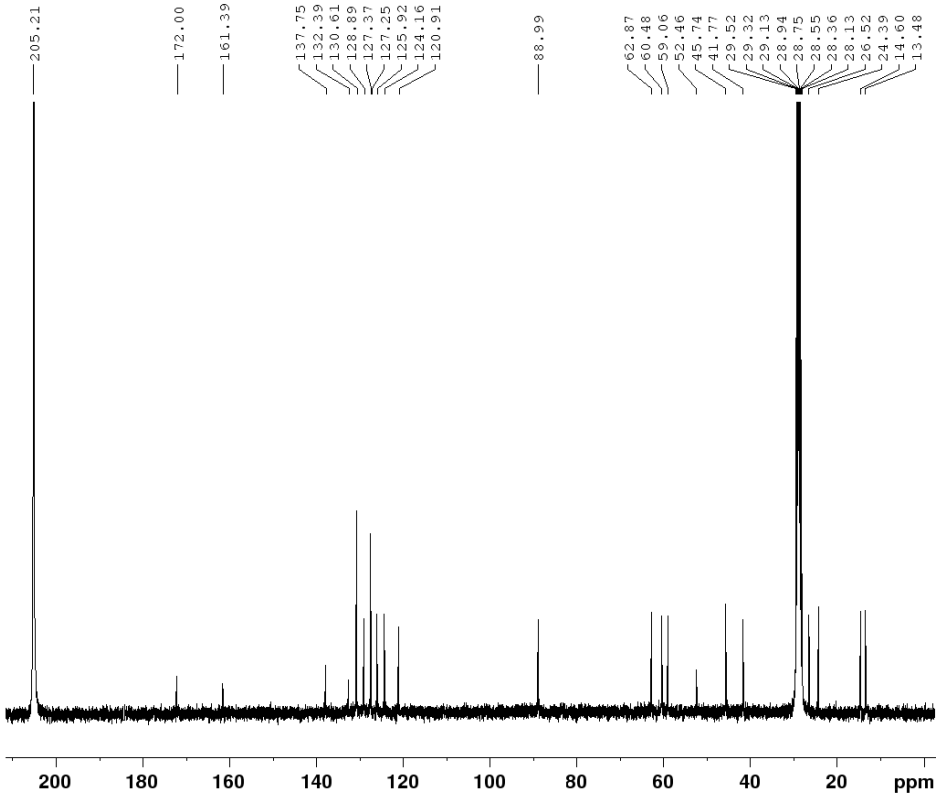
^{1}H NMR (400 MHz, acetone–d_6)



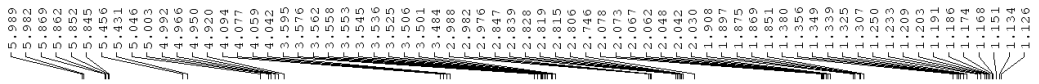
Anti-**196b**



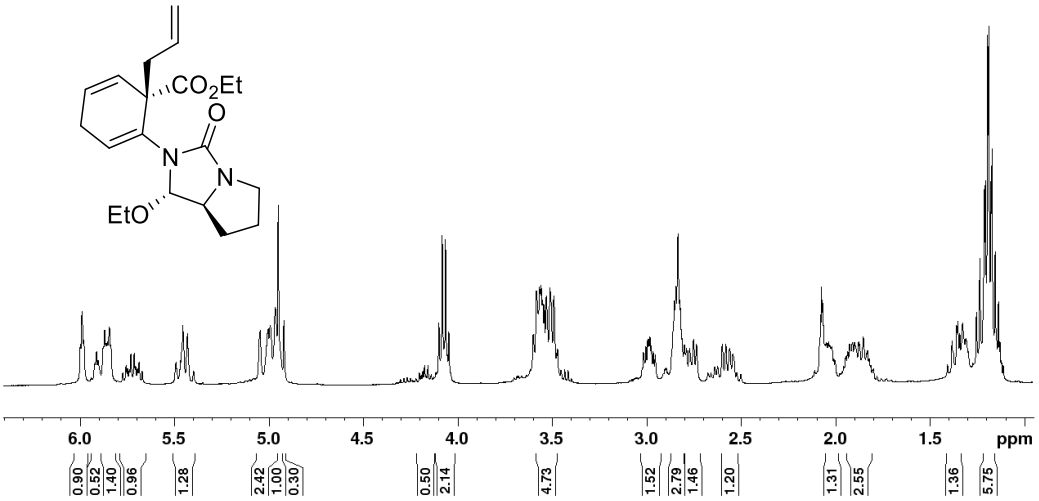
^{13}C NMR (100.7 MHz, acetone–d_6)



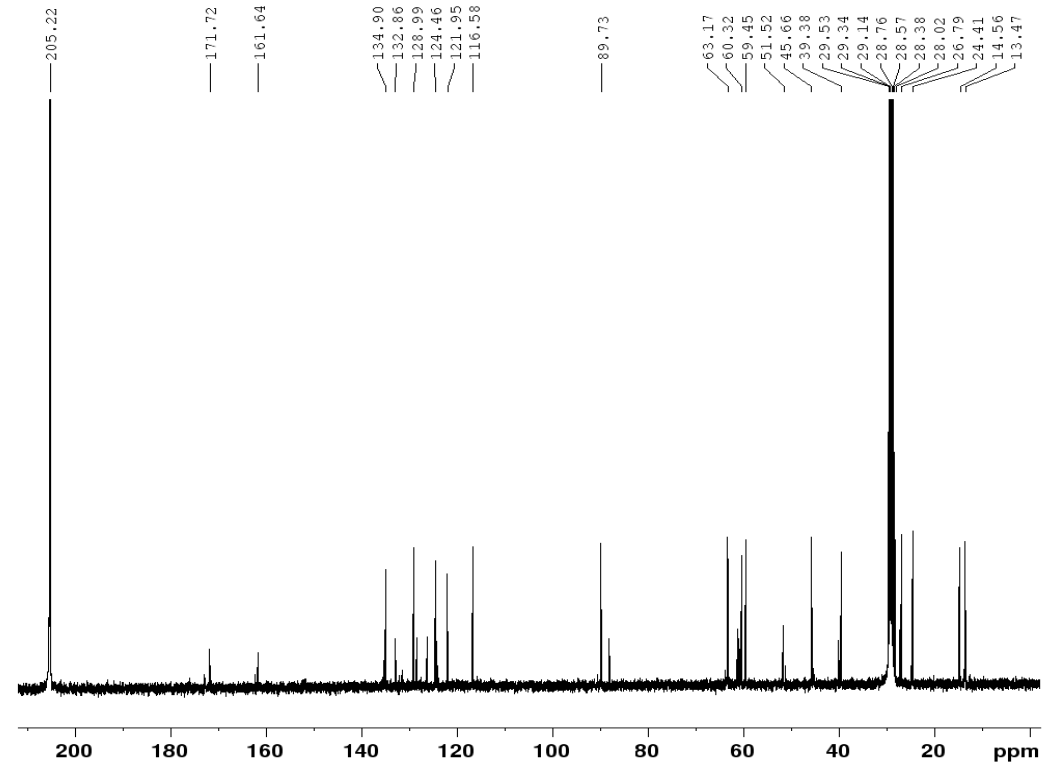
^{1}H NMR (400 MHz, acetone–d_6)



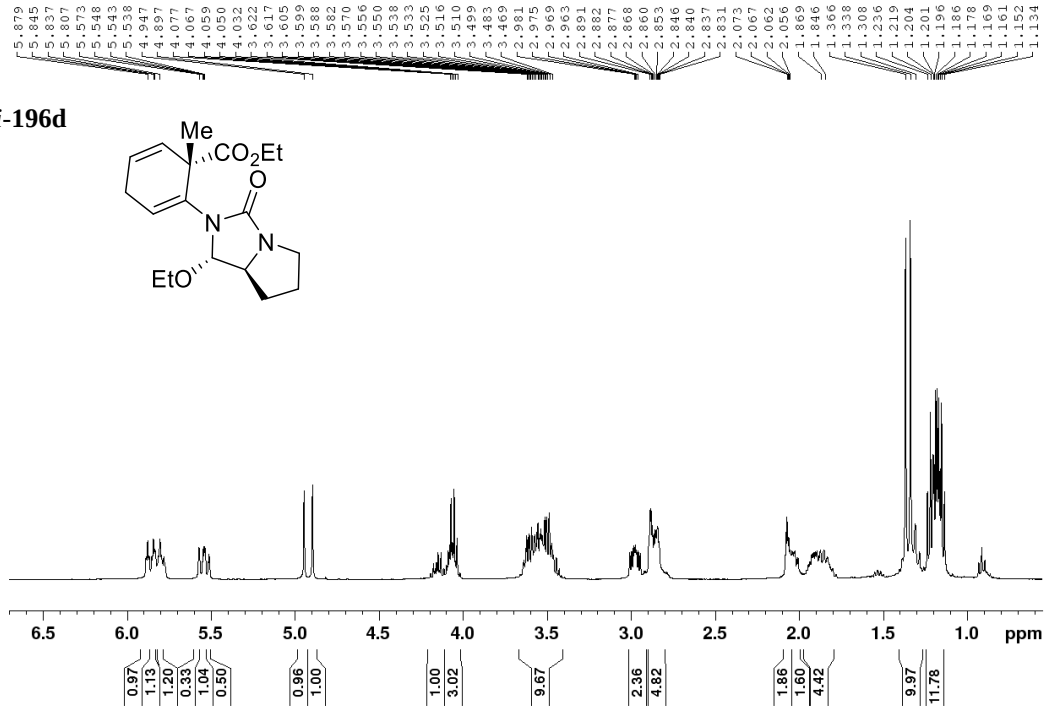
Anti-**196c**



^{13}C NMR (100.7 MHz, acetone–d_6)

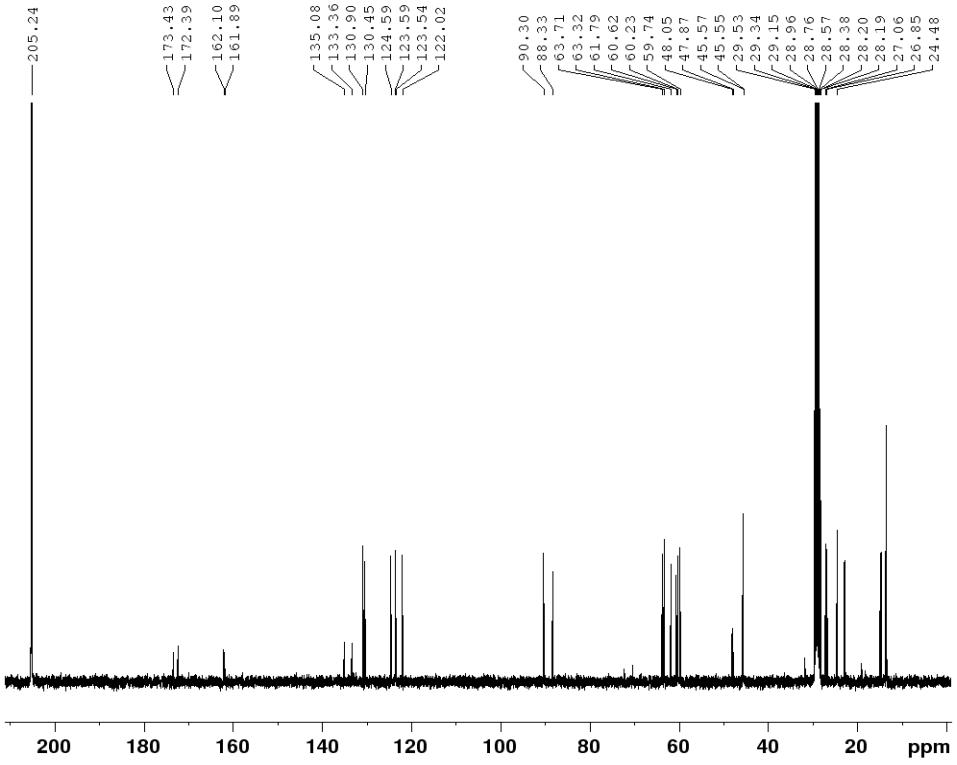


^{1}H NMR (400 MHz, acetone–d_6)

