Development of Novel Transition Metal Catalyzed Transformations Involving Small, Strained Carbocycles

BY

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LIST OF ABBREVIATIONS

ACS	American Chemical Society
AHF	Asymmetric Hydroformylation
AHR	Asymmetric Heck Reaction
Ar	Aryl Ring
β-HE	Beta Hydride Elimination
BINAP	Binaphthyl
BIPHEP	biphenylphosphine
BITIANP	2,2'-bis(diphenylphosphino)-3,3'-bi(benzo[*b*]thiophene)
Calcd	Calculated
Bn	Benzyl
^{t}Bu	*tert*-Butyl
cat.	Catalytic Amount
cm^{-1}	Inverse Centimeters
CPDUL	dual carbon proton cryoprobe
Cy	Cyclohexyl
δ	Chemical shifts in ppm downfield from tetramethylsilane (NMR)
Δ	Heat
d	Doublet

LIST OF ABBREVIATIONS (Continued)

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
DOSP	*N*-(dodecylbenzenesulfonyl)prolinate)
DPTI	diphenyltrifylimidazolidinone
ee	Enantiomeric Excess
Et	ethyl
eq, equiv	molar equivalent
EWG	electron withdrawing group
FID	Flame Ionization Detector
FT	Fourier Transform
g	gram
GC	gas chromatography
GCMS	gas chromatography/mass spectrometry
h, hr, hrs	hours
HRMS	high resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	Hertz

LIST OF ABBREVIATIONS (Continued)

IR	infra-red spectroscopy
J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
m	multiplet
mp	melting point
μ	micro
M	molar
MS	mass spectrometry
Me	methyl
MEPY	methyl-2-oxopyrrolidine-5-carboxylate
mg	milligram
min	minute
MIRC	Michael initiated ring closure
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MOM	methoxymethyl

LIST OF ABBREVIATIONS (Continued)

MHz	megahertz
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OAc	Acetate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate
Ph	Phenyl Ring
PHOX	Phosphanyl-oxazoline
ppm	parts per million
Pr	propyl
^{i}Pr	isopropyl
ps.t.	pseudo triplet or overlapping doublet of doublets (NMR)
q	quartet (NMR)
QNP	Quadruple-band Gradient Probe
rt	room temperature
R_t	retention time
s	singlet (NMR)
SAR	Structure and Activity Relationships
t	triplet (NMR)

LIST OF ABBREVIATIONS (Continued)

TDTAB	tetradecyltrimethylammonium bromide
TDMPP	tris(2,6-dimethoxylphenyl)phosphine
Tf	trifluoromethylsulfonyl (triflate)
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMBTP	4,4A-bis(diphenylphosphino)-2,2',5,5'-tetramethyl-3,3A-bithiophene
TMS	trimethylsilyl
Tol, tol	tolyl
TPP	triphenylphosphine
TPP$^+$	electron deficient triphenylphosphine
Ts	tosyl
UV	ultra-violet

SUMMARY

This thesis deals with 3-membered carbocycles; their use as ligands for the asymmetric Heck reaction (AHR), the development of novel methods and reactions for their synthesis and use. It is broken into three chapters, each one devoted to different aspects of the chemistry of these uniquely interesting small carbocycles.

The first chapter discusses the development of a novel class of chiral, non-racemic, phosphorous containing, cyclopropyl oxazolidinones and their use as ligands in the asymmetric Heck reaction. It gives a brief overview of the Heck reaction and describes how these ligands influence the outcome of the reaction. This is then followed with a discussion of the synthetic methodology used in developing the PHOX ligands and ultimately their application to the asymmetric Heck reaction.

Chapter two covers the development of a high throughput screening method for the hydroformylation of olefins. The method described makes use of a multi-reactor array and rapid analysis via GCMS which allowed for the screening of a library of approximately fifty chiral phosphine ligands in the hydroformylation of styrenes as well as the development of solvent and temperature screening optimization protocols.

Chapter three can be broken down into three parts. The first deals with the improvement on a 1,2-elimination procedure for the synthesis of cyclopropenes which has been known since the 1960's. Through careful optimization of the reaction conditions it was possible to improve the method and correspondingly increase the

SUMMARY (Continued)

yield of the cyclopropenes. Part two divulges a novel methodology for the synthesis

of cyclopropenes which replaces DMSO with THF as the solvent in the base assisted

1,2-elimination step. It also shows how this change ultimately allowed for an overall

improvement in yield especially for cyclopropenes bearing a hydrophilic amido

moiety. The final portion of chapter three discusses the application of the high-

throughput screening method shown in chapter one to cyclopropenes. While

hydroformylation of cyclopropenes is a precedented process, until recently this was

done with the assistance of a stoichiometric amount of a transition metal. The

method divulged herein is the first catalytic hydroformylation which has been done

on strained, small carbocycles both in a racemic and asymmetric fashion.

Chapter 1. Development of Chiral, non-racemic cyclopropyl PHOX ligands

1.1. Introduction

The asymmetric Heck reaction is one of the most powerful and versatile processes for the enantioselective construction of new carbon-carbon bonds. Intramolecular versions of this reaction catalyzed by palladium complexes with BINAP and related diphosphine ligands[1] allow for efficient installation of tertiary and quaternary chiral centers leading to a rapid increase of molecular complexity.[2] To date, various modes of this transformation are being successfully employed in the synthesis of complex organic molecules.[3] Considerable achievements have also been made towards the application of BINAP type ligands in the intermolecular asymmetric Heck reaction.[4] This reaction was pioneered by Hayashi,[5] who demonstrated the arylation of dihydrofuran **1** with phenyl triflate **2a** (Scheme 1) in the presence of (R)-BINAP[5,6] produced isomeric dihydrofurans **3a** and **4a**, with the latter being the major product, due to substantial isomerization of the double bond. Depending on the reaction conditions, moderate to good selectivities toward formation of **4a** were observed. Remarkably, the obtained products, "normal" **3a** and "isomerized" **4a**, had the opposite absolute configurations of the stereogenic center at C2. Moreover, it was found that the enantioselectivity improved during the reaction course. The mechanistic rationale proposed by Hayashi[5] fully accounts for the observed stereoselectivity change (Scheme 2).

Scheme 1.
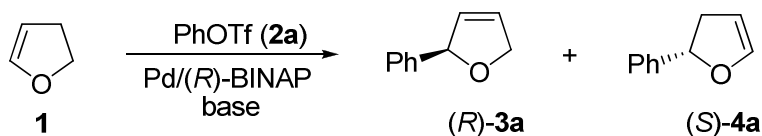
The catalytic cycle begins with the oxidative addition of Pd(0) species **5** into the aryl triflate **2** resulting in the formation of cationic complex **6**. The latter can coordinate to either of the prochiral faces of dihydrofuran (**1**) affording diastereomeric $^2\eta$-complexes **7** and **10**. Subsequent carbopalladation, followed by β-hydride elimination, produces species **9** and **12**, respectively. It was proposed that the diastereomeric complex **12** has a higher propensity toward further hydropalladation than **9**. Accordingly, the latter species releases the (*S*)-enantiomer of 2,5-dihydrofuran **3** (Path I), while the former undergoes a series of reversible hydropalladations and β-hydride eliminations, resulting in the formation of a thermodynamically more favored $^2\eta$-complex **14**, which ultimately produces (*R*)-enantiomer of the isomeric product **4**.

Later, a number of research groups pursued the design of alternative diphosphine ligands to achieve better regio- and enantioselectivity in the intramolecular Heck reaction. Several derivatives of BINAP[7] and other chiral diphosphines[8,9] including TMBTP,[10] BIPHEP,[11] BITIANP[12] (Scheme 3) were tested, some of which provided improved selectivity. Nevertheless, in all cases predominant or exclusive formation of the isomerized product **4** was observed.

Scheme 2.

Scheme 3.

BIPHEP   TMBTP   BITIANP
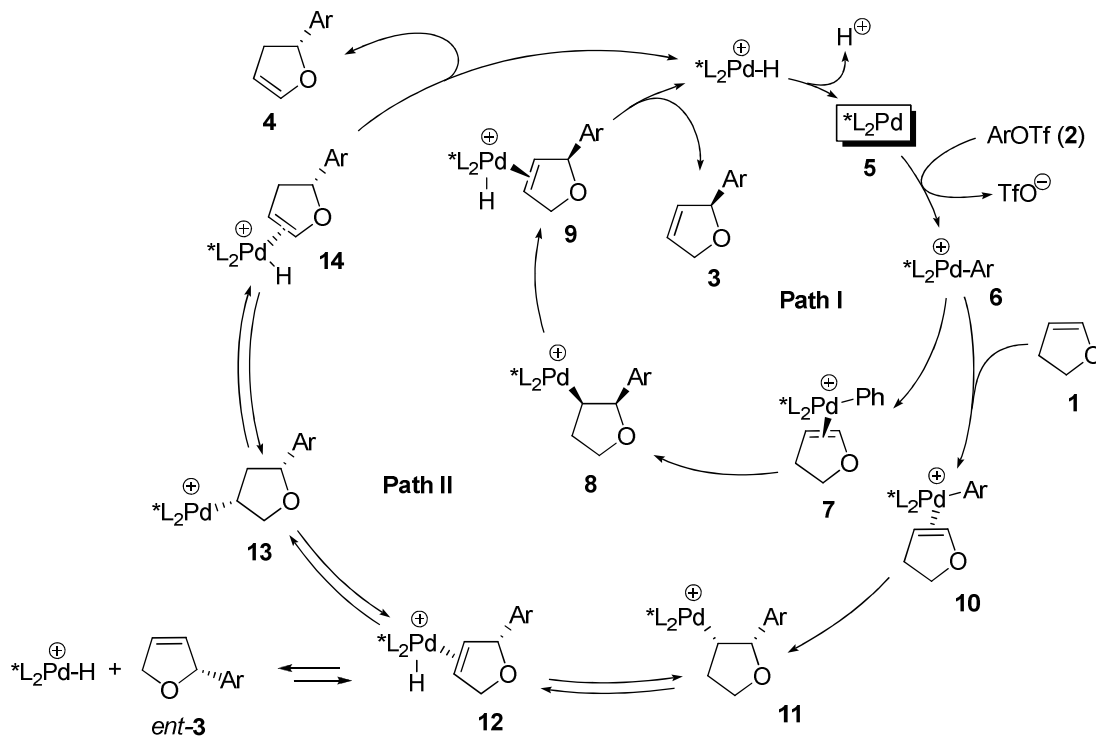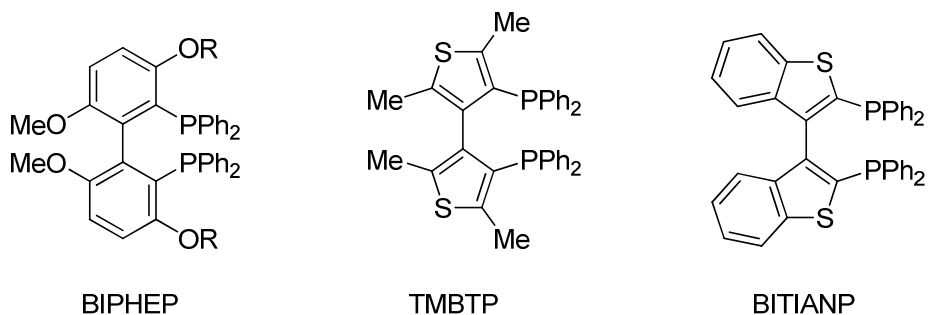
At the same time, several mixed heteroatom ligands of the P-S,[13] P-O,[14] and N-N[15] type have also been explored in the intermolecular Heck arylation; however, they demonstrated only marginal regio- and enantioselectivities. On the other hand,

superior results were obtained using chiral ligands of the P,N-type.[16] Particularly, excellent enantioselectivities were achieved using different variations of phosphanyl-oxazoline (PHOX) ligands,[17] originally introduced by Pfaltz (Scheme 4).[18] The remarkable, yet not fully understood feature of PHOX ligands is their low tendency to promote C=C bond isomerization.[17] In contrast to the diphosphines, PHOX ligands produced dihydrofuran **3** with very high selectivity. Structural modification of the flat *ortho*-phenylene tether in the Pfaltz ligand through the incorporation of additional chirality elements into the ligand backbone allowed for significant improvement of the enantioselectivity. Thus, ferrocene-based ligands introduced by Dai and Hou,[19] and Guiry[20] (Scheme 4) were employed in the asymmetric Heck reaction of different cyclic olefins. Furthermore, Gilbertson demonstrated PHOX ligands featuring apobornene backbone (Scheme 4) exhibit outstanding activities and selectivities in the arylation and alkenylation of different cyclic substrates.[21] Recently, a highly efficient asymmetric arylation in the presence of sugar-derived phosphite-oxazoline ligands was reported by Diéguez and Pàmies.[17c,d]

Scheme 4.

Pfaltz ligands   Ferrocene based ligands   Gilbertson ligands   Diéguez and Pàmies ligands
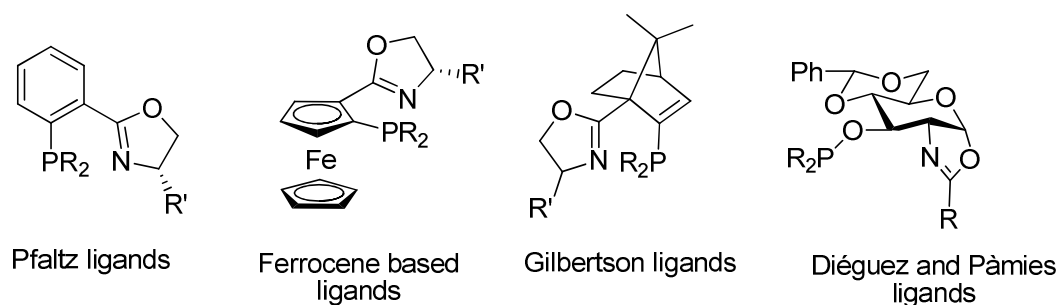
PHOX ligands are very appealing due to their high catalytic potential and modular design, which permits easy preparation of a series of analogs via the same synthetic route. To date; however, the general approach to the ligand design has been largely empirical due to a poor understanding of the factors affecting the activity and selectivity of the corresponding catalytic systems.

1.2. Results and Discussion

Our approach to the PHOX ligands with a chiral cyclopropyl backbone is presented in Scheme 5. The synthesis began from optically active 1-methyl-2,2-dibromocyclopropanecarboxylic acid (**15**)[22] readily available in both enantiomeric forms. The *S*-enantiomer of acid **15** was converted into acyl chloride (S)-**16**. Subsequent acylation of (*R*)-phenyl glycinol with (*S*)-**16** afforded amide **17**, which was subjected to cyclization in the presence of mesyl chloride and a base providing dihydrooxazole **18**. Diastereoselective partial reduction of the dibromocyclopropane moiety with zinc dust in glacial acetic acid produced a 1:4 mixture of *trans-* and *cis-*bromocyclopropanes **19**, which were separated by column chromatography. Lithium to halogen exchange followed by trapping of the resulting cyclopropyllithium species with chlorophosphine produced ligand **L1** (Scheme 5).

Scheme 5.
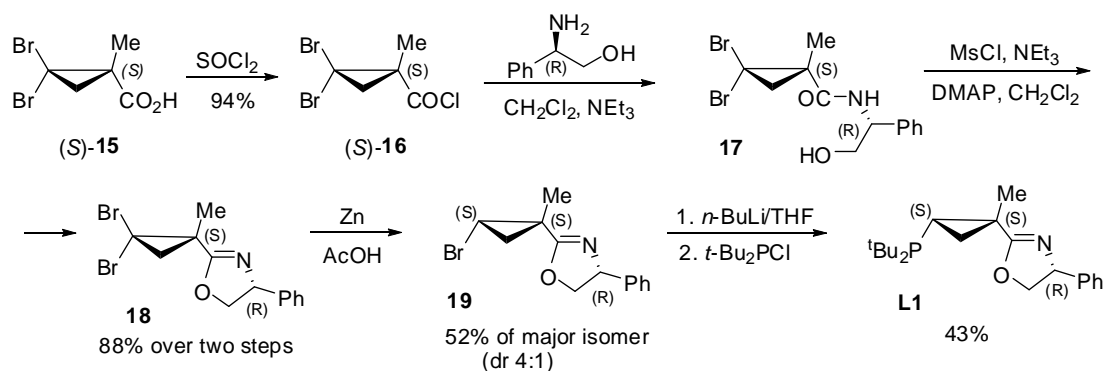
Ligand **L1** once obtained, was tested in the asymmetric arylation reaction of 2,3-dihydrofuran under various reaction conditions (Table 1). It was found that the reaction proceeded efficiently, yet with only moderate enantioselectivity, in the presence of palladium acetate and Hünig's base (Table 1, entry 3). Interestingly, the employment of proton sponge as a base resulted in significant isomerization of product **3a** into more thermodynamically stable dihydrofurans **4a** and **20a**. Close monitoring of the reaction by chiral GC revealed the reaction begins with formation of "normal" product **3a** (Table 1, entry 4); however, at the time of complete consumption of the starting material **1**, the entire amount of **3a** produced was converted into **4a** (Table 1, entry 5). Remarkably, all through the reaction course, the absolute configuration of the stereogenic center at C2 remained the same; furthermore, the optical purity of both products **3a** and **4a** did not change significantly (Table 1, entries 4,5). This feature makes this isomerization mechanistically distinct from the one reported by Hayashi (*vide supra*).

Table 1. Selected Results on Optimization of the Reaction Conditions for Asymmetric Heck Arylation Using **L1**

Ph–OTf + (1, furan) $\xrightarrow[\text{base (2 equiv)}]{\text{Pd/L1 (6 mol\%)}}$ (R)-3a + (R)-4a + 20a

2a　　**1**　　　　　　　　　　(R)-**3a**　　(R)-**4a**　　**20a**
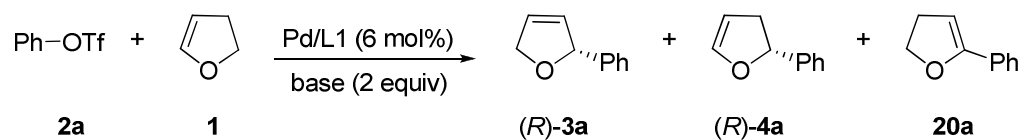
#	Pd-cat.	Base	Solvent	Time/Temp	3a:4a	ee, %	conv, %[a]
1	Pd₂dba₃·CHCl₃	EtN^{i}Pr₂	benzene	3 days/70 °C	19:1	90 (A)	15
2	Pd₂dba₃·CHCl₃	EtN^{i}Pr₂	THF	20 hrs/85 °C	10:1	85 (A)	60
3	Pd(OAc)₂	EtN^{i}Pr₂	THF	20 hrs/85 °C	11:1	83 (A)	99
4	Pd(OAc)₂	Proton sponge	THF	20 hrs/60 °C	10:1	88 (A)	45
5	Pd(OAc)₂	Proton sponge	THF	70 hrs/60 °C	>1:50[b]	85 (B)	99
6	Pd(OAc)₂	Proton sponge	THF	20 hrs/90 °C	>1:50[b]	82 (B)	99

[a] Conversion by GC. [b] Formation of small amounts of dihydrofuran 20a was observed.

To better understand the factors affecting the selectivity and efficiency of the asymmetric arylation, we have prepared two more analogs of **L1**: ligand **L2**, possessing a diphenylphosphanyl group; and ligand **L3** derived from *tert*-leucinol (Scheme 6).[25]

Scheme 6.
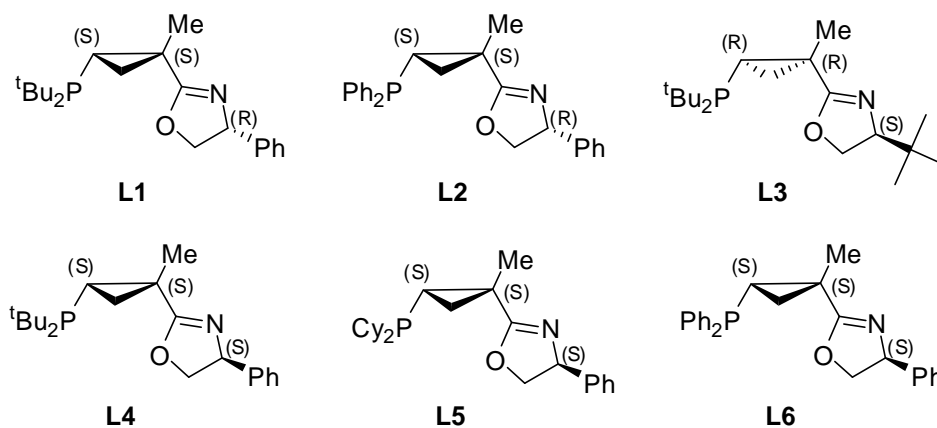
Not surprisingly, installation of the less hindered phosphorus moiety in **L2** negatively affected the asymmetric induction the corresponding product **3a** was obtained in only 78-79 % ee (Table 2, entries 3,4). However, in contrast to **L1** (Table 2, entries 1,2) the selectivity toward **3a** in the reaction using **L2** remained high regardless of the base used.

Table 2. Screening of **L1-L3** in the Asymmetric Heck Arylation of Dihydrofuran **1**

#	Ligand	Base	3a:4a	ee, %[b]	conv, %[c]
1	**L1**[a]	EtN^{i}Pr$_2$	11:1	83	99
2	**L1**[a]	Proton sponge	>1:50	82	99
3	**L2**	EtN^{i}Pr$_2$	20:1	79	99
4	**L2**	Proton sponge	15:1	78	99
5	**L3**	EtN^{i}Pr$_2$	7:1	87	35
6	**L3**	Proton sponge	1.4:1	84[d]	80

[a] Results from Table 1. [b] Enantioselectivity of a major product. [c] Conversions by GC.
[d] Enantioselectivity of product (R)-**4a** was 80 %.

Modification of the dihydrooxazole moiety by installation of a bulky *tert-*butyl group was pursued in attempt to improve the enantioinduction of our catalytic system. Indeed, a number of previously reported PHOX ligands derived from *tert-*leucinol were shown to provide superior enantioselectivities compared to their analogs obtained from less bulky amino alcohols.[18b,20,21] However, the arylation

carried out in the presence of **L3** proceeded much more sluggishly (Table 2, entries 5,6), and allowed for only insignificant improvement in enantioselectivity (84-87 % ee). Most remarkably, the same (*R*)-enantiomer of product **3** was obtained, despite the opposite absolute configuration of **L3** with respect to **L1** (Scheme 6). In other words, switching from Ph to a *t*Bu substituent in the dihydrooxazole ring of the ligand resulted in a reversal of enantioselectivity.

Such an unexpected change in the catalyst selectivity motivated us to perform structural analysis of the key intermediate complexes invoked in the catalytic cycle of the Heck arylation. First, we assessed the possibility of conformational equilibrium for the six-membered arylpalladium species bearing **L1** (Scheme 7). The non-planar six-membered palladacycle[23] can potentially adopt one of two conformations: **I1**, in which the syn-*tert*-Bu-substituent at phosphorus assumes a pseudo-equatorial position, whereas the anti-*tert*-Bu-substituent is pseudo-axial; and **I2**, where this relationship is reversed (Scheme 7). Analysis of these two conformations suggests steric repulsions between the axial syn-substituent and the methylene group in cyclopropane makes conformation **I2** thermodynamically disfavored compared to **I1**. This hypothesis was also supported by a single crystal X-ray analysis of (**L1**)PdCl$_2$ complex (Figure 1). The resolved crystal structure clearly shows the syn- (C14) and anti-substituent (C18) at phosphorus adopt a pseudo-equatorial and a pseudo-axial position, respectively. It would be reasonable to assume the strained and rigid cyclopropyl backbone renders the six-membered palladacycle particularly inflexible, thus significantly suppressing conformational fluctuations throughout the catalytic

cycle. Furthermore, coordination of the soft π-ligand dihydrofuran should take place predominantly *trans-* to a soft phosphorus atom[24] (Scheme 8.). In this case, the re-face approach (**I4**) is encumbered by a large pseudo-axial *tert*-butyl group, while the *si*-face approach (**I3**) is also somewhat hindered by a pseudo-axial syn-phenyl substituent in dihydrooxazole ring. As a result, the (*R*)-enantiomer of the product was predominantly formed, albeit with moderate enantioselectivity. Analogously, in the intermediate **I5** derived from chiral ligand **L2**, the less bulky pseudo-axial phenyl substituent at phosphorus blocks the re-face approach even less efficiently, which ultimately results in a further decrease of enantioselectivity (Scheme 8.).

Scheme 7. Conformational equilibrium in cationic arylpalladium(II) complexes with chiral ligand **L1**.
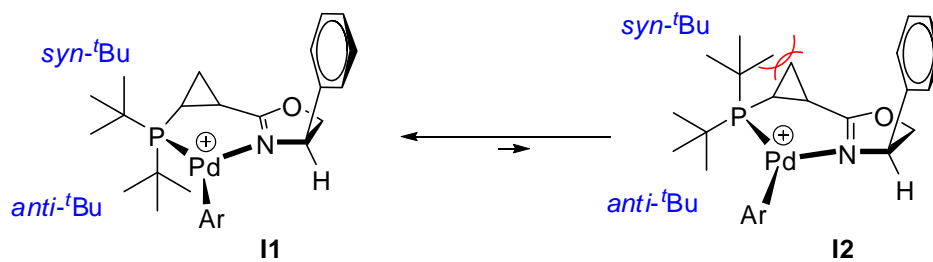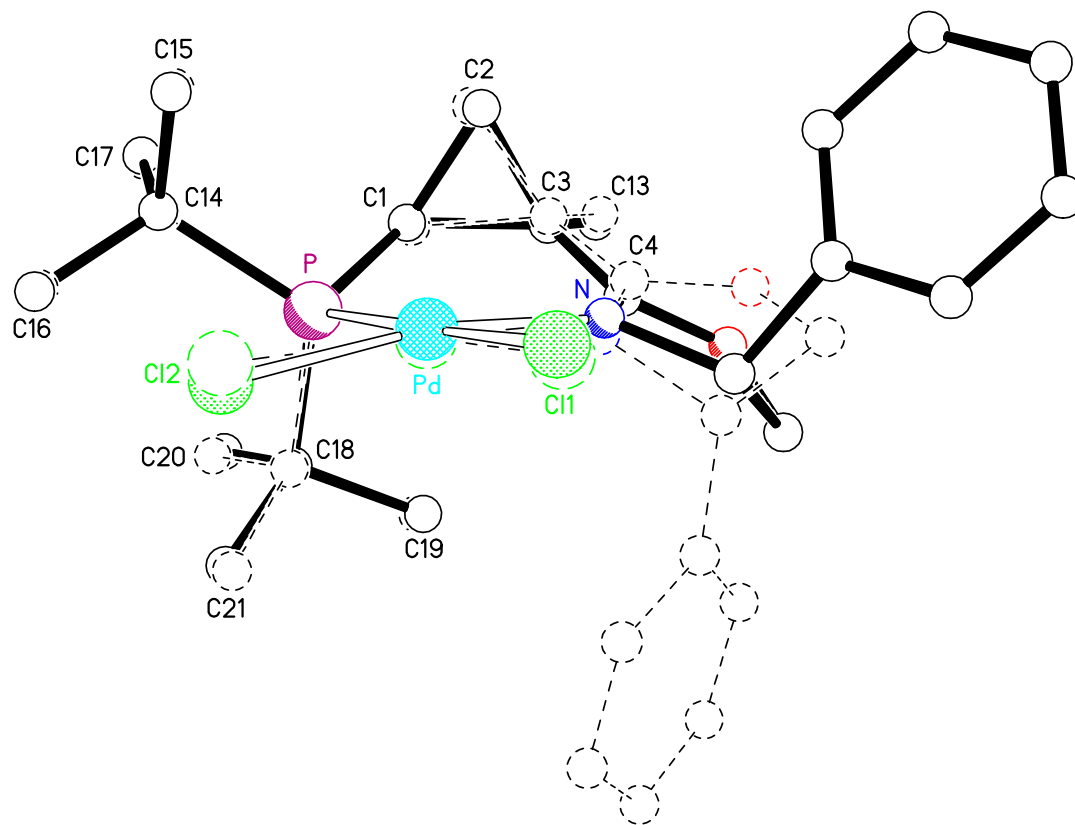
Figure 1.

Overlay of X-ray structures of complexes (**L1**)PdCl$_2$ (solid lines) and (**L4**)PdCl$_2$ (dashed lines, molecule A). The 18 conformationally-similar non-hydrogen atoms [Pd, Cl(1), Cl(2), P, N, C(1)→C(4), C(13)→C(21)] in the two isomers can be superimposed with a rms deviation of 0.12 Å and a maximum deviation of 0.22 Å for any pair of these atoms.

Similar considerations were used to account for the observed reversal of enantioselectivity in the reaction carried out in the presence of **L3** (Table 2, entries 5,6, Scheme 9). Thus, the increased sterics created by a bulky *tert*-butyl group in the dihydrooxazole ring does not allow for the *si*-face approach resulting in the reaction proceeding predominantly from the *re*-face, providing the (*S*)-enantiomer of **3**

(Scheme 9). The fact that in both intermediates **I7** and **I8** dihydrofuran experiences certain impediment on approach to palladium may also be responsible for the observed decrease in the reaction rate.

Scheme 8.
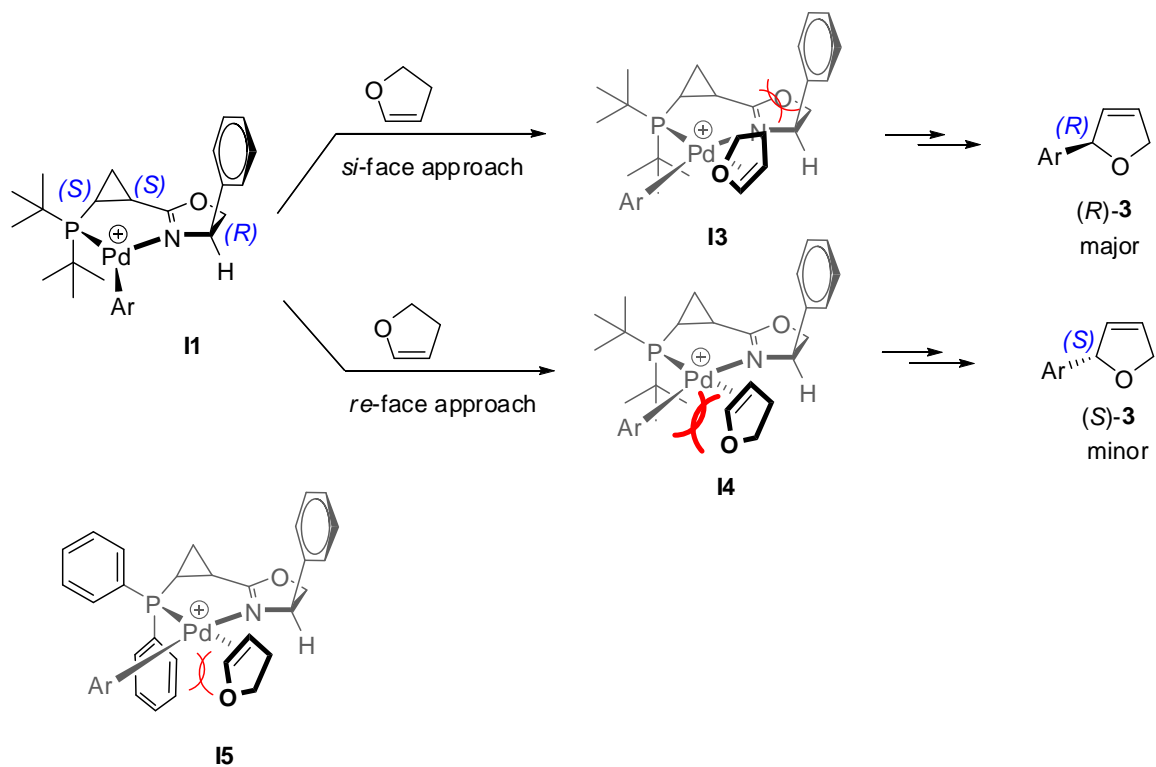
Scheme 9.
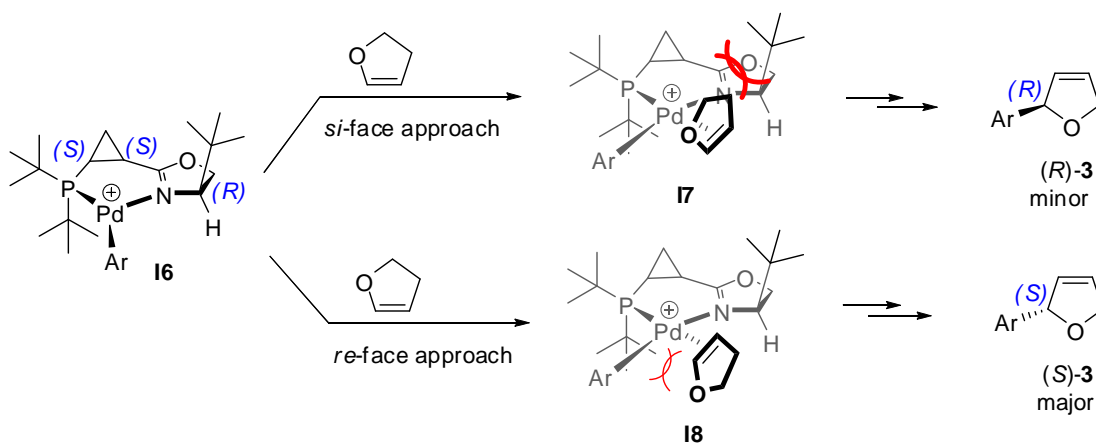
Based on this analysis, we rationalized that the "wrong" relative configuration of the stereogenic centers in ligands **L1**, **L2**, **L3** could be responsible for the observed marginal enantioselectivity of the corresponding catalytic systems. We envisioned inverting the absolute configuration of the asymmetric center at C4 in the dihydrooxazole ring may potentially help improve enantioselectivity of the arylation reaction. Indeed, it is reasonable to propose inversion of the stereogenic center in the dihydrooxazole ring should not significantly affect the thermodynamic equilibrium of the corresponding palladacycle conformations **I9** and **I10** (Scheme 10), as compared to **I1** and **I2** (Scheme 7). Thus, the cationic palladacycle with (*S*,*S*,*S*)-ligand **L4** would still predominantly adopt conformation **I9** to avoid the unfavorable steric interaction between the pseudo-axial syn-*tert*-butyl group and the methylene group of the cyclopropane (Scheme 10). Accordingly, the axial P-*t*Bu group and a bulky substituent at C4 in dihydrooxazolyl moiety in the alternative, (*S*,*S*,*S*)-configuration of the ligand would now act synergistically to provide efficient blocking of both bottom quadrants thereby completely preventing the *re*-face attack (**I12**, Scheme 11).

On the other hand, the *si*-face attack should become more favorable after the removal of a bulky group obstructing the top right quadrant (**I11**, Scheme 11 vs. **I3**, Scheme 8). Ultimately, if the above assumptions are correct, this change should result in enhanced enantioselectivity of the asymmetric arylation in the presence of ligand **L4** in favor of the (*R*)-enantiomer of the product **3**.

Scheme 10.
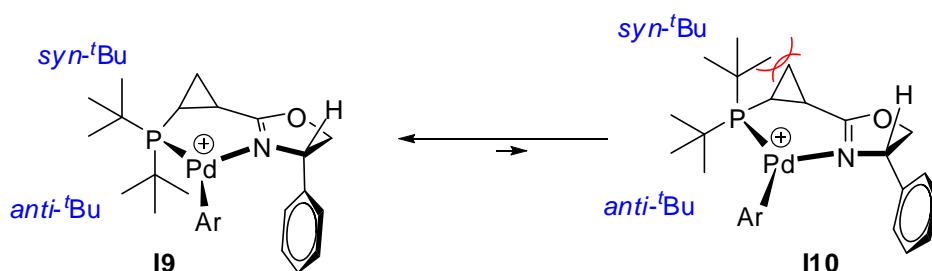
Scheme 11.
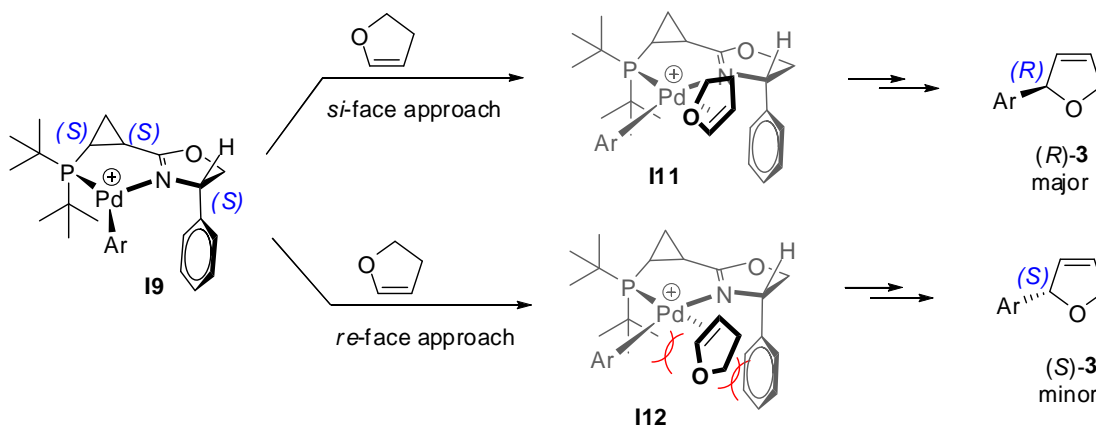
With this idea in mind, we prepared a new series of ligands with the (*S,S,S*) absolute configuration using the synthetic approach described above (Scheme 5),

starting from acid chloride (*S*)-**16** and (*S*)-phenyl glycinol.[25] Additional diversification of the ligand structure was achieved by varying the chlorophosphine source. Thus, employment of di-*tert*-butylchlorophosphine, chlorodicyclo-hexylphosphine, and chlorodiphenylphosphine at the last step of the sequence provided ligands **L4**, **L5**, and **L6**, respectively (Scheme 6).[25] Crystallographic data obtained for the (**L4**)PdCl$_2$ complex (Figure 1) completely confirmed the preference of conformation **I9** vs. **I10** (Scheme 10).[26,27] Remarkably, X-ray analysis has also demonstrated that the phenyl substituent at C4 of dihydrooxazole ring adopts a pseudo-axial position thereby completely blocking any potential re-face attack (Scheme 11). Ligands **L4**, **L5**, **L6** once obtained were tested in the asymmetric arylation of dihydrofuran **1** (Table 3). Gratifyingly, right along with our expectations, the entire series of (*S*,*S*,*S*) ligands **L4**-**L6** not only provided a significant improvement in enantioselectivity, but also helped suppress the unwanted isomerization of **3** into **4**, as compared to the diastereomeric ligand series (**L1**-**L3**, Table 2). Remarkably, changing the absolute configuration of the stereocenter in the dihydrooxazole ring did not cause the change of the absolute configuration of the product. This is in contrast to the reactions performed using most known PHOX ligands, in which configuration of the oxazoline moiety usually determines the stereochemical outcome of the reaction.[28] Thus, employment of **L4** and **L5** afforded dihydrofuran (*R*)-**3** with very high enantioselectivity regardless of the base used (entries 1-6); however, the reactions proceeded more sluggishly in the presence of Hünig's base (Table 3, entries 2,5). Making use of a proton sponge helped boost the reaction rate in the arylation

catalyzed by both **L4** and **L5** (Table 3, entries 3,6) yet, significant isomerization of **3** into **4** was observed with this base when the reaction catalyzed by Pd/**L4** complex was allowed to run for an additional 20 hrs (Table 3, note c). Employment of the diphenylphosphanyl ligand **L6** provided lower enantioselectivity (Table 3, entries 7,8), which can be attributed to decreased steric demands created by phenyl groups at phosphorus as compared to the *tert*-butyl (**L4**) and cyclohexyl (**L5**) substituents.

The different tendencies of Pd/**L1** and Pd/**L4** catalyst systems to promote isomerization of product **3** into **4** can be rationalized as follows: as discussed above (Scheme 2), the isomerization process involves reversible hydropalladation of the double bond of product **3**. The migration of the double bond can be realized only when hydropalladation of **3** occurs with addition of palladium to C4 (Scheme 12, path A), whereas the opposite regioselectivity of hydropalladation would ultimately lead, after the subsequent β-hydride elimination, back to compound **3** (Scheme 12, path B). The diastereoselectivity of the hydropalladation of **3** by Pd/**L1** hydride species **I13** is controlled as shown in Scheme 13. Thus, the *si*-face approach of palladium hydride species **I13** to the double bond of **3** cannot be realized due to severe steric clashes between the di(*tert*-butyl)phospanyl group of the ligand and the aryl substituent in **3** on one side, and between the phenyl substituent in dihydrooxazole ring and C5-methylene of dihydrofuran **3** on the other (**I15**, Scheme 13). However, the alternative *re*-face approach is not associated with any steric hindrance, making this mechanistic channel available for isomerization (**I14**, Scheme 13).

Table 3. Screening of **L4-L6** in the Asymmetric Heck Arylation Reaction
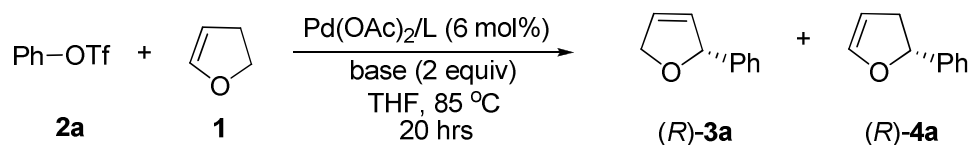
#	Ligand	Base	3a:4a	ee (3a), %	Conv, %[a]
1	**L4**	EtN^{i}Pr$_2$	>50:1	98	53
2	**L4**	EtN^{i}Pr$_2$	16:1	98	97[b]
3	**L4**	Proton sponge	>50:1[c]	98	74
4	**L5**	EtN^{i}Pr$_2$	>50:1	94	71
5	**L5**	EtN^{i}Pr$_2$	40:1	94	90[b]
6	**L5**	Proton sponge	29:1	95	99
7	**L6**	EtN^{i}Pr$_2$	16:1	88	76
8	**L6**	Proton sponge	>50:1	86	83

[a] Conversions by GC. [b] Conversion after 2 days at 85 °C. [c] When the reaction was allowed to stir for an additional 20 hrs, the product ratio changed to 2:1. The enantioselectivities of products (*R*)-**3a** and (*R*)-**4a** in this case were found to be 98 % and 97 %, respectively.

Two potential pathways for hydropalladation of **3** by the diastereomeric Pd/**L4** hydride species **I16** are shown in Scheme 14. In conjunction with **L1**-derived complex **I15** (Scheme 13), complex **I18** produced via the *si*-face approach should be highly disfavored (Scheme 14). In this case; however, an alternative complex **I17**

resulting from the *re*-face attack should also experience steric repulsion between the C5-methylene of dihydrofuran **3** and a pseudo-equatorial phenyl substituent in dihydrooxazole ring (Scheme 14). Accordingly, complex **I17** should be much more unfavorable compared to **L1**-derived complex **I14**, where such interaction does not occur (Scheme 13). As a result, both mechanistic channels for isomerization of compound **3** into **4** should be suppressed in this case. It should be mentioned; however, that electronic density at the phosphine moiety of the ligand also notably affects the propensity of the corresponding catalyst to promote the isomerization.

Scheme 12.
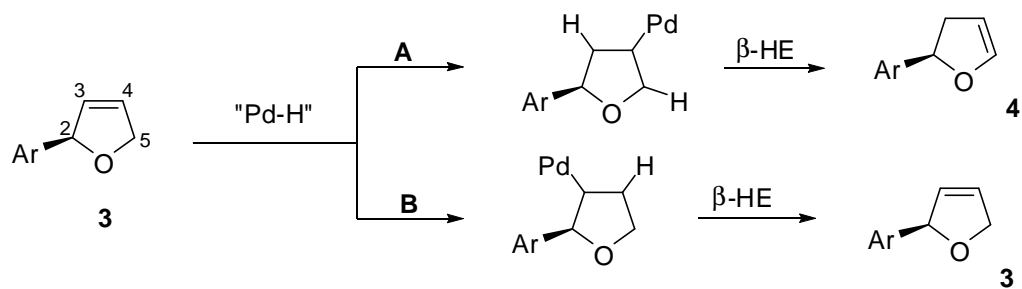
Scheme 13.
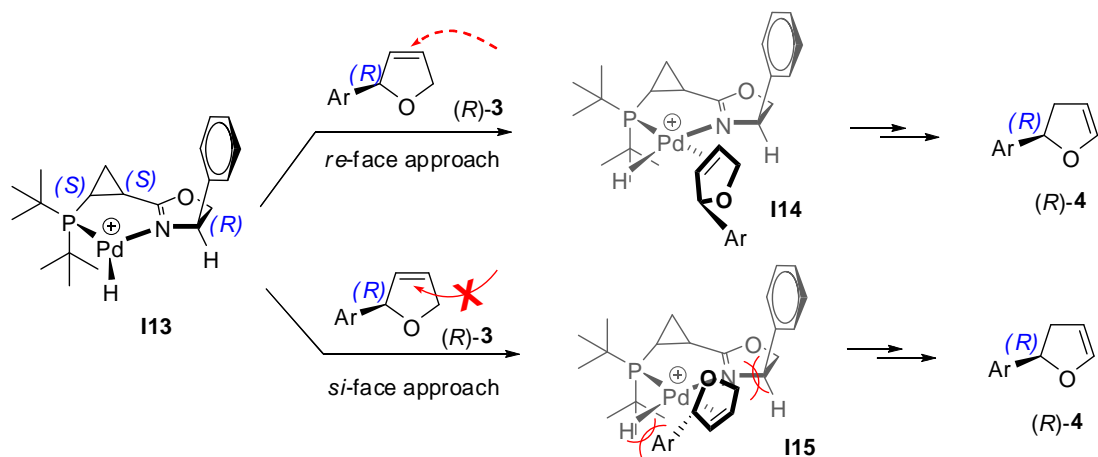
Our experiments indicate in the series of di(*tert*-butyl)-, dicyclohexyl-, and diphenylphosphanyl-containing ligands (**L4→L6**), the former has the highest tendency to induce isomerization while the latter has the lowest (Table 3). A similar electronic effect was previously observed in the asymmetric Heck arylation in the presence of diphosphine-oxazoline ferrocenyl ligands.[19a]

Scheme 14.
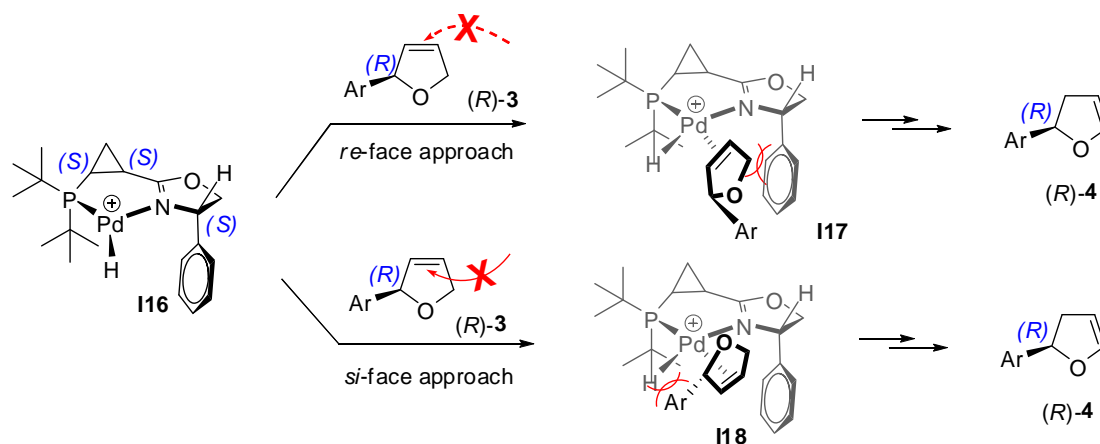
Next, the most efficient ligands **L4** and **L5** were tested in the asymmetric arylation of dihydrofuran **1** against various aryl triflates (Table 4). It was found that all reactions catalyzed by Pd/**L4** provided excellent enantioselectivities (98-99 % ee) regardless of the nature of the aryl triflate (Table 4, entries 1-5). However, the reactions carried out in the presence of **L4**/Hünig's base combination proceeded much more sluggishly; as a result, the selectivity toward formation of **3** was slightly lower in these cases. Reactions performed in the presence of Pd/**L5** catalyst and proton sponge proceeded much faster, albeit providing somewhat lower ee's (Table 4,

entries 6-10). In contrast to the Pd/**L4** catalyzed reactions, enantioselectivities in this case varied slightly depending on the aryl triflate used, with the highest value obtained from 1-naphthyl triflate (96 % ee, entry 9) and the lowest from 2-naphthyl triflate (87 % ee, entry 10). Interestingly, the electronic nature of the aryl triflate had a pronounced effect on the reaction rate, which is best seen in the Pd/**L5** series of catalyzed reactions. Thus, electron-rich aryl triflates (entries 6,7,9) reacted much faster than the electron-poor analog **2d** (entry 8). Furthermore, a remarkable difference between the reactivity of 1- and 2-naphthyl triflates was also observed, suggesting the reaction is also sensitive to sterics (entries 9 and 10).

We also tested all new ligands **L1**-**L6** in the asymmetric Heck arylation of cyclopentene (Table 5). Initial experiments conducted under the conditions optimized for arylation of dihydrofuran **1** (Table 4) provided no reaction with cyclopentene **19**. Additional optimization revealed reasonable reaction rates can be achieved only in the presence of Pd(dba)$_2$ catalyst and proton sponge (Table 6).[29] Generally, the enantioselectivities obtained in this transformation (Table 5) were somewhat lower than those obtained in the arylation of dihydrofuran (Tables 2,3) for all ligands tested except **L4**. Notably, similarly to the arylation of dihydrofuran (Tables 2,3), the isomerization rates (**22**→**23**) in this transformation were significantly lower in the reactions carried out in the presence of ligands with the (*S*,*S*,*S*) absolute configuration (**L4**-**L6**, Table 5, entries 4-6), as compared to the ligands in the diastereomeric series (**L1**-**L3**, Table 5, entries 1-3).

Table 4. Asymmetric Arylation of Dihydrofuran with Aryl Triflates
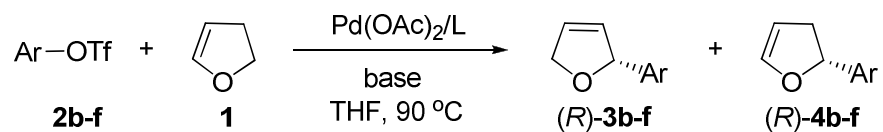
#	Aryl		Ligand/Base	Time, h	**3:4**	ee (**3**), %	Conv, %[a]
1	p-Me-C$_6$H$_4$	**2b**	**L4**/Hünig's base	48	16:1	99	96
2	p-MeO-C$_6$H$_4$	**2c**	**L4**/Hünig's base	20	17:1	98	98
3	p-CF$_3$-C$_6$H$_4$	**2d**	**L4**/Hünig's base	48	>50:1	98	58
4	1-Naphthyl	**2e**	**L4**/Hünig's base	48	18:1	98	70[b]
5	2-Naphthyl	**2f**	**L4**/Hünig's base	20	>50:1	98	32[b]
6	p-Me-C$_6$H$_4$	**2b**	**L5**/Proton sponge	6	39:1	95	93
7	p-MeO-C$_6$H$_4$	**2c**	**L5**/Proton sponge	6	35:1	92	99
8	p-CF$_3$-C$_6$H$_4$	**2d**	**L5**/Proton sponge	20	42:1	91	95
9	1-Naphthyl	**2e**	**L5**/Proton sponge	6	31:1	96	94[b]
10	2-Naphthyl	**2f**	**L5**/Proton sponge	20	17:1	87	100[c]

[a] Conversion by GC. [b] Formation of ca.10 % of naphthalene was observed. [c] Formation of ca.20 % of naphthalene was observed.

Table 5. Evaluation of Ligands **L1**-**L6** in the Intermolecular Asymmetric Heck Reaction of Phenyl Triflate (**2a**) with Cyclopentene (**21**)
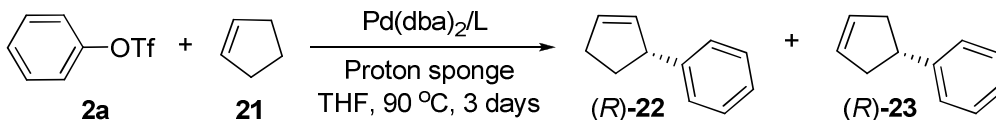
#	Ligand	**22:23**	ee (**22**), %	Conv, %[a]
1	**L1**	12:1	81	99
2	**L2**	15:1	86	95
3	**L3**	13:1	82	15
4	**L4**	27:1	92	32
5	**L5**	44:1	89	96
6	**L6**	40:1	80	60

[a] Conversion by GC.

1.3. Conclusions

In conclusion, a series of novel PHOX ligands featuring a chiral cyclopropyl backbone have been synthesized and examined in the intermolecular asymmetric Heck arylation of cyclic olefins. By lowering degrees of freedom in the catalyst structure through the introduction of additional conformation constraints, we have created a model catalytic system with predictable, tunable and easily adjustable properties. Structure-activity relationship studies allowed for identifying the key topological and stereochemical features of the ligands, responsible for achieving high enantioselectivity and for suppressing product isomerization. This has resulted in the

development of efficient catalytic systems demonstrating excellent enantioselectivities in the asymmetric arylation of dihydrofuran with various aryl triflates. It was also shown that product isomerization in the presence of these ligands has a different nature from that reported previously using chiral diphosphine ligands. Furthermore, a number of factors were shown to affect the isomerization rate including the absolute configuration of the ligand, its electronic properties, and the base employed.

1.4. Experimental

1.4.1. General Information

NMR spectra were recorded on a Bruker Avance DPX-400 instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C and ^{31}P NMR spectra were registered with broad-band decoupling. The (+) and (-) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments.

GC/MS analyses were performed on a Shimadzu GC-2010 gas chromatograph interfaced to a Shimadzu GCMS 2010S mass selective detector and equipped with an AOC-20i auto-injector and an AOC-20S auto-sampler tray (150 vials). 30 m x 0.25 mm x 0.25 μm capillary column, SHR5XLB, polydimethylsiloxane, 5 % Ph was employed. Helium (99.96 %), additionally purified by passing consecutively through a CRS oxygen/moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap

(P100-1), was used as a carrier gas. The same model of gas chromatograph, equipped with the same auto-injector, FID detector, and J&W CyclosilB column (30 m x 0.25 mm x 0.25 μm) or J&W CyclodexB column (30 m x 0.25 mm x 0.25 μm) was employed for chiral GC analyses. Hydrogen gas was used as both carrier gas and FID fuel; zero-grade air and zero-grade nitrogen were used as an oxidant and make-up gas, respectively, for the FID. All these gases were purified by passing through CRS #202839 traps.

Glassware employed in moisture-free syntheses was flame-dried in vacuum prior to use. Water was purified by dual stage deionization, followed by dual stage reverse osmosis. Anhydrous hexane, dichloromethane, and tetrahydrofuran were obtained by passing degassed HPLC-grade commercially available solvents consecutively through two columns filled with activated alumina (Innovative Technology). Anhydrous triethylamine was obtained by distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. Glacial acetic acid was purchased from Acros Organics and used as received. Palladium complexes were obtained from Strem Chemicals. Racemic 2,2-dibromocyclpopanecarboxylic acid (*rac*-**15**) was obtained according to the literature procedure.[30] All other reagents were purchased from Sigma-Aldrich or Acros Organics.

1.4.2. Preparation of the Homochiral Dibromocyclopropylcarboxylic Acid: Scale up Procedure

Resolution of racemic 2,2-dibromo-1-methylcyclopropanecarboxylic acid (*rac*-**15**) with (+)-dehydroabiethylamine was performed using previously published protocol.[31] Our modifications allowed for preparation of large quantities of optically active material. (Scheme 15)

Scheme 15. Chiral Resolution of Racemic Dibromoacid **15**
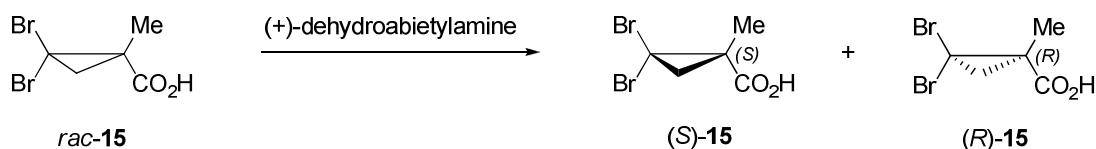
Commercially available technical grade (60 % essay)[32] (+)-dehydroabiethylamine (500 g) was stirred in toluene (2500 mL) at 0 °C, and a solution of glacial acetic acid (121 mL) in toluene (1000 mL) was added over 1 hr. The solution was stirred for 2.5 hrs at 0 °C and the resulting precipitate was collected by suction filtration. The filter cake was washed with ice-cold toluene (2 x 250 mL) and then was air dried. The waxy off-white solid was re-crystallized from refluxing toluene (2000 mL) to obtain acetate as fine colorless needles (yield 429 g, 57 %). To this material dissolved in distilled water (1300 mL) was slowly added a 10 % aqueous solution of NaOH (1100 mL). The resulting solution was stirred for 1 hr in water/ice bath, after which the free amine was extracted with ether (3 x 700 mL). Combined

ethereal phases were washed with brine (500 mL), dried with anhydrous K_2CO_3, filtered, and concentrated in vacuum. After removal of residual solvent in high vacuum (<20 μm Hg), pure (+)-dehydroabiethylamine (340 g) was obtained as a highly viscous yellow oil, which slowly crystallized upon standing. This material was used in further operations.

To a stirred hot solution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (*rac*-**15**) (317 g, 1.23 mol) in aqueous methanol (water, 310 mL + methanol, 1240 mL) was added a hot solution of (+)-dehydroabiethylamine (88.8 g, 310 mmol) in methanol (1500 mL). The mixture was stirred for 1 min, until crystals began to precipitate. Then stirring was stopped, the flask was closed and covered with insulating blanket to allow slow crystallization (over ca. 8 hrs). The resulting crystalline precipitate was collected by suction filtration; the mother liquor was saved for further isolation of the (*R*)-enantiomer of cyclopropylcarboxylic acid. The filter cake was washed with ice cold methanol (2 x 100 mL) and air dried to provide 207 g of salt as white needles. A second re-crystallization from 90 % aqueous methanol (2000 mL) afforded 141 g of crystalline salt, m.p. 209-210 °C. This material was partitioned between 20 % aqueous NaOH (1500 mL) and dichloromethane (500 mL). Organic phase was separated; aqueous layer was extracted with dichloromethane (2 x 500 mL). Combined organic phases were evaporated to regenerate (+)-dehydro-abiethylamine, which can be re-used as is without additional purification. The aqueous phase was acidified with 30 % aqueous sulfuric acid and extracted with dichloromethane (3 x 500 mL). The combined organic phases were washed with

brine (500 mL), dried with MgSO$_4$, filtered, and concentrated to afford (*S*)-2,2-dibromo-1-methylcyclopropanecarboxylic acid ((*S*)-**15**) (91 g, 353 mmol, 57 %), m.p. 62-62.5 °C, ee > 99 % (determined by chiral GC of the corresponding methyl ester).

The combined mother liquors obtained in the described above crystallizations were evaporated. (+)-Dehydroabiethylamine amine and the acid enriched with the (*R*)-enantiomer was regenerated from the obtained crystalline mass by acid/base extraction, analogous to the procedure described above. The crude acid was slowly re-crystallized from hot *n*-hexane. The flask was closed and allowed to cool down to room temperature. Crystallization (over ca. 15 hrs at 5 °C) produced a precipitate of a nearly racemic acid, which was filtered off. Evaporation of the mother liquor afforded enantiomerically pure (*R*)-2,2-dibromo-1-methylcyclopropanecarboxylic acid ((*R*)-**15**) as a yellowish oil, which solidified upon standing. Yield 87 g, 337 mmol, 55 %; ee > 99 % (determined by chiral GC of the corresponding methyl ester).

1.4.3. Installation of the Chiral Dihydrooxazole Moiety

(*S*)-2,2-Dibromo-1-methylcyclopropylcarbonyl chloride, (*S*)-**16**: (*S*)-2,2-dibromo-1-methylcyclopropanecarboxylic acid ((*S*)-**15**) (49.8 g, 193 mmol) and freshly distilled thionyl chloride (50 mL) were stirred at room temperature overnight. Excess thionyl chloride was distilled off at ambient pressure. The residue was distilled in vacuum, b.p. 57-60 °C (1.7 mm Hg). Yield 49.9 g (180.5 mmol, 94 %).