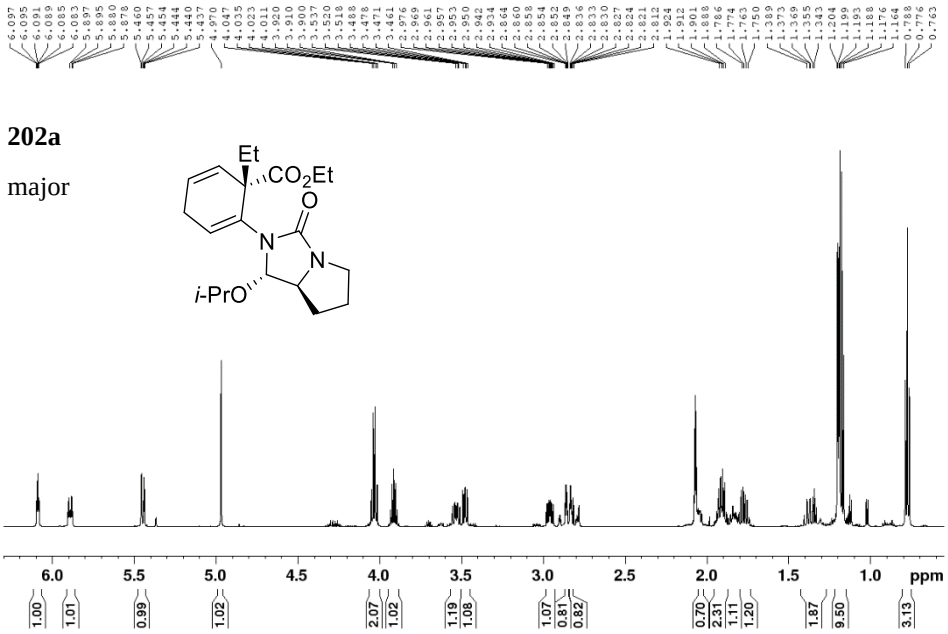


Anti-**196d**

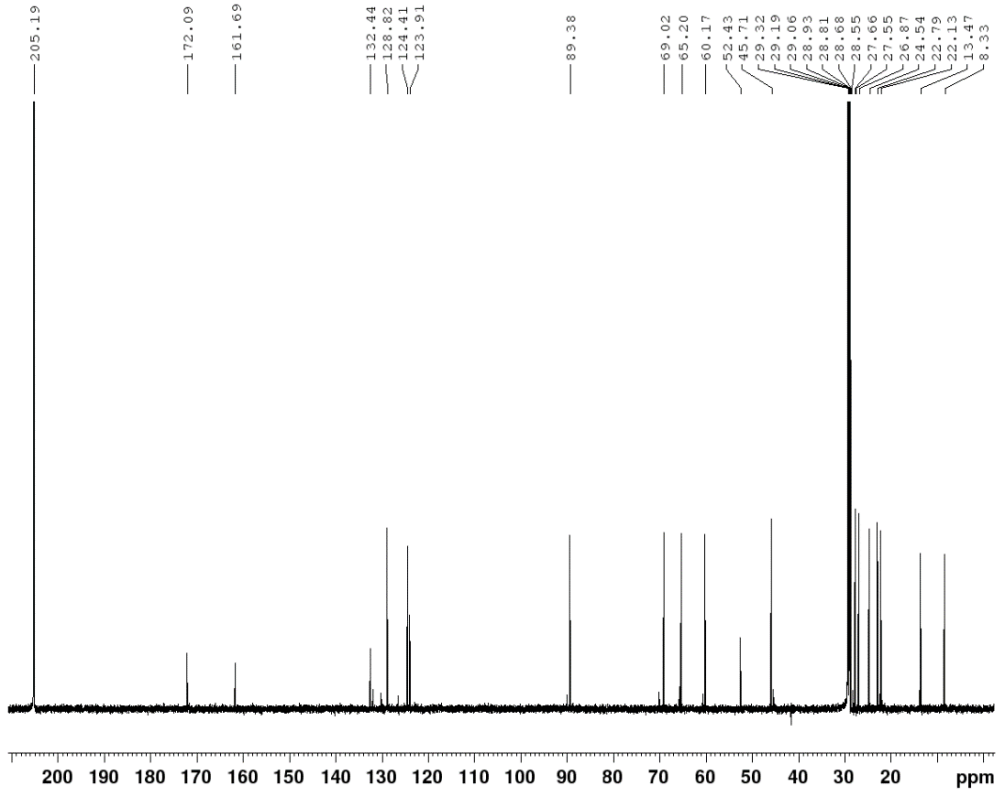
^{13}C NMR (100.7 MHz, acetone–d_6)



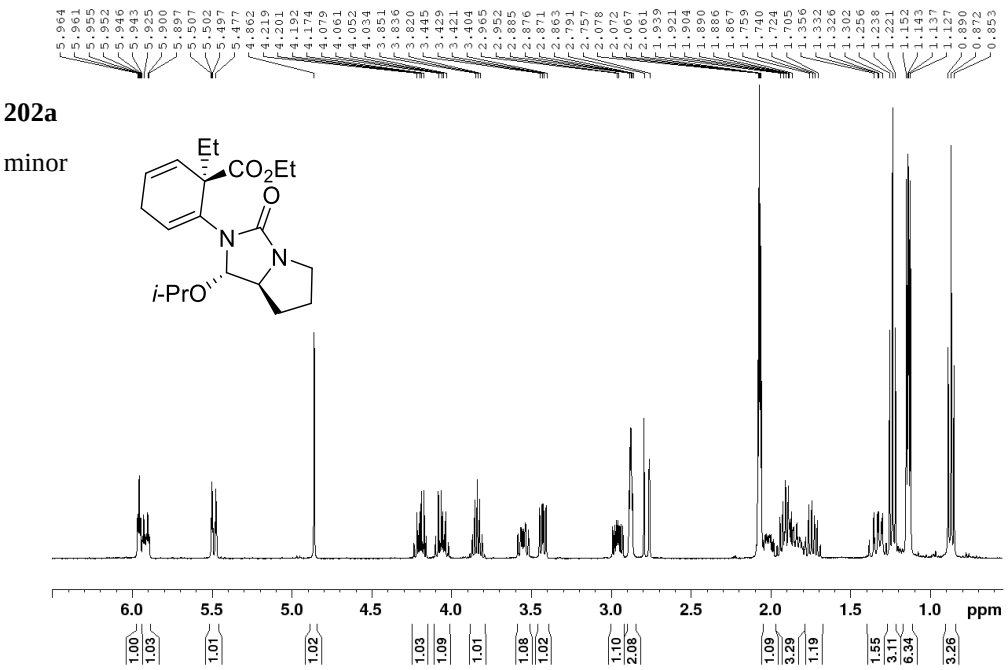
^{1}H NMR (600 MHz, acetone–d_6)



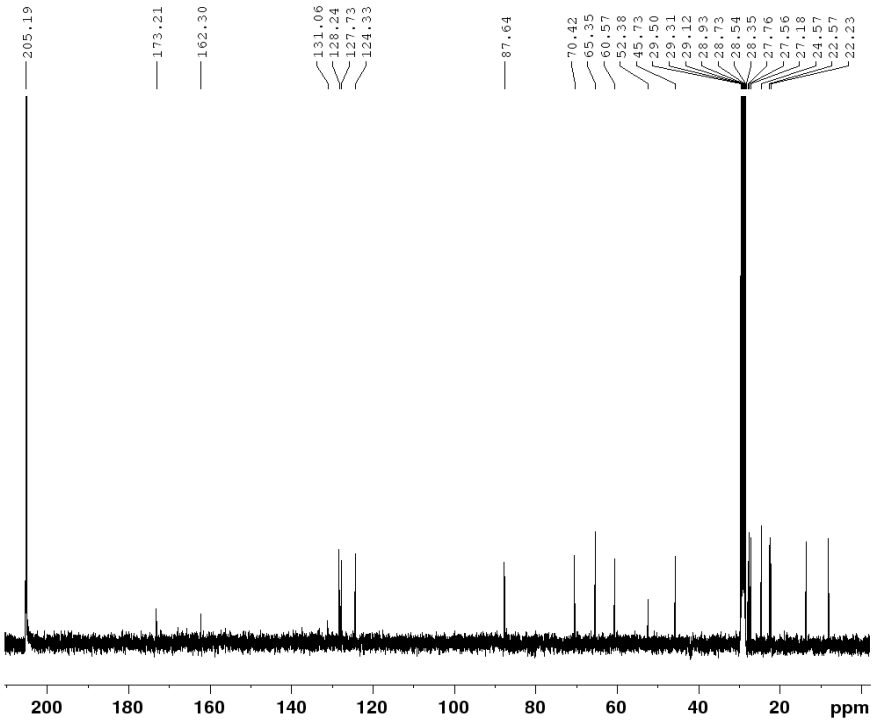
^{13}C NMR (100.7 MHz, acetone–d_6)



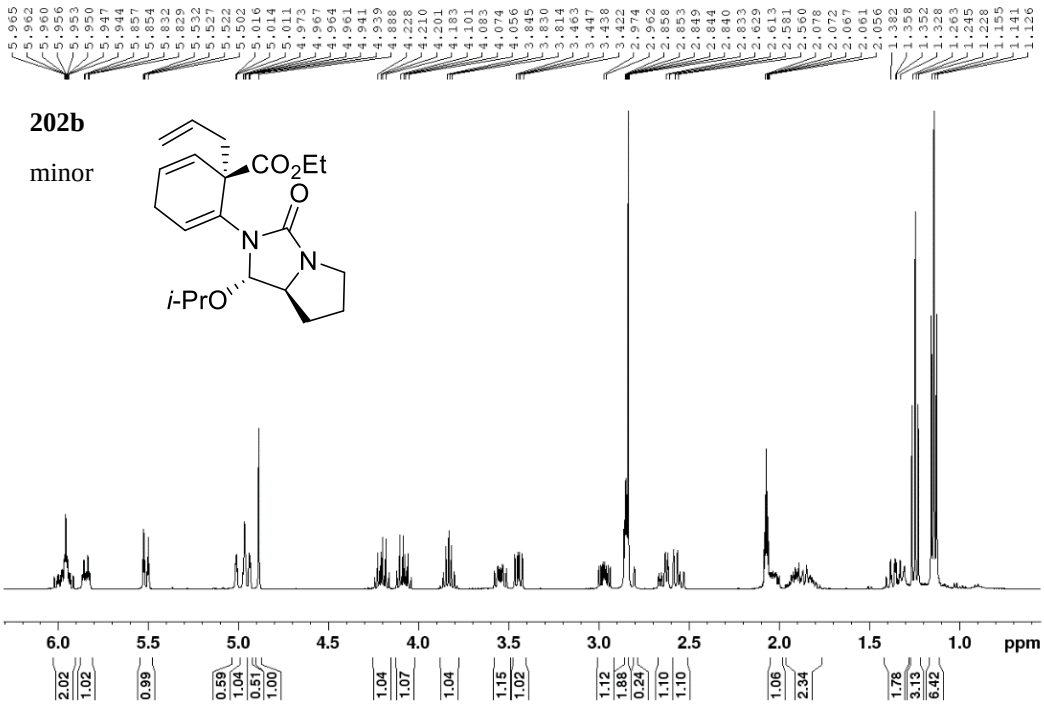
^{1}H NMR (400 MHz, acetone–d_6)



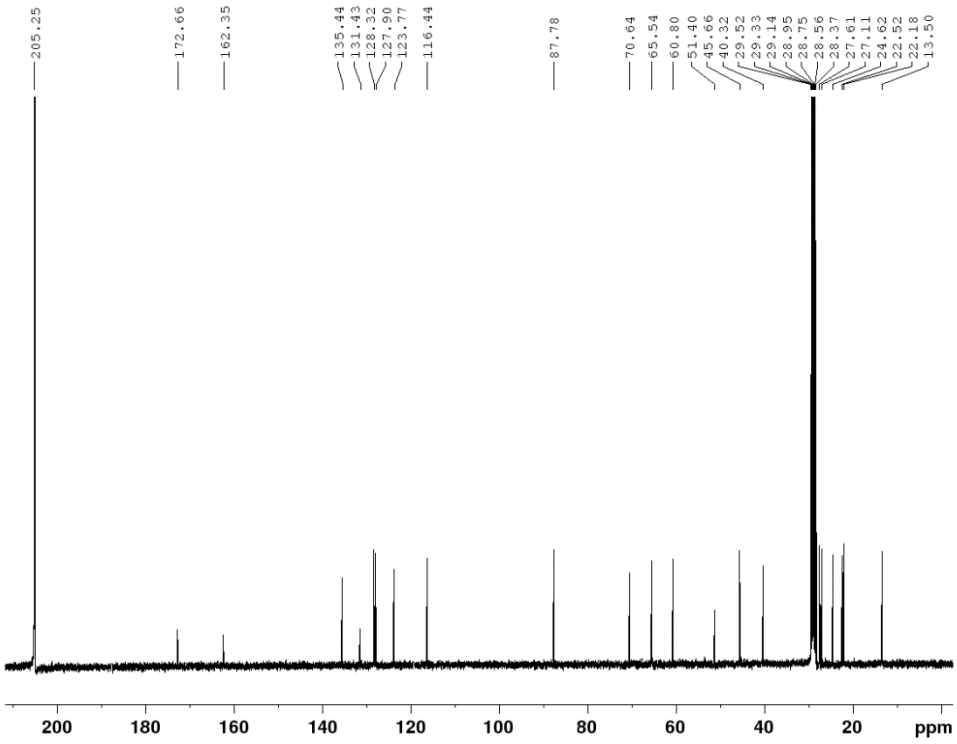
^{13}C NMR (100.7 MHz, acetone–d_6)



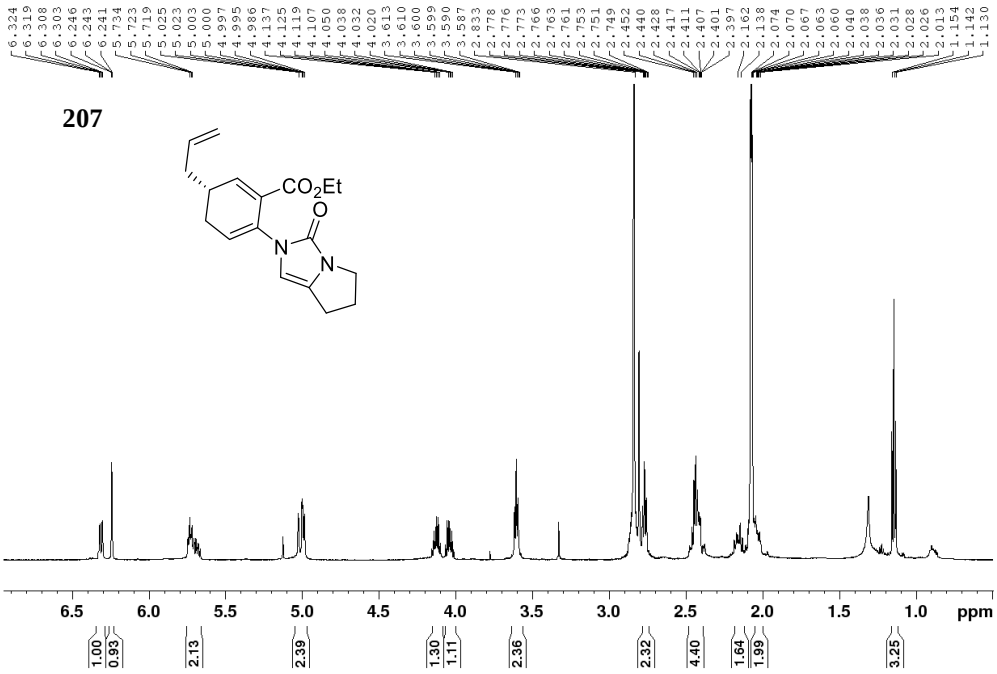
^{1}H NMR (600 MHz, acetone–d_6)