(R)-2,2-dibromo-1-methylcyclopropylcarbonyl chloride, (R)-**16**: was obtained using the procedure described above, starting from (R)-2,2-dibromo-1-methyl-cyclopropanecarboxylic acid ((R)-**15**).
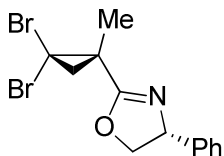
18: To a stirred solution of (S)-2,2-dibromo-1-methylcyclopropyl-carbonyl chloride (7.760 g, 28 mmol) in anhydrous methylene chloride (75 mL) was added at 0 $^{\circ}$C a solution of (R)-phenylglycinol (3.848 g, 28 mmol) in dry methylene chloride (15 mL), to obtain a thick suspension. Then triethylamine (7.8 mL, 56.1 mmol) was added dropwise at 0 $^{\circ}$C, and the resulting clear solution was warmed to room temperature and stirred for 3 hrs. Solvent was removed in vacuum and the residue was partitioned between water and EtOAc. Combined organic extracts were washed consecutively with water and brine, dried with $MgSO_4$, filtered, and concentrated to give (1S)-2,2-dibromo-N[(1R)-2-hydroxy-1-phenylethyl]-1-methylcyclopropanecarboxamide (**17**) as a white crystalline solid (> 95 % pure by NMR).[33] This material was dissolved in anhydrous dichloromethane (200 mL) and dry triethylamine (6 mL) was added, followed by aminomethylpyridine (114 μL). Mesyl chloride (3.25 mL, 42 mmol) was added dropwise at 0 $^{\circ}$C, and the remaining dry triethylamine (36 mL) was added in one portion. The mixture was warmed up to room temperature and stirred for 20 hrs, until TLC analysis showed complete conversion. The reaction mixture was quenched with 10 % aqueous HCl, the organic phase was separated, and the aqueous layer was extracted with dichloromethane. Combined organic extracts were washed

consecutively with water and brine, dried with MgSO$_4$, filtered, and concentrated. The oily residue was purified by short column chromatography on Silica gel, eluting hexane/EtOAc (4:1). The titled compound **18** was obtained as yellowish oil. Yield 8.896 g (25.8 mmol, 88 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.40-7.37 (m, 2H), 7.33-7.28 (m, 3H), 5.24 (ps.-t, J = 10.1 Hz, 9.1 Hz, 1H); 4.75 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 4.18 (ps.t, J = 9.1 Hz, 8.3 Hz, 1H), 2.54 (d, J = 7.8 Hz, 1H), 1.73 (s, 3H), 1.72 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 167.1, 141.5, 128.7 (+, 2C), 127.7 (+), 126.8 (+, 2C), 75.3 (-), 69.7 (+), 33.3 (-), 31.7, 29.5, 21.3 (+).
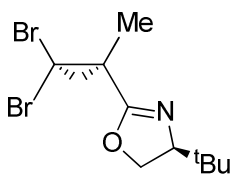
24: Was prepared in a similar manner from 5.62 g (20.3 mmol) of (*R*)-2,2-dibromo-1-methylcyclopropylcarbonyl chloride ((*R*)-**16**) and 2.38 g (20.3 mmol) of (*S*)-*tert*-leucinol. However, the cyclization step required heating overnight at 40 ^{o}C for complete conversion. Purification of final product by preparative column chromatography was performed using hexane/EtOAc (4.5:1) as an eluent. Yield 3.67 g (10.8 mmol, 54 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 4.27 (dd, J = 9.9 Hz, 8.8 Hz, 1H), 4.13 (ps.-t, J = 8.8 Hz, 8.6 Hz, 1H), 3.87 (dd, J = 9.9 Hz, 8.6 Hz, 1H), 2.43 (d, J = 7.8 Hz, 1H), 1.64 (d, J = 7.8 Hz, 1H), 1.61 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 165.4, 75.6 (+), 69.2 (-), 33.3 (-), 31.8, 29.7, 25.9 (+, 3C), 21.3 (+).
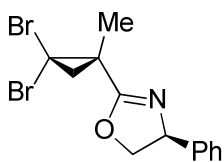
25: Was prepared in a similar manner from 4.65 g (16.8 mmol) of (*S*)-2,2-dibromo-1-methylcyclopropylcarbonyl chloride ((*S*)-**16**) and 2.92 g (16.8 mmol) of (*R*)-phenylglycinol. Purification of final product by preparative column chromatography was performed using hexane/EtOAc (2.5:1) as an eluent. Yield 4.14 g (11.5 mmol, 69 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.40-7.26 (m, 5H), 5.25 (dd, *J* = 10.4 Hz, 9.1 Hz, 1H), 4.76 (dd, *J* = 10.4 Hz, 8.6 Hz, 1H), 4.20 (ps.-t, *J* = 9.1 Hz, 8.6 Hz, 1H), 2.52 (d, *J* = 7.8 Hz, 1H), 1.71 (d, *J* = 7.8 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 167.1, 141.4, 128.5 (+, 2C), 127.5 (+), 126.8 (+, 2C), 75.4 (-), 69.6 (+), 33.0 (-), 31.6, 29.5, 21.2 (+).

1.4.4. Diastereoselective Partial Reduction of Dibromocyclopropane

Various reducing agents for partial reduction of dibromocyclopropanes into bromocyclopropanes were tested. Depending on the nature of the reducing agent and the substitution pattern of the substrate, the reaction can be controlled by steric or directing effects, which greatly affects the diastereoselectivity of the reaction. A number of reports demonstrated employment of different alkyllithium reagents,[34] which normally results in predominant formation of *trans*-bromocyclopropanes[35] in the case where a suitable directing group is present in the substrate. In our case, employment of *tert*-BuLi produced the *trans*- product with very good selectivity

(Table 6, entry 1). Radical hydrodebromination with tin hydride[36] (entry 2), as well as the titanium-catalyzed reduction with Grignard reagent[37] (entry 3) produced equimolar mixtures of isomeric products. Employment of a more sterically hindered hydride source, tris(trimethylsilyl)silane,[38] in the presence of 1,1'-azobis(cyanocyclohexane) (V-40) as a radical initiator allowed for a significant improvement of the diastereoselectivity in favor of the desired *cis*-product (entry 4). Reductions with zinc dust activated by aqueous HCl in ethanol[39] or by glacial AcOH[40] were also explored. While the former protocol produced the required monobromide in moderate yield and poor diastereoselectivity (entry 5), the latter procedure provided satisfactory results (entry 6). It was found that reaction temperature significantly affected the selectivity, providing the best cis/trans ratio at ca. + 5 $^{\circ}$C. Accordingly, this protocol was employed in the ligand synthesis as the most selective and cost-efficient method.

Optimization protocol: An oven dried 3 mL Wheaton vial was charged with (4*S*)-2-[(1*S*)-2,2-dibromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**25**) (100 mg, 0.28 mmol), followed by an appropriate solvent. The reducing agent was added (see Table 1), and the reaction was stirred for a time indicated in Table 1, until GC/MS showed complete conversion of the starting material. The diastereoselectivities were determined by ^{1}H NMR.

Table 6. Optimization of the Reaction Conditions for Partial Reduction of

Dibromocyclopropanes

#	Reducing agent	Solvent	Temperature	Time, hrs	cis/trans	Yield, %
1	^{t}BuLi (1.05 equiv)	Et$_2$O	-85 - 90 ^{o}C	1	1:13	N/D
2	Bu$_3$SnH (1.01 equiv)	none	r.t.	1	1:1	N/D
3	EtMgBr (1.1 equiv) Ti(OPr^i)$_4$ (5 mol %)	Et$_2$O	r.t	1	1:1	N/D
4	V-40 (20 mol%) TMS$_3$SiH (3 equiv)	pyridine	r.t	3	5.3:1	N/D
5	Zn (2.5 equiv) HCl (10 mol%)	EtOH	r.t.	2	2:1	54
6	Zn (2.5 equiv)	AcOH	+5 ^{o}C	2	5.3:1	70

Diastereomeric (4*R*)-2-[(1*S*)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazoles (**19** and **19'**)*:* To a stirred at +5 ^{o}C solution of (4*R*)-2-[(1*S*)-2,2-dibromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**18**) (8.90 g, 25.8

mmol) in glacial acetic acid (100 mL) was added zinc dust (4.2 g, 64.5 mmol, 2.5 equiv) in small portions. The mixture was stirred for 1.5 hr, while the temperature was slowly raised to 20 $^{\circ}$C. When judged complete by GC/MS, the mixture was filtered and concentrated in vacuum. The residue was dissolved in EtOAc (150 mL), washed consecutively with water (2x100 mL) and brine (100 mL), dried with MgSO$_4$, filtered, and concentrated. Preparative column chromatography of the residue on Silica gel (eluent hexane/EtOAc 5:1 → 2:1) afforded two fractions.
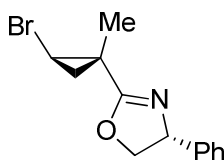
19' minor: Yield 1.13 g (4.0 mmol, 16 %); R$_f$ = 0.37 (hexane-EtOAc, 4:1); ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.39-7.35 (m, 2H), 7.32-7.28 (m, 1H), 7.26-7.23 (m, 2H), 5.18 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 4.61 (dd, J = 10.1 Hz, 8.6 Hz, 1H), 4.07 (ps.-t, J = 8.6 Hz, 8.3 Hz, 1H), 3.62 (dd, J = 8.1 Hz, 5.3 Hz, 1H), 1.91 (dd, J = 8.1 Hz, 6.1 Hz, 1H), 1.63 (s, 3H), 1.10 (ps.-t, J = 6.1 Hz, 5.3 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 169.1, 142.1, 128.7 (+, 2C), 127.6 (+), 126.5 (+, 2C), 75.1 (-), 69.7 (+), 28.2 (+), 24.2 (-), 19.5, 18.1 (+).
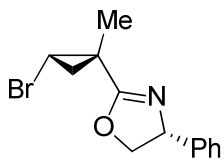
19 major: Yield 3.76 g (13.4 mmol, 52 %); R$_f$ = 0.27 (hexane-EtOAc, 4:1); ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.40-7.33 (m, 4H), 7.32-7.28 (m, 1H), 5.26 (ps.-t, J = 10.1 Hz, 9.1 Hz, 1H), 4.70 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 4.12 (ps.-t, J = 9.1 Hz, 8.3 Hz, 1H), 3.02 (dd, J = 7.6 Hz, 5.1 Hz, 1H), 1.88 (dd, J = 6.8 Hz, 5.1 Hz, 1H), 1.51 (s, 3H), 1.33 (dd, J = 7.6 Hz,

6.8 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 167.9, 142.0, 128.6 (+, 2C), 127.5 (+), 126.9 (+, 2C), 74.9 (-), 69.9 (+), 26.0 (+), 21.9 (-), 21.9, 20.8 (+).
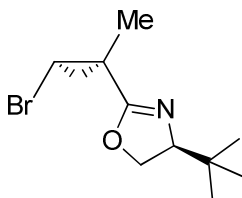
26: Was prepared in a similar manner from 3.67 g (10.8 mmol) of (4S)-4-$tert$-butyl-2-[(1R)-2,2-dibromo-1-methylcyclopropyl]-4,5-dihydro-1,3-oxazole (**24**). Purification of the final product by preparative column chromatography was performed using hexane/EtOAc (4:1) as eluent. Yield 1.05 g (4.03 mmol, 37 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 4.23 (dd, J = 10.1 Hz, 8.6 Hz, 1H), 4.08 (ps.-t, J = 8.6 Hz, 8.3 Hz, 1H), 3.91 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 2.92 (dd, J = 7.6 Hz, 5.1 Hz, 1H), 1.74 (dd, J = 6.6 Hz, 5.1 Hz, 1H), 1.41 (s, 3H), 1.25 (dd, J = 7.6 Hz, 6.6 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 166.1, 75.8 (+), 68.3 (-), 33.1, 25.9 (+, 3C), 22.0, 21.7 (-), 21.0 (+).
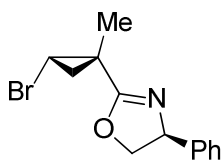
27: Was prepared in a similar manner from 4.14 g (11.5 mmol) of (4S)-2-[(1S)-2,2-dibromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**26**). Purification of the final product by preparative column chromatography was performed using hexane/EtOAc (3:1) as an eluent. Yield 1.92 g (6.86 mmol, 59 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.40-7.25 (m, 5H), 5.26 (dd, J = 10.4 Hz, 8.6 Hz, 1H), 4.71 (dd, J = 10.4 Hz, 8.3 Hz, 1H), 4.17 (ps.t, J = 8.6 Hz, 8.3 Hz, 1H), 3.01 (dd,

J = 7.6 Hz, 5.1 Hz, 1H), 1.87 (dd, J = 6.8 Hz, 5.1 Hz, 1H), 1.49 (s, 3H), 1.33 (dd, J =

7.6 Hz, 6.8 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 167.9, 142.1, 128.5 (+, 2C),

127.4 (+), 126.8 (+, 2C), 75.2 (-), 70.0 (+), 26.0 (+), 21.9, 21.8 (-), 20.7 (+).

1.4.5. Installation of the Phosphine Moiety
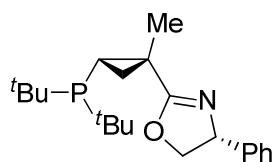
L1: To a stirred at -80 $^{\circ}$C solution of (4R)-2-[(1S,2S)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**19**) (2.67 g, 9.52 mmol) in anhydrous THF (25 mL) was added dropwise a solution of n-BuLi in hexane (2.5M, 4.2 mL, 10.5 mmol).

The mixture was allowed to warm up to -30 $^{\circ}$C (within 0.5 hr), after which di-*tert*-butylchlorophosphine (2 mL, 10.53 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at room temperature. The mixture was quenched with saturated aqueous solution of NH$_4$Cl (100 mL), and extracted with ether (3 x 50 mL). The combined ethereal phases were washed with brine, dried with MgSO$_4$ and concentrated.[41] Preparative column chromatography was performed in a nitrogen-filled glove box, using degassed Silica gel and degassed dry solvents (hexane/EtOAc/CH$_2$Cl$_2$ 10:1:1). Yield 1.41 g (4.1 mmol, 43 %).

^{1}H NMR (400.13 MHz, C$_6$D$_6$) δ 7.43-7.41 (m, 2H), 7.30-7.27 (m, 2H), 7.21-7.17 (m, 1H), 5.18 (ps.-t, J = 10.1 Hz, 9.6 Hz, 1H), 4.29 (dd, J = 10.1 Hz, 8.2 Hz, 1H), 3.96 (dd, J = 9.6 Hz, 8.2 Hz, 1H), 2.02-1.99 (m, 1H), 1.59 (d, $^4J_{PH}$ = 1.8 Hz, 3H), 1.32 (d,

$^3J_{PH}$ = 4.3 Hz, 9H), 1.29 (d, $^3J_{PH}$ = 4.3 Hz, 9H), 1.01-0.92 (m, 2H); ^{13}C NMR (100.67

MHz, C$_6$D$_6$) δ 169.8 (d, $^3J_{CP}$ = 2.2 Hz), 143.8, 129.0 (+, 2C), 127.8 (+, 2C), 127.7 (+),

74.4 (-), 70.8 (+), 32.7 (d, $^1J_{CP}$ = 22.7 Hz), 31.4 (d, $^1J_{CP}$ = 20.5 Hz), 30.7 (d, $^2J_{CP}$ =

13.2 Hz, +, 3C), 30.4 (d, $^2J_{CP}$ = 13.9 Hz, +, 3C), 23.3, 23.2 (d, $^1J_{CP}$ = 27.1 Hz, +),

21.2 (d, $^2J_{CP}$ = 8.8 Hz, -), 19.4 (d, $^3J_{CP}$ = 4.4 Hz, +); ^{31}P NMR (161.98 MHz, C$_6$D$_6$) δ

22.4; α_D^{25} +56.7° (c 1.15, CH$_2$Cl$_2$); HRMS (TOF ES) Calculated for C$_{21}$H$_{33}$NOP

(M+H) 346.2300, Found 346.2283 (4.9 ppm).
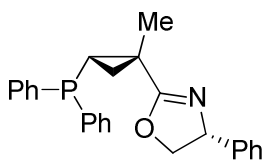
L2: was prepared in a similar manner from 733 mg (2.62 mmol) of (4R)-2-[(1S,2S)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**19**). Purification of the final product by preparative column chromatography was performed in a nitrogen-filled glove box using degassed Silica gel and CH$_2$Cl$_2$/EtOAc (40:1) as an eluent. Yield 200 mg (0.52 mmol, 20 %).

^{1}H NMR (400.13 MHz, C$_6$D$_6$) δ 7.72-7.68 (m, 2H), 7.67-7.63 (m, 2H), 7.29-7.15 (m, 11H), 5.15 (t, J = 8.3 Hz, 1H), 4.23 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 3.86 (dd, J = 9.6 Hz, 8.3 Hz, 1H), 1.99 (ddd, $^2J_{PH}$ = 13.1 Hz, J = 7.1 Hz, 4.5 Hz, 1H), 1.62 (d, $^4J_{PH}$ = 1.5 Hz), 1.48 (ddd, $^3J_{PH}$ = 6.3 Hz, J = 9.1 Hz, 7.1 Hz, 1H), 0.94 (ddd, $^3J_{PH}$ = 7.3 Hz, J = 9.1 Hz, 4.5 Hz, 1H); ^{13}C NMR (100.67 MHz, C$_6$D$_6$) δ 169.0 (d, $^3J_{CP}$ = 3.7 Hz), 143.2, 140.8 (d, $^1J_{CP}$ = 12.5 Hz), 140.3 (d, $^1J_{CP}$ = 13.2 Hz), 133.6 (d, $^2J_{CP}$ = 19.8 Hz, +, 2C), 132.2 (d, $^2J_{CP}$ = 17.6 Hz, +, 2C), 128.8 (d, $^3J_{CP}$ = 9.5 Hz, +, 2C), 128.70 (+),

128.65 (+), 128.6 (+, 2C), 128.1 (d, $^3J_{CP}$ = 9.5 Hz, +, 2C), 127.3 (+), 127.2 (+, 2C), 74.5 (-), 70.4 (+), 26.9 (d, $^1J_{CP}$ = 12.4 Hz, +), 23.0 (d, $^3J_{CP}$ = 1.5 Hz, +), 22.3 (d, $^2J_{CP}$ = 6.6 Hz), 19.1 (d, $^2J_{CP}$ = 11.0 Hz, -); ^{31}P NMR (161.98 MHz, C_6D_6) δ -9.23; α_D^{25} -84.7° (c 1.15, CH_2Cl_2); HRMS (TOF ES) Calculated for $C_{25}H_{24}NOPNa$ (M+Na) 408.1493, Found 408.1483 (2.5 ppm).
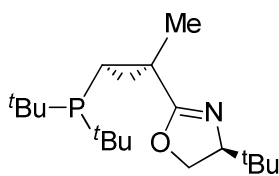
L3: was prepared in a similar manner from 840 mg (3.22 mmol) of (4S)-2-[(1R,2R)-2-bromo-1-methylcyclopropyl]-4-tert-butyl-4,5-dihydro-1,3-oxazole (**26**). Purification of the final product by preparative column chromatography was performed in a nitrogen-filled glove box using degassed Silica gel and hexane/EtOAc (9:1) as an eluent. Yield 204 mg (0.63 mmol, 19 %); α_D^{25} -84.0° (c 0.55, CH_2Cl_2).

^{1}H NMR (400.13 MHz, C_6D_6) δ 4.02-3.82 (m, 3H), 1.96 (m, 1H), 1.55 (d, $^4J_{PH}$ = 1.5 Hz, 3H), 1.33 (d, $^3J_{PH}$ = 10.4 Hz, 9H), 1.30 (d, $^3J_{PH}$ = 10.4 Hz, 9H), 1.00 (s, 9H), 0.97-0.89 (m, 2H); ^{13}C NMR (100.67 MHz, C_6D_6) δ 168.5, 76.7 (+), 68.5 (-), 33.8, 32.7 (d, $^1J_{CP}$ = 22.7 Hz), 31.4 (d, $^1J_{CP}$ = 20.5 Hz), 30.7 (d, $^2J_{CP}$ = 13.9 Hz, +, 3C), 30.5 (d, $^2J_{CP}$ = 14.6 Hz, +, 3C), 26.9 (s, +, 3C), 23.3, 23.0 (d, $^1J_{CP}$ = 27.8 Hz, +), 21.2 (d, $^2J_{CP}$ = 8.8 Hz, -), 19.2 (d, $^3J_{CP}$ = 3.7 Hz, +); HRMS (TOF ES) Calculated for $C_{19}H_{37}NOP$ (M+H) 326.2613, Found 326.2603 (3.1 ppm).
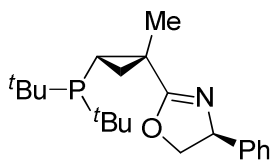
L4: Was prepared in a similar manner from 564 mg (2.0 mmol) of (4*S*)-2-[(1*S*,2*S*)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**27**). Purification of the final product by preparative column chromatography was performed in a nitrogen-filled glove box using degassed Silica gel and hexane/EtOAc/CH$_2$Cl$_2$ (10:1:1) as an eluent. Yield 370 mg (1.07 mmol, 54 %).

^{1}H NMR (400.13 MHz, C$_6$D$_6$) δ 7.47-7.45 (m, 2H), 7.32-7.28 (m, 2H), 7.21-7.18 (m, 1H), 5.14 (dd, *J* = 10.1 Hz. 8.2 Hz, 1H), 4.35 (dd, *J* = 10.2 Hz, 8.2 Hz, 1H), 3.90 (ps.-t, *J* = 8.2 Hz, 8.0 Hz, 1H), 2.02-1.98 (m, 1H), 1.59 (d, $^4J_{PH}$ = 1.5 Hz, 3H), 1.33 (d, $^3J_{PH}$ = 8.7 Hz, 9H), 1.31 (d, $^3J_{PH}$ = 8.7 Hz, 9H), 0.99-0.96 (m, 2H); ^{13}C NMR (100.67 MHz, C$_6$D$_6$) δ 169.5, 143.7, 128.4 (+, 2C), 127.12 (+), 127.08 (+, 2C), 74.3 (-), 70.2 (+), 32.2 (d, $^1J_{CP}$ = 22.0 Hz), 30.9 (d, $^1J_{CP}$ = 20.8 Hz), 30.1 (d, $^2J_{CP}$ = 13.3 Hz, +, 3C), 29.8 (d, $^2J_{CP}$ = 14.4 Hz, +, 3C), 22.8, 22.5 (d, $^1J_{CP}$ = 27.6 Hz, +), 20.5 (d, $^2J_{CP}$ = 7.6 Hz, -), 19.0 (d, $^3J_{CP}$ = 5.2 Hz, +); ^{31}P NMR (161.98 MHz, C$_6$D$_6$) δ 22.7; α_D^{25} -80.2° (c 1.15, CH$_2$Cl$_2$); HRMS (TOF ES) Calculated for C$_{21}$H$_{32}$NOPNa (M+Na) 368.2119, Found 368.2109 (2.7 ppm).
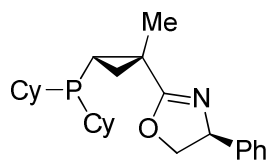
L5: was prepared in a similar manner from 590 mg (2.10 mmol) of (4*S*)-2-[(1*S*,2*S*)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**27**) and 539 mg (2.32 mmol, 1.1 equiv) of dicyclohexylchlorophosphine. Purification of final product by

preparative column chromatography was performed in a nitrogen-filled glove box using degassed Silica gel and CH_2Cl_2/EtOAc (100:1) as an eluent. Yield 228 mg (0.57 mmol, 27 %).

^{1}H NMR (400.13 MHz, C_6D_6) δ 7.49 (d, J = 7.3 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.19 (d, J = 7.3 Hz, 1H), 5.18 (dd, J = 10.0 Hz, 8.3 Hz, 1H), 4.38 (dd, J = 10.8 Hz, 8.3 Hz, 1H), 3.93 (t, J = 8.3 Hz, 1H), 2.11-1.70 (m, 12H), 1.59 (s, 3H), 1.54-1.31 (m, 10H), 1.02-0.92 (m, 2H), 0.84-0.78 (m, 1H); ^{13}C NMR (100.67 MHz, C_6D_6) δ 169.6 (d, $^3J_{CP}$ = 2.9 Hz), 143.9, 128.6 (+, 2C), 127.44 (+), 127.40 (+), 127.3 (+), 74.6 (-), 70.5 (+), 35.1 (d, $^1J_{CP}$ = 13.9 Hz, +), 34.7 (d, $^1J_{CP}$ = 11.7 Hz, +), 31.2 (d, J_{CP} = 16.1 Hz, -), 30.9 (d, J_{CP} = 17.6 Hz, -), 29.6 (d, J_{CP} = 8.9 Hz, -), 29.5 (d, J_{CP} = 6.6 Hz, -), 27.9-27.6 (m, -, 5C), 27.0 (d, J_{CP} = 2.9 Hz, -), 23.0 (+), 22.2 (d, $^1J_{CP}$ = 22.0 Hz, +), 20.0 (d, $^2J_{CP}$ = 7.3 Hz), 18.6 (d, $^2J_{CP}$ = 7.3 Hz, -), ^{31}P NMR (161.98 MHz, C_6D_6) δ -4.02; α_D^{25} -116.7^o (c 1.00, CH_2Cl_2); HRMS (TOF ES) Calculated for $C_{25}H_{37}NOP$ (M+H) 398.2613, Found 398.2604 (2.3 ppm).
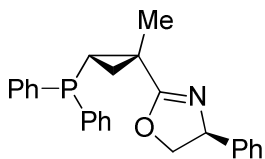
L6: was prepared in a similar manner from 666 mg (2.38 mmol) of (4S)-2-[(1S,2S)-2-bromo-1-methylcyclopropyl]-4-phenyl-4,5-dihydro-1,3-oxazole (**27**). Purification of the final product by preparative column chromatography was performed in a nitrogen-filled glove box using degassed Silica gel and CH_2Cl_2/EtOAc (40:1) as an eluent. Yield 354 mg (0.92 mmol, 39 %).

^{1}H NMR (400.13 MHz, C_6D_6) δ 7.73-7.64 (m, 4H), 7.44-7.42 (m, 2H), 7.31-7.15 (m, 9H), 5.07 (dd, J = 10.1 Hz, 8.3 Hz, 1H), 4.27 (dd, J = 10.1 Hz, 8.1 Hz, 1H), 3.85 (ps.-t, J = 8.3 Hz, 8.1 Hz, 1H), 1.98 (ddd, $^2J_{PH}$ = 12.9 Hz, J = 6.8 Hz, 4.6 Hz, 1H), 1.58 (d, $^4J_{PH}$ = 1.5 Hz, 3H), 1.46 (ddd, $^3J_{PH}$ = 6.1 Hz, J = 9.1 Hz, 6.8 Hz, 1H), 0.93 (ddd, $^3J_{PH}$ = 7.3 Hz, J = 9.1 Hz, 4.6 Hz, 1H); ^{13}C NMR (100.67 MHz, C_6D_6) δ 169.1 (d, $^3J_{CP}$ = 3.7 Hz), 143.5, 141.0 (d, $^1J_{CP}$ = 11.7 Hz), 140.1 (d, $^1J_{CP}$ = 12.4 Hz), 133.6 (d, $^2J_{CP}$ = 19.8 Hz, +, 2C), 132.2 (d, $^2J_{CP}$ = 17.6 Hz, +, 2C), 128.8 (d, $^3J_{CP}$ = 8.8 Hz, +, 2C), 128.7 (d, $^3J_{CP}$ = 10.3 Hz, +, 2C), 128.7 (+), 128.6 (+, 2C), 128.1 (+), 127.4 (+, 2C), 127.3 (+), 74.7 (-), 70.4 (+), 26.8 (d, $^1J_{CP}$ = 11.7 Hz, +), 22.9 (d, $^3J_{CP}$ = 1.5 Hz, +), 22.4 (d, $^2J_{CP}$ = 7.3 Hz), 18.9 (d, $^2J_{CP}$ = 11.0 Hz, -); ^{31}P NMR (161.98 MHz, C_6D_6) δ -9.03; α_D^{25} -178.7^o (c 1.25, CH_2Cl_2); HRMS (TOF ES) Calculated for $C_{25}H_{25}NOP$ (M+H) 386.1674, Found 386.1680 (1.6 ppm).

X-Ray crystallography data from Pd(**L1**) and Pd (**L4**) complexes are detailed in the appendix.

Chapter 2. Asymmetric Hydroformylation of Styrenes

2.1. Introduction

2.1.1 Rhodium Catalyzed Hydroformylation

Hydroformylation, also known as oxo synthesis, is an important industrial process for the direct transformation of olefins into aldehydes. This chemical reaction entails the transition metal-catalyzed addition of a formyl group (CHO) and a hydrogen atom to a carbon-carbon double bond.[42,43] Many of the early examples of this process made use of stoichiometric amounts of metals such as cobalt and manganese. Otto Roelen first described his cobalt catalyzed "oxo" reaction toward the end of the 1930's.[44] Since the discovery of the reaction, much has been done to advance the state of the art of this important process which is still being actively investigated by many research groups around the world.

The first examples of rhodium catalyzed hydroformylations were published toward the middle of the 1960's.[45] In these studies, $RhCl_3$ and Rh/Al_2O_3 showed significantly higher catalytic activity under milder conditions than did the analogous cobalt catalysts,[43] which justified the transition to rhodium catalysis for this class of reactions in most of the further applications in spite of the higher cost for Rh-complexes.

Hydroformylation was significantly advanced by the discovery that the addition of phosphine ligands on the rhodium greatly enhanced the rate and

corresponding yields of the reactions. An early example of utilizing a phosphorus containing ligand in rhodium catalyzed hydroformylations is documented in a patent issued to the Shell Oil Company in 1966.[45] It was noted in this patent that $RhCl_3$ in the presence of tributylphosphine gave reasonable conversions of 1-pentene to the corresponding aldehydes while a similar system devoid of the phosphine resulted in no conversion.

Wilkinson was instrumental in bringing rhodium catalysis to the forefront of hydroformylation through his discovery that arylphosphine ligands further activate the metal and make the process proceed under much milder conditions than were previously known.[46]

Around the same period that Wilkinson was investigating the effects of arylphosphines on hydroformylation, Pruett, a chemist working at Union Carbide, found phosphite ligands are also capable of affecting the reaction.[47] By varying the steric and electronic nature of the phosphites, Pruett was able to fine tune the reaction and successfully demonstrated higher conversions in some cases than had been previously reported by Wilkinson.

Pruett's and Wilkinson's investigations were primarily focused on different classes of monodentate phosphorous-containing ligands. However, in other metal-catalyzed processes there was beginning to be a shift away from monodentate ligands toward ligands capable of binding to a metal center in multiple coordination sites. These new ligands began appearing in processes such as asymmetric hydrogenation, but it was not until later that these ligands began to be used in asymmetric

hydroformylation. Many of the bidentate ligands currently used in hydroformylation began as hydrogenation ligands. It was not until the 1980's that bidentate phosphorus ligands became mainstream in rhodium catalyzed hydroformylation.

2.1.2 Mechanism/Mechanistic Discussion

The general mechanism of rhodium-catalyzed hydroformylation[43] is depicted in Scheme 16. The process begins with the coordination of the olefin as an $^2\eta$-ligand to the rhodium hydride species **28** (**LE^1**), followed by a migratory insertion or hydrometallation of the olefin into the metal-hydrogen bond (**MI^1**). Regiochemistry of this migratory insertion determines the outcome of the reaction. Thus, new carbon-metal bond can be installed either at the terminal position of the olefin (path **A**), leading to alkylmetal complex **30**, and ultimately to the linear aldehyde. Alternatively, installation of metal-carbon bond at the internal position (path **B**) results in formation of complex **34**, which provides the branched aldehyde. Hydrometallation (**MI^1**) is followed by coordination of a CO-ligand onto the metal center (**LE^2**) to form complexes **31** and **35**, after which migratory insertion of CO into the C-Rh bond (**MI^2**) provides acylrhodium species **32** and **36**, respectively. Insertion of the metal into a molecule of H_2 (**OA**) followed by reductive elimination (**RE**) yields the product aldehydes and regenerates the Rh-H active catalyst.