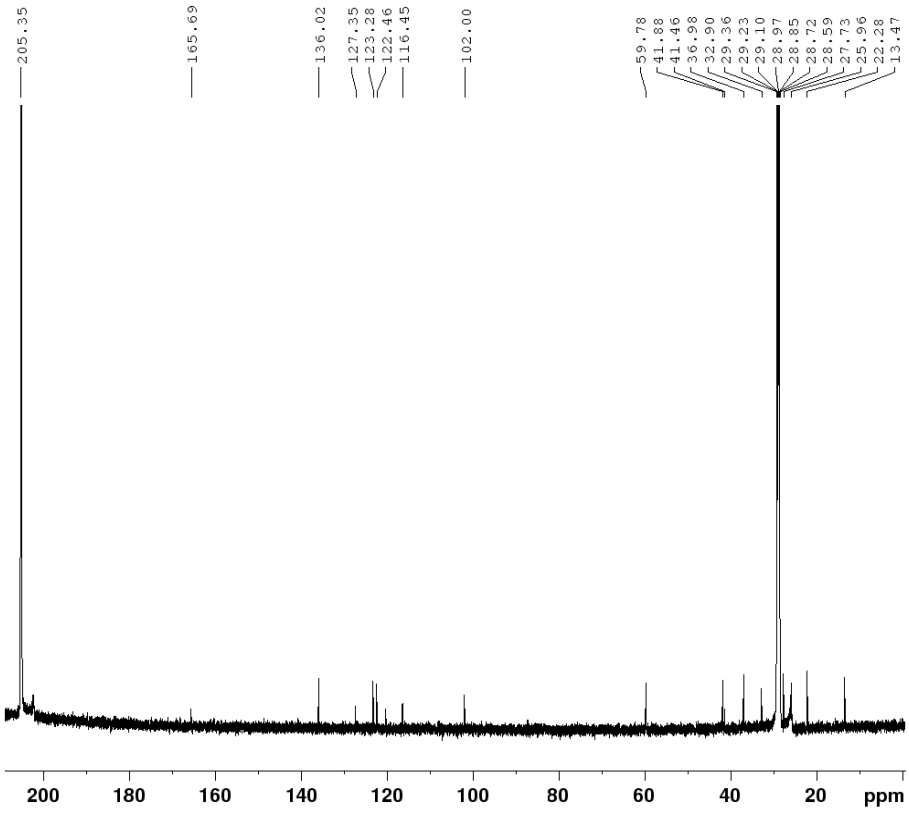
^{13}C NMR (100.7 MHz, acetone–d_6)



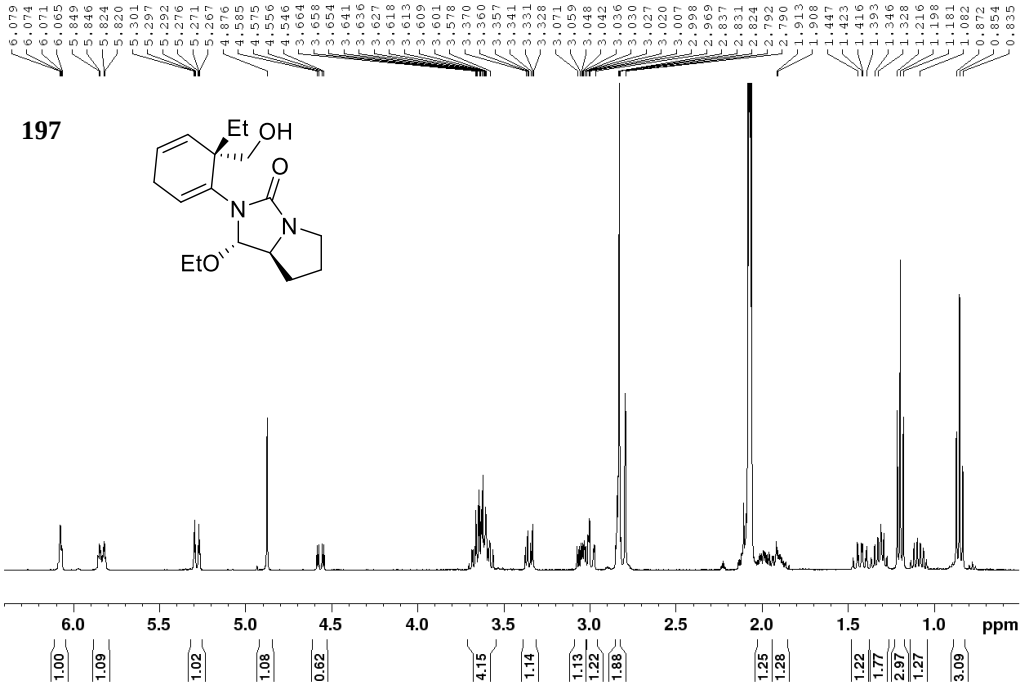
^{1}H NMR (600 MHz, acetone–d_6)



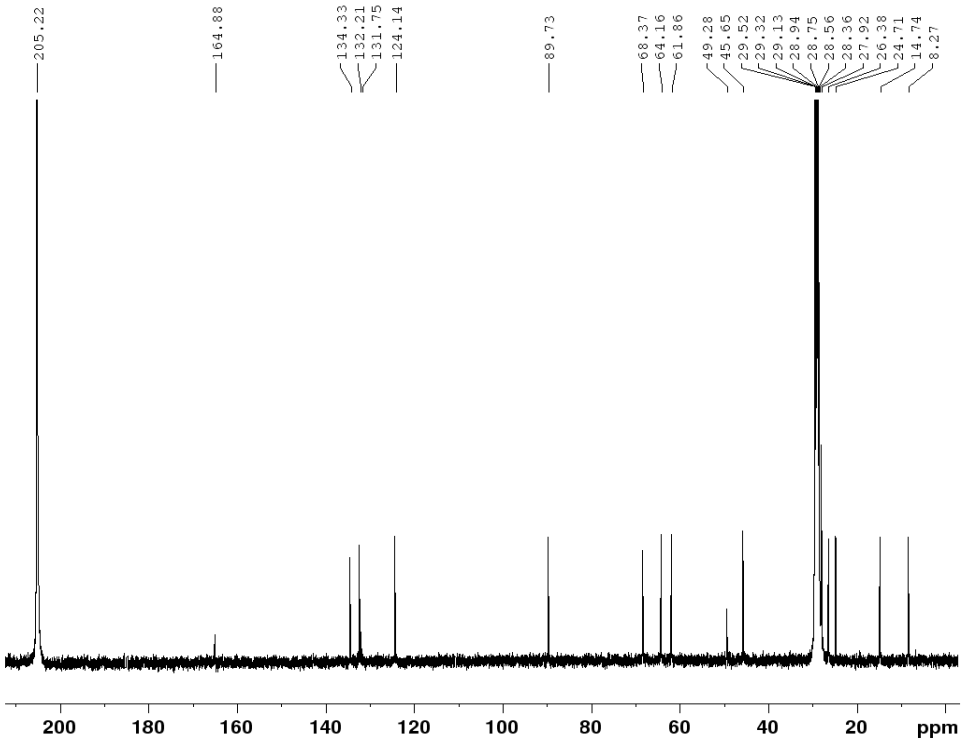
^{13}C NMR (100.7 MHz, acetone–d_6)



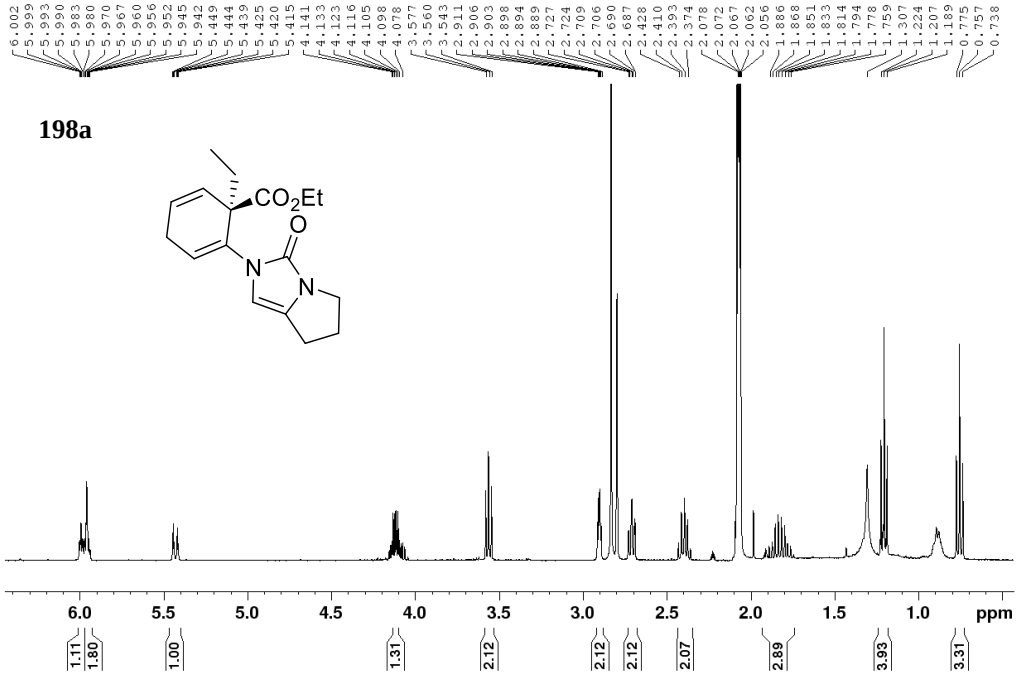
^{1}H NMR (400 MHz, acetone–d_6)



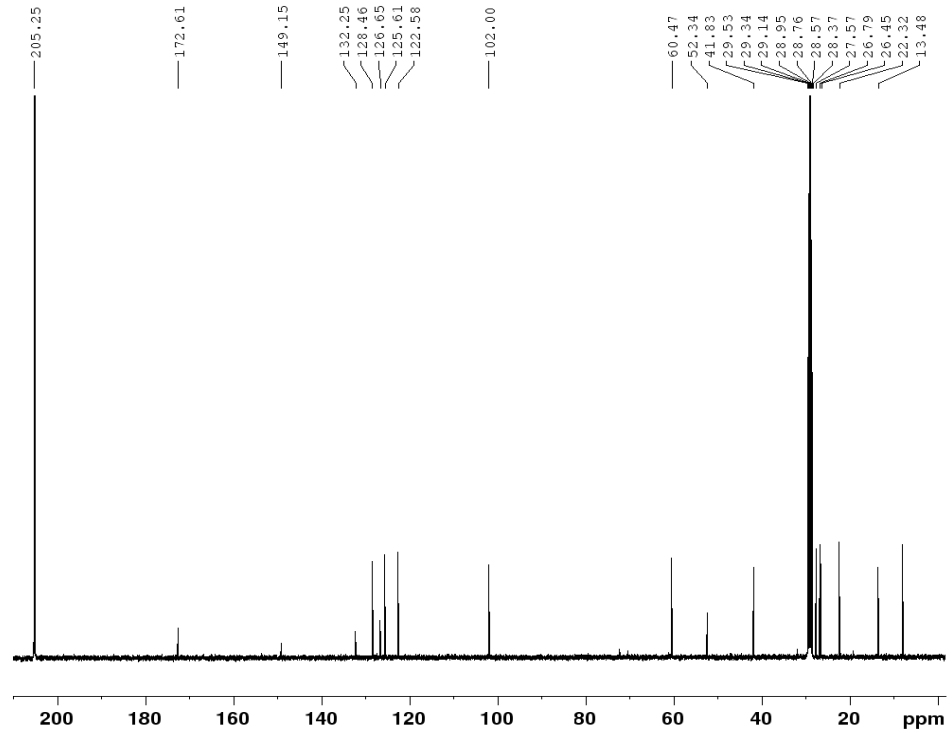
^{13}C NMR (100.7 MHz, acetone–d_6)



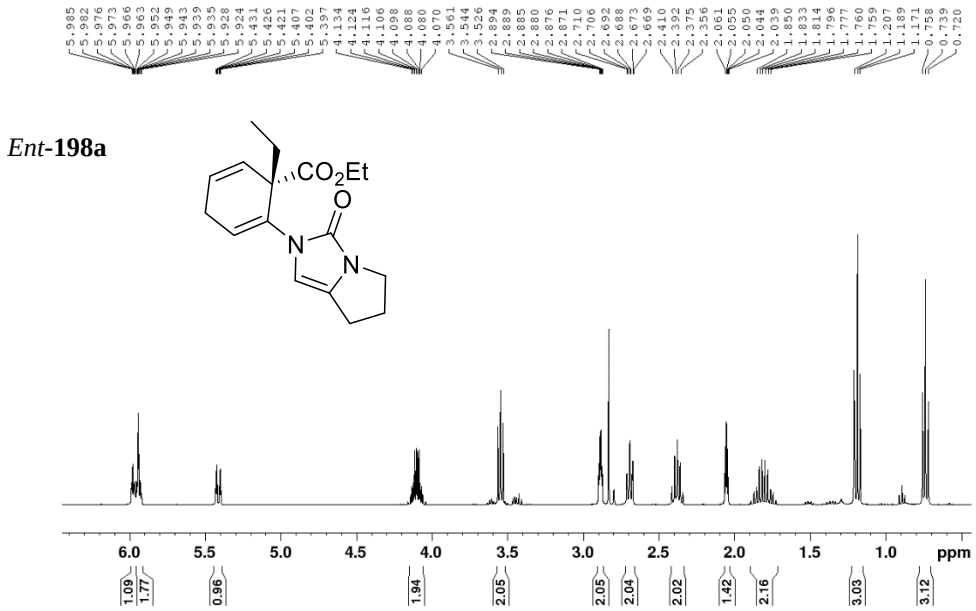
^{1}H NMR (400 MHz, acetone–d_6)