Scheme 16. Mechanism of Hydroformylation
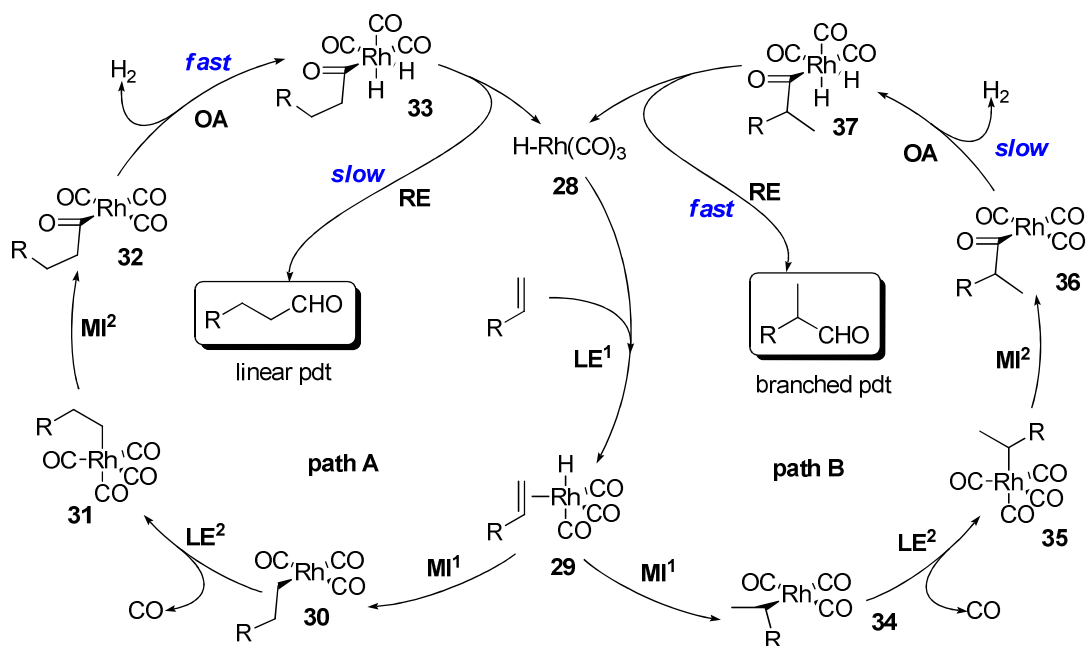
The rate determining step of each one of the pathways depicted in Scheme 16 has a different rate depending upon the steric environment surrounding the metal center. In the case of pathway **A** (the linear product), oxidative addition of the metal into H_2 is significantly more facile than that of the metal species associated with the same step in pathway **B**. This phenomenon can be explained by the different steric environments of the metal in the two key intermediate acyl complexes **33** and **37** (Scheme 16). In pathway **A,** the primary alkyl substituent in species **33** results in a significant decrease in the steric environment around the metal center compared to complex **37**, which possesses a secondary alkyl group. Accordingly, associative process **OA**, proceeds much faster, when it leads to less sterically hindered species **33** (path **A**) compared to a similar process resulting in a more encumbered species **37**

(path **B**). On the other hand, a dissociative process, such as reductive elimination (**RE**), is also sensitive to sterics. At this step, however, the steric driving force of the reaction producing the linear product from species **33** (path **A**) is lower compared to the analogous process, providing branched product from species **37** (path **B**). Accordingly, the kinetic rate of the latter process is higher.

In addition to changing the steric environments around the metal, the relative rates of the reaction can also be controlled by changing the effective concentration of either CO or H_2 present in the system. According to the rate equation shown in Scheme 17, the rate of the reaction is directly proportional to the partial pressure of H_2 while it is inversely proportional to the concentration of CO. This is because 16-electron acylrhodium complexes **32**,**36** in the presence of excess CO form catalytically inactive 18-electron species **38** (Scheme 17), inhibiting oxidative addition of hydrogen (**OA**). When a bulky phosphine ligand is present on the metal center **39**, the slow step of the catalytic cycle becomes the ligand exchange **LE**[1] of a CO for the olefin. This is due primarily to the increased sterics around the metal center that comes with the presence of the phosphine ligand. Also, increased steric demand renders the formation of the branched alkylrhodium species **41** unfavorable, and the fast reverse β-hydride elimination process shuts down the channel for formation of the branched product, resulting in significantly improved regioselectivity favoring linear product **40**. For α-olefins possessing allylic C-H bonds, β-hydride elimination in an alternative direction is possible, leading to the formation of

isomerized internal olefin byproduct, which is inactive in catalytic hydroformylation under normal reaction conditions.

Scheme 17. Relative Rates of Reaction
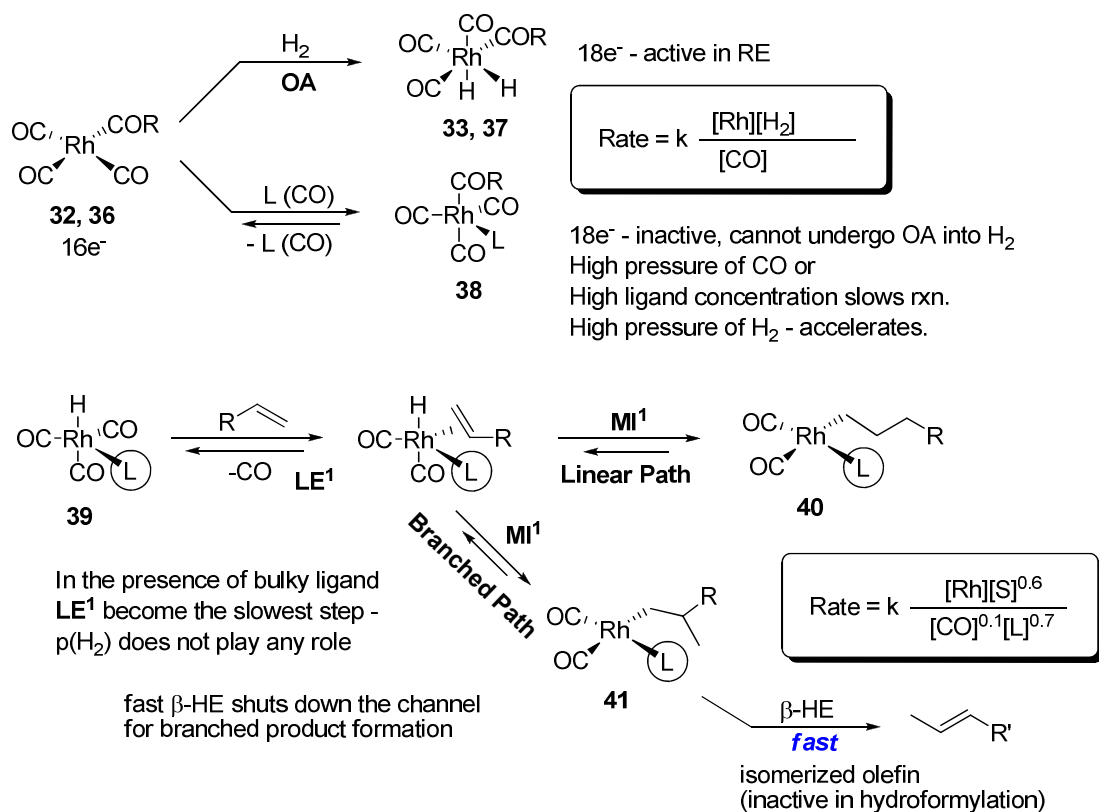
The enantioselectivity of the reaction is governed primarily by steric factors in the asymmetric environment created by the chiral ligands bound to the metal center. Steric bulk on the metal restricts the orientation in which the substrate coordinates to the metal in such a way as to allow a minimum number of favorable diastereomeric complexes. By changing the structure of the ligands on the metal, the chiral pocket can be finely tuned to require substrate orientation in a single fashion for each iteration of the catalytic cycle resulting in the formation of a single enantiomer. An

example of how the asymmetric control could be realized in Rh-catalyzed hydroformylation of styrene in the presence of chiral phosphinoxazoline ligand is shown in Figure 2. The favorable orientation of the olefin substrate in the trigonal bipyramidal Rh(I) complex is such that it minimizes any unfavorable steric interactions. The approach of the styrene molecule to the catalytically active rhodium species from the North-West (Figure 2, model I), ultimately resulting in the formation of linear aldehydes, would be accompanied by significant steric interactions between the phenyl ring of the styrene and the aromatic group on the phosphine ligand. These interactions are visualized on the model as a break in the mesh representing the solvent accessible surface of the ligand. In a similar manner, upon North-East approach, which would also result in formation of linear product, (Figure 2, model II), the steric hindrance is experienced between the phenyl group of the styrene and the phenyl substituent on the oxazolidine. As the result, the amount of linear product formed is diminished. The approach from the South-West (Figure 2, model III), is the most favorable, as there is very little unfavorable steric interaction between the substrate and the bidentate ligand on the metal, accordingly the (*S*)-enantiomer of the branched product formed from this approach is the major product in the reaction. Finally, approach from the South-East (Figure 2, model IV) is accompanied by a significantly more unfavorable interaction compared to model III, resulting in formation of minute amounts of the branched product with opposite absolute configuration (*R*). While the example below (Figure 2) on the origins of enantioselectivity in this reaction uses a specific oxazolidinone ligand, it is believed

the same rationale governs the enantioselectivity of rhodium species in the vast majority of catalytically active, bidentate rhodium species used in the hydroformylation of olefins.
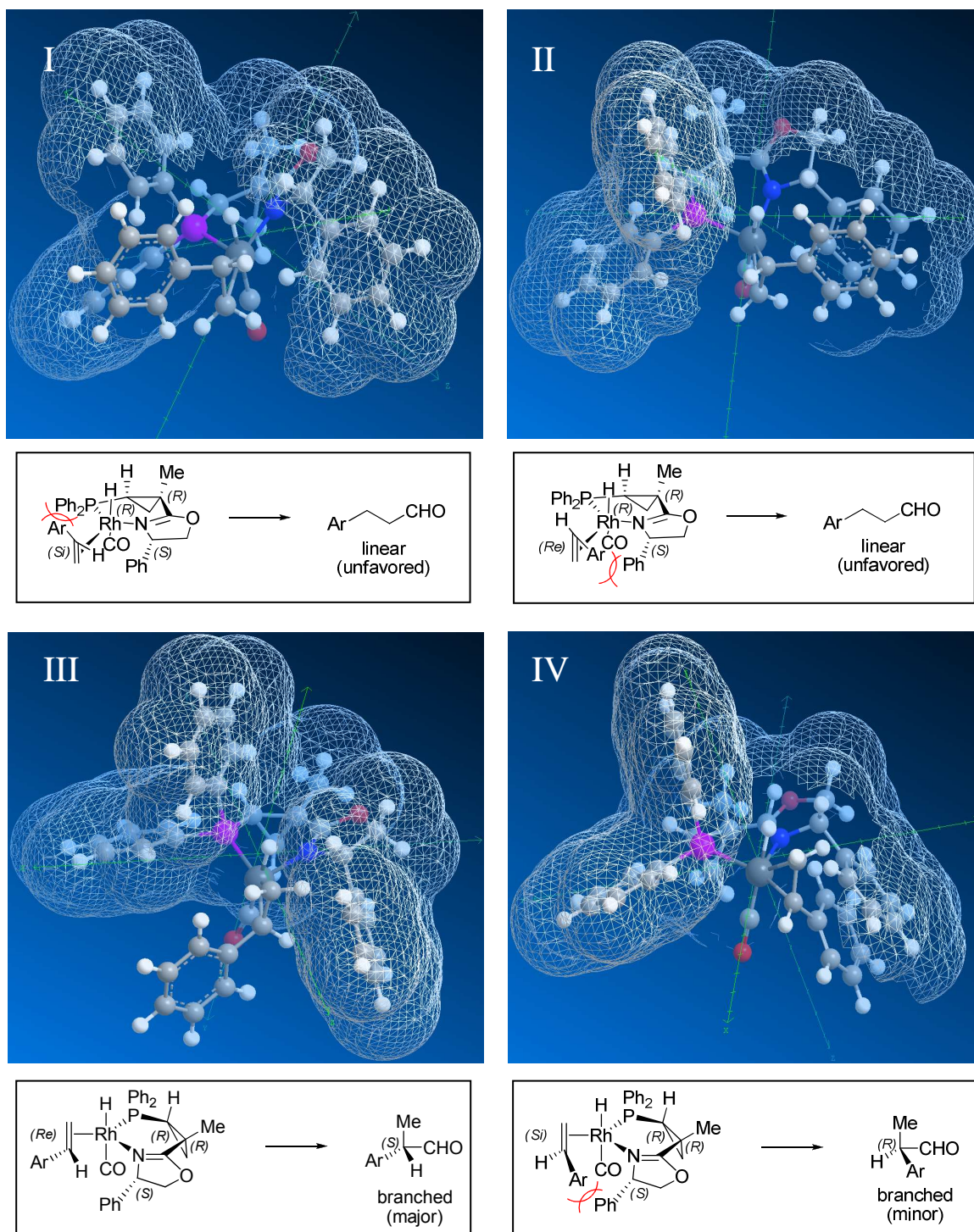
Figure 2. Enantioinduction in Rh-catalyzed asymmetric hydroformylation reaction in the presence of chiral ligands.

2.2 Ligands/Accomplishments in Asymmetric Hydroformylation

2.2.1. Phosphine-Phosphites

The members of this class of ligands for asymmetric hydroformylation are the highest performing yet discovered. (*R*,*S*)-BINAPHOS **42** (Figure 3) is the current benchmark standard in this process as it exhibits not only high selectivity, but is also effective on a wide array of substrates making it one of the most useful chiral ligands to aid in this transformation.

42
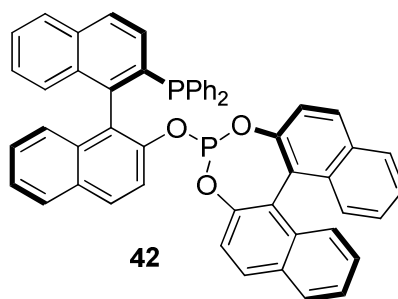
Figure 3. (*R*,*S*)-BINAPHOS

A significant advancement in the technology of asymmetric hydroformylation was made by Takaya in 1993.[48] He synthesized a novel class of phosphine-phosphite ligands that revolutionized the way asymmetric hydroformylations were performed. Prior to the discovery of (*R*,*S*)-BINAPHOS in 1993, the best ee's from all the known rhodium catalyzed asymmetric processes had been no higher than 60 %.[42] The ligand was extraordinary not only in the ee's it produces out of the process but also due to

the ease of preparation. Starting from optically active 1,1'-binaphthalene-2-2'-diol

BINAPHOS can be obtained on a preparative scale in three high yielding steps

(Scheme 18). In the seminal paper, asymmetric hydroformylation of a variety of

substrates ranging from vinyl acetates to substituted styrenes gave ee's ranging from

73 – 95 %.[48,49]

Scheme 18. Preparation of (*R*,*S*)-BINAPHOS
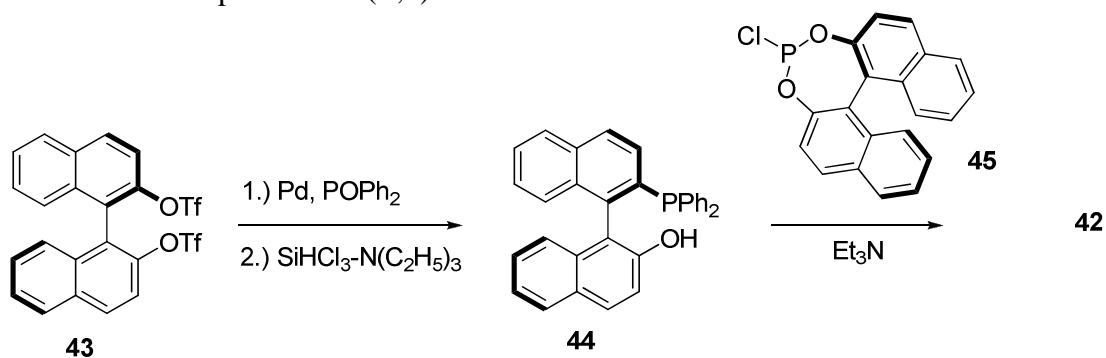
A recent trend in the hydroformylation of olefins has been the immobilization

of the catalyst using polymer bound chiral ligands. This keeps the catalyst bound to

the polymer support and facilitates its easy separation and recovery while not

necessarily adversely affecting the outcome of the reaction. Hiyama successfully

bound BINAPHOS to polystyrene linkers to create a polymer bound version of the

Rh-BINAPHOS catalyst.[50] He observed there was little difference when the ligand

was linked into the polymer in a single place (**46,** Figure 4) between first complexing

the metal to the ligand followed by polymerization or in first polymerizing the ligand

and then complexing the metal to it.
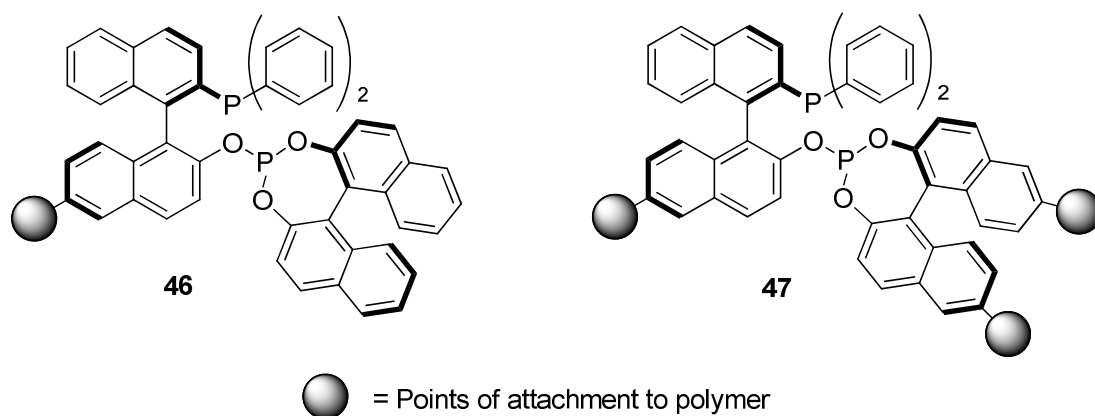
Figure 4. Polymer Bound Ligands

The only marked difference came when there were three points of attachment between the ligand and polymer **47** (Figure 4). In that case, where polymerization occurred prior to the complexation of the metal, significant loss of enantioselectivity was observed. This is due to the loss of flexibility in the ligand that is tethered in three positions. Since it can no longer flex to reach the optimum orientation with respect to the metal center, there is a corresponding decrease in the enantioinduction. When the metal is complexed prior to the polymerization of the ligand, there is little change in the ee, since the ligand is able to orient itself prior to being incorporated in the polymer. These polymer bound ligands were then applied to solventless hydroformylation using vapor phase techniques and the results were promising. Not only were the selectivities in the reaction high, the authors also demonstrated the reusability of the catalyst by running subsequent hydroformylation batches with the

same catalyst and a variety of olefins. The drawback to this process is the percent conversion. The branched-to-linear (B:L) ratio is normally high as is the ee, but the typical conversions are less than 50 %.[51] BINAPHOS has been successfully applied in the asymmetric hydroformylation of a wide range of substrates including enol ethers.[52]

Variations of BINAPHOS have been developed including a class of ligands containing perfluorinated alkyl pony tails for the use in supercritical CO_2 ($scCO_2$) or perfluorinated solvents. Ligand **48** (Figure 5) gave 73 % conversion with a 91:0 B:L and > 82 % ee employing perfluorinated toluene as the solvent.[53]
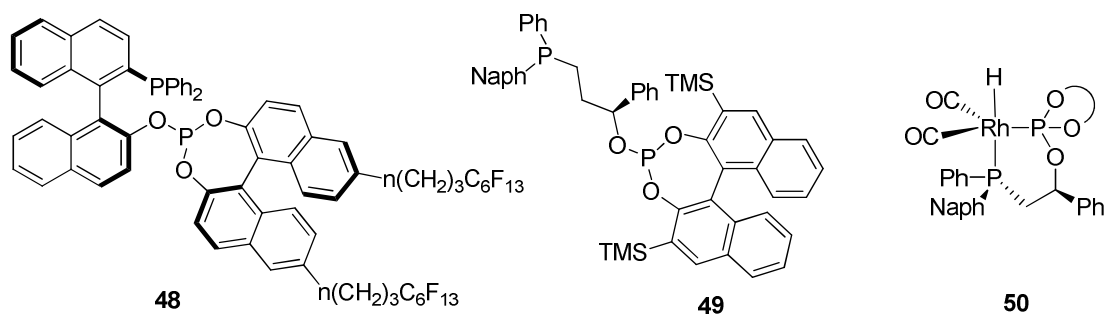
Figure 5.

The binding orientation of the BINAPHOS to the metal center is one of the keys to its success as a chiral ligand. In 2000, a derivative of BINAPHOS was reported (**49**) in which a remote chiral center was incorporated into an alkyl tether (Figure 5). It was hypothesized that ligand **49** would operate in a fashion similar to

BINAPHOS and due to the increased sterics at the remote site could potentially result in an enhancement of enantioselectivity. However, a decrease in the enantioinduction of the catalyst was observed, and upon closer inspection it was found to be due to the increased sterics of the remote chiral center, the new ligand coordinated to the Rh in reverse fashion compared to how BINAPHOS is known to bind. In the case of the Rh complex **50** (Figure 5) formed from ligand **49,** the phosphite moiety is bound in the equatorial position while the phosphine is bound apically. The resulting catalytic system gave moderate conversions (~ 50 %), moderate B:L ratios (~ 10:1) and moderate ee's (~ 50 %). This is in direct contrast to BINAPHOS which typically gives excellent results.[54]

2.2.2. Diphosphines

One of the interesting phenomena observed with the use of bidentate ligands is the effect the ligand bite angle has on not only the regioselectivity of the catalytic cycle, but on the enantioselectivity as well. Whiteker and his colleagues discovered there is indeed a documentable relationship between the outcome of the reaction and bite angle of the ligand. They determined ligands with a more flexible backbone, allowing for a smaller bite angle, yielded higher branched selectivity and a higher enantioselectivity as well, but they also concluded the optimum ligand for each process is greatly dependent upon the identity of the substrate itself.[55] It has also been observed for diphosphine ligands that the selectivity of the reaction is related to both the size of the metallacycle formed from the ligand and the metal as well as the

concentration of the ligand present in the system. For ligands forming five-membered metallacycles it has been observed that a decrease in the concentration of the ligand favorably affects the outcome of the reaction, while for ligands forming a six-membered cycle the process benefits from an increase in the ligand concentration. This difference is believed to arise from the equilibrium established between species **51** and **52** in Figure 6. Species of type **51** are known to be present in Rh/P ligand systems and they have been characterized for the (*S,S*)-2,4-bis(diphenylphosphine)pentane (bdpp) ligand.[56] It is believed an excess of additional phosphine ligand shifts the equilibrium in favor of **52** which, in turn, makes coordination to the olefin significantly more difficult. Since enantio- and regiodifferentiation in the reaction take place at the stage of coordination of the olefin substrate, any modifications to the ligand sphere on the metal during this event would drastically affect the selectivities of the reaction. Since its unfavorable sterics would prevent coordination of the olefin to a Rh species of type **52,** the active species in the catalytic cycle in the case of increased phosphine ligand concentration is proposed to be **53** where one of the arms of the bidentate ligand has been replaced with another phosphine (Figure 6). Existence of this equilibrium could account for the change in selectivity by varying the metal to ligand ratio.[57]
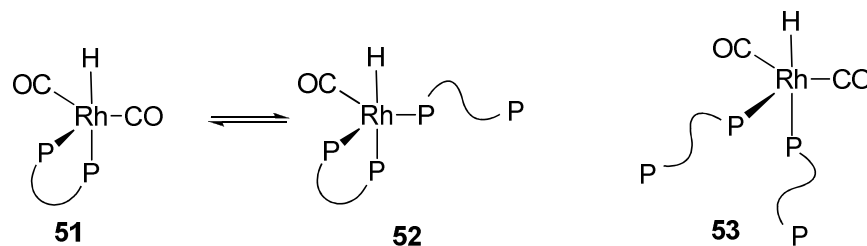
Figure 6.

An example of using a racemic, cationic Rh(I) species in the hydroformylation of a variety of olefins is given by Yamamoto.[58] His group synthesized racemic ligand **54** and prepared cationic complex [Rh(nbd)(**54**)]$^+$ClO$_4^-$ by mixing **54** with Rh(nbd)(acac) in the presence of perchloric acid (Figure 7).   This species was then used in the hydroformylation of substituted styrenes and vinylnaphthalenes in high yields and high branched to linear ratios.[59]
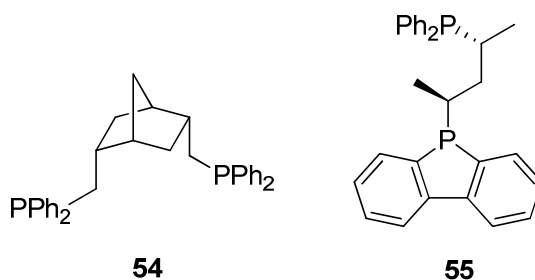
Figure 7.

Bakos and his group successfully demonstrated the use of a C$_1$-symmetric diphosphine ligand **55** in the hydroformylation of styrene. This reaction afforded a branched to linear ratio of 92/8 although their conversions and ee's were moderate

(57 % conv., 47 % ee).[60] An early example of the employment of an achiral diphosphine comes from a comparative study between the activity and selectivity of a Rh complex from bis(diphenylphosphino)ethane (dppe) to that of an active species formed from triphenylphosphine (tpp). It was determined the complex with dppe tended to give lower branched to linear ratios than the analogous tpp complex. A build-up of a significant amount of internal olefin by-product in the hydroformylation of linear α-olefins in the presence of dppe revealed the ability of the dppe complex to promote the isomerization of the alkene. This was explained by more difficult coordination of CO to the metal center in the presence of chelating dppe-ligand; moreover, the corresponding sterics-driven β-hydride elimination becomes more facile resulting in the formation of isomerized olefinic products.[61]

2.2.3. Pholanes

This is a class of ligands which has generated a significant amount of interest in the last few years. This is largely due to one member of this class (*R,R*)-phenyl-bis-phospholanoethane (Ph-BPE **56**, Figure 8). This ligand was discovered by Zanotti-Gerosa, from the Dow Chemical Company and was first reported as an asymmetric hydrogenation ligand in 2003.[62] In 2005, it was reported to be active in the asymmetric hydroformylation of styrenes.[63,64] Ph-BPE is one of the few challengers which can compete with the numbers chemists have been generating with BINAPHOS over the last fifteen years. This ligand is finding increased use not only in the AHF of styrenes and other vinyl arenes, but also with such functionalized

alkenes as allyl cyanides and vinyl acetates. Klosin and co-workers have demonstrated the versatility of the ligand by conducting concurrent hydroformylation experiments on the mixture of three substrates; styrene, allyl cyanide, and vinyl acetate. Under the conditions they describe, they were successfully able to demonstrate the AHF of all three substrates in excellent conversion, B:L ratio and ee.[65] Due to its high enantioselectivity, substrate scope, and faster kinetic rate than BINAPHOS, this is the ligand chosen to be the benchmark for the ligand screening experiments described in the coming sections.
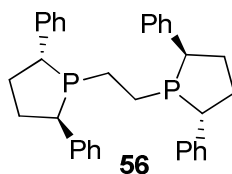
Figure 8. (*R,R,R,R*)-Ph-BPE

2.2.4. Diphosphinites.

This class of ligands has been used in asymmetric hydrogenation[66] and hydroboration,[67] but only recently has their use in asymmetric hydroformylation been evaluated. While a substantial amount of work has been done to determine the potential of this class of ligands, thus far, the demonstrated activities and selectivities are inferior when compared to the diphosphine class of ligands.

Some recent work by Claver has demonstrated the usefulness of chiral diphosphinites in the asymmetric hydroformylation of styrenes. His design is based

on using furanoses as modular scaffolds for the preparation of their sugar based ligands. They successfully demonstrated the use of two of these ligands (**57,58**) on a number of different olefins giving moderate yields albeit with quite low enantioselectivities. The outcome of the reaction depended heavily on the nature of the substrate. Thus, with styrene and its derivatives the enantioselectivity of the reaction was very poor; however, for vinylnaphthalenes the enantioselectivities improved greatly.[68] In the case of ligand **59**, conversions of substituted styrenes up to > 80 % with excellent regioselectivity and ee's > 78 % were achieved.[69]
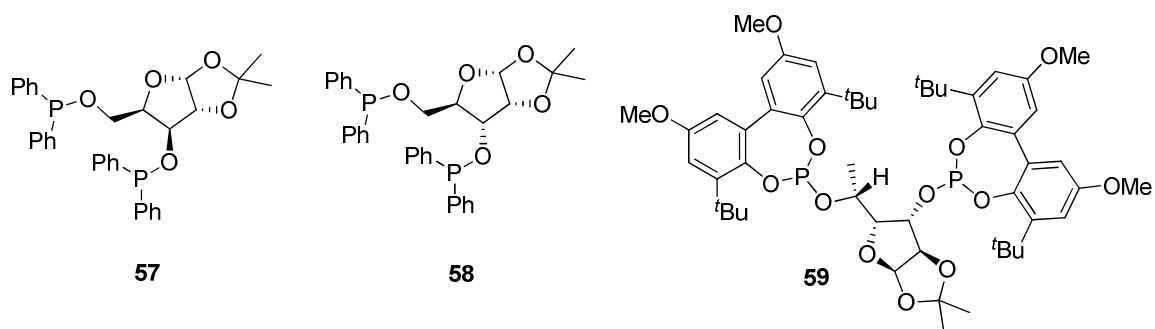
Figure 9.

2.2.5. Diphosphites.

This class of ligand suffers from many of the same drawbacks which plague the diphosphinites. Work done by Sunchi demonstrates diphosphites which are tethered together through a binaphthyl type moiety **60** (Figure 10) give excellent conversions (> 99 %) and very high branched to linear ratios (> 75 %), albeit with marginal enantioselectivities.[70]
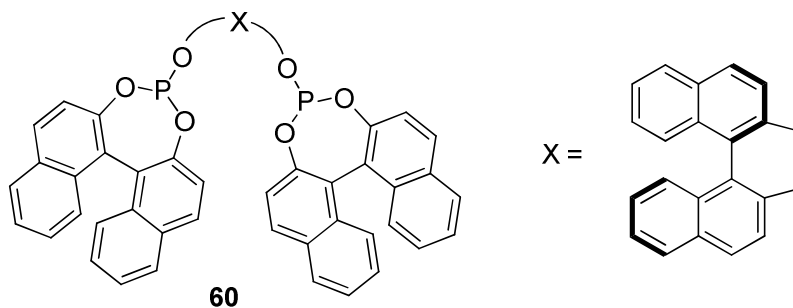
Figure 10.

Furanoside based diphosphinite ligands originally appeared to offer significant advantages over other diphosphinites. While many phosphinites suffer from low ee's, the furanoside based diphosphite ligand **59** (Figure 9) seems to offer excellent conversions, regioselectivity, and respectable ee's > 78 %.[69] Unfortunately, this ligand seems to be the exceptional example as a subsequent paper published by the same authors included the screening results of fifteen novel furanoside ligands. All of the new ligands paled in comparison to **59**. The authors explained these results based on the coordination of the ligands to the metal. Based on the authors' observations, they determined ligands binding in a bis-equatorial fashion exhibited significantly higher ee's than ligands binding in the equatorial-axial fashion.[71]

2.2.6. P,N-Type Bidentate Ligands

This is a rather broad class of hydroformylation ligands that includes aminophosphines, aminophosphine-phosphinites, phosphine-phosphoramidites. A library of nine different P-chiral ligands was synthesized and tested in the AHF of

styrene in order to evaluate the effect of bringing the ligand's center of chirality as close to the metal as possible. It was found that ligand **61** (Figure 11) was able to give a B:L of 98:2 and an ee of 75 %. This is in direct comparison to (*R*,*S*)-BINAPHOS which under the same reaction conditions was found to yield an ee of 92 %. Complete conversion of the olefin was achieved by allowing longer reaction times, and the authors did not note any appreciable deterioration in the final ee of the product.[72]

61
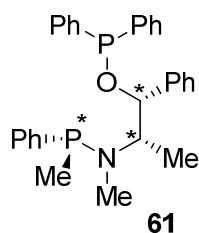
Figure 11.