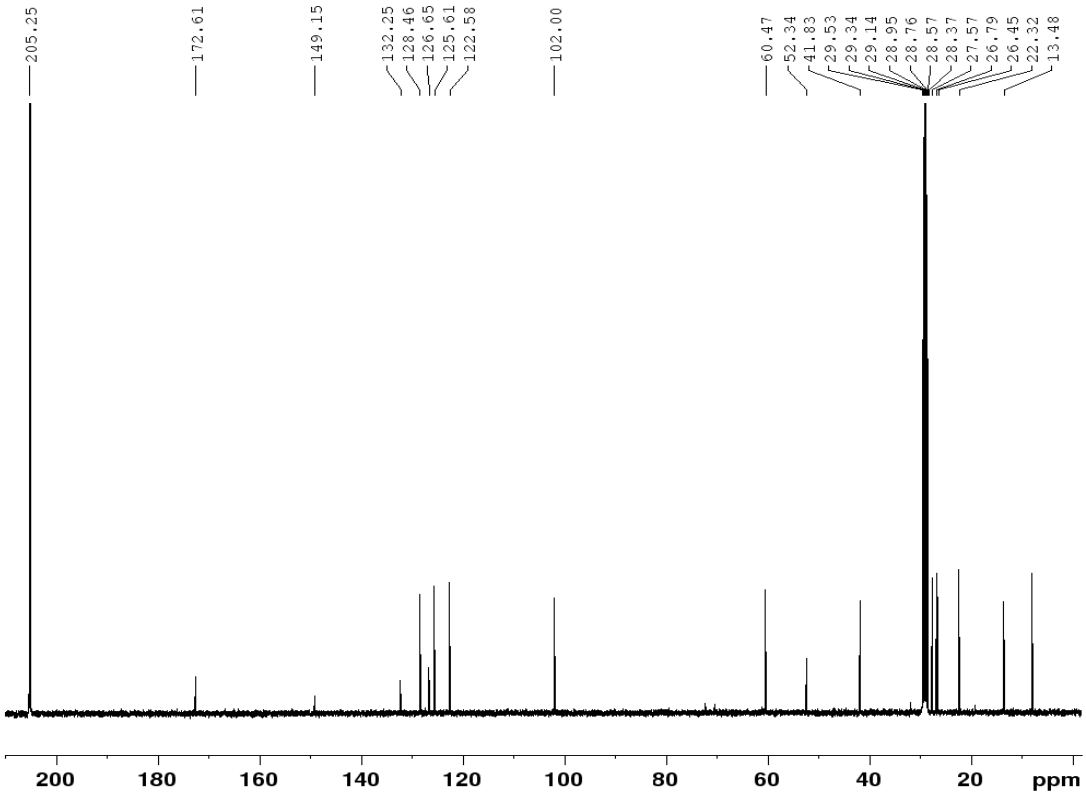
^{13}C NMR (100.7 MHz, acetone–d_6)



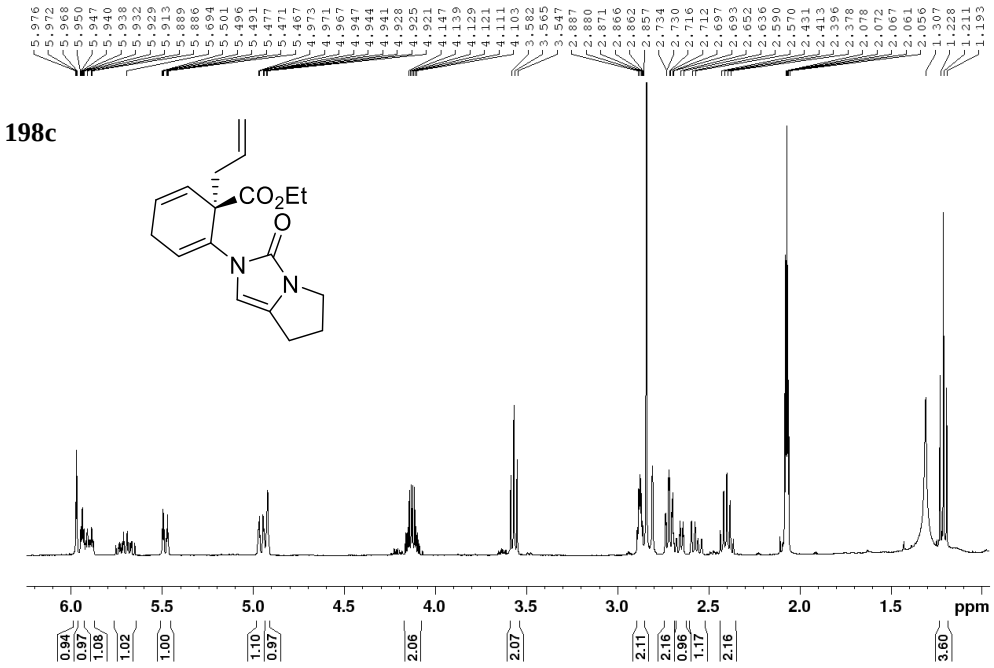
^{1}H NMR (400 MHz, acetone–d_6)



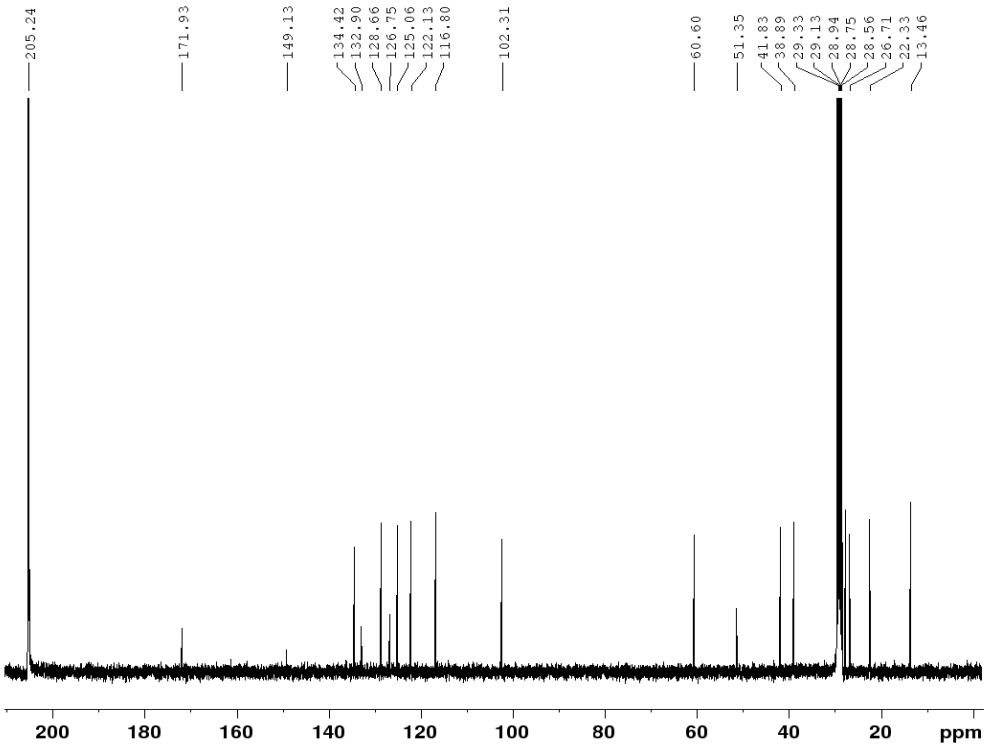
^{13}C NMR (100.7 MHz, acetone–d_6)



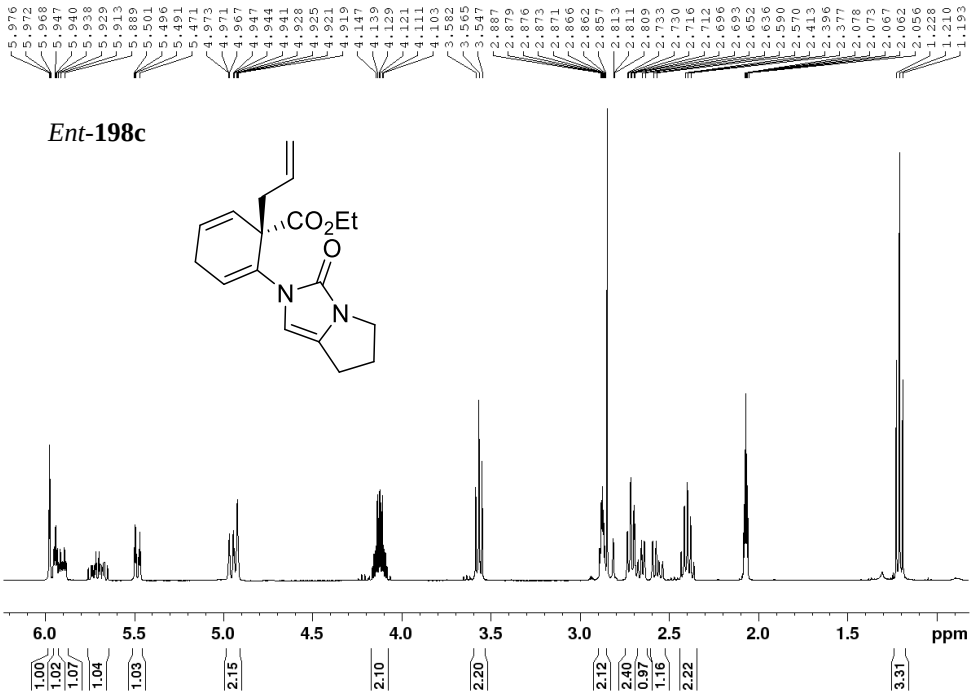
^{1}H NMR (400 MHz, acetone–d_6)



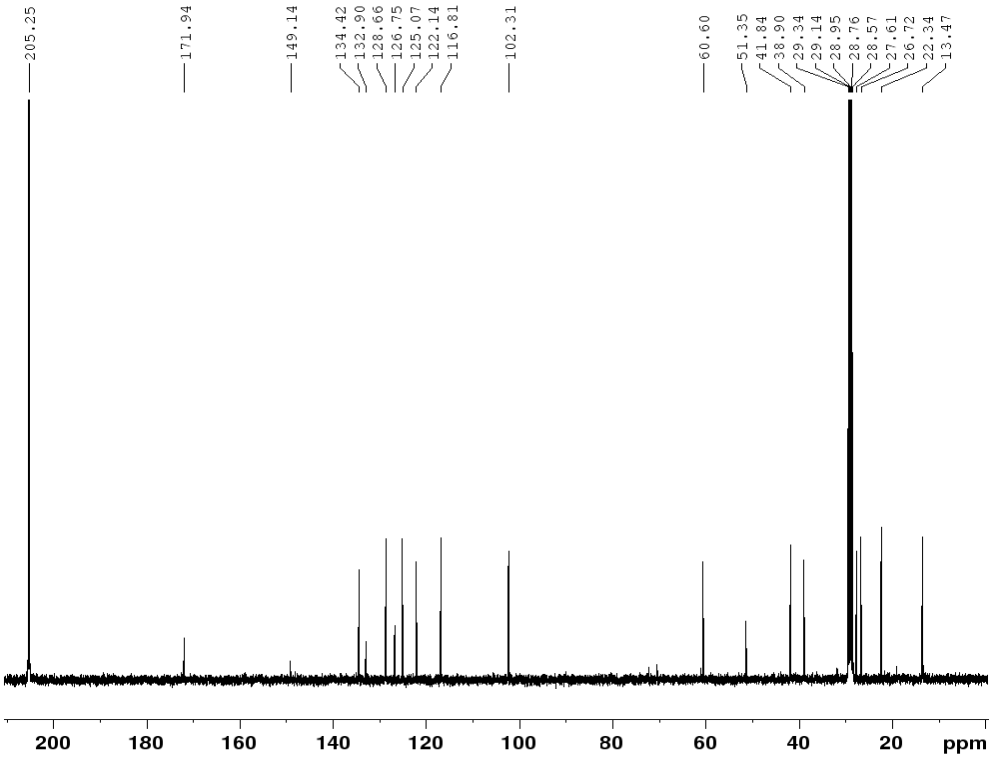
^{13}C NMR (100.7 MHz, acetone–d_6)



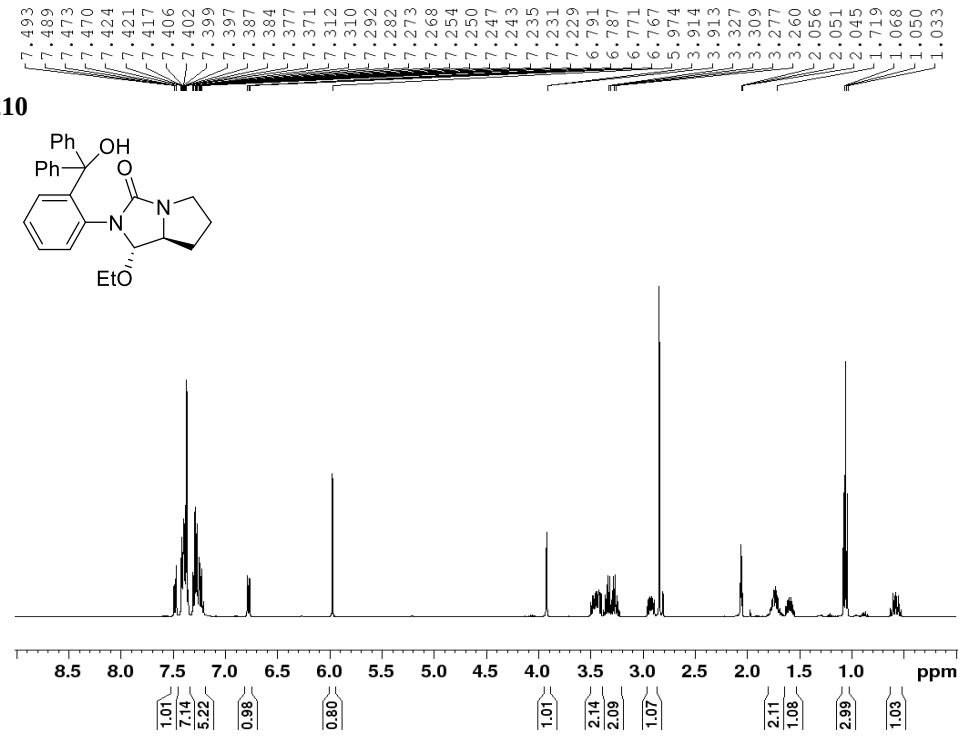
^{1}H NMR (400 MHz, acetone–d_6)



^{13}C NMR (100.7 MHz, acetone–d_6)

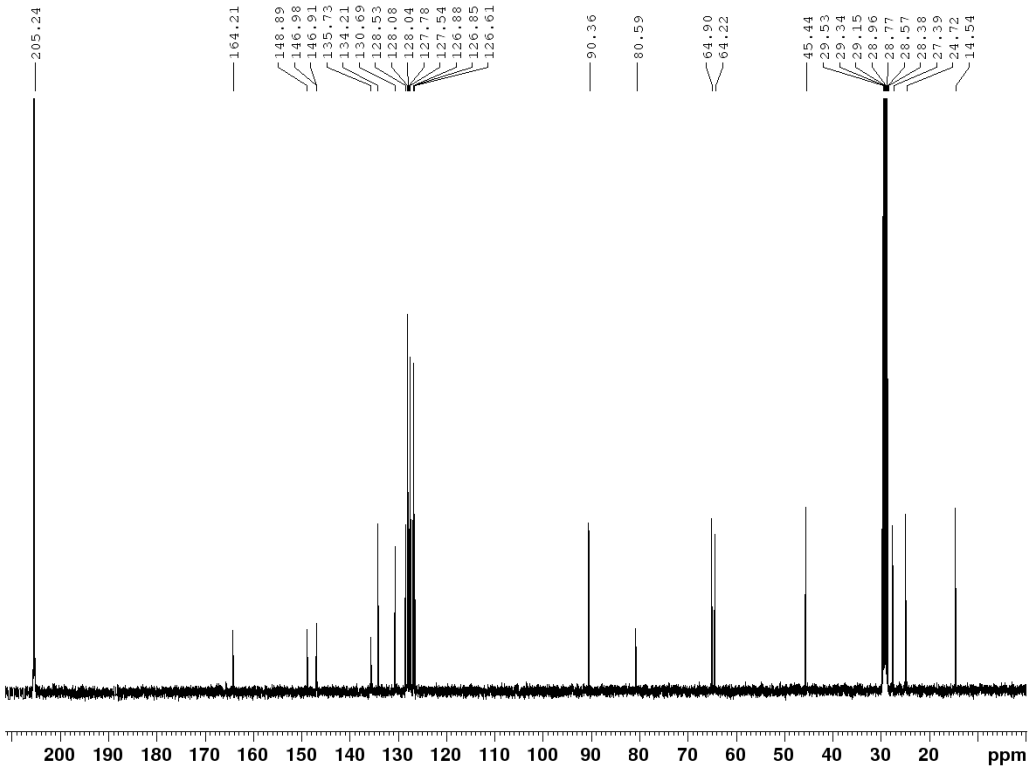


^{1}H NMR (400 MHz, acetone–d_6)

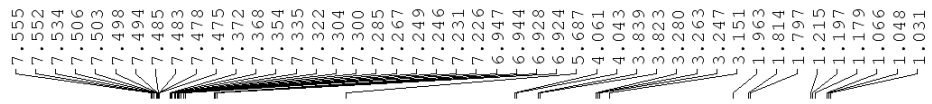


Anti-**210**

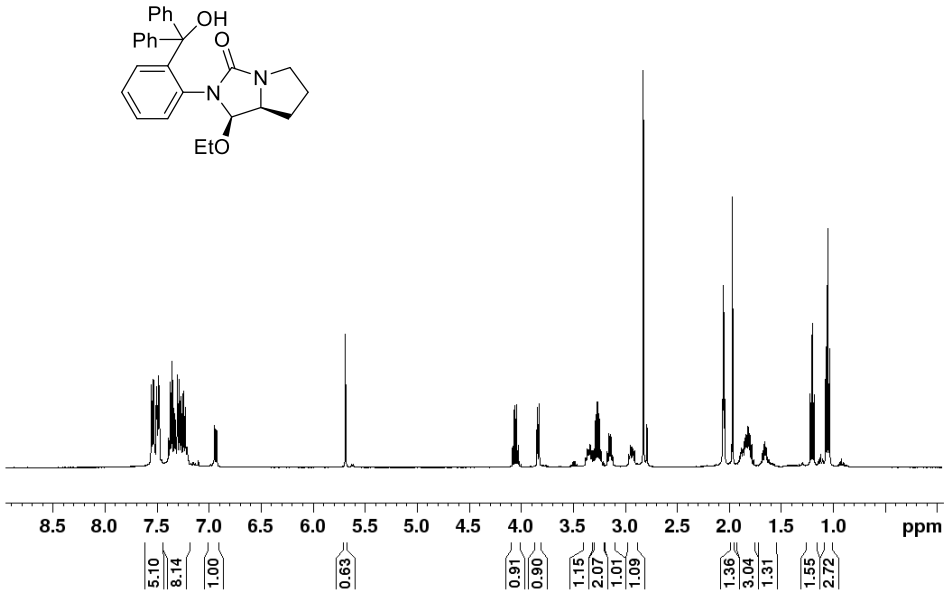
^{13}C NMR (100.7 MHz, acetone–d_6)



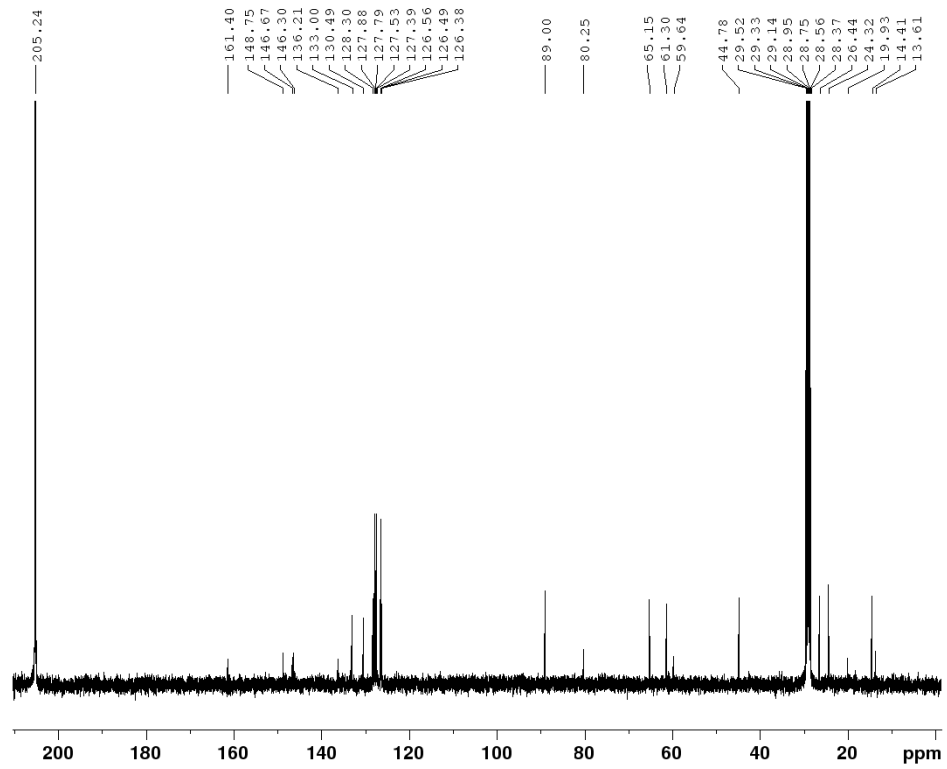
^{1}H NMR (400 MHz, acetone–d_6)



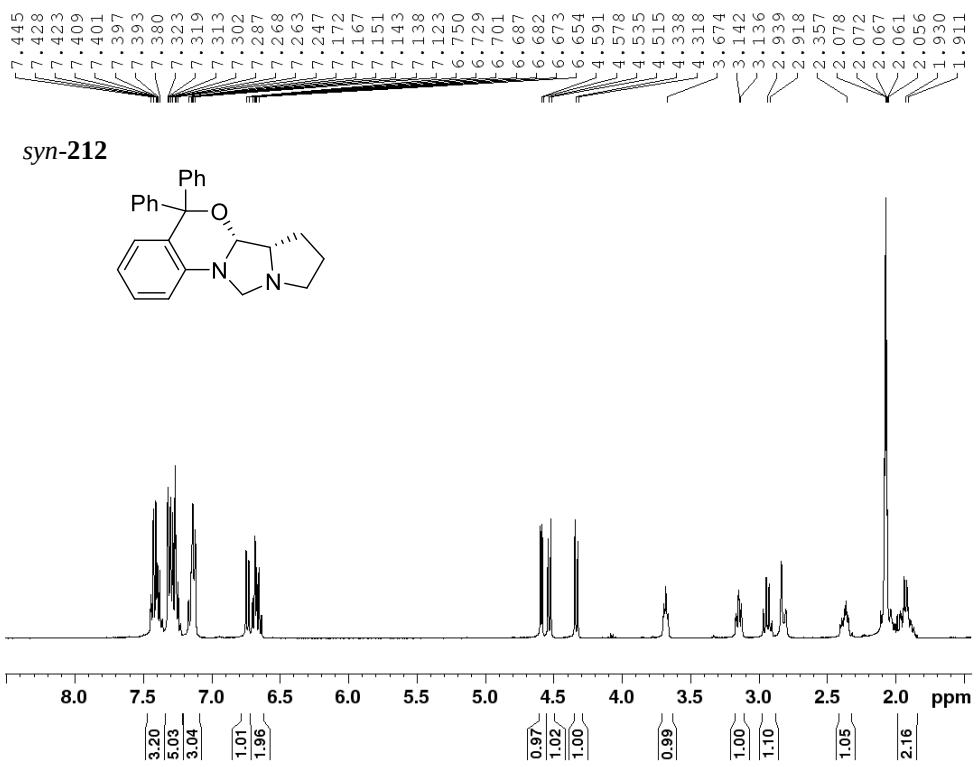
syn-**210**



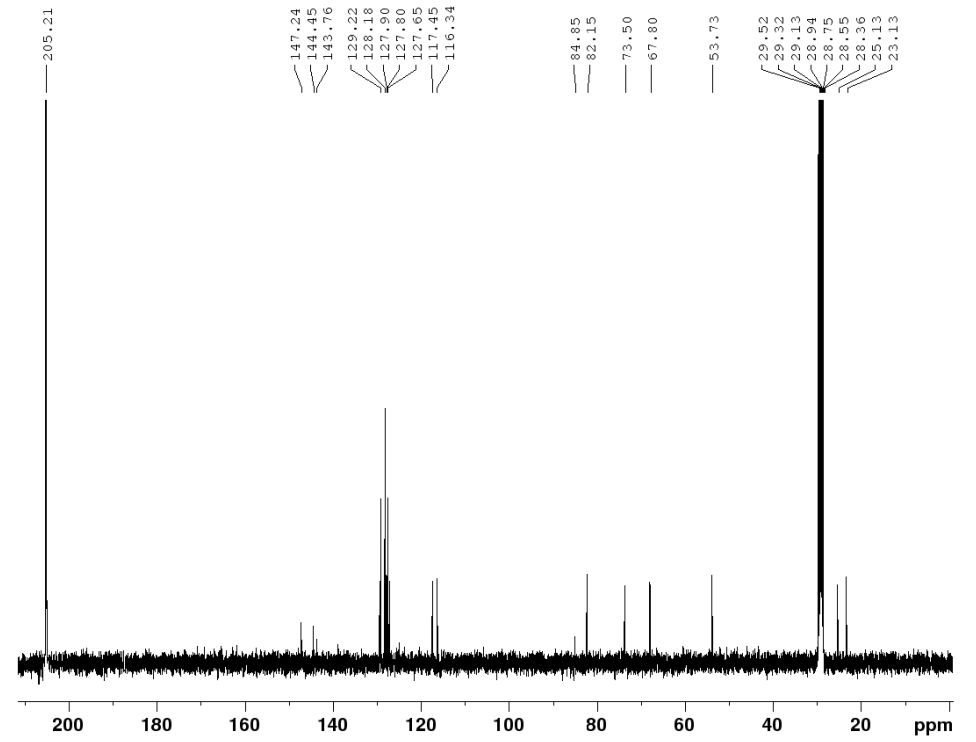
^{13}C NMR (100.7 MHz, acetone–d_6)



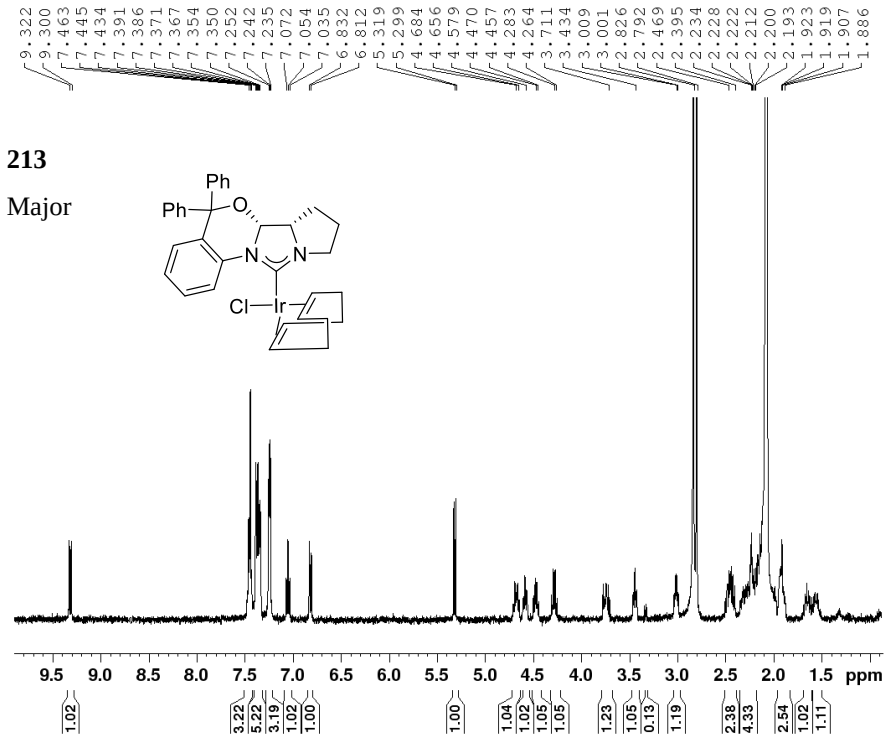
^{1}H NMR (400 MHz, acetone–d_6)