An extension of the furanoside chemistry discussed previously (Figure 9) is the development of phosphite-phosphoramidite ligands based upon the naturally occurring carbohydrate D-(+)-xylose. These ligands are easily prepared from naturally occurring furanosides and the desired chlorophosphines. This type of ligand falls well short of the performance characteristics of the phosphine-phosphite furanosides. The conversions were reasonable at ~ 70 % with excellent B:L ratio > 96 %, but the enantioselectivity of this type of ligands is significantly lacking. The highest ee obtained with a ligand of this type was 65 % with a conversion of 12 % while the average ee of a reaction with a reasonable conversion was ~ 20 %.[73]

2.2.7. Applications of asymmetric hydroformylation

There are a number of reasons catalytic, asymmetric hydroformylations have become increasingly attractive recently. One of the biggest drivers behind this surge comes from the ability to use this process as a key transformation in the synthesis of various non-steroidal anti-inflammatory drugs (NSAIDs). Such common over the counter pain relievers as ketoprofen **62**, ibuprofen **63**, and naproxen **64** (Figure 12) can all be easily synthesized from the hydroformylation of the corresponding vinyl arenes followed by the subsequent oxidation of the chiral aldehydes.

Ketoprofen **62**   Ibuprofen **63**   Naproxen **64**
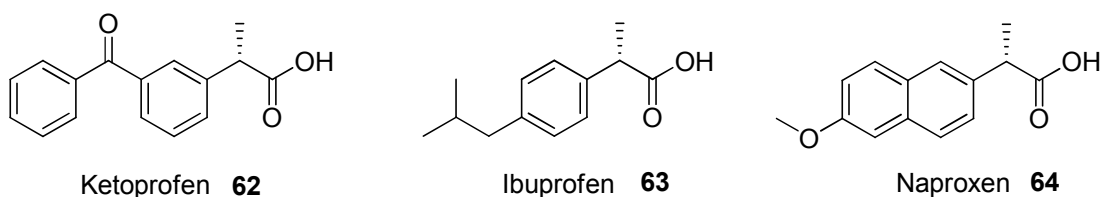
Figure 12.

AHF is also being used in industry as a method for the synthesis of a number of different chemicals which are important to agriculture and fragrances. Recently, AHF was published as a method for obtaining Florhydral® **68**. The investigation began by looking at the possibility of selectively hydroformylating only one of the olefins in 1,3-diisopropenylbenzene **65** to obtain the aldehyde **66** or in the event of dihydroformylation dialdehyde **67**. A mixture of these compounds could potentially be reduced to yield the desired product Florhydral® **68** (Scheme 19).

Scheme 19.
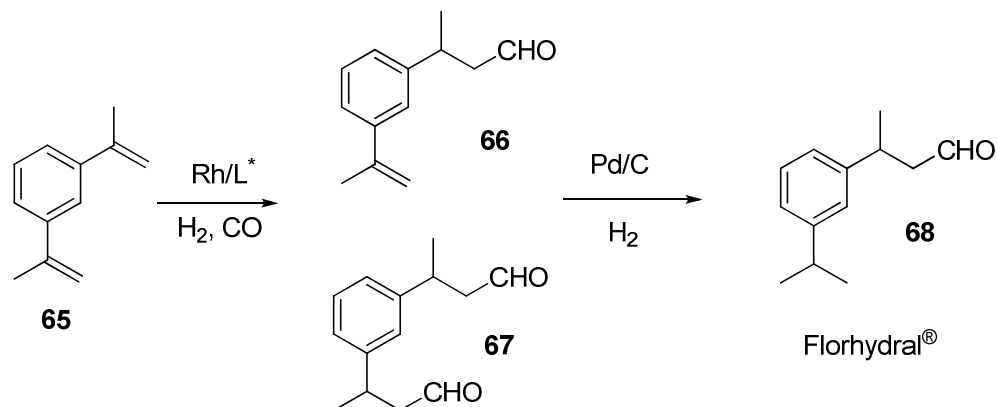
The major challenge associated with the synthetic route outlined in Scheme 19 proved to be finding a set of conditions to optimize the ratio of the products formed in the hydroformylation step. Due to the presence of two olefins in the substrate **65**, the catalyst must produce only the monohydroformylated product **66** in preference to the dihydroformylated product **67**. This proved to be an insurmountable obstacle and resulted in the proposal of a different synthetic route involving the α-methylstyrene derivative **70** having only a single olefin. (Scheme 20.) For the attempted AHF of **70,** three different ligands were screened, (*R*)-BINAP and two representative examples of the JOSIPHOS class of chiral ferrocenyl diphosphine ligands. Unfortunately, none of the three ligands were able to yield anything higher than a 5 % ee although the yield on the transformation was 94 %.[74]

Scheme 20.
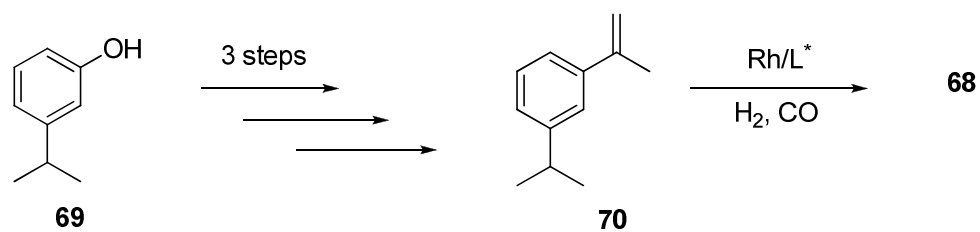
Abboud and co-workers have recently published the synthesis of optically active isoxazolines and imidazoles obtained from the hydroformylation of vinylacetates **71** (Scheme 21).   Using diazophospholane type ligand **72** they successfully demonstrated the AHF of vinylacetate with a 94 % conversion, 29:1 B:L and 96 % ee in scales up to 180 g. These chiral aldehydes were then subjected to a series of synthetic steps finally yielding the chiral isoxazolines **74** and imidazoles **75**.[75]

Scheme 21. Synthesis of isoxazoline and imidazoles
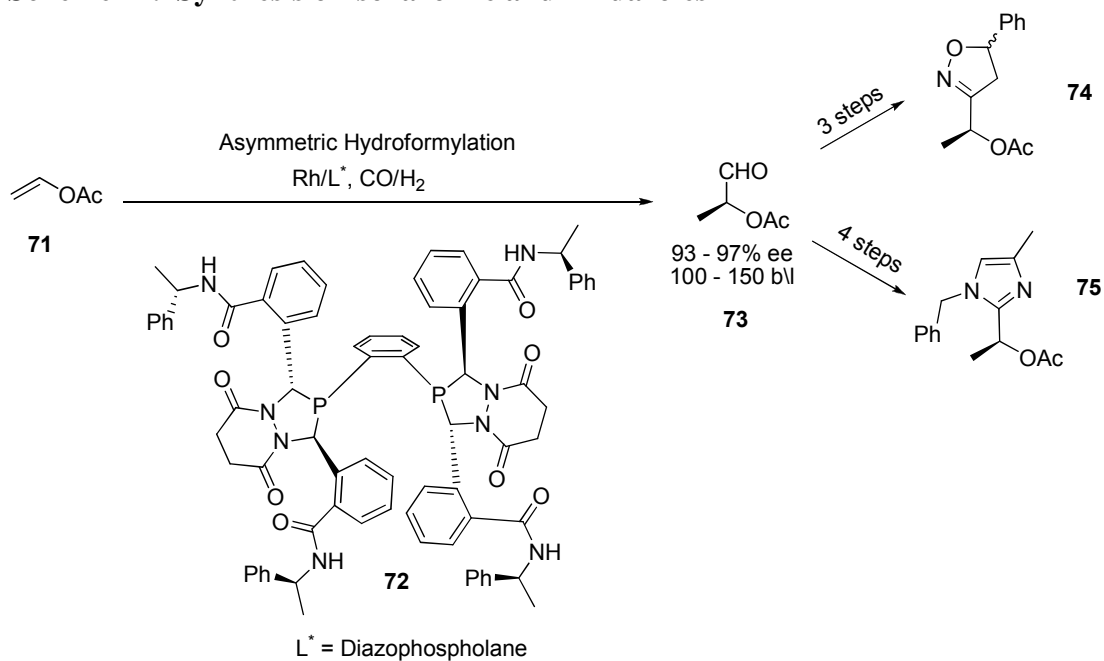
An example of the usefulness of AHF in the preparation of difficult to access biologically active materials is in the synthesis of 1-methylcarbapenem precursors. 1-methylcarbapenem (Scheme 22) is known to have a variety of different biological properties, namely strong anti-bacterial attributes. It is a member of the β-lactam class of antibiotics, one of the most famous of which is penicillin. One of the first attempts to prepare this compound using AHF was done by Nozaki in 1996.[76] In that paper, they described the synthesis using BINAPHOS which resulted in good diastereoselectivity, but the regioselectivity of the reaction (**77,78** to **79**) Scheme 22 was rather poor. Park and co-workers revisited the AHF in an attempt to further optimize the process for use in the preparation of 1-methyl carbapenem precursors (**77,78** Scheme 22). A number of different ligands were screened and it was found

that excellent regio- and diastereoselectivities could be obtained when the ligand was (*S*,*S*)-bis(diphenylphosphino)pentane ((*S*,*S*)-BDPP). This was an important improvement over the results originally obtained by Nozaki as it was also discovered that BDPP is useful in catalyzing this transformation and the regioselectivity issues which were present in Nozaki's protocol can be eliminated based upon the choosing of the proper chiral ligands.[77]

Scheme 22.

1-methylcarbapenem
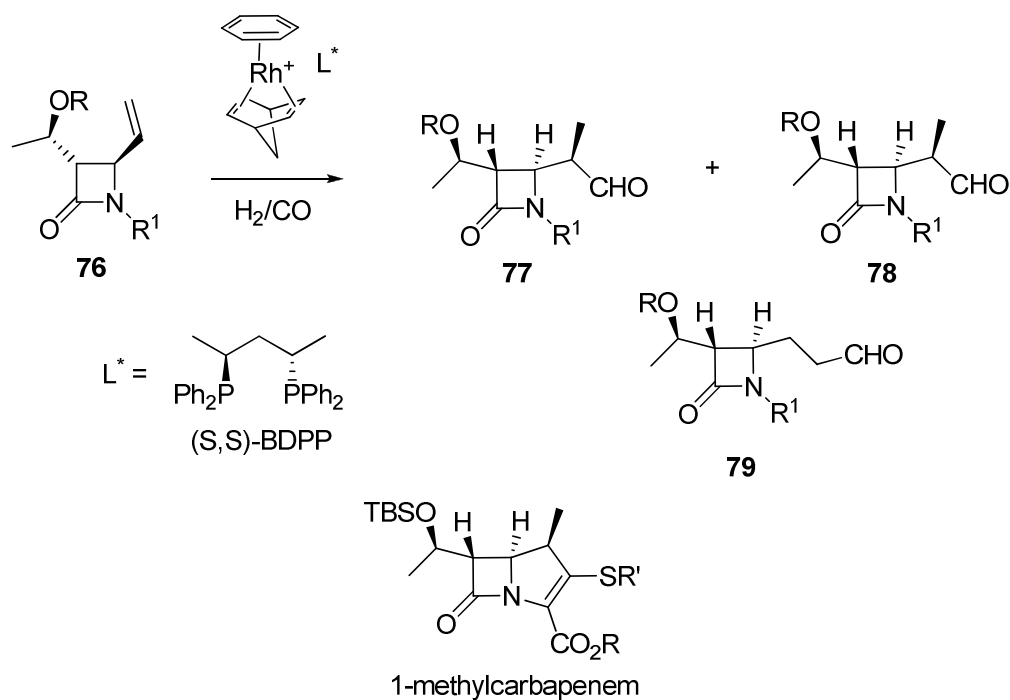
2.2.8. Conclusions

Asymmetric hydroformylation is a powerful tool for the synthesis of chiral aldehydes and their derivatives. A number of classes of chiral ligands have been developed which allow this process to be applicable to a wide array of substrates containing many different functional groups. A lot of effort has been invested into the potential of this method to serve as a convenient way to make NSAIDs such as those shown in Figure 12. The ability to convert various olefins into readily functionalizable, synthetically useful, biologically active compounds is one of the many attractive qualities that have drawn and will continue to draw research efforts into this essential process.

Chiral ligands such as (*R,S*)-BINAPHOS, a member of the phosphine-phosphite class of ligands, and (*R,R*)-Ph-BPE of the phospholane family have demonstrated exceptional B:L ratios while providing high yields and very high enantioselectivities across numerous different substrates under a wide variety of conditions.

2.3. High Throughput Optimization of the Rhodium-Catalyzed Asymmetric Hydroformylation of Styrene

2.3.1. Introduction

Catalytic asymmetric hydroformylation (AHF) of olefins is a powerful synthetic method allowing for simultaneous installation of a stereogenic center and a new C-C bond in a highly atom economic fashion. Synthesis of chiral aldehydes via AHF is very attractive from the standpoint of cost-effectiveness, due to the ready availability of olefins as compared to other substrates used in production of aldehydes.[42,43] However, a number of challenges associated with AHF, such as low reaction rates and problems of simultaneous control of regio- and stereoselectivity, which thus far have been only partially addressed,[78] significantly limit practical application of this method.   Accordingly, a major challenge exists in multidimensional optimization of chemo-, diastereo-, and enantioselectivity, as well as overall catalyst efficiency (or turnover frequency, TOF), which is usually tackled through rational ligand design. Due to the cost-related issues associated with the metals and ligands used in this process, as well as technical requirements for an industrial reactor design, it is essential for the transition metal complex to catalyze this process efficiently while operating at elevated temperatures and low catalyst loadings. However, in contrast to other transition metal catalyzed asymmetric processes, there is general lack of effective and selective chiral ligands suitable for AHF. As it was demonstrated earlier, a few classes of ligands are known to catalyze this process and they include: phospholanes (Chapter 2.2.3.),[79] phosphinites (Chapter

2.2.4.), [80] phosphines (Chapter 2.2.2.), [81] diazophospholine, [82] bis-diazophospholanes,[75,83] phosphine-phosphites (Chapter 2.2.1),[84] and phosphite-phos-phoramidites.[73] Unfortunately, most of them are very substrate-specific, which necessitates empirical optimization of the catalyst and reaction conditions for every given olefin. From this perspective, a high throughput screening method serves as an excellent tool for rapid evaluation of the most promising ligands and optimization of the reaction parameters. Along this line, Klosin recently reported the results of parallel ligand screening, which led to the discovery of a highly efficient and selective catalyst system for AHF of olefins, employing phospholane ligand Ph-BPE (**83**).[79,85,86] To intensify the screening routine, an equimolar mixture of three different substrates was employed in each run. While this approach certainly allows shortening of the screening time, it does not guarantee that the selectivities obtained using mixtures of olefins will be the same as in the reactions with individual alkenes.
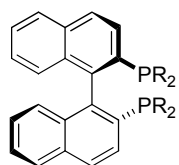
BINAP series
R= Ph   (*R*)-BINAP   (**80**)
R= p-Tol   (*R*)-Tol-BINAP   (**81**)
R= 3,5 xylyl   (*R*)-Xylyl-BINAP   (**82**)
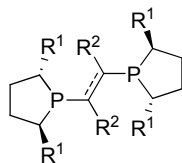
BPE series and related pholanes
R^1= Ph R^2= H$_2$ (*R,R*)-Ph-BPE   (**83**)
R^1= Me R^2= H$_2$ (*R,R*)-Me-BPE   (**84**)
R^1= Et R^2 = H$_2$ (*R,R*)-Et-BPE   (**85**)
R^1= Me R^2= COOCO   catASium m(R) (**86**)
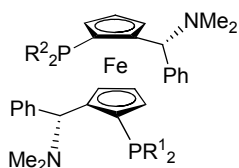
Mandyphos series
R^1, R^2= Ph   M001-1 (**87**)
R^1, R^2= 4-MeO-3,5-Xylyl   M004-1 (**88**)
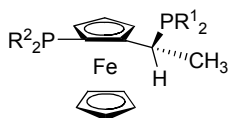
Josiphos series
R^1= Cy, R^2= Ph   SL-J001-1 (**89**)
R^1 = *t*-Bu, R^2 = Ph   SL-J002-1 (**90**)
R^1, R^2= Cy   SL-J003-1 (**91**)
R^1 = 3,5-Xylyl, R^2= Ph   SL-J005-1 (**92**)
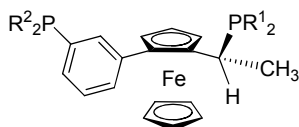
Walphos series
R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$, R^2 = Ph SL-W001-1 (**93**)
R^1 = Ph, R^2 = Ph   SL-W002-1 (**94**)
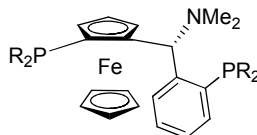
Taniaphos series
R = Ph   SL-T001-1 (**95**)
R = Cy   SL-T002-1 (**96**)
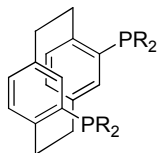
PHANEPHOS series
R= Ph   (*S*)-PHANEPHOS (**97**)
R= 3,5-Xylyl   CTH-(*S*)-Xylyl-PHANEPHOS (**98**)
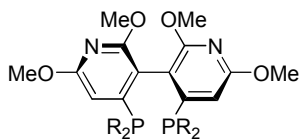
P-PHOS series
R= Ph   CTH-(*R*)-P-PHOS (**99**)
R= 3,5-Xylyl   CTH-(*R*)-Xylyl-P-PHOS (**100**)
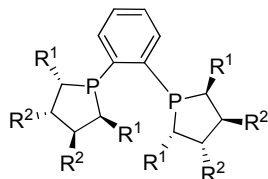
DUPHOS and RHOPHOS series
R^1= Me R^2= H$_2$ (*S,S*)-Me-DUPHOS (**101**)
R^1= Et R^2= H$_2$ (*S,S*)-Et-DUPHOS (**102**)
R^1=Me R^2= OH   SL-P001-2   (**103**)
     (Phosphonium Salt with Triflate)
R^1= *i*-Pr R^2 = H$_2$ (*R,R*) *i*-Pr-DUPHOS (**104**)

R^4= PPh$_2$ R^1-R^3 = H   (R,R)-NORPHOS (105)
R^1 = Me, R^2= 3-diphienylphosphino-2,5-dimethyl-4-thienyl
R^3 = (3,5-Xylyl)$_2$P, R^4 = H   catASium T2 (106)

(S,S)-CHIRAPHOS (107)

CARBOPHOS (108)

(R)-iPr-PHOX (109)

R^1= NHPPh$_2$, R^{2}R^3= (CH$_2$)$_4$ CTH-(R)-BINAM (110)
R^1= PPh$_2$ R^{2}R^3= O(CH$_2$)$_2$O   (R)-SYNPHOS (111)
R^1= PPh$_2$ R^{2}R^3=MeN(CH$_2$)$_2$O   (R)-SOLPHOS (112)
R^1= P(3,5-Xylyl)$_2$ R^{2}R^3 = MeN(CH$_2$)$_2$O   (R)-Xylyl-SOLPHOS (113)
R^1= PPh$_2$, R^{2}R^3 = OCF$_2$O   (R,R)-Difluorophos (114)
R^1= PPh$_2$, R^2 = H, R^3= OMe   SL-A101-1 (115)
R^1= P[3,5-(t-Bu)$_2$-4-MeOC$_6$H$_2$]$_2$,
        R^2= H, R^3= OMe   SL-A109-1 (116)
R^1= PPh$_2$, R^2= Cl, R^3 = OMe   (R)-Cl-MeO-BIPHEP (117)
R^1= PPh$_2$, R^2 = H, R^{3}R^3 = O(CH$_2$)$_3$O   (R)-C3-TUNEPHOS (118)

(S)-BINAPINE (121)

R^1,R^3= OPPh$_2$ R^2, R^4, R^5= H$_2$ CTH-(R)-Spiro-P (119)
R^{2}R^3 = R^{5}R^4 = (CH)$_3$C(PPh$_2$), R^1= H$_2$ (R)-SDP (120)

(R,R)-BINAPHANE (122)

R^1 = CH$_2$PPh$_2$, X= O, Y= CMe$_2$ (R,R)-DIOP (123)
R^1 = PPh$_2$, X= CH$_2$, Y= NBn   catASium d(R) (124)

catASium I (125)

(R,R,S,S)-DUANPHOS (126)

(R,R,S,S)-TANGPHOS (127)

Figure 13. Chiral Phosphine Ligands Tested in the Asymmetric Hydroformylation of Styrenes

Indeed, some olefins, especially those possessing functional groups, might act as co-solvents or ligands, thereby altering the polarity of the reaction media and the coordination sphere of a chiral catalyst. However, the additive effect on the enantioselectivity of hydroformylation has never been systematically investigated.[87]

2.3.2. Results and Discussion

Accordingly, the primary focus of this work was (1) to develop an express screening protocol for the asymmetric hydroformylation reaction that would permit quick and efficient assessment of chiral ligand efficacy; and (2) to evaluate the influence of various reaction parameters on the AHF of olefins using a single olefin substrate. For our studies we selected asymmetric hydroformylation of styrene (**128**) as a model process (Table 7). A ten parallel reactor array was used for screening and the obtained data were analyzed using an automated GC/MS and a chiral GC. All reactions were stopped at 3 h, which significantly accelerated the screening process and permitted direct comparison with literature data.[79,85,86] The initial screening involved testing 48 different commercially available ligands (Figure 13) known to provide high enantioselectivities in the asymmetric hydrogenation[88] of olefins (Table 7). The apparent difference between our results on AHF of styrene as a sole substrate and Klosin's data obtained in the analogous runs carried out with a 1:1:1 mixture of styrene, vinyl acetate, and allylcyanide (provided in parentheses), is noteworthy.

Table 7. Selected Results of Ligand Screening
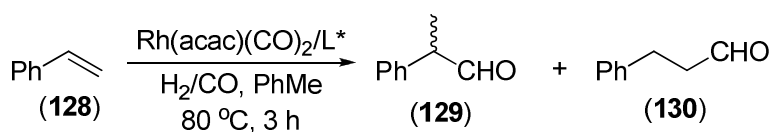
No.	Ligand[a]	ee (%)[b]	X(B)[e]	TOF (h^{-1})[c]	A
1	(**83**)	90 (94)	0.96 (0.98)	759 (740)	656
2	(**86**)	61	0.94	187	109
3	(**87**)	28 (-24)	0.78 (0.85)	473 (470)	106
4	(**88**)	10 (-10)	0.74 (0.87)	220 (150)	17.7
5	(**92**)	40 (38)	0.95 (0.95)	606 (450)	231
6	(**95**)	-42	0.68	251	75.7
7	(**101**)[d]	-33 (-44)	0.62 (0.94)	13 (100)	2.84
8	(**104**)[d]	-30 (-83)	0.57 (0.92)	54 (150)	10.0
9	(**114**)	29	0.77	222	51.4
10	(**124**)	32 (-10)	0.87 (0.95)	139 (240)	39.9
11	(**125**)	16 (-29)	0.74 (0.81)	505 (190)	61.3
12	(**126**)	79	0.93	378	280

[a] Reaction conditions: $Rh(acac)(CO)_2$ (2.9 µmol, stock solution, 0.05 M), ligand (5.8 µmol), octane (internal standard, 2.60 mmol), styrene (8.73 mmol), PhMe (4 mL), syn gas (1:1 $CO:H_2$, 150 psi isobaric); 80 °C; 800 rpm stirring rate. [b] Negative ee's represent predominant formation of the (S)-enantiomer. [c] Literature values given in parentheses (refs 79,85,86). [d] Used the opposite enantiomer to that employed in the comparison literature experiments. [e] Mol fraction of the branched products.
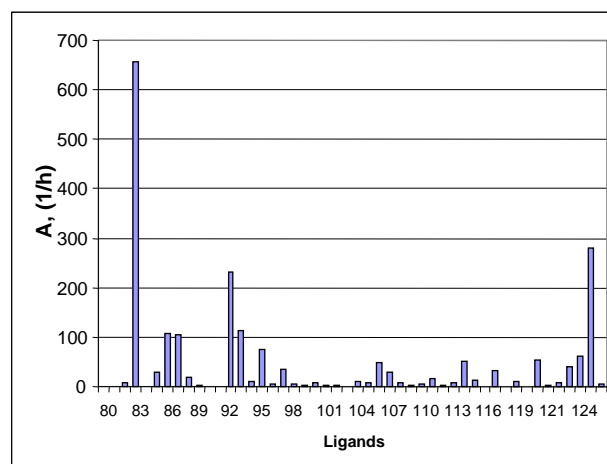
$$A = \frac{\%ee * TOF * x(B)}{100\%}$$

Figure 14. A-values obtained in the ligand screening.

Thus, while the outstanding performance of Ph-BPE (**83**) was essentially reproduced (entry 1), another ligand regarded as potent,[79] ^{i}Pr-DUPHOS (**104**), showed only moderate enantioselectivity in our experiments.[89] Remarkably, in several cases the opposite enantiomer of the branched aldehyde **129** was obtained in our studies (entries 3,4,10,11), compared to that reported by Klosin in his multi-substrate screening protocol,[79,85,86] while using the same enantiomers of the chiral ligands. Conversely, products with the same absolute stereochemistry were obtained in some cases using chiral ligands of the opposite configurations to those reported in the literature[79,85,86] (entries 7,8). The significant discrepancy between our data and the previously reported results strongly suggest involvement of one of the co-substrates, vinyl acetate or allylcyanide, in the stereodifferentiation step of AHF of

styrene in the latter case. This finding prompted us to investigate the solvent effect on the selectivity of AHF. Since three parameters have to be taken into account simultaneously (enantioselectivity, mole fraction of branched product, X(**B**), and TOF, see Figure 14 for equation), a single parameter **A** defined as the product of these three values was introduced, which served as criterion for assessing the overall ligand efficiency (Figure 14). Four chiral ligands have been selected for solvent screening as leads (**86,92,95,126**).[90] Three other ligands (**101,104,124**), which provided significantly different enantioselectivities in our hands (Table 7) compared to the data obtained in the multisubstrate AHF,[79,85,86] were also included in the test. The selected series was screened against 14 different solvents (Figure 15). It was found that the solvent nature had indeed a profound effect on the reactivity and selectivity of the AHF. Interestingly, several ligands demonstrated improved performance in hexane (**104,124,126**). However, due to limited solubility of some rhodium diphosphine complexes, the effective concentration of catalyst in this solvent was affected by other factors, such as reaction temperature and conversion, which led to irreproducible results.

More remarkably, EtOAc appeared to be a superior solvent for many ligands tested, providing comparable or higher values of A than those obtained in toluene (Figure 15). Thus, significant improvement of the reaction efficiency was observed for Taniaphos (**95**), (*R*,*R*)-*i*Pr-DUPHOS (**104**), and catASium® d(R) (**124**) upon switching from toluene to EtOAc (A = 139, 253, 171 vs 76, 10, 40, respectively, Figure 15). Notably, the enantioselectivity and X(**B**) obtained for **104** in EtOAc

(ee = 85 %, X(**B**) = 0.90) were very close to the corresponding values reported by

Klosin[79,85,86] in the AHF of styrene performed in toluene with the olefin mixture (ee =

83 %, X(**B**) = 0.92), which may suggest EtOAc and vinyl acetate indeed have a

similar solvation effect on this hydroformylation catalyst.
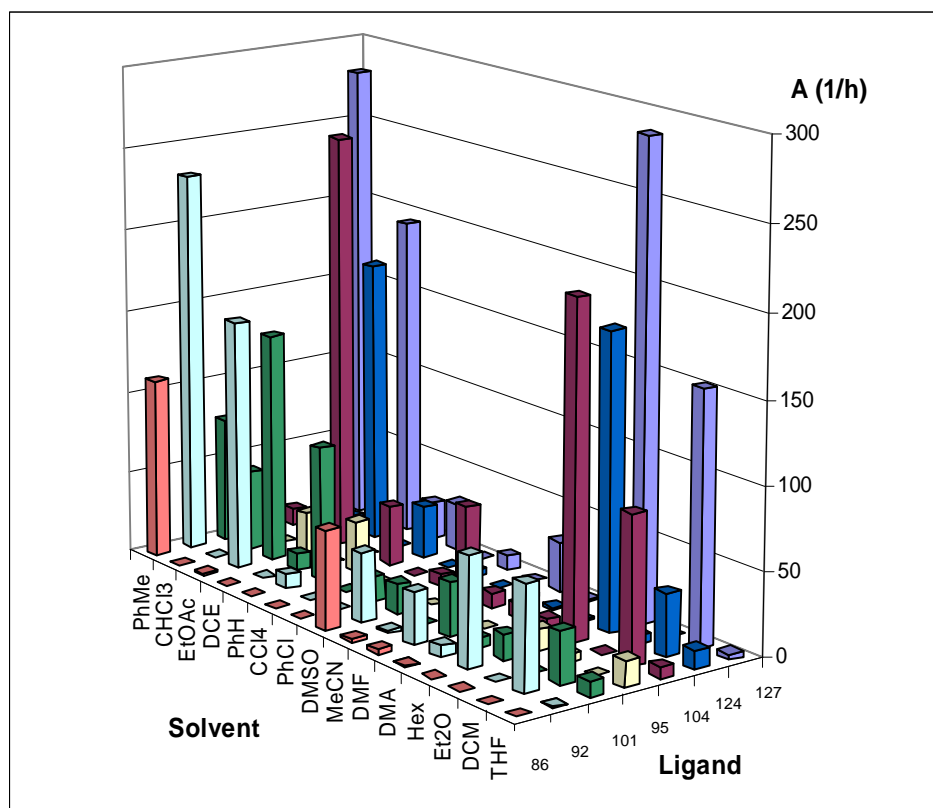
Figure 15. A-values obtained in the solvent screening.

The results of solvent screening demonstrated that a single ligand, (*R,R,S,S*)-

Duanphos (**126**), outperforms all others in both enantioselectivity and regioselectivity

in a range of different solvents although, the TOF attained for this ligand under the

conditions tested remained moderate. This discovery of **126** as a good candidate for the AHF of styrenes is not completely surprising since it is a structural derivative of (*R,R,S,S*)-TANGPHOS (**127**) a ligand which has been demonstrated to be very active the AHF of olefins.[91] The discrepancies between the numbers that were obtained in this study for **127** versus what has been published can be attributed to a difference in the ligand to Rh ratio under our screening conditions. It has been demonstrated that for small, electron rich diphosphines, an increase in the ligand to Rh ratio can have a detrimental effect on the selectivity of the catalytically active species.[86]

With the best ligand-solvent combinations in hand, we investigated whether the efficiency of the AHF catalyzed by Rh-**126** complex could be further improved by adjusting the reaction temperature (Table 8).[92] Screening of this catalyst system in toluene and EtOAc[93] in the range from 50 to 110 °C revealed a similar temperature profile for both solvents (Table 8). Thus, a significant improvement in branched-to-linear ratios, but dramatically decreased reaction rates were observed in AHF in these solvents at low temperatures. In contrast, the enantioselectivities remained essentially unchanged within a wide temperature range and deteriorated only slightly above 95 °C (Table 8). At the same time, the reaction rates reached practical values at temperatures above 80 °C,[94] and nearly complete conversions were observed after 3 h at 110 °C in both solvents (entries 5,10). Although the reactions in EtOAc were somewhat more sluggish than in toluene, the corresponding ee's and branched-to-linear ratios were higher in the former solvent (Table 8).