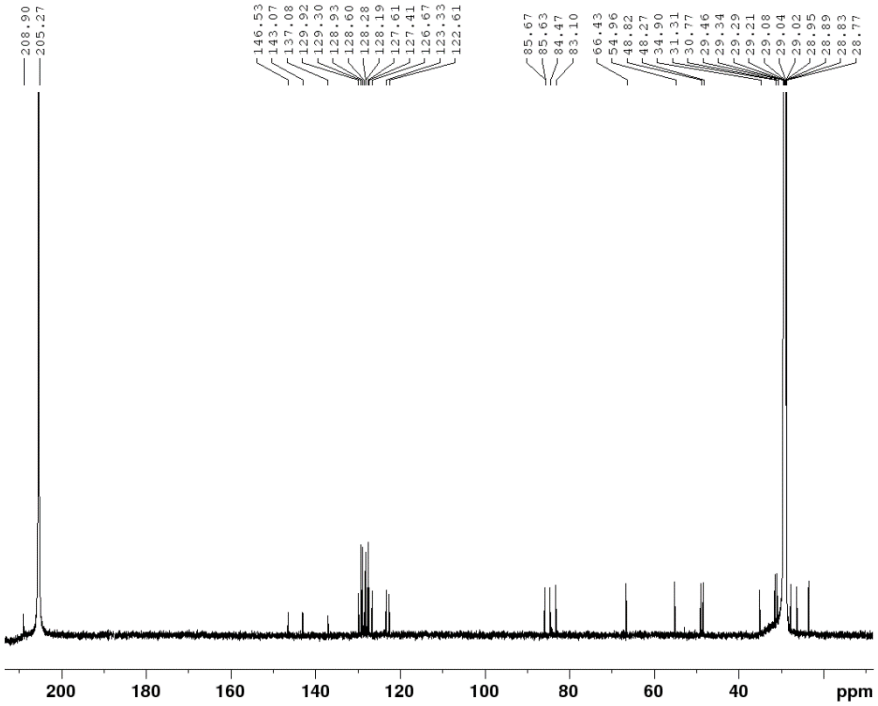
^{13}C NMR (100.7 MHz, acetone–d_6)



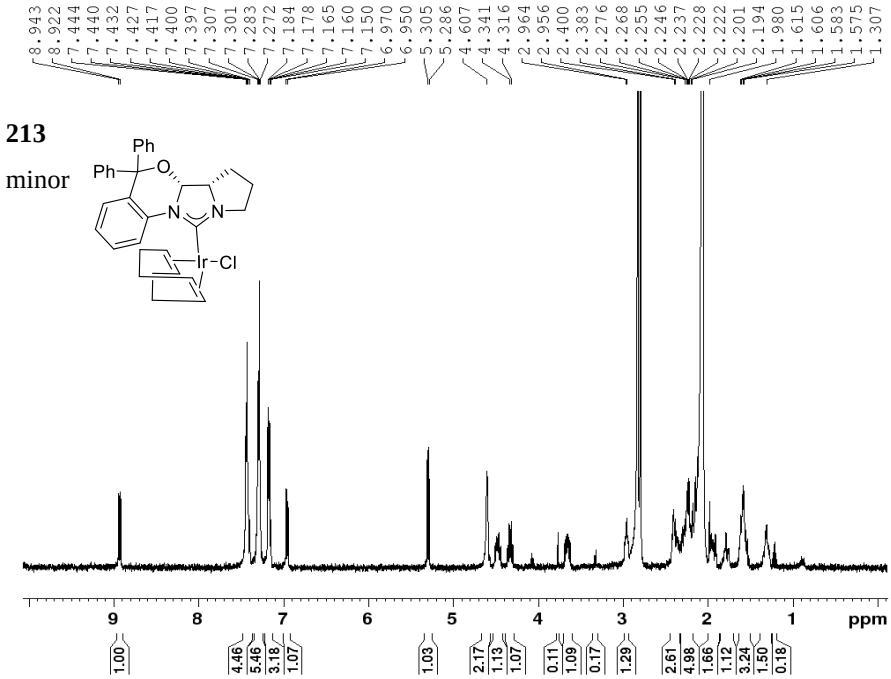
^{1}H NMR (600 MHz, acetone–d_6)



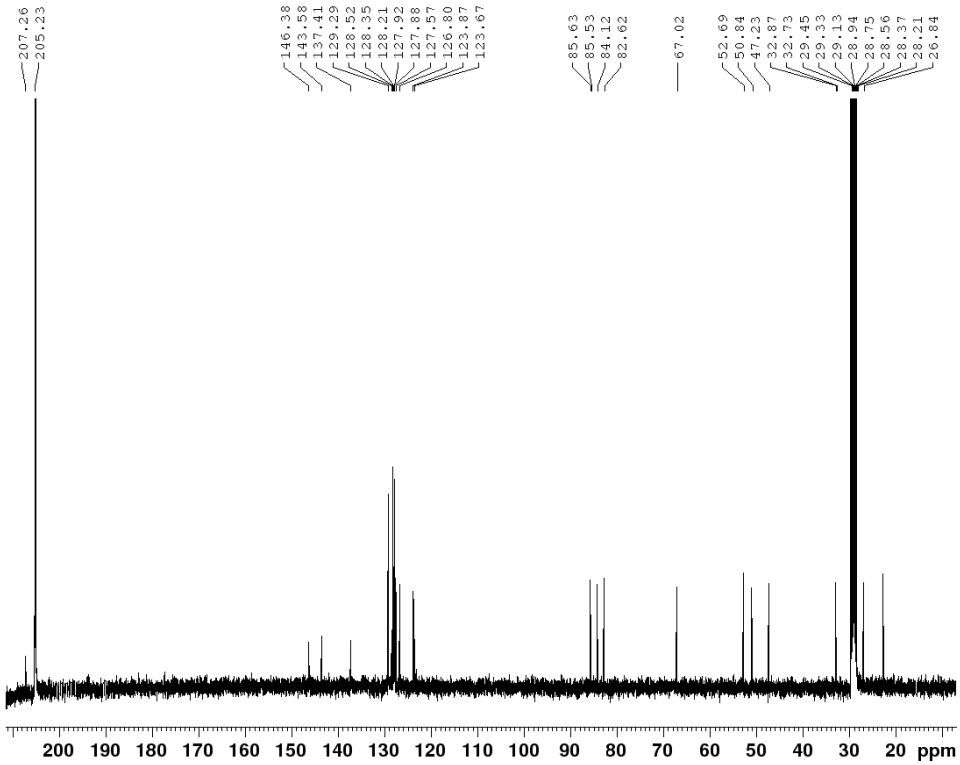
^{13}C NMR (100.7 MHz, acetone–d_6)



^{1}H NMR (600 MHz, acetone–d_6)

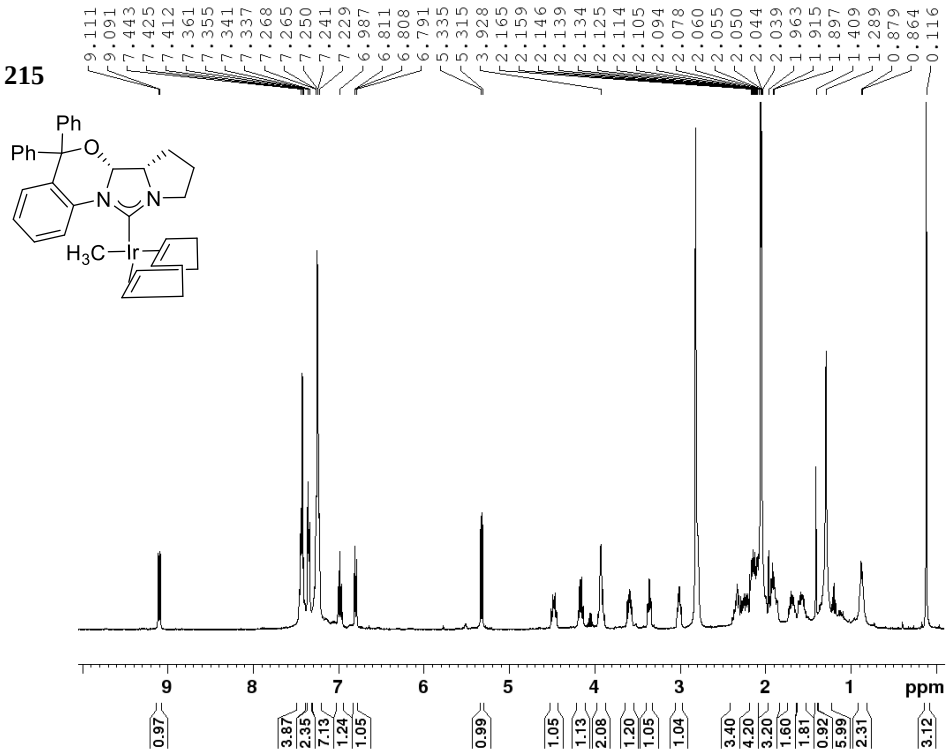


^{13}C NMR (100.7 MHz, acetone–d_6)

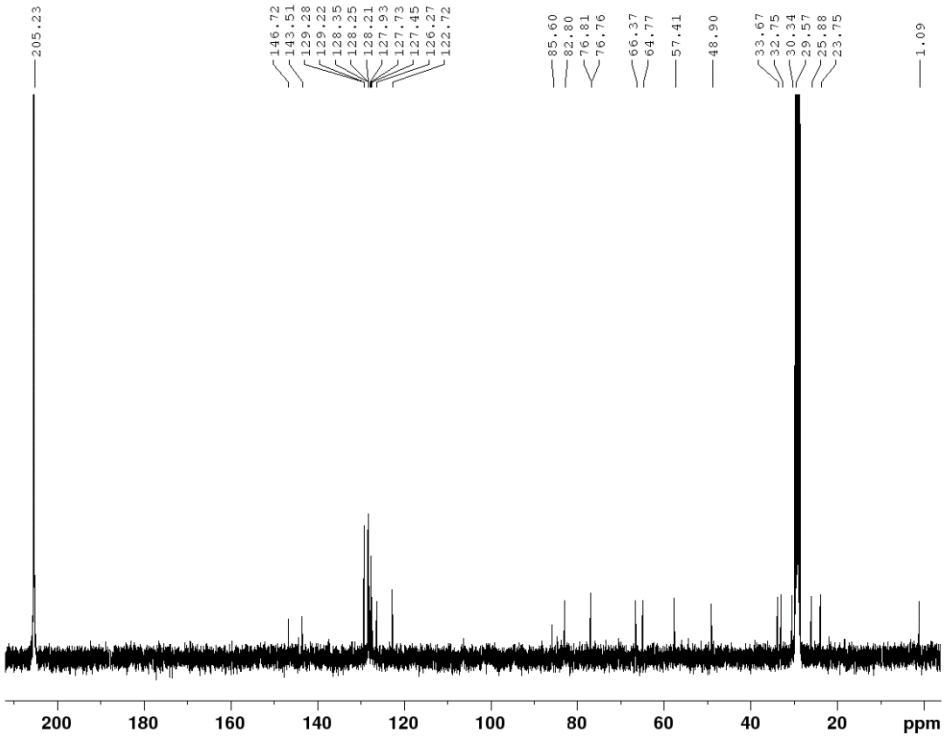


^{1}H NMR (600 MHz, acetone–d_6)

215

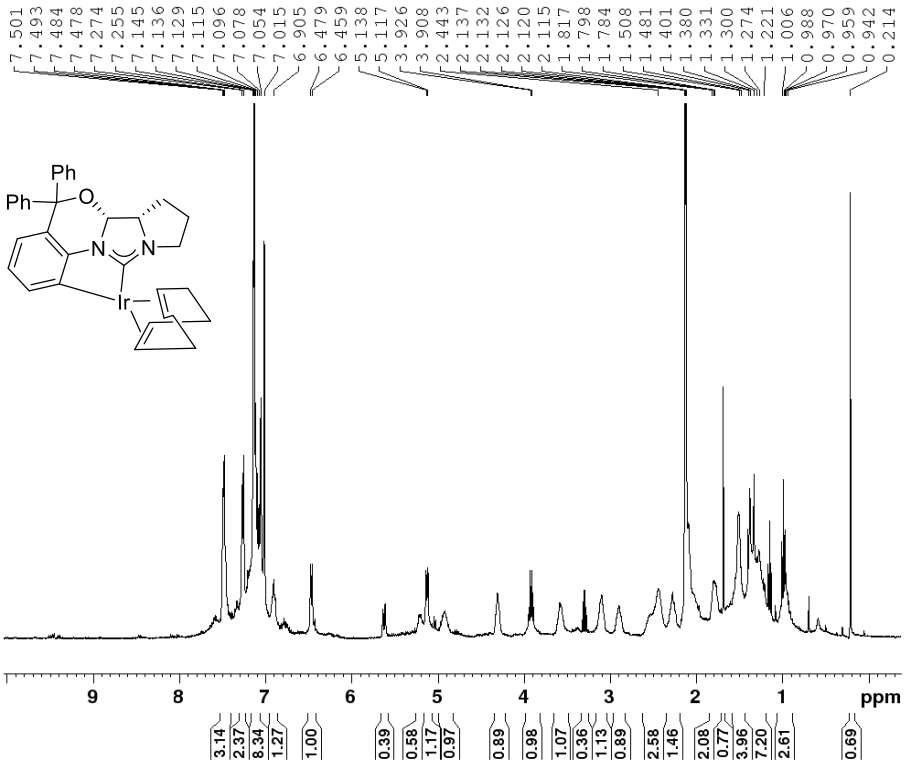


^{13}C NMR (100.7 MHz, acetone–d_6)

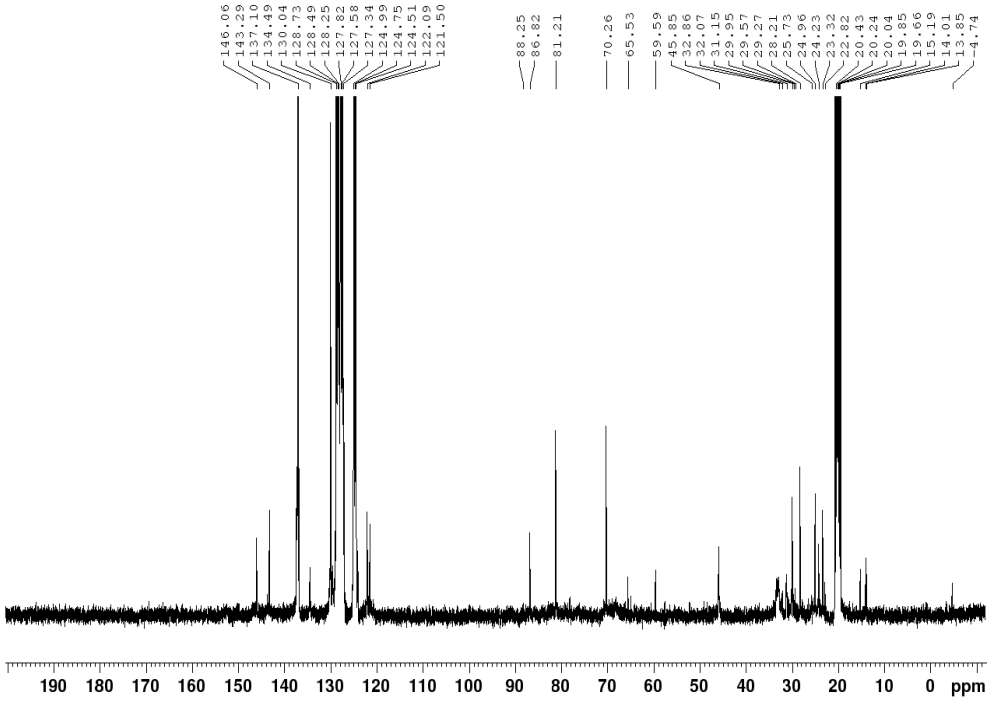


^{1}H NMR (600 MHz, toluene–d_8)

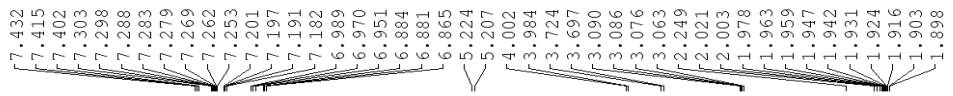
216



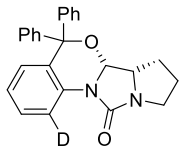
^{13}C NMR (100.7 MHz, toluene–d_8)

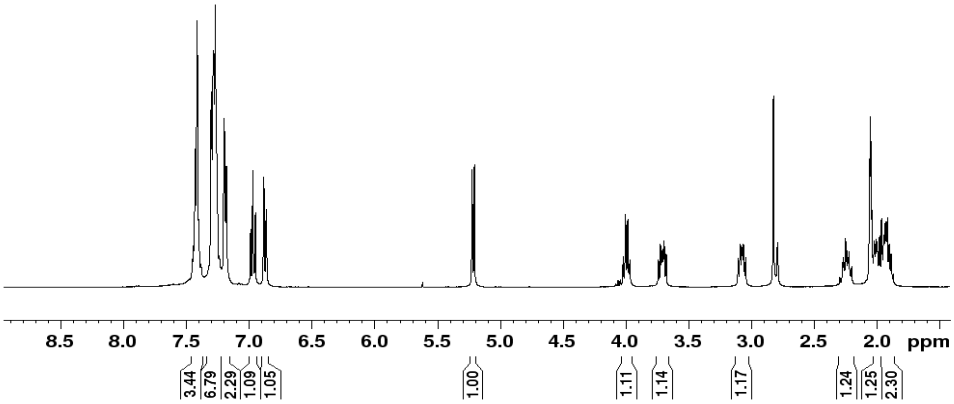


^{1}H NMR (600 MHz, acetone–d_6)

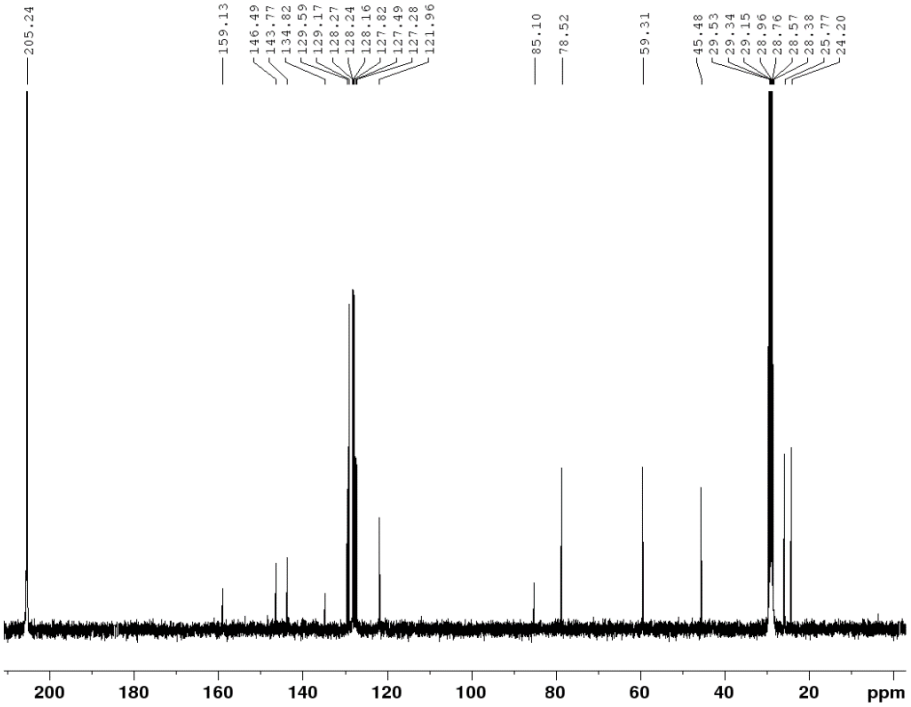


217

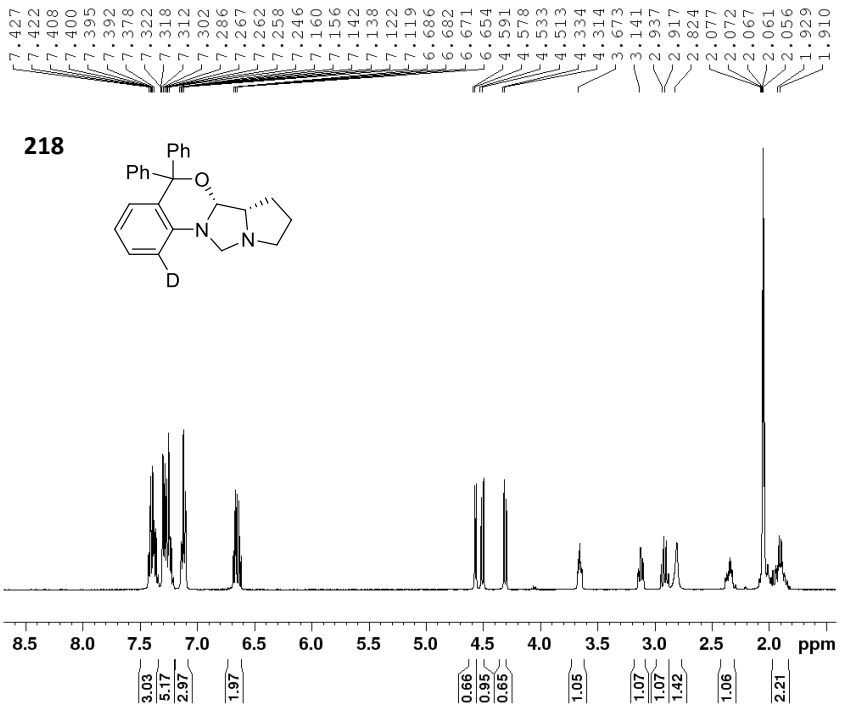




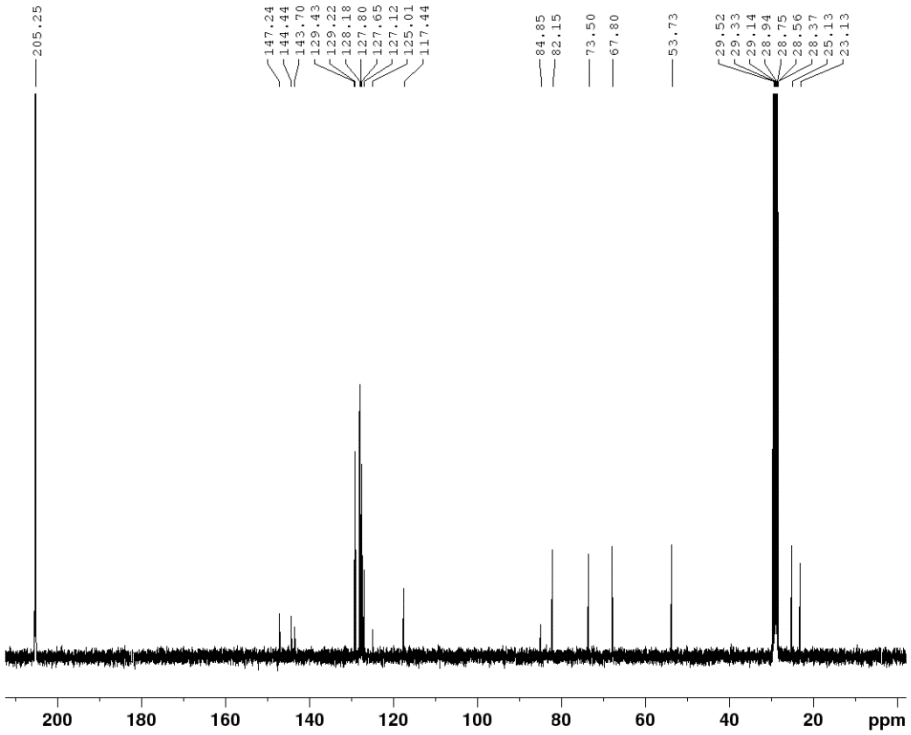
^{13}C NMR (100.7 MHz, acetone–d_6)



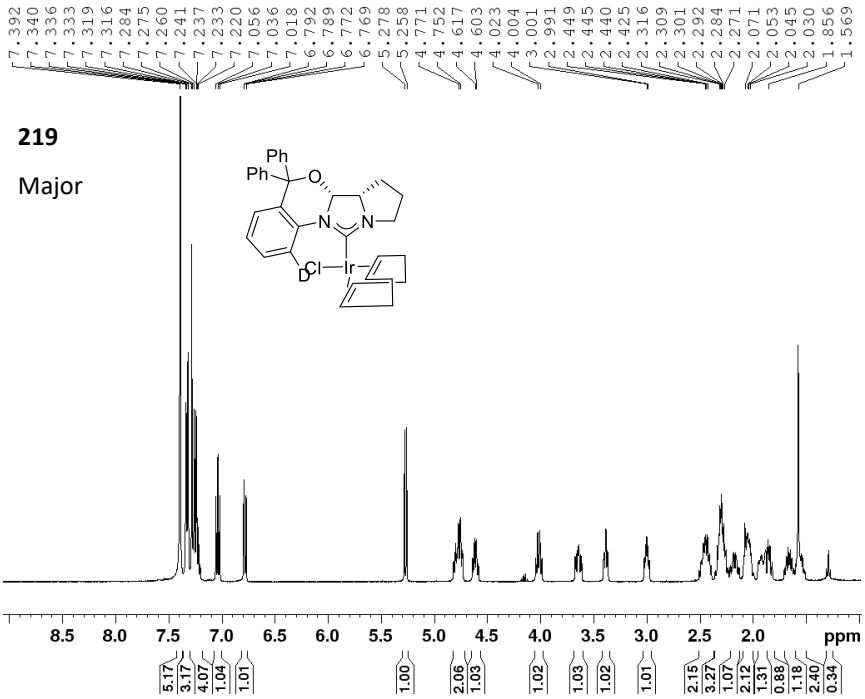
^{1}H NMR (400 MHz, acetone–d_6)



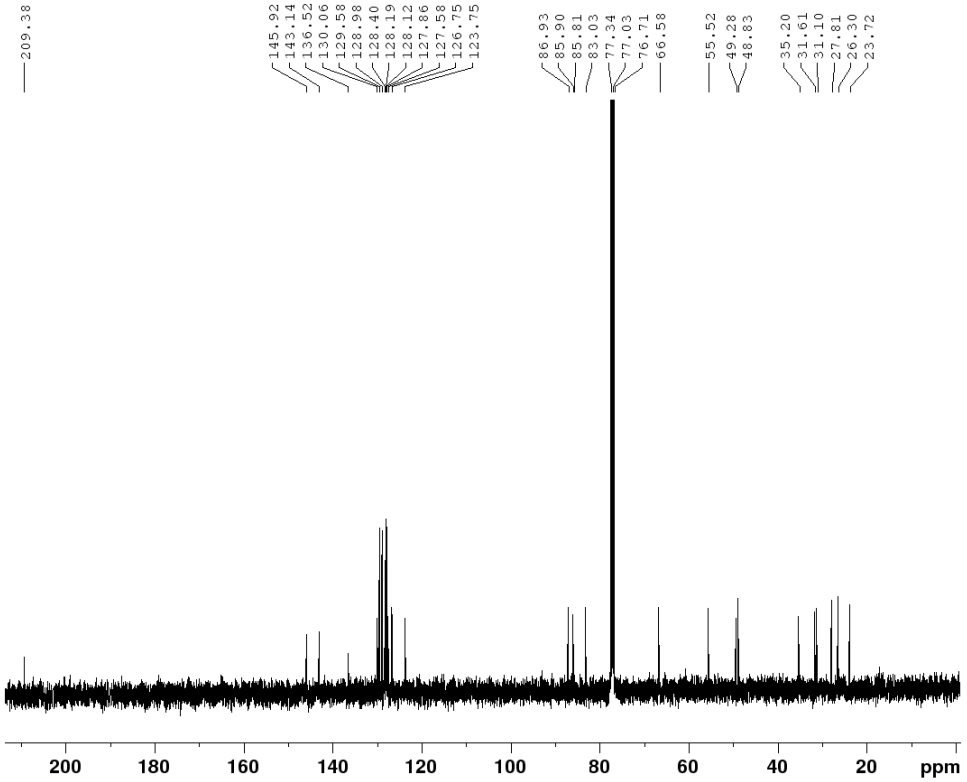
^{13}C NMR (100.7 MHz, acetone–d_6)



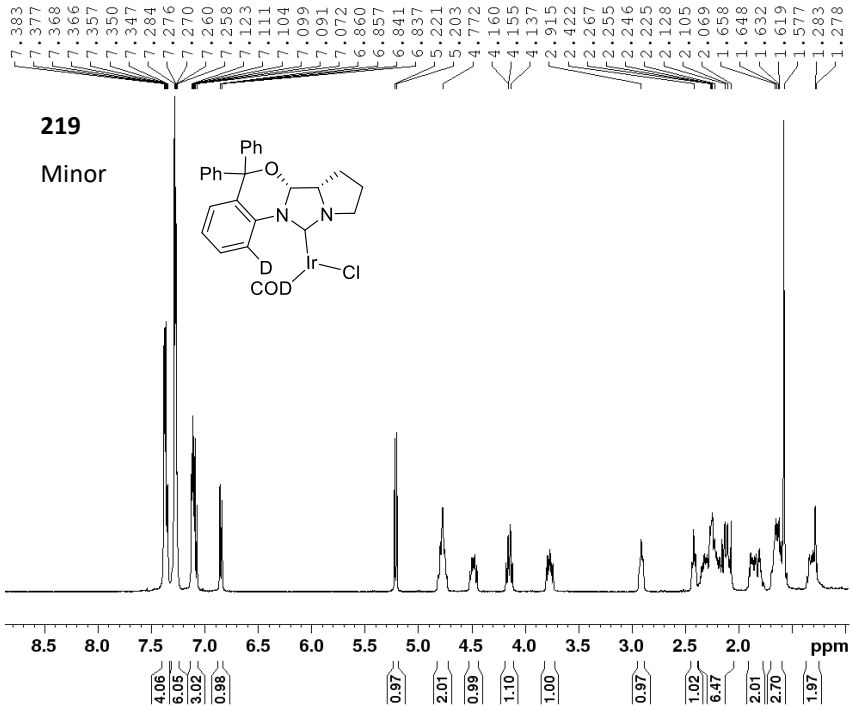
^{1}H NMR (400 MHz, $CDCl_3$)