Table 8. Results of Temperature Screening
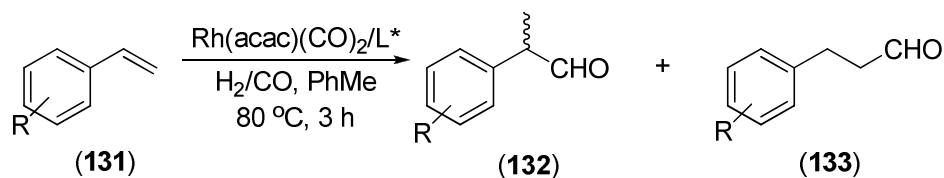
No.	T,°C[a]	(R,R,S,S)-Duanphos (126) in EtOAc				
		%ee	x(B)	Conv., %	TOF, h^{-1}	A, h^{-1}
1	50	87	0.954	1.3	13	10.8
2	65	86	0.943	7.2	72	58.4
3	80	82	0.930	26.3	263	201
4	95	82	0.904	58.3	583	432
5	110	68	0.818	96.8	968	538
(R,R,S,S)-Duanphos (126) in toluene						
6	50	78	0.935	2.0	20	14.6
7	65	80	0.940	8.9	89	66.9
8	80	79	0.930	37.8	378	278
9	95	71	0.888	78.7	787	496
10	110	62	0.815	99.2	992	501

[a] Reaction conditions: Rh(acac)(CO)$_2$ (2.9 µmol, stock solution, 0.05 M), ligand (5.8 µmol), octane (internal standard, 2.60 mmol), styrene (8.73 mmol), solvent (4 M), syn gas (1:1 CO:H2, 150 psi, constant supply), 800 rpm stirring rate, 3 hrs.

Once the high-throughput screening routine described above was developed, we decided to investigate the effects of substituents in the aromatic ring system on the reaction performance and selectivity. A unique feature of our high throughput screening method is the ability to screen multiple ligands side by side in the same process and obtain all the results simultaneously. This cuts down on any inconsistencies which can potentially arise from running ligands in different batches at different points in time. It also allows for much faster generation and comparison of data as all of the reactions are completed at the same time and are quickly ready for analysis. For the investigation of substrate scope, we screened a variety of substituted styrenes. We were looking to directly compare the activity of two ligands: Ph-BPE (**83**), the benchmark ligand for this study, and DUANPHOS (**126**), the closest competitor as determined from earlier optimization studies. The optimized conditions for (**83**), reported by Klosin, and the conditions found within this study for (**126**) were used. The results are summarized in Table 9. It was determined in reactions catalyzed by BPE-complexes, substituents in the *ortho*-position of the ring yield higher ee's than the same substituents placed at other locations on the ring. This could possibly arise from an increase in steric interactions between the aryl rings of the ligand and the substituent, thereby increasing the enantioselectivity of the reaction (Table 9 entries 2,4,7,12). Strongly electron withdrawing groups such as NO_2 (entry 11) drastically decrease the yield of the reaction while still maintaining a reasonably high ee's. This most likely results from the inability of the metal to efficiently insert into the electron deficient olefin at the beginning of the catalytic

cycle, dramatically decreasing the rate and subsequent conversion of the reaction. It was also found that (**126**) gave very similar yields regardless of the substituent on the aryl ring, but in all cases the B:L of the product was not as high as that obtained for Ph-BPE. The ee's of the reactions were also very similar with some notable exceptions. When the substituent was 4-Cl or 4-OMe, (**126**) gave slightly higher ee's than Ph-BPE (Table 9 entries 5,8) and when the substituent was 4-F, (**126**) gave a racemic mixture. When substituents on the aryl ring were methyl or *tert*-butyl (entries 9,12), there was very little difference in either the activity or enantioselectivity of the catalysts. However, placing fluorine in either the *ortho*- or *para*- position resulted in higher yields and significantly higher ee's from (**83**) (entries 2,3). That was reversed when the substituents were either a chlorine or methoxy group in the para position (entries 5,8). The reason for this phenomenon is not clearly understood, and further investigations are ongoing in our laboratories. It was generally determined that (**83**) is the ligand of choice for a wide variety of substrates, but it was discovered that through careful optimization of the reaction conditions, it is possible to further enhance the selectivity of ligands that may have been previously overlooked in the AHF of olefins.

Table 9. (*R*,*R*)-Ph-BPE vs. (*R*,*R*,*S*,*S*)-DUANPhos Substituted Styrenes Results

No.	R	NMR Yield (%)	B:L	%ee	Yield (%)[c,d]
1	H	>99 (28)	22:1 (12:1)	90 (79)	64[a] (N/D)
2	2-F	99 (46)	15:1 (1:1)	>99 (N/D)	84 (N/D)
3	4-F	93 (>99)	16:1 (4:1)	74 (0)	85 (87)
4	2-Cl	>99	156:1	89	96
5	4-Cl	99 (99)	6:1 (5:1)	38 (81)	99 (99)
6	3-OMe	>99	20:1	N/D[b]	99
7	2-OMe	>99 (>99)	8:1 (0.66:1)	80 (N/D)	96 (N/D)
8	4-OMe	>99 (>99)	10:1 (3:1)	68 (88)	96 (94)
9	4-^{t}Bu	>99 (99)	4:1 (2:1)	>99 (94)	>99 (91)
10	4-CF$_3$	>99	8:1	20	90
11	4-NO$_2$	28	7:1	97	<12
12	2-CH$_3$	>99 (99)	17:1 (1:1)	81 (83)	93 (92)
13	3-CH$_3$	>99	44:1	N/D[b]	90
14	4-CH$_3$	>99 (99)	36:1 (1:1)	81 (N/D)	95 (N/D)
15	4-^{i}Bu	>99	7:1	60	97
16	6-MeO-2-Naph	>99	8:1	N/D[b]	99

[a] This isolation has not been optimized. [b] Unable to separate enantiomers via chiral GC. [c] Isolated Yield. [d] Data shown in parenthesis represent DUANPHOS catalyzed reactions.

2.3.2. Conclusions

In conclusion, application of the high throughput technique to ligand screening and optimization of the reaction conditions of the Rh-catalyzed asymmetric hydroformylation of styrene was demonstrated. Direct comparison of the obtained data with the previously reported results of multi-substrate AHF screening reveals a number of discrepancies putatively arising from interference of functionalized co-substrates with some of the chiral catalyst systems. Although not comprehensive by any means, the described screening protocol allowed express analysis of a large series of chiral ligands, which led to the discovery of a novel efficient catalyst system, [Rh(CO)$_2$acac]-Duanphos, for the asymmetric hydroformylation of styrene, and highlighted the dramatic effect of reaction conditions on the efficiency of the AHF.

2.4. Experimental

High Throughput Optimization of the Rhodium-Catalyzed Asymmetric Hydroformylation of Styrenes

2.4.1. General Information

See Chapter 1.4.1. for instrumentation details.

Anhydrous hexane, dichloromethane, toluene, diethyl ether, tetrahydrofuran, and acetonitrile were obtained by passing degassed HPLC-grade commercially

available solvents consecutively through two columns with activated alumina (Innovative Technology).   Anhydrous benzene, chlorobenzene, and carbon tetrachloride were obtained by distillation of ACS-grade commercially available materials over calcium hydride in a nitrogen atmosphere. Anhydrous chloroform and EtOAc were obtained by drying ACS-grade commercially available solvents over activated 4Å molecular sieves. All manually dried solvents were degassed using a N_2 spurge. Anhydrous dimethylformamide, dimethylacetamide, 1,2-dichloroethane, and dimethylsulfoxide were purchased form Sigma-Aldrich or Acros Organics and used as received.   The $Rh(CO)_2(acac)$ complex and chiral ligands were obtained from Strem Chemicals and Solvias. Styrene was purchased from Sigma-Aldrich.

All materials were handled in nitrogen-filled glovebox (< 8 ppm residual oxygen and moisture).

2.4.2. Special Equipment

Ten reactions were run concurrently in a BarnStead RS10 ten cell control unit. This unit allows for individual programming and control of heating and stirring regimens in all reaction vessels. The pressure vessels used were custom-made by Parr Instrument and were obtained from BarnStead. Each pressure vessel is made from stainless steel, has a total reactor volume of 10 mL (8mL if using the optional glass liners), and is rated to a maximum pressure of 2000 psi at 150 $^{\circ}$C. The pressure in the vessel can be monitored by an analog pressure gauge which is mounted to the

top of each pressure vessel. The ten vessels were attached to a high-pressure manifold which facilitates the delivery of the syn gas into the system by means of a quick disconnect valve stem. The construction of this manifold including technical drawings is detailed in the following section.

Figure 16. Barnstead RS10 Reactor

2.4.3. Synthesis Gas Manifold Construction

All of the parts used in the construction of this manifold are made from stainless steel and are obtainable from Swagelok. (The following CAD drawing shows the various pieces needed for construction Figure 17):
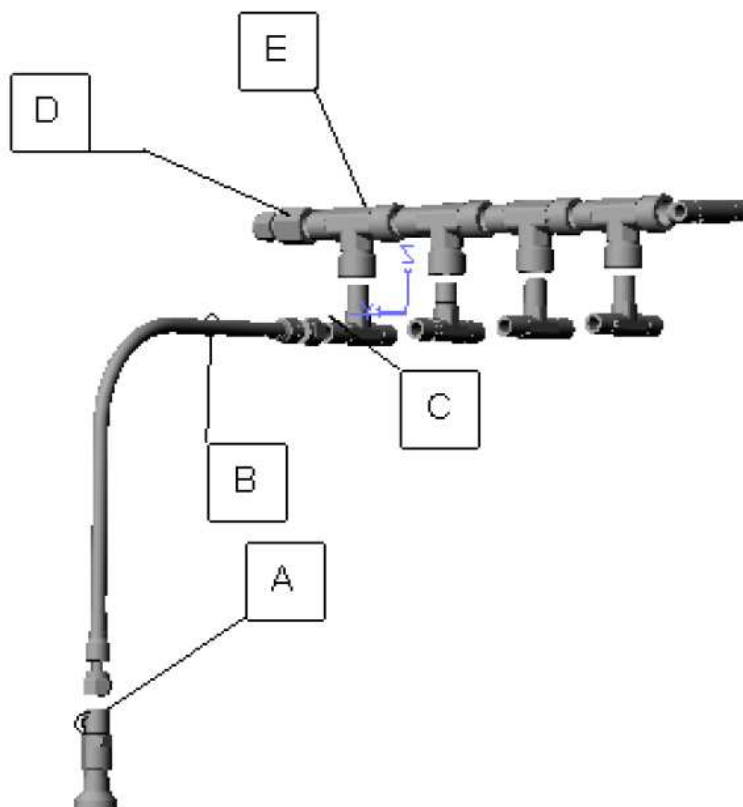
Figure 17. Synthesis Gas Delivery Manifold

Part numbers for the labeled pieces are provided in bold and the numbers of pieces needed for construction have been place in parenthesis.

(A) **SS-QC4-B-4PM**; Quick connect body 0.2 CV, 1/4" male NPT (10);

(B) **SS-TH4PF4PF4**; PTFE-Lined stainless braided hose 1/4" female NPT fittings 3/16" hose, 24" long (10);

(C) **SS-4-mt**; Male tee, 1/4" NPT (5);

(D) **SS-400-7-4**; 1/4" female NPT, 1/4" tube OD Swagelok tube fitting adapter (1);

(E) **SS-4-st**; tee 1/4" female NPT, 1/4" male NPT, 1/4" female NPT (4).

This manifold is designed to attach to a standard ¼" OD soft copper tubing. It should be noted that using this manifold does not allow for individual control of the syn gas pressure in each pressure vessel since the overall pressure of the system is set using a pressure regulator attached to the syn gas tank.

2.4.4. General Procedure for Ligand Screening

For the ligand screening procedure all of the reactor vessels were loaded in a glovebox under a N_2 atmosphere. The optional glass liners were used in each of the pressure vessels and were found to double nicely as weighing vials. To each of the glass liners was added 5.82 µmol of ligand and 2.91 µmol of the Rh source (58 µL of a 0.05 molar Rh(acac)(CO)$_2$ stock solution in toluene)[95] followed by 3.5 mL of dry toluene and 423 µL (2.60 mmol) of octane as an internal standard. Styrene (1 mL, 8.73 mmol) was then added to give a total vessel volume of ~ 4.5 mL and a substrate to catalyst ratio of 3000:1. The vessels were removed from the glove box and placed in the RS10 unit. The reactions were stirred at 800 rpm and heated to 80 °C for three hours. A constant supply of syn gas (1:1 H_2:CO) was provided through the manifold at a pressure of 150 psi. After three hours the temperature was crashed to 15 °C and the vessels were vented and opened (after this point all the operations were performed in air). Aliquots (5 µL) were taken from the crude reaction mixtures and dissolved in dichloromethane (1 mL) for GC/MS and chiral GC analysis.

2.4.5. Analytical Procedure

Yields of hydroformylation and branched-to-linear ratios were determined by quantitative high throughput GC/MS analysis. The temperature of the oven was started at 50 °C held for two minutes then ramped to 200 °C at a rate of 20 °C/min. The flow rate through the column was 0.68 mL/min with a constant linear velocity of 29.9 cm/sec. Total flow rate for the system was 15.3 ml/min with a 20:1 split ratio. The following parameters were set: injector temperature 275 ^{o}C, MS interface temperature 275 ^{o}C, and ion source temperature 225 ^{o}C. To accelerate the analytical sequence, the length of each run was limited to 9.5 minutes. To remove heavy materials from the analytical column, after every 10 runs a conditioning program was performed (20 minutes heating to 320 ^{o}C, MS acquisition turned off). Quantitative measurements were performed based on 7-point TIC calibration curve *vs n*-octane as internal standard (Figure 18). TIC integration was performed in automatic mode (max number of peaks: 12; peak width: 2 sec; max height: 0) using the batch processing option, integrated in Shimadzu's GCMS Solution suite.[96] Components were identified using NIST05 Mass-Spec Library,[97] and independently by comparison with GC/MS data of authentic samples, purchased from Sigma-Aldrich. A typical chromatogram shows the retention times, integration parameters and NIST library search results for the major components in crude reaction mixture. Enantioselectivities were assessed by quantitative GC on a J&W CyclosilB chiral column. Baseline separation was achieved using a 75 ^{o}C isothermic program. The

flow rate through the column was 1.19 ml/min with a constant linear velocity of 30.0 cm/sec. Total flow rate for the system was 27.9 mL/min with a 20:1 split ratio. To save time, the method of overlapping GC runs was employed. The interval between automatic injections was set for 40 min, i.e. each new analysis was beginning shortly after both enantiomers of the branched products were coming out of the column. Under these conditions, the elution of linear isomer was observed at the beginning of the next run. A typical chromatogram is depicted in Figure 20.

Calibration Curve

Styrene (green) – slope 1.932, $R^2 = 0.9855$

Ethylbenzene (purple) –

slope 1.979

$R^2 = 0.9893$

Linear product (red) –

slope 2.320

$R^2 = 0.9961$

Branched product

(blue) –

slope 2.014

$R^2 = 0.9856$
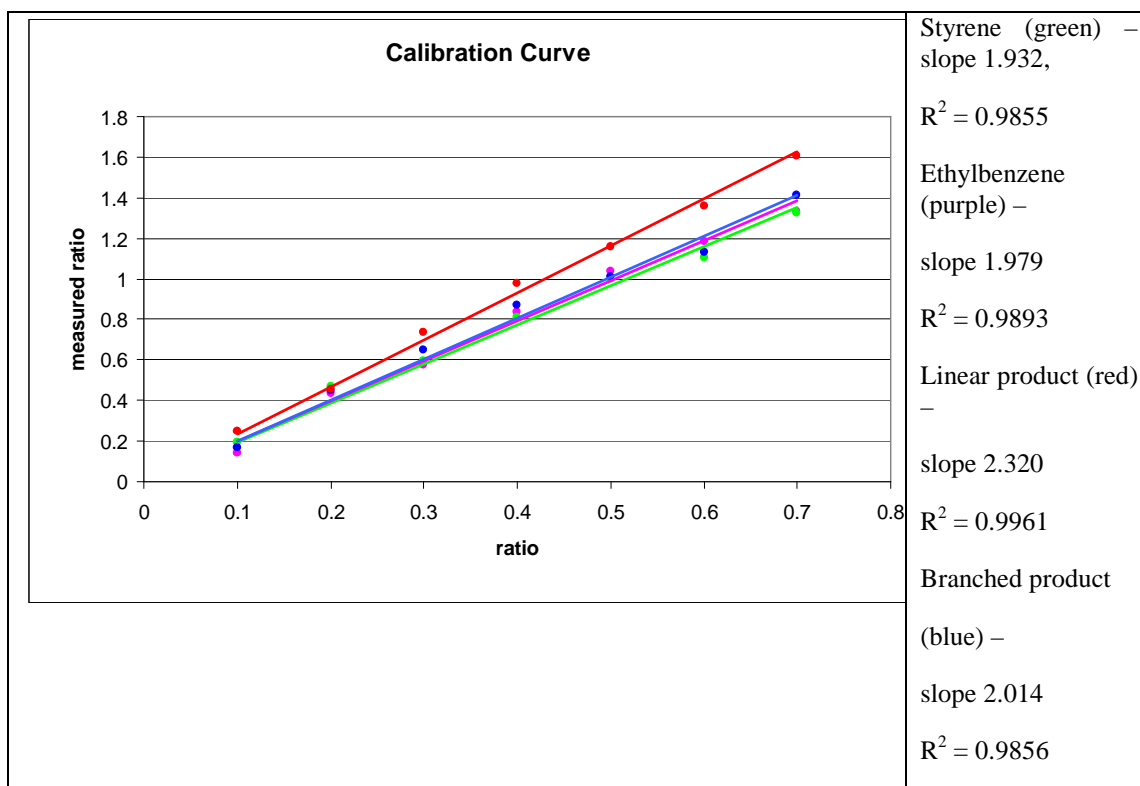
Figure 18. GC/MS calibration data for Styrene (starting material), Ethylbenzene (reduction product), Phenylpropanal (linear product), and α-Methylphenylacetaldehyde (branched product) *vs n*-Octane.
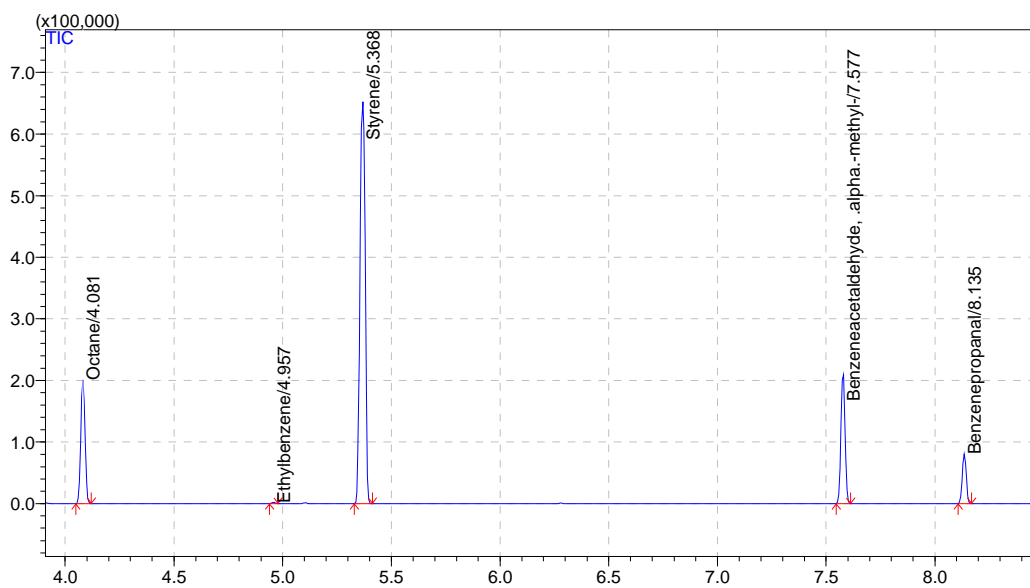
Peak #	R. Time	I. Time	F. Time	Area	%Area	Compound
1	4.081	4.048	4.12	270172	15.31	Octane
2	4.957	4.94	4.978	2238	0.13	Ethylbenzene
3	5.368	5.33	5.413	1103733	62.53	Styrene
4	7.577	7.547	7.613	285488	16.18	Benzeneacetaldehyde, α-methyl-
5	8.135	8.107	8.168	103286	5.85	Benzenepropanal

Figure 19. Typical TIC trace, integration and NIST library search report obtained in high throughput GC/MS analysis of crude reaction mixtures in the asymmetric hydroformylation reaction.
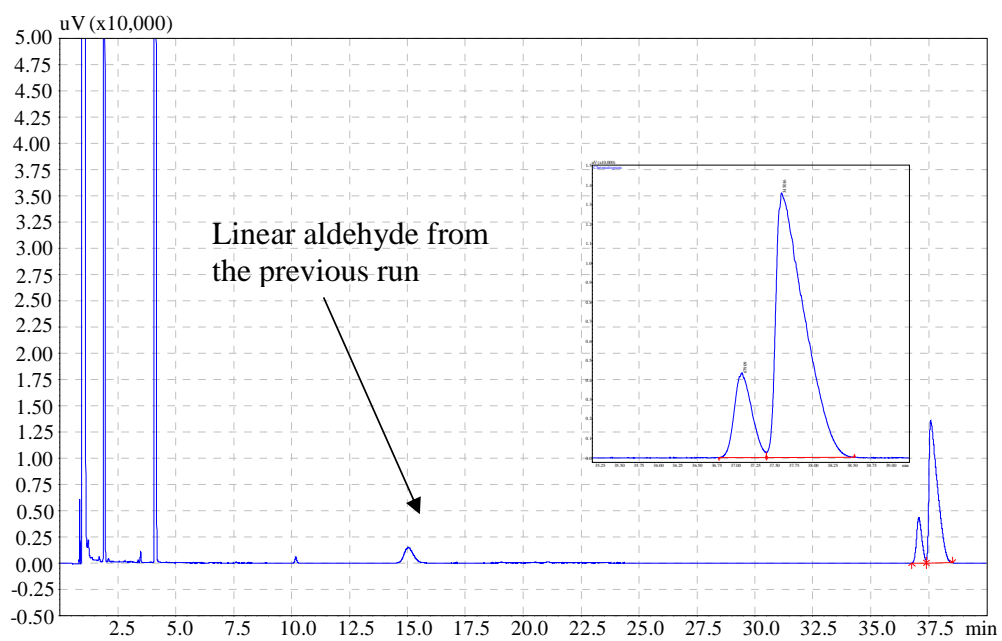
Figure 20. A typical chiral chromatogram with integration showing the % ee of the branched aldehydes and the linear aldehyde from the previous run**.**

Table 10. Results for General Ligand Screening

Ligand	ee,[c,d] %	x(B)	TOF, h^{-1}	A, h^{-1}
(*R*)-BINAP (**80**)[86]	-3(28)	0.444(0.911)	66(80)	0.88(20.4)
(*R*)-Tol-BINAP (**81**)	1	0.444	89	0.40
(*R*)-Xylyl-BINAP (**82**)	3	0.583	389	6.80
(*R,R*)-Ph-BPE (**83**)[86]	90(94)	0.959(0.978)	761(740)	657(680)
(*R,R*)-Me-BPE (**84**)[63]	2(-43)	0.524(0.933)	66(80)	0.69(32.1)
(*R,R*)-Et-BPE (**85**)[63]	14(52)	0.756(0.919)	290(100)	30.7(50.5)
catASium m(R) (**86**)	61	0.939	190	109
SL-M001-1 (**87**)[86]	20(-24)	0.778(0.848)	486(470)	106(95.7)
SL-M004-1 (**88**)[86]	10(-10)	0.737(0.868)	240(150)	17.7(13.0)
SL-J001-1 (**89**)[86]	-2(39)	0.583(0.922)	157(140)	1.83(50.3)
SL-J002-1 (**90**)[86]	-4(43)	0.474(0.844)	23(50)	0.44(18.1)
SL-J003-1 (**91**)[86]	0(-47)	0.000(0.844)	1(30)	0(11.9)
SL-J005-1 (**92**)[86]	40(38)	0.949(0.952)	609(450)	231(162)
SL-W001-1 (**93**)[86]	27(44)	0.565(0.706)	743(980)	113(304)
SL-W002-1 (**94**)	-3	0.677	550	11.2
SL-T001-1 (**95**)	-42	0.677	266	75.7
SL-T002-1 (**96**)	3	0.762	294	6.72
(*S*)-Phanephos (**97**)	-14	0.744	325	33.8
CTH-(S)-Xylylphanephos (**98**)	-8	0.600	116	5.57

Table 10. Continued

CTH-(*R*)-P-Phos (**99**)	7	0.500	51	1.79
CTH-(*R*)-Xylyl-P-Phos (**100**)[86]	17(-8)	0.600(0.898)	81(270)	8.26(19.4)
(*S*,*S*)-Me-DUPHOS (**101**)[63,(R,R)a]	-33(-44)	0.615(0.940)	14(100)	2.84(41.4)
(*S*,*S*)-Et-DUPHOS (**102**)[63,(R,R),a]	-5(-52)	0.615(0.932)	126(140)	3.88(67.8)
Rhophos SL-P001-2 (**103**)	0	0	15	0
(*R*,*R*)-(*i*Pr)-DUPHOS (**104**)[63,(S,S),a]	-30(-83)	0.565(0.919)	59(150)	10.0(114)
(*R*,*R*)-NORPHOS (**105**)[86]	6(-17)	0.750(0.940)	179(230)	8.06(36.8)
(*R*)- catASium T2 (**106**)[86]	18(-26)	0.875(0.897)	309(120)	48.7(28.0)
(*S*,*S*)-CHIRAPHOS (**107**)[57,86]	-12(2)	0.722(0.941)	352(50)	30.5(0.94)
CARBOPHOS (**108**)[86]	2(-6)	0.629(0.859)	583(610)	7.34(31.4)
(*R*)-(*i*Pr)-PHOX (**109**)	1	0.920	153	1.41
CTH-(*R*)-BINAM (**110**)[86]	-5(2)	0.667(0.677)	171(120)	5.70(1.62)
(*R*)-SYNPHOS (**111**)	20	0.919	86	15.8
(*R*)-SOLPHOS (**112**)	4	0.807	120	3.88
(*R*)-Xylyl-SOLPHOS (**113**)	18	0.892	48	7.71
(*R*)-DIFLUOROPHOS (**114**)	29	0.767	231	51.4
SL-A101-1 (**115**)	21	0.882	68	12.6
SL-A109-1 (**116**)	0	0.697	527	0
(*R*)-Cl-MeO-BIPHEP (**117**)	14	0.923	242	31.3

Table 10. Continued

(*R*)-C$_3$-TUNEPHOS (**118**)[86]	2(-19)	0.444(0.917)	70(80)	0.622(13.9)
CTH-(*R*)-SPIRO-P (**119**)[86]	7(-14)	0.583(0.667)	261(400)	10.7(37.6)
(*R*)-SDP (**120**)	-2	0.545	123	1.34
(*S*)-BINAPINE (**121**)[86]	21(-94)	0.697(0.905)	363(120)	53.1(102)
(*S*)-BINAPHANE (**122**)	-16	0.600	31	2.98
(*R,R*)-DIOP (**123**)[86 ,(*S,S*),a]	-8(13)	0.565(0.600)	150(480)	6.78(37.4)
catASium D(R) (**124**)[86]	32(-10)	0.872(0.949)	143(240)	39.9(22.8)
catASium I(R) (**125**)[86]	16(-29)	0.737(0.808)	520(190)	61.3(44.5)
(*S,S,R,R*)-DUANPHOS (**126**)	79	0.956	383	280
(*S,S,R,R*)-TANGPHOS (**127**)[86,b]	21(65)	0.600(0.937)	42(100)	5.29(60.9)

[a] Absolute configuration of the corresponding ligand employed in the multi-substrate screening. [b] The ratio of ligand to Rh described in this reference is 1.2:1 which differs from the 2:1 loading that was used in this study as dictated by the optimum conditions for the benchmark ligand 4. This could account for the significant difference in efficacy as compared to the literature data. [c] Negative ee's represent predominant formation of the (*S*)-enantiomer. [d] Data shown in parenthesis represent DUANPHOS catalyzed reactions.

2.4.6. General Procedure for Solvent Screening

All reactor vessels were loaded in the glove box under an inert atmosphere. The stock solution of Rh(acac)(CO)$_2$ (0.05 M) was prepared in the solvent to be used in the screening run. The remaining parameters were the same as previously described in the general reaction conditions outlined above with the exception of substituting the solvent to be screened in the place of PhMe used in the general procedure.

2.4.7. Results of the Solvent Screening Procedure

Table 11. Results of Solvent Screening

No.	Solvent	SL-T001-1 (95)				SL-J005-1 (92)			
		%ee	X(B)	TOF, h^{-1}	A, h^{-1}	%ee	X(B)	TOF, h^{-1}	A, h^{-1}
1	THF	-53	0.833	22	9.71	-2	0.947	12	0.227
2	DCM	-77	0.949	43	31.4	32	0.972	205	63.8
3	Et$_2$O	0	0.565	21	0	0	0.792	8	0
4	Hex	-57	0.961	28	15.3	44	0.982	154	66.5
5	DMA	-21	0.836	31	5.44	5	0.969	139	6.73
6	DMF	-65	0.875	57	32.4	21	0.954	159	31.9
7	MeCN	0	0.500	56	0	5	0.971	35	1.70
8	DMSO	-63	0.767	37	17.9	22	0.973	194	41.5
9	PhCl	-68	0.767	30	15.7	2	0.444	37	0.33
10	CCl$_4$	0	0	0	0	0	0	0	0
11	PhH	-73	0.808	139	82.0	-3	0.655	442	8.69
12	DCE	-70	0.821	18	10.4	0	0	0	0
13	EtOAc	-76	0.815	225	139	38	0.912	437	151
14	CHCl$_3$	-78	0.756	83	48.9	0	0	0	0

Table 11. Continued

No.	Solvent	catASium m(R) (86)				catASium d(R) (124)			
		%ee	X(B)	TOF, h^{-1}	A, h^{-1}	%ee	X(B)	TOF, h^{-1}	A, h^{-1}
15	THF	3	0.500	22	0.33	20	0.744	76	11.3
16	DCM	0	0.474	102	0	35	0.946	114	37.8
17	Et$_2$O	0	0.474	10	0	36	0.714	22	5.66
18	Hex	0	0.500	68	0	44	0.944	431	179
19	DMA	-2	0.706	16	0.23	1	0.954	151	1.44
20	DMF	6	0.821	67	3.30	1	0.957	205	1.96
21	MeCN	19	0.697	15	1.99	4	0.976	80	3.12
22	DMSO	62	0.950	102	60.1	1	0.968	84	0.81
23	PhCl	3	0.474	23	0.33	17	0.565	43	4.13
24	CCl$_4$	0	0	0	0	0	0	0	0
25	PhH	4	0.474	31	0.59	29	0.744	147	31.7
26	DCE	-3	0.444	22	0.29	36	0	9	0
27	EtOAc	1	0.583	166	0.97	42	0.938	435	171
28	CHCl$_3$	0	0.583	7	0	49	0.951	14	6.52

Table 11. Continued

No.	Solvent	(R)-Difluorophos (114)				(S,S,R,R)-DUANPHOS (126)			
		%ee	X(B)	TOF, h^{-1}	A, h^{-1}	%ee	X(B)	TOF, h^{-1}	A, h^{-1}
29	THF	3	0.474	54	0.77	7	0.583	86	3.51
30	DCM	34	0.895	205	62.4	79	0.926	208	152
31	Et$_2$O	0	0.444	7	0	0	0.500	13	0
32	Hex	18	0.744	299	40.0	80	0.917	392	287
33	DMA	7	0.643	26	1.17	7	0.930	123	8.00
34	DMF	16	0.851	82	11.2	2	0.944	83	1.57
35	MeCN	24	0.878	46	9.69	34	0.818	109	30.3
36	DMSO	29	0.926	164	44.0	0	0.969	31	0
37	PhCl	6	0.444	79	2.11	28	0.524	60	8.80
38	CCl$_4$	0	0	0	0	0	0	0	0
39	PhH	35	0.877	183	56.1	38	0.600	127	29.0
40	DCE	18	0.545	69	6.77	83	0.929	30	23.1
41	EtOAc	4	0.677	404	11.0	82	0.925	256	194
42	CHCl$_3$	39	0.907	10.4	36.8	0	0	1	0

Table 11. Continued

No.	Solvent	(R,R)-*i*Pr-DUPHOS (104)				(*S*,*S*)-Me-DUPHOS (101)			
		%ee	X(B)	TOF, h^{-1}	A, h^{-1}	%ee	X(B)	TOF, h^{-1}	A, h^{-1}
43	THF	-33	0.545	38	6.84	-40	0.706	86	16.1
44	DCM	-67	0.921	144	88.8	0	0	208	0
45	Et$_2$O	0	0.583	9	0	-40	0.583	13	5.37
46	Hex	-81	0.915	273	202	-9	0.941	392	13.0
47	DMA	-24	0.859	34	7.01	9	0	123	0
48	DMF	-13	0.933	76	9.22	1	0	83	0
49	MeCN	-52	0.970	18	9.08	0	0	109	0
50	DMSO	-25	0.991	222	55.0	0	0	31	0
51	PhCl	-29	0.565	43	7.05	0	0	60	0
52	CCl$_4$	0	0	0	0.00	0	0	0	0
53	PhH	-67	0.825	66	36.5	-70	0.961	127	31.6
54	DCE	-82	0	6	0	0	0	30	0
55	EtOAc	-85	0.901	331	253	-13	0.939	256	24.3
56	CHCl$_3$	0	0	0	0	0	0	1	0

2.4.8. Typical Procedure for Temperature Screening

All reactor vessels were loaded in a glove box under an inert atmosphere. The stock solution of Rh(acac)(CO)$_2$ (0.05 M) was prepared in EtOAc. Five reactor vessels were loaded with the same amount of material as described in the general procedure section, employing (*R,R,S,S*)-Duanphos (**126**) as a ligand. They were then run at 15 °C increments in a range from 50 °C to 110 °C for 3 hours at a stirring speed of 800 rpm. After 3 hours the reactions were worked up and analyzed according to the general procedure method.

2.4.9. Typical Preparative Procedure
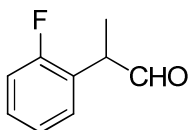
134[98]: In a glove box under an atmosphere of N$_2$ a stock solution of 0.05 M Rh(acac)CO$_2$ was prepared (12.9 mg of Rh(acac)CO$_2$ in 1 mL of dry PhMe) and was allowed to stir at room temperature overnight. In a glove box under N$_2$ to one of the 8 mL glass inserts for the Parr stainless steel reactors was added 5.67 mg (11.0 μmol) of (*R,R*)Ph-BPE followed by 58 μL of the 0.05M Rh stock solution (5.59 μmol). Upon mixing the evolution of CO gas was observed. This was diluted with 3.5 mL of dry PhMe, and 1 mL (1.025 g, 8.39 mmol) of *o*-fluorostyrene was added and the vessel was placed into the reactor and sealed. The reactor was placed into the Barnstead RS10 stirring unit and hooked to the gas

manifold. It was charged with 150 psi of syn gas (H_2/CO 1:1) and stirred at 800 rpm at 80 °C for 18 hrs. Then, the reactor was cooled down to room temperature, vented under a fumehood, and the reaction mixture was condensed under vacuum. The compound was purified by vacuum distillation in a Kugelröhr apparatus at an oven temperature of 80 °C and 0.6 torr. Obtained as a colorless oil 1.07 g (7.00 mmol, 84 %, 15:1 B:L).
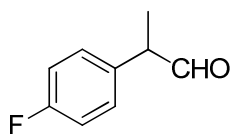
135[98]: This compound was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus at 83 °C and 0.6 torr. It was obtained as a clear oil. 1.08 g (7.12 mmol, 85 %, 20:1 B:L)
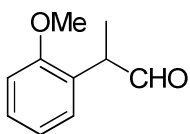
136: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 100 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.17 g (7.13 mmol, 96 %, 8:1 B:L).
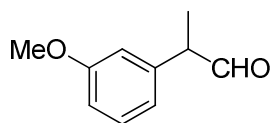
137[99]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 110 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.17 g (7.12 mmol, 99 %, 20:1 B:L).
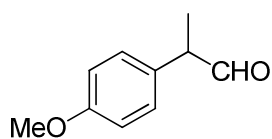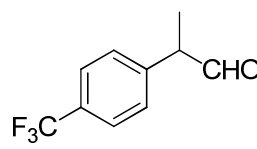
138[100]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 115 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.17 g (7.12 mmol, 96 %, 10:1 B:L).
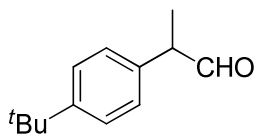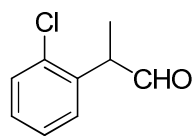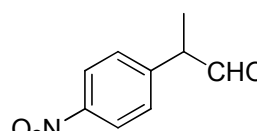
139[101]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 130 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.11 g (5.83 mmol, > 99 %, 4:1 B:L).
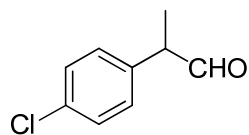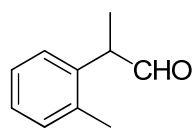
140[101]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 142 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.24 g (7.36 mmol, 99 %, 14:1 B:L)

141[99]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 132 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.23 g (6.07 mmol, 90 %, 8:1 B:L)

142[102]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 138 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.27 g (7.51 mmol, 96 %, single)

143[103]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 163 °C and pressure of 0.2 torr. It was obtained as a yellow oil. 0.16 g (0.893 mmol, < 12 %, 7:1 B:L)

144[104]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 124 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.07 g (7.23 mmol, 93 %, 8:1 B:L)
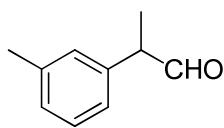
145 [105] : The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 126 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.00 g (6.78 mmol, 90 %, 44:1 B:L)
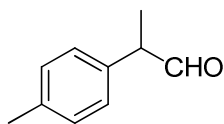
146 [101]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a kugelrohr apparatus with an oven temp of 128 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.07 g (7.19 mmol, 95 %, 36:1 B:L)
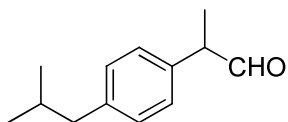
147 [106]: The product was obtained according to the typical procedure. In order to push the reaction of completion it was necessary to allow the reaction to run for 48 hrs at 800 rpm of stirring, 80 °C, and 150 psi of 1:1 H_2\CO. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 158 °C and pressure of 0.6 torr. It was obtained as a clear oil. 1.01 g (5.31 mmol, 97 %, 7:1 B:L)
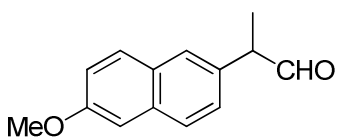
148 [106]: The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 168 °C and pressure of 0.2 torr. It was obtained as an off white solid. 1.15 g (5.37 mmol, 99 %, 8:1 B:L)
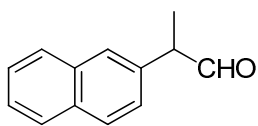
 149 [107] : The product was obtained according to the typical procedure. It was purified by vacuum distillation in a Kugelröhr apparatus with an oven temp of 162 °C and pressure of 0.2 torr. It was obtained as an off white solid. 1.20 g (6.42 mmol, 99%, 8:1 B:L)

Chapter 3. Hydroformylation of Cyclopropenes

3.1. Synthesis of Cyclopropenes

Cyclopropenes are known to be useful in a variety of processes and are found in different compounds and precursors used in the pharmaceutical and agriculture industries. They are finding increased utility owing to a number of unique properties which they posses. Cyclopropenes are highly strained small cycles which possess ~ 60 kcal/mol of energy in the C=C π-bond.[108] This strain energy makes the olefin much more reactive than analogous non-strained alkenes. It also makes potentially reversible reactions unfavorable in the reverse direction since the energy of activation needed for the reaction to proceed in reverse is high. The nature of the three membered cycle makes the species completely rigid allowing it to maintain a high degree of stereochemical information, yet due to its small size, it does not drastically add to the molecular weight or complexity of the molecule.

A number of methods exist for the synthesis of cyclopropenes.[109] One of the more useful of these approaches is the rhodium catalyzed [2+1] cycloaddition (Chapter 3.1.1.) of a diazo compound to an alkyne[110] (**A**, Scheme 23). Other methods which have been used include: cycloisomerizations of vinyl carbenes **B** (Chapter 3.1.2.) [111], 1,2-elmination from dihalocyclopropanes **C** (Chapter 3.1.4.), silicon migrations **D** (Chapter 3.1.5.)[112], and derivatization of pre-formed cyclopropenes **E** (Chapter 3.1.7.).

Scheme 23.
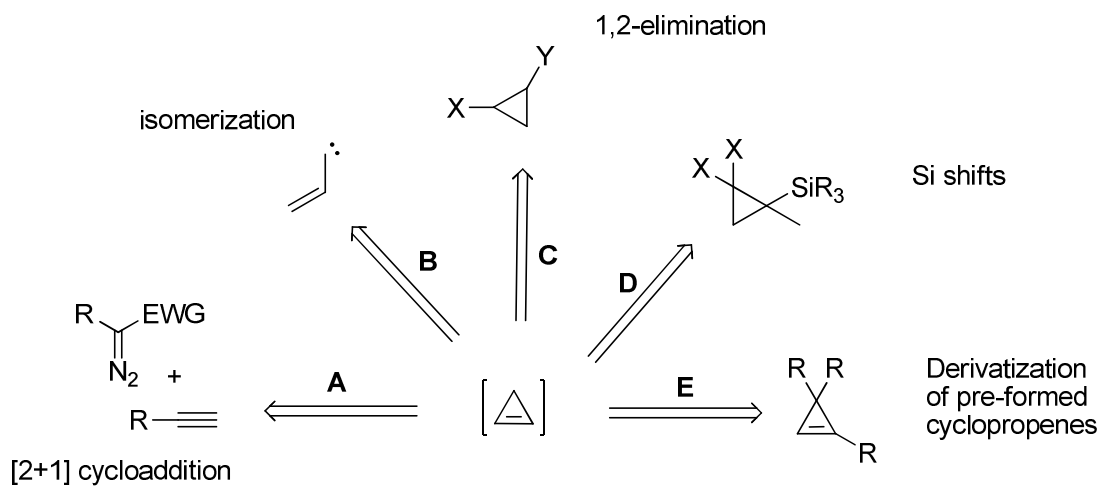
3.1.1. [2+1] Cycloadditions

One of the more common methods for the formation of cyclopropenes is the [2+1] cycloaddition of carbene equivalents to olefins.[110a,c] Most of the carbenoids used in this reaction are metal carbene complexes formed primarily using either rhodium or copper catalysts with an empty coordination site and diazocompounds. Coordination of the diazocompound with the empty site of the metal and extrusion of N_2 results in the formation of the metal carbene used in the transformations. For cyclopropenation, Rh is the first metal of choice and the best catalysts found to affect this transformation are those which are Rh dimers bearing multiple identical ligands. Doyle reported one of the first highly enantioselective dirhodium catalysts for the asymmetric cyclopropenation using diazoacetates and alkynes dirhodium(II) tetrakis [methyl 2-oxopyrrolidine-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$ **150** (Figure 21). This

catalyst was found to promote the cyclopropenation of terminal alkynes in moderate yields with the ee's ranging from ~ 40 % to as high as 98 %.[113]

Davies also has demonstrated a rhodium catalyst that is highly effective at the asymmetric cyclopropenation of alkynes with diazoesters.[114] His catalyst, dirhodium tetrakis ((S)-N-(dodecylbenzenesulfonyl)prolinate) $Rh_2(DOSP)_4$ **151** (Figure 21), enables the transformation in yields as high as 74 % and ee's up to 92 %. This catalyst has been utilized with a number of different aryl-diazoesters and terminal alkynes with great success.

Corey has shown the catalyst he developed, $Rh_2(OAc)(DPTI)_3$ (diphenyltriflylimidazolindinone, DPTI) **152,** catalyzes the asymmetric cyclopropenation of a number of terminal acetylenes in reasonable yield (> 60 %) and high ee (> 92 %).[115]
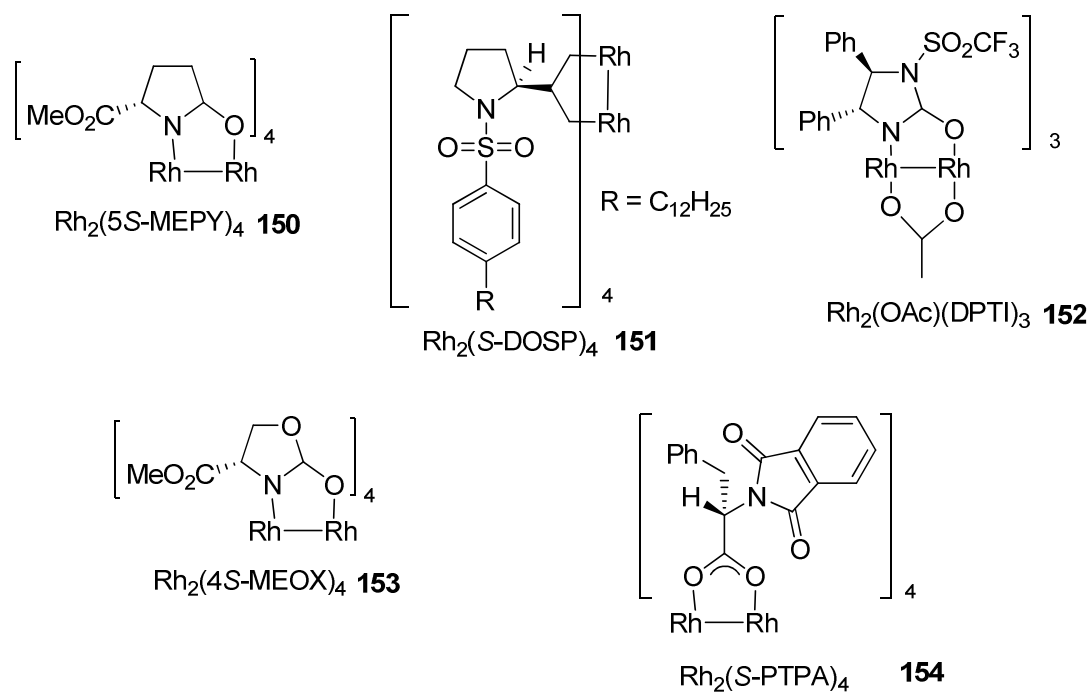
Figure 21.

Until recently, one of the major drawbacks associated with the use of diazo-compounds in cyclopropenations stemmed from their intolerance to β-hydrogens (**155,** Scheme 24**).** It has been known for a while there is a significant amount of elimination to yield α,β-unsaturated esters that takes place with these substrates resulting in a significantly decreased yield of cyclopropene compared to substrates without β-hydrogens. Research from Fox and coworkers[116] has recently addressed this problem and found a workable solution. They found the rate of elimination depends significantly on the steric environment created around the metal center by the ligands. The bulkier the ligands on the metal are, the less favorable the β-elimination is. They screened a number of structurally diverse ligands on Rh and found two ligands which gave them modest yield in the cyclopropenation of

α-ethyldiazobutanoate with phenylacetylene. Through their studies, $Rh_2(Piv)_4$ and

$Rh_2(CO_2Me_2Ph)_4$ were found to give the best ratio of cyclopropenation to elimination,

with the pivalate structure giving a slightly improved yield of the cyclopropene. It is

also noteworthy that catalysts which are known to give a high yield of cyclopropenes

and high enantioselectivity using diazoacetates without β-hydrogens such as Rh_2(S-

DOSP)$_4$ **151**, Rh_2(S-PTPA)$_4$ **154**, Rh_2(4S-MEOX)$_4$ **153**, and Rh_2(5S-MEPY)$_4$ **150**

(Figure 21) gave absolutely no formation of the cyclopropene product using **155**. The

pivalate catalyst was tested on a variety of diazoesters and acetylenes **156** and was

able to produce cyclopropenes **157** in moderate to good yields (43 – 75 %) while

limiting the amount of acrylate product **158** formed.[116]

Scheme 24.
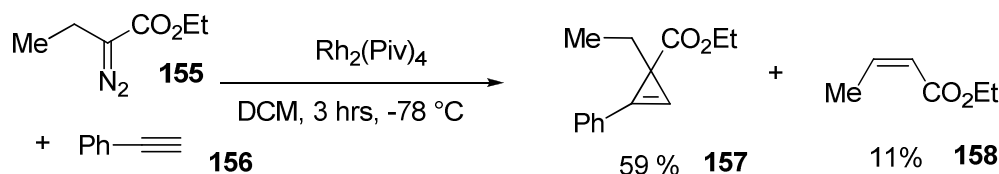
Gevorgyan has recently reported the use of the Davies' Rh_2(S-DOSP) catalyst

to promote the insertion of triazoles **159** (Scheme 25) into alkynes resulting in the

formation of cyclopropenes **160**.[117] This method is extremely efficient in producing

pryidyl containing cyclopropenes which are difficult to obtain by more conventional

methods.[118] This method for their production is very general and is tolerant of both

electron rich and poor triazoles and provides alkynes in yields often exceeding 80 %.

Scheme 25.

X = Halogen
R = Aryl, EWG, EDG
R^1 = Aryl, EWG, EDG
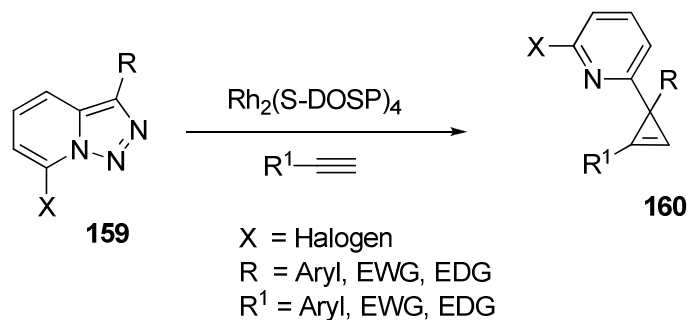
3.1.2. Cycloisomerizations.

One of the key intermediates in the cyclization to form cyclopropenes is vinyl carbenes (Path **B**, Scheme 23). [119] The latter are readily generated through Graham's procedure for the halogenation of alkyl- or arylamidines and isoureas (Scheme 26).[120] The resulting diazirines then give the vinyl carbene and release N_2 upon thermal treatment. A limited number of these carbenes have been characterized in their singlet state via spectroscopic methods including IR, NMR, and UV/VIS.

Scheme 26.
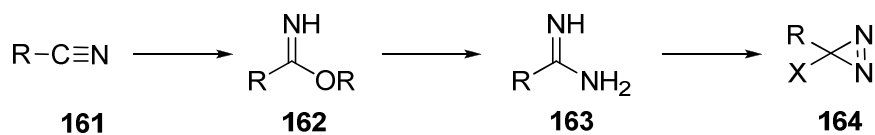
Vinylcarbenes in the singlet state are primarily responsible for the isomerization into cyclopropenes, and halogens have been demonstrated to exhibit a

stabilizing effect on the singlet state of the carbene.[121] As a result of this, the carbenes that have been examined are primarily halovinylcarbenes.[122]

Vinylcarbenes have also been observed resulting from the flash vacuum pyrolysis of anhydride **165** (Scheme 27) in argon producing the vinylcarbene **166**, which quickly isomerized into difluorocyclopropenone **167**, CO_2, and a negligible amount of difluoroacetylene **168**.[123]

Scheme 27.
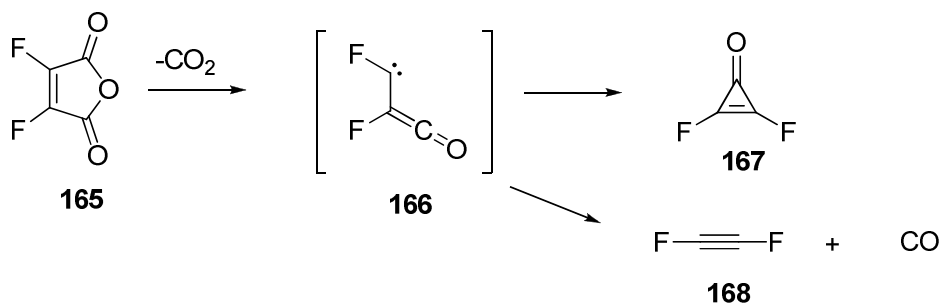
Cycloisomerizations resulting in the formation of cyclopropenes are also known to occur from allenyl structures (Scheme 28).[124] Allenes upon exposure to light can rearrange into vinyl carbenes which potentially undergo cycloisomerizations to produce cyclopropenes. Homolytic cleavage of the allenyl π-bond **169** results in the formation of a diradical intermediate **170,171** which can then form the carbene in two possible conformations **172,173**. The more thermodynamically favored form **172** resulted in the formation of the desired cyclopropene, while the disfavored carbene **173** resulted in the formation of the substituted acetylene (Scheme 28). The reasoning for the observed ratio of product formation is the steric repulsion exhibited between the ^{t}Bu group and the phenyl rings. When the ^{t}Bu group is farthest away

from the phenyl substituents (*anti-*) **172,** these steric factors are markedly decreased

compared to when the *t*Bu group is close to the phenyl rings (*syn-*) **173** (Scheme 28).

The difference in the energy associated with these conformations as determined by

DFT calculations was found to be ~18 kcal/mol making the *syn-* conformation

significantly less stable.[124]

Scheme 28.
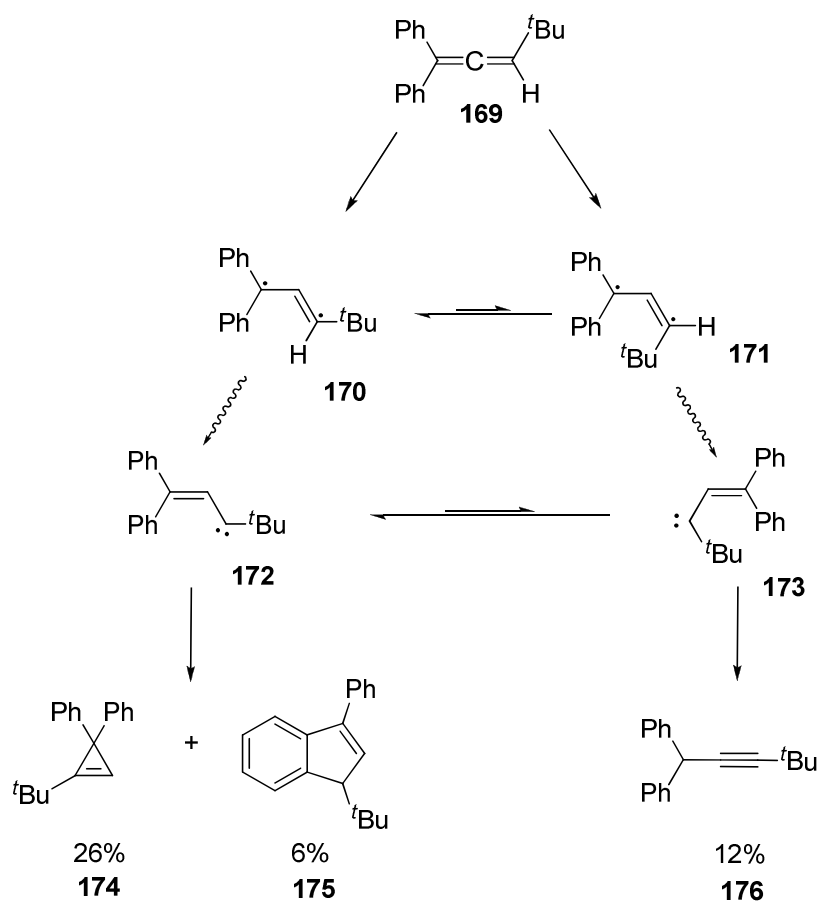
Vinylcarbenes can be stabilized in a singlet form via formation of

organometallic vinylidene complexes. These complexes, usually formed with Ru or

Mo metals, undergo rearrangements into cyclopropenes mediated by a number of different bases including tetrabutylammonium fluoride, tetrabutylammonium hydroxide, DBU, and potassium hydroxide. The plausible mechanism of this transformation (Scheme 29) begins with deprotonation at the β-position to the vinylidene **177** the resulting anion **178** then can attack the electrophilic carbenoid moiety to afford cyclopropenyl metal species **179**.[125]

Scheme 29.
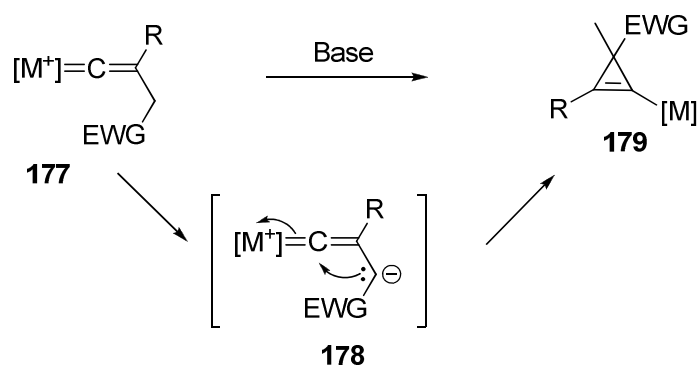
An example of isomerizations of methylenecyclopropanes to cyclopropenes was reported by Bubnov.[126] He demonstrated the rearrangement of a methylene-cyclopropylborane **180** into a cyclopropene **182** under solvolytic conditions in methanol (Scheme 30). When the reaction was carried out in the presence of deuterated methanol, incorporation of a deuterium label in the methyl group of the cyclopropene was observed.[126]

Scheme 30.
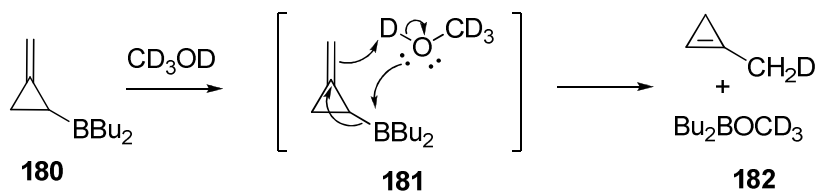
Examples of cycloisomerization to produce cyclopropenes under photolytic conditions are also known. By irradiating methano-epoxydienes **183** (Scheme 31) it is possible to induce the formation of vinyl carbenes which can then isomerize into cyclopropenes. The first step is the photoinduced heterolytic cleavage of the epoxide resulting in ring expansion and the formation of the zwitterionic species **184**. Cleavage of the seven-membered ring affords the more stable vinylcarbene **185** which then undergoes the cycloisomerization to form the cyclopropene **186** in a 44 % yield.[127]

Scheme 31.
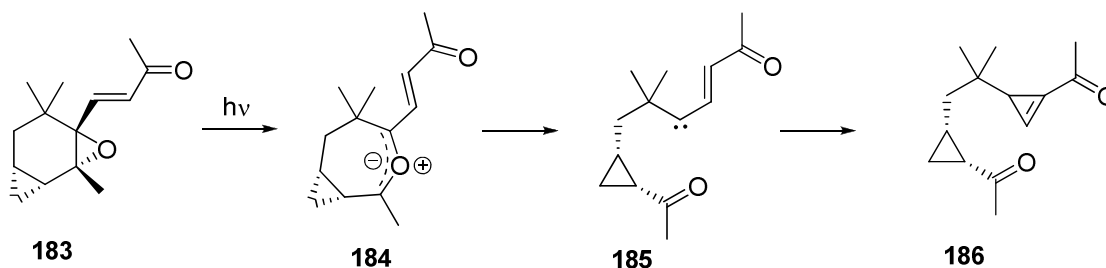
3.1.3. Elimination from dihalopropanes

Another method for the preparation of cyclopropenes is from the elimination of dihalopropanes. By treating the dihalopropanes with a base under the right conditions, these substrates can be made to undergo first a cyclization to form the halocyclopropane, followed by a subsequent dehydrohalogenation to generate the cyclopropene.

An example of this process has been discussed by Breslow where he describes the synthesis of the dihalopropane **188** starting from alkene **186** (Scheme 32). By treating **188** with KNH_2 in liquid NH_3 he succeeded in isolating 3,3-dimethoxypropene **189** in 40 – 65 % yield which upon further treatment with acid could yield cyclopropanone **190**.[128]

Scheme 32.
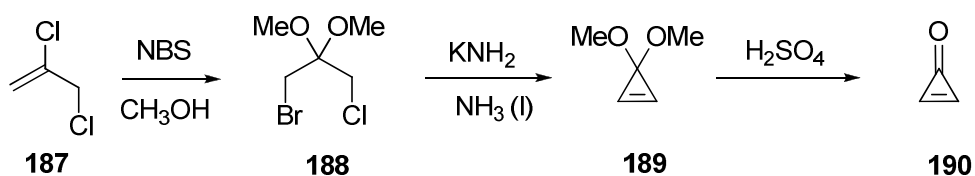
3.1.4. 1,2-Elimination from halocyclopropanes

This is a well established method for the formation of cyclopropenes. One of the more common ways of forming cyclopropenes, via a dehydrohalogenation, was developed using primarily bases, such as ^tBuOK and KOH in DMSO, although other leaving groups such as sulphones have also been employed.[129] Dehydrohalogenation

works well for the synthesis of non-polar substrates containing alkyl or aryl substituents. Cyclopropenes with polar groups, such as esters, amides, or groups not stable in the presence of strong bases suffer from diminished yields in this process.[136] When the cyclopropyl precursor contains such polar groups as amide, it becomes difficult to separate the resulting cyclopropenes from the solvent which results in significantly lower yields of the product than what could be obtained from other methods.