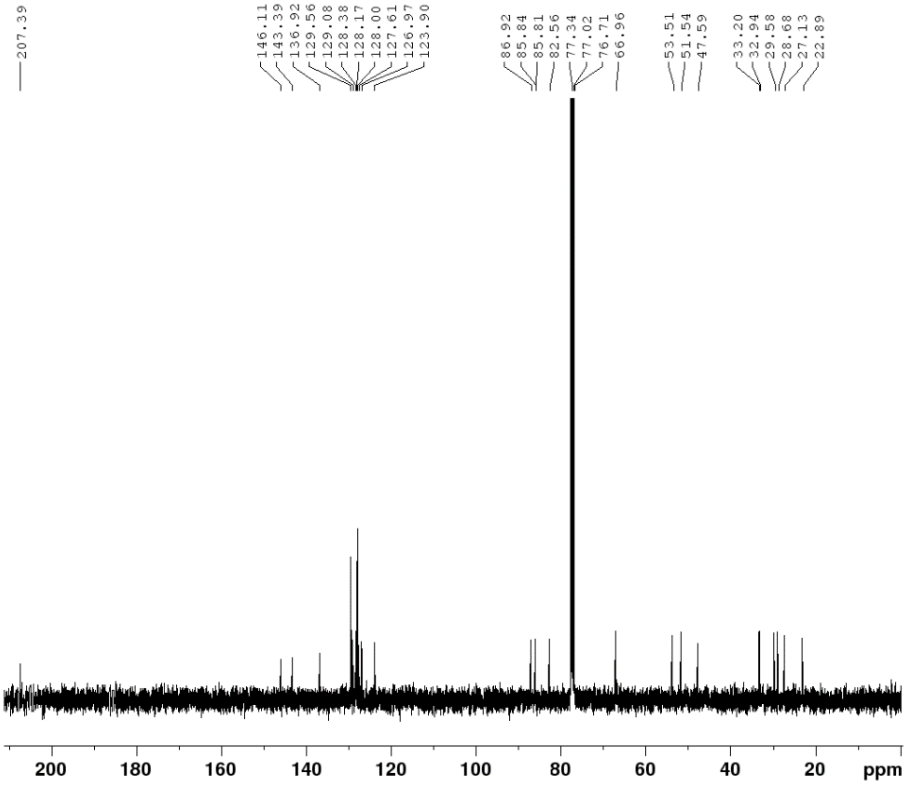
^{13}C NMR (100.7 MHz, $CDCl_3$



^{1} H NMR (400 MHz, $CDCl_3$)

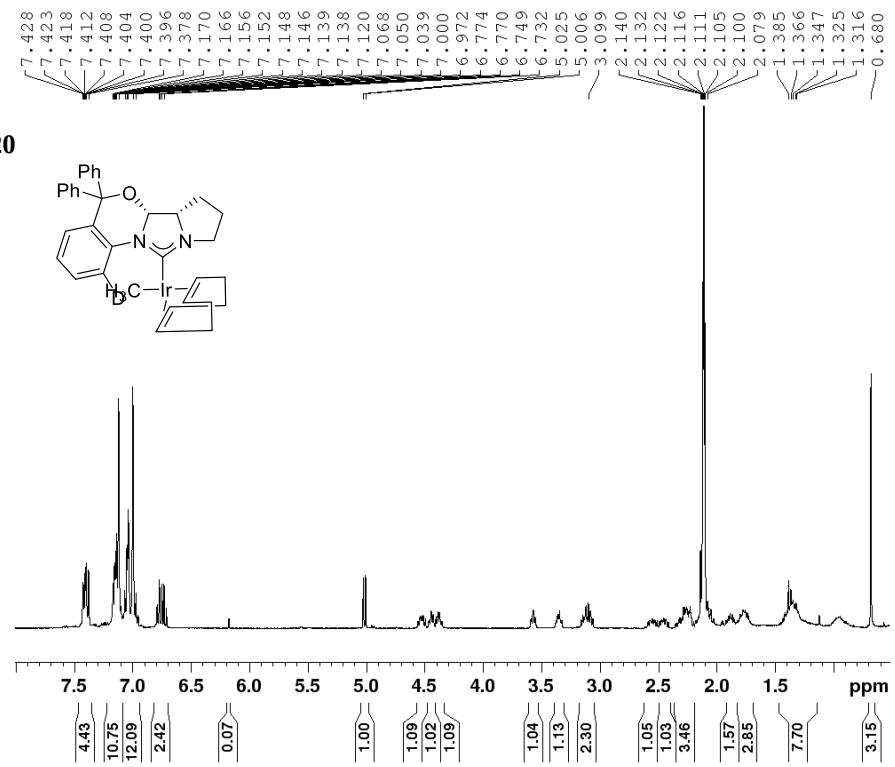


^{13}C NMR (100.7 MHz, $CDCl_3$)

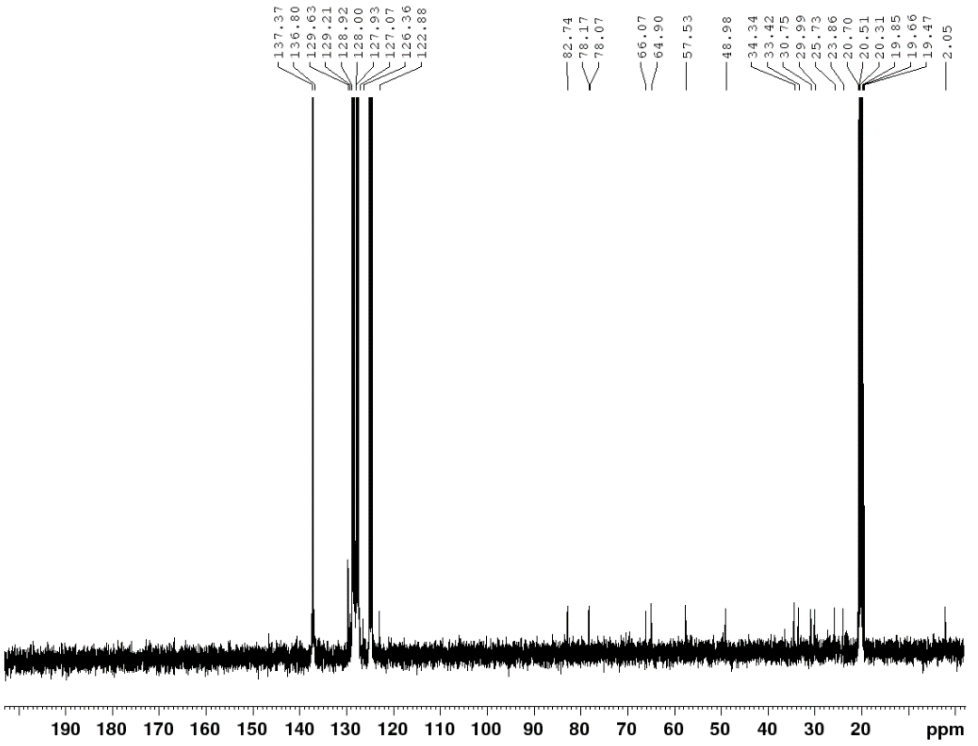


^{1}H NMR (400 MHz, toluene–d_8)

220

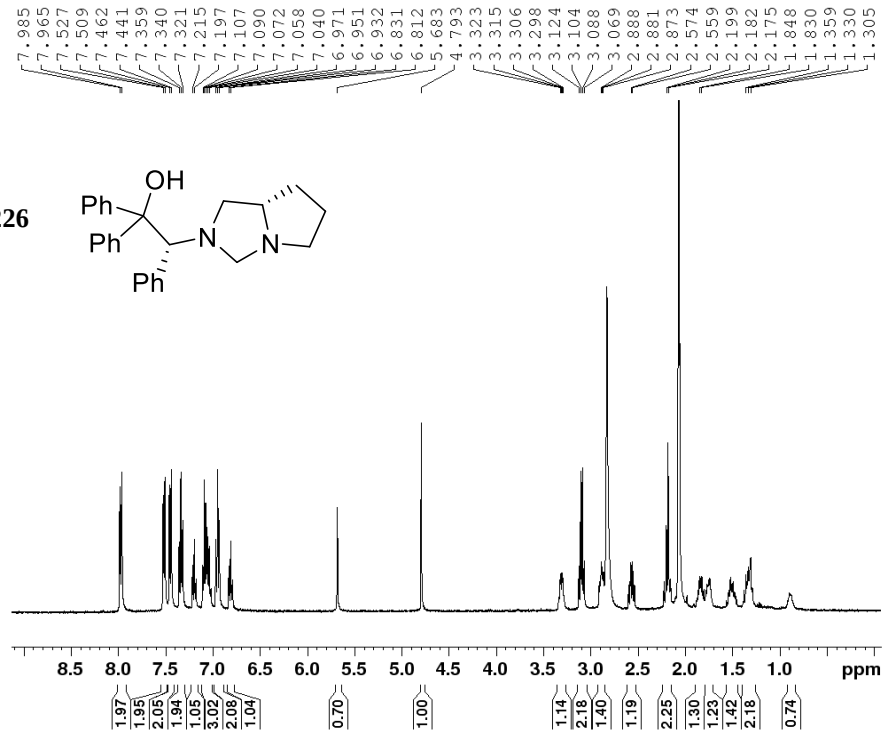


^{13}C NMR (100.7 MHz, toluene–d_8)

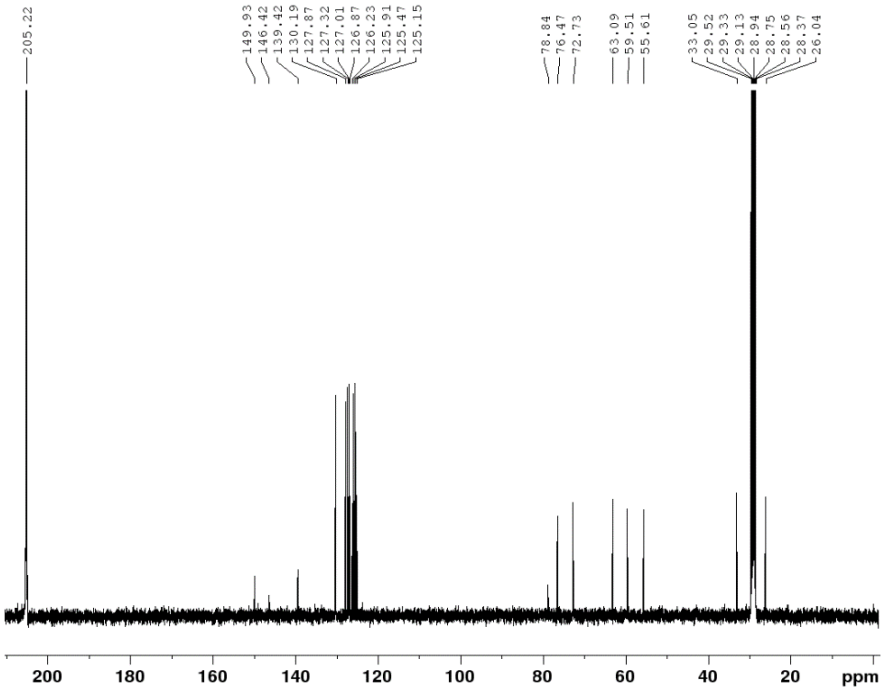


^{1}H NMR (400 MHz, acetone–d_6)

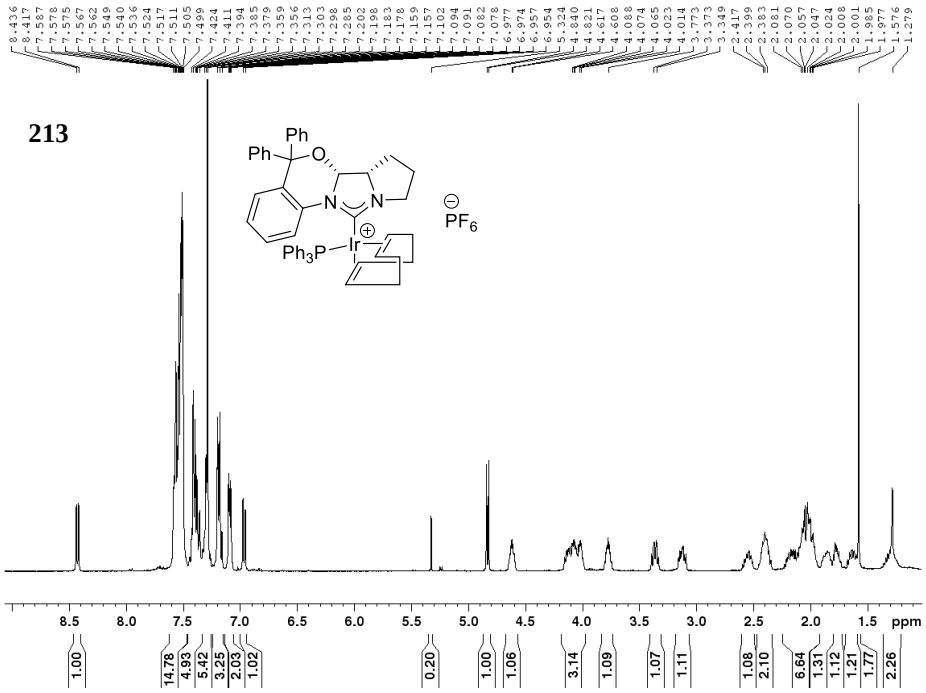
226



^{13}C NMR (100.7 MHz, acetone–d_6)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.7 MHz, $CDCl_3$)