1,2-elimination of dihalocyclopropanes **191** (Scheme 33) to yield halocyclopropenes upon treatment with a potassium alkoxide base using either alcohols or DMSO as a solvent afforded essentially no cyclopropenyl product due to the propensity of halocyclopropenes **192**, under the reaction conditions, to undergo a proton shift forcing the opening of the ring and resulting in the formation of β-halo-alkynes which can then undergo a second dehydrohalogenation to give enynes **193**.[130]

Scheme 33.
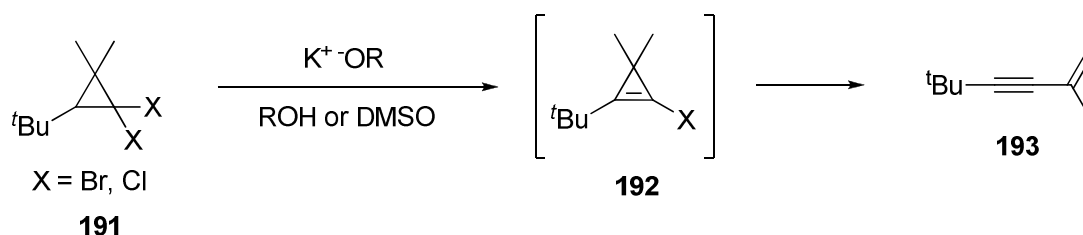
While this process was widely believed to proceed via a halocyclopropenyl intermediate **192**, there was little success at hindering the subsequent rearrangements

and eliminations. Baird found that by treating **191** with MeLi the reaction was able to be stopped at **192** with a 52 % yield. [130] He later adapted his method for 1,2-elimination to tri-halocyclopropenes **194** (Scheme 34) and found this method was able to generate cyclopropenes **196** from many different substrates. It is believed the first step of the reaction is the lithium-halogen exchange forming the metallocyclopropane **195** which can then eliminate X^- from the β-position and yield the cyclopropene.

Scheme 34.
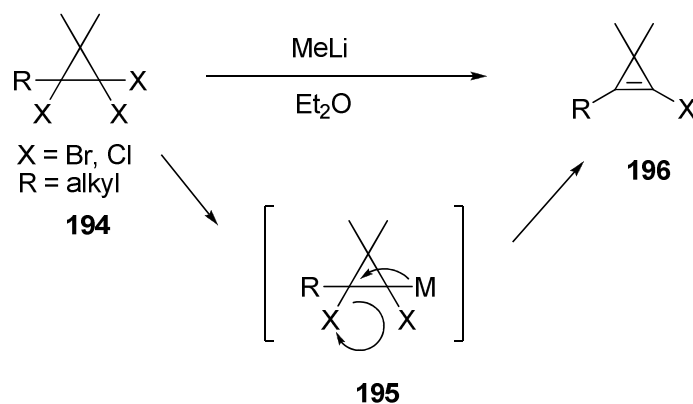
3.1.5. Silicon Shifts

Silicon shifts involve the migration of a silyl group usually, in either a 1,2- or 1,3-fashion, and result in the formation of a cyclopropene. An example of a 1,2-silyl migration starts with a dibromocyclopropane **197** (Scheme 35). When this species is treated with methyl lithium, it undergoes a lithium-bromine exchange followed by α-elimination to form a cyclopropylidene **198**. This carbene then undergoes a 1,2-

silyl shift moving the silyl group to the carbon which previously held the geminal bromines to give silylcyclopropene **199**. This type of shift has been demonstrated on variously substituted cyclopropanes with reasonable yields (48 – 94 %).[112]

Scheme 35.

$$
\begin{array}{ccc}
\mathbf{197} & \mathbf{198} & \mathbf{199}
\end{array}
$$
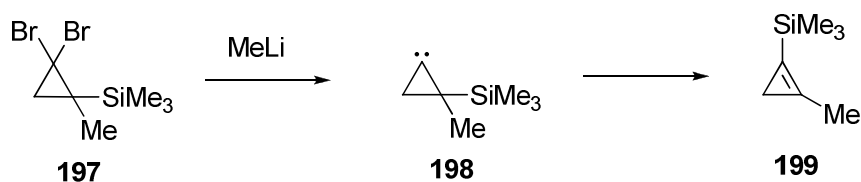
3.1.6. Extrusion of N_2

Lai and coworkers demonstrated the photoinduced electron transfer and extrusion of N_2 from 3*H*-pyrazoles resulting in the formation of cyclopropenes.[131] The mechanism of this transformation is thought to begin with light and an electron deficient Ph_3P^+ abstracting an electron from the C-N σ-bond of pyrazole **200** to give radical cation **201**. This undergoes the loss of nitrogen to form the resonance stabilized radical cation **202** which, through a single electron transfer process, can gain an electron to form the carbene **203**. By closely monitoring the exposure of the system to light, they were successfully able to produce predominantly the photoextrusion product **204**. When the reaction was allowed to remain exposed to light for longer periods of time they observed the formation of dimer **205**, but they observed very little formation of the solvent adduct **206**. The amount of **206** formed

in the reaction can also be controlled by the electronic nature of the substituents on the C4 and C5 positions of pyrazole **200** (Scheme 36). By placing withdrawing substituents on both the C4 and C5 positions or by replacing an electron withdrawing group at the C4 position with a phenyl ring, the amount of **206** formed was minimal.

Scheme 36.
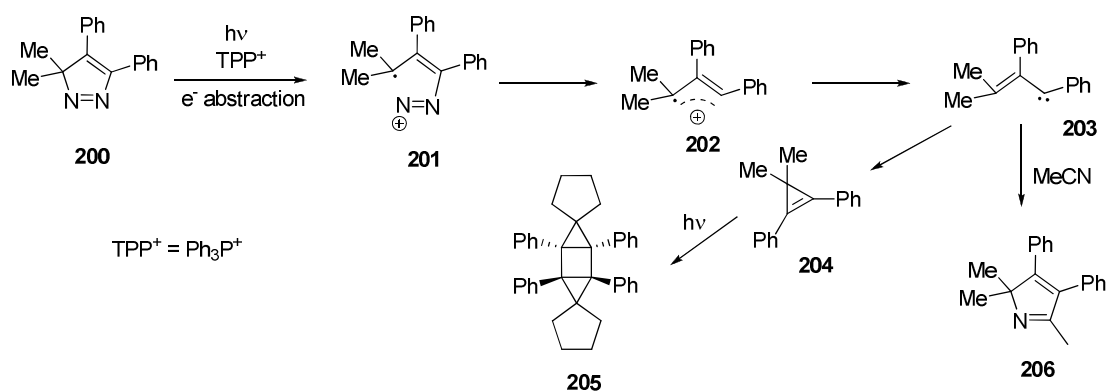
3.1.7. Derivatization of Pre-formed Cyclopropenes

Another method for the preparation of cyclopropenes stems from the derivatization of cyclopropenes which have already been formed. This includes such reactions as functional group transformations, deprotonation of the cyclopropene and subsequent trapping with electrophiles, and ene-type oligomerization reactions (Scheme 37).

Scheme 37. Functionalization of Pre-formed Cyclopropenes

Deprotonation and E$^+$ trapping   Ene reaction
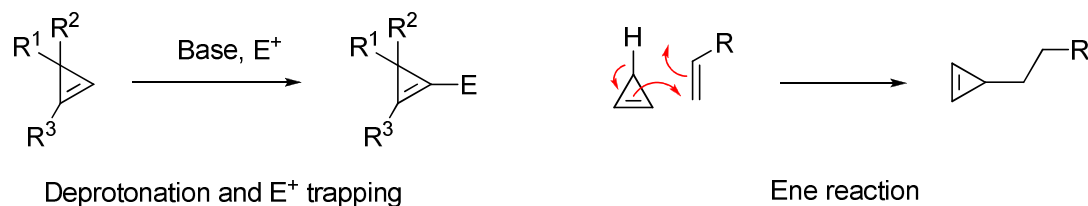
A paper describing an example of oligomerization reactions of cyclopropenes while still maintaining the integrity of the C=C double bond in the cyclopropene appeared in 2008 by Plemenkov.[132] In it he describes the oligomerization of 3,3-disubstituted cyclopropenes bearing a CN group as one of the substituents **207** (Scheme 38). This tetramerization is the first example of Alder-ene chemistry to ever be demonstrated on a 3,3-disubtituted cyclopropene. Another key feature of this reaction is migration of the CN group from one cyclopropenyl moiety to the other. This reaction is believed to proceed via the diradical intermediate **209**. The upper radical can abstract the CN group generating a radical on the carbon bearing the methyl group. This radical can then combine with the one on the β carbon and regenerate the cyclopropene.[132]

Scheme 38.
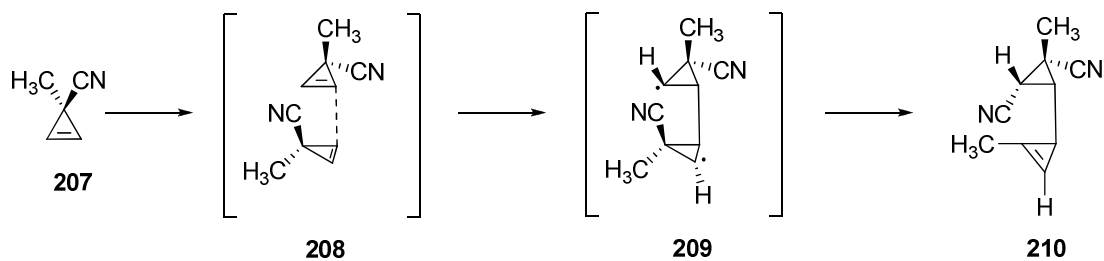
There has been a renewed interest recently in the ability to functionalize cyclopropenes through deprotonation of one or both of the acidic sp^2-H bonds and then trap the resulting cyclopropenyl anion with various electrophiles. This chemistry has been around since the 1960's when alkyl- and aryl-Li species were being used to deprotonate cyclopropenes and the resulting cyclopropenyl lithium species were subsequently trapped with electrophiles. [133, 134] However, there are significant challenges associated with using this process on substituted cyclopropenes, especially those containing carbonyl functionalities. These substrates, upon deprotonation, readily ring open and give isomerized products rather than the desired cyclopropenes. Much of the knowledge of this process has come through the contributions of Fox and his group from the University of Delaware. [135] He has described the formation of a dianion **216** (Scheme 39) resulting from the double deprotonation of the cyclopropenyl carboxylic acid both on the carbons of the olefin and to form the carboxylate. One of the problems inherent with this process is the ability of a cyclopropenyl anion **212** to rearrange into an alkyne **214** much faster than it undergoes electrophilic trapping **213**. This appears to be the case when at least one of

the substituents at the position 3 of the cyclopropene is an ester **211**. When the ester

is hydrolyzed to form the acid, the Columbic repulsion between the carboxylate and

the cyclopropenyl anion is sufficient to keep the ring intact allowing electrophilic

trapping to occur resulting in very little isomerization to **215** and shifting the major

product of the reaction to be the electrophilically trapped species **217**. The yields in

this process are reasonably high (> 65 %) and in the case of a chiral starting material,

the reaction proceeds with retention of configuration of the substrate.[135]

Scheme 39.
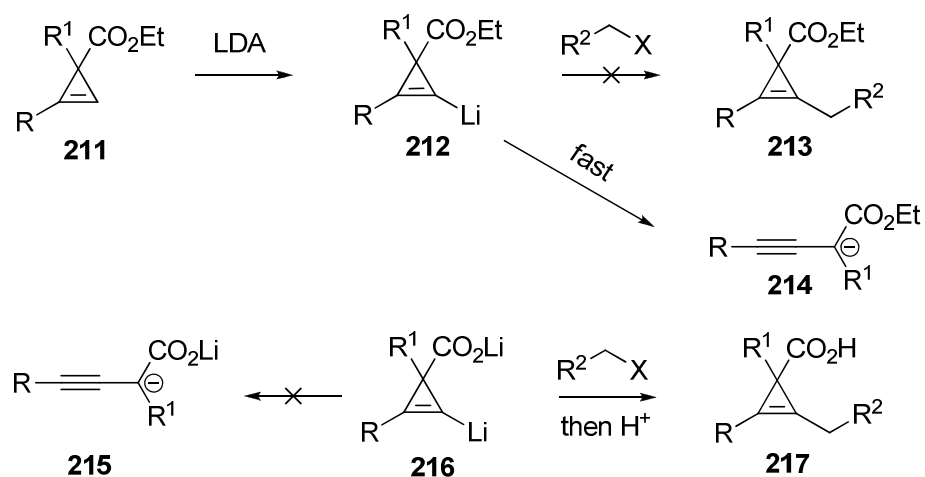
It has also been recently discovered that cyclopropenyl carboxamide can

undergo the same kind of deprotenation/electrophilic trapping process as the

carboxylic acids with a negligible amount of ring opening (Scheme 40). [136] This is

believed to be due to reduced electron withdrawing capability of the amides, which

destabilizes the buildup of negative charge β to the amide making the isomerization

to **218** more energetically disfavored allowing for the electrophilic trapping to occur (**220**).

Scheme 40.
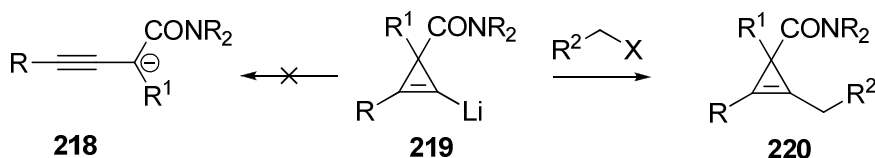
Gevorgyan showed in 2005 (Scheme 41) that by taking trisubstituted cyclopropenes, with at least one of the substituents in the 3 position being an ester **221**, in the presence of a palladium catalyst and an aryl halide; a coupling process analogous to Heck coupling occurs between the CH of the olefin in the cyclopropene and the aryl halide in reasonable yields **222**. Starting with a chiral cyclopropene, it was demonstrated the coupling proceeded uneventfully and with full retention of the stereochemistry. This reaction proceeds under mild conditions and gives moderate to high yields.[137]

Scheme 41.

When R^2 = Ar yields > 65%
When R^2 = alk yield ~40%

222
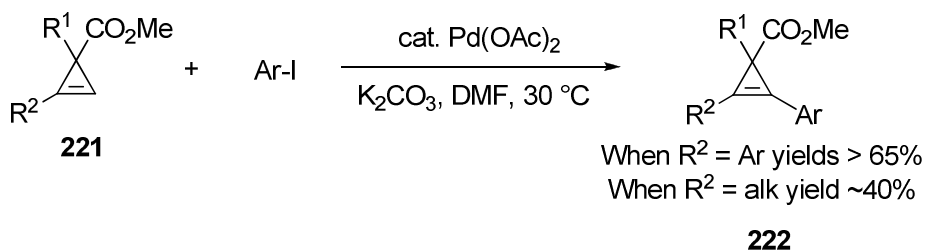
3.1.8. Conclusions

Functionalized cyclopropenes are increasingly becoming available from a variety of different processes. These important substrates possess unique characteristics due to the rigidity of the small cycle and the amount of ring strain inherent in the system. By harnessing their reactivity and unique properties, it is possible to use cyclopropenes in processes which normal olefins will not undergo. Many of these processes proceed irreversibly due to the amount of energy required to form the C=C π-bond in the cycle. This makes cyclopropenes interesting and useful candidates for metal catalyzed, asymmetric processes in which β-hydride elimination can cause racemization of the stereocenter set during the reaction. As more people realize the ease of preparing them, and their synthetic utility, new processes involving cyclopropenes will continue to arise.

3.2. Improved preparative route toward 3-arylcyclopropenes

3.2.1. Introduction

The chemistry of cyclopropenes has increasingly become a focus of research in the past decade, as these unique synthons often provide an inimitable opportunity for preparation of stereodefined cyclopropyl scaffolds with otherwise inaccessible substitution patterns.[138] Development of powerful methods for catalytic enantioselective cyclopropenation of alkynes,[113,114,115,139,140] as well as novel efficient

protocols for chiral separation [141] and chiral kinetic resolution [142] of racemic cyclopropenes opened new opportunities for the use of optically active cyclopropenes in asymmetric synthesis.[137,138a,143] On the other hand, several efficient diastereo- and enantioselective transformations involving prochiral C_S-symmetric 3,3-disubsituted cyclopropenes have been recently reported, which highlight the remarkable versatility of these compounds (Scheme 42). They include: the Alder-ene reaction with homochiral alkenes (**a**);[144] asymmetric carbomagnesation in the presence of chiral amino alcohols (**b**);[145] iron-catalyzed asymmetric alkylzincation (**c**)[146] and ROM-CM reaction (**d**).[147] Furthermore, this type of substrate was also used in preparation of optically active cyclopropyltins and cyclopropylboronates via the Rh(I)-catalyzed asymmetric hydrometallations (**e**,**f**),[148] as well as in catalytic hydroformylation of cyclopropenes (**g**).[149]

Scheme 42.
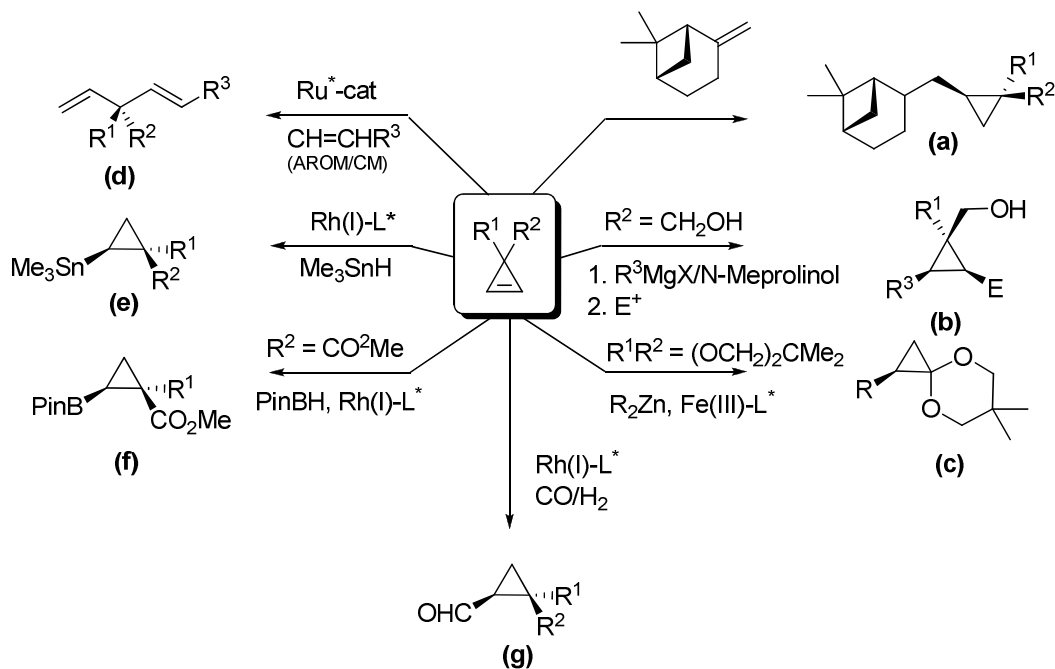
With the growing number of impressive novel methodologies utilizing 3,3-disubstituted cyclopropenes, the question is repeatedly raised as to whether these strained and very reactive synthons can be efficiently prepared in a multigram scale. Herein we disclose a detailed improved synthetic procedure applicable for medium and large scale preparation of a series of 3-arylcyclopropenes. We also comment on the stability and reactivity of 3-arylcyclopropenes, as well as the corresponding precursors, possessing various substituents in the aryl group at C3.

Scheme 43.

Method A

Method B
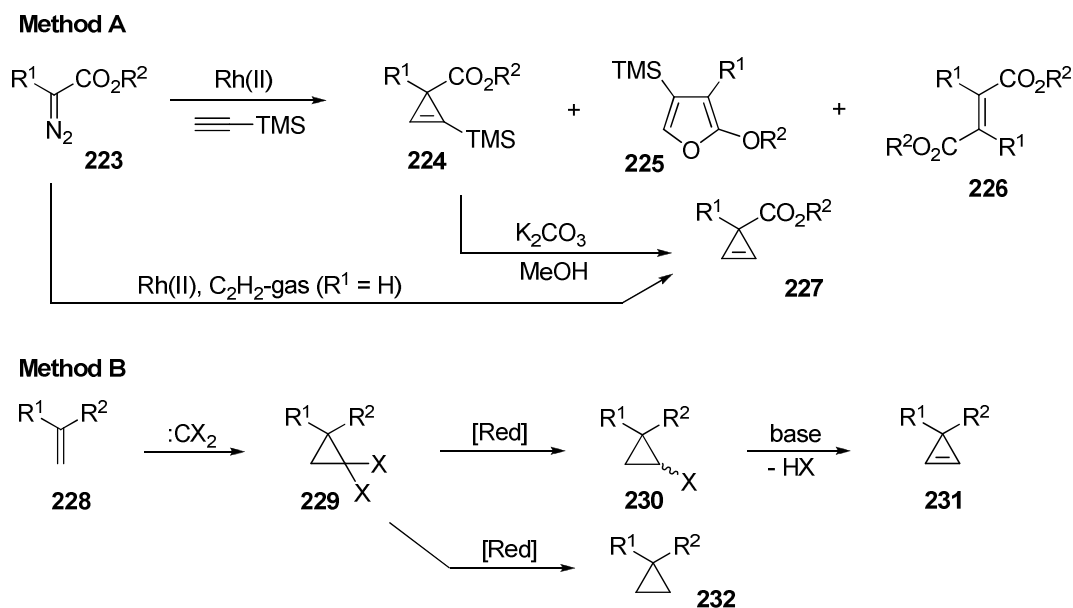
3.2.2. Results and Discussion

Two general approaches to cyclopropenes unsubstituted at the double bond are depicted in Scheme 43. The first approach involves the Rh-catalyzed [2 + 1] cycloaddition of carbenoid species to acetylene gas. This method provides rapid access to monosubstituted cyclopropenes possessing an ester function at C3.[150] Alternatively, 3,3-disubstituted ester-containing cyclopropenes can be prepared via the Cu- or Rh-catalyzed reaction between a diazocarbonyl compound and bis-trimethylsilylacetylene or trimethylsilylacetylene, followed by in situ protio-desilylation of the resulting trisubstituted cyclopropene **224** (Scheme 43, Method A).[151] The latter route provides high yields with phenyl diazoacetate and electron poor aryl diazoacetates; however, our experience suggests that it is poorly applicable

to the synthesis of analogs possessing electron-donating substituents in the aryl ring. The main problem lies in the poor chemoselectivity of the reaction, which produces significant amounts of fumarates **226** or diazines via the concurrent Rh-catalyzed dimerization of diazoacetate **223**.[152] Furthermore, cyclopropenes **224** possessing electron-rich aryl groups are more prone to partial decomposition in the presence of Rh(II) via the ring expansion into furans **225**.[153]

An alternative synthetic approach toward 3,3-disubstituted cyclopropenes involves a three-step sequence, including initial [2 + 1] cycloaddition of a dihalocarbene to 1,1-disubstituted olefin **228**,[154] followed by partial reduction of the resulting dibromocyclopropane **229** to afford bromocyclopropane **230**, and 1,2-elimination of HBr with an appropriate base (Scheme 43, Method **B**). Method **B** was successfully utilized to assemble cyclopropenes possessing aryl,[155] alkenyl,[156] alkynyl,[157] and ferrocenyl[158] substituents at C3. Furthermore, this protocol was demonstrated to be compatible with several functional groups, such as ethers,[159] silyl ethers,[147] acetals,[148a, 160] carboxylates,[148b, 161] and nitriles.[162] A few rather exotic compounds containing a spiro-bicyclic scaffold,[36a, 163] and tethered bis-cyclopropenes[40c, 164] were also obtained via this method. Until recently, one substantial limitation of the described approach was the lack of highly selective and general methods for preparative partial reduction of dibromocyclopropanes **229** into monobromides **230**. Although a plethora of various reduction protocols has been developed, most of them provide an insufficient degree of chemoselectivity, as judged by our own experience and the data in the literature.[165] Thus, to avoid product

loss associated with purification, the chemoselectivity of the reduction method should exceed 98 %. Specifically, the method should allow for complete control over eventual overreduction, which results in inevitable contamination of the target cyclopropene with a cyclopropane side product. A few known, highly chemoselective reducing agents, such as $(EtO)_2POH$[166] and Bu_3SnH,[167] are extremely toxic, which becomes a major liability for synthesis scale-up. A viable, more environmentally benign alternative to the latter methods was suggested by Baird and Bolesov who demonstrated the possibility of selective partial reduction of geminal dihalocyclopropanes **229** into monohalocyclopropanes **230** by use of ethylmagnesium bromide in the presence of catalytic amounts of titanium(IV).[37] This reduction protocol was successfully incorporated into Method **B** and used in the synthesis of a few 3,3-disubstituted cyclopropenes.[147,148,151]

Our studies of novel synthetic transformations involving cyclopropenes[143g,149,168] stimulated us to develop a general and practical approach to a series of 3-arylcyclopropenes possessing differently substituted aromatic ring. It should be mentioned that, although the parent 3-methyl-3-phenylcyclopropene was previously synthesized from the commercially available α-methylstyrene on a multigram scale,[151] no preparative syntheses of analogs functionalized at the aryl group have been reported to date.[169]

3.2.3. Synthesis of α-methyl styrenes

Multigram scale preparation of diverse 3,3-disubstituted cyclopropenes via the 1,2-elimination protocol (Scheme 43, Method **B**) greatly relies on the availability of the corresponding 1,1-disubstituted olefins. While α-methylstyrene (**225a**) is a monomer industrially produced in a multi-ton scale, the corresponding substituted analogs are not available from commercial sources. Most of styrenes **228** described in this report were prepared from the readily available alkyl benzoates (**233**) or acetophenones (**234**) via a two-step sequence including addition of Grignard reagent followed by the acid-catalyzed dehydration of the resulting tertiary alcohols (**235**) (Scheme 44). Maintaining the temperature around 80 °C during the dehydration step allowed for minimizing the concurrent acid-catalyzed cationic polymerization. The reaction times varied significantly depending on the electronic properties of the substituents at the aromatic ring of styrenes **228**. Thus, substrates possessing electron-rich groups (**235b-e,i**) reacted within 1 hr, the chlorosubstituted analogs **235f,g** required 2-3 hrs for complete conversion, while dehydration of the electron poor alcohol **235h** took almost 9 days (Scheme 44). Preparation of olefins highly susceptible to acid-catalyzed cationic polymerization (**228k,l**) was carried out via the Wittig olefination (Scheme 45). Although this route is somewhat more expensive, it avoids exposing olefins **228** to strong acid. We found it convenient to carry out steps **233→ 228** without purification, which dramatically expedited the synthesis, and

helped to significantly improve the overall yields, mainly by avoiding partial polymerization of olefin **228** upon purification.

Scheme 44.

228b: R = p-MeC$_6$H$_4$ **228f**: R = p-ClC$_6$H$_4$
228c: R = m-MeC$_6$H$_4$ **228g**: R = o-ClC$_6$H$_4$
228d: R = o-MeC$_6$H$_4$ **228h**: R = p-CF$_3$C$_6$H$_4$
228e: R = p-(t-Bu)C$_6$H$_4$ **228i**: R = 1-Naphthyl

Scheme 45.

228j: R = p-FC$_6$H$_4$
228k: R = p-MeOC$_6$H$_4$
228l: R = o-MeOC$_6$H$_4$
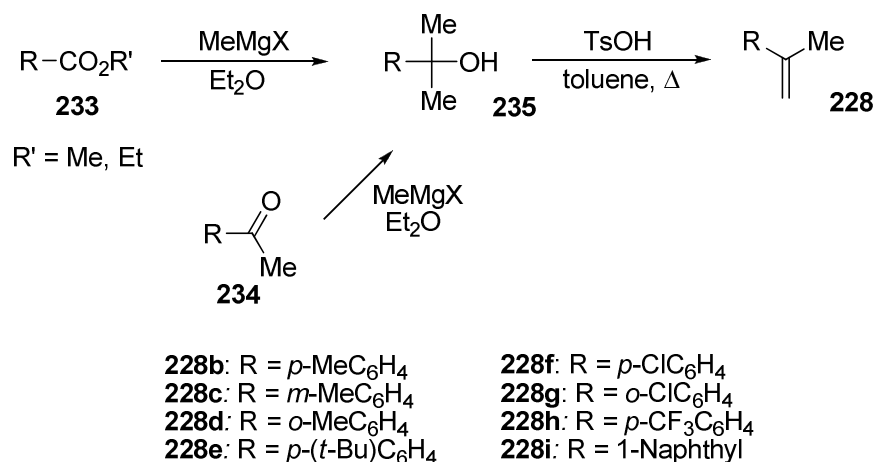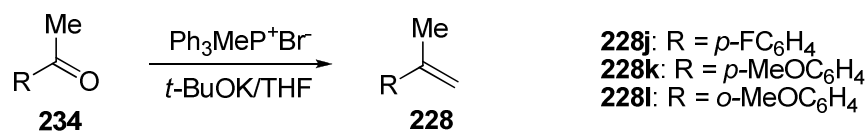
3.2.4. Synthesis of dibromocyclopropanes

Dibromocyclopropanes **229** were prepared by cyclopropanation of crude olefins **228** with dibromocarbene generated under modified Makosza's PTC conditions[170] (Table 12). It was found that employment of the addition mode opposite to that originally described by Makosza (i.e., the dropwise addition of

concentrated aqueous base solution to a vigorously stirred mixture of the organic components) was also beneficial for the reaction yields. This modification allowed for significantly suppressing the formation of resins and, accordingly, for more efficient isolation of the product. To control the intensive heat released at the initial stages of the reaction, it was found convenient to carry out the reaction in a 1:1 (v/v) mixture of bromoform and dichloromethane, refluxing of which prevented overheating of the reaction mixtures above 40 - 45 °C. At the later stages of the process, after the intense exothermic effects have ceased, the remaining dichloromethane was boiled off by heating the reaction mixture at 50 °C.

It is well documented that kinetic rates of cyclopropanation under the phase transfer conditions greatly depend on the structure of the phase transfer catalyst. Thus, the highest rates and best conversions are normally obtained with benzyl-triethylammonium (TEBA) salts.[170] We found, however, that employment of tetrabutylammonium (TBA) and TEBA salts brings about additional problems with excessive foaming and formation of steady emulsions during aqueous workup, when the reaction is performed in a large scale. In contrast, much better separation of the biphasic solutions was observed when hexadecyl- or tetradecyltrimethylammonium salts were employed as catalysts. As a result, extraction could be done faster and more efficiently, which ultimately provided better overall yields. Isolation of the final product in a large scale was done using short-path vacuum distillation at temperatures below 100 °C. In smaller scale (up to 10 g) a simple filtration through a short pad of silica gel was used instead. Albeit this isolation method does not allow

for removal of all the residual bromoform, it was found that small amounts of this impurity do not compromise the next step. [171] Therefore, simple removal of bromoform in vacuum followed by filtration afforded material sufficiently pure to use in the following transformations.

Table 12. Dibromocyclopropanes **229** via [2 + 1] cycloaddition to styrenes.
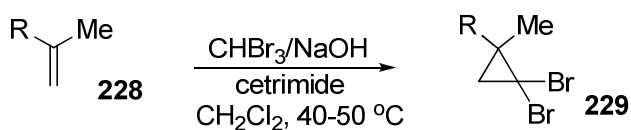
#	R		time, h	scale, mmol	Isolated yield of **229**, %	
					based on **228**	overall[a]
1	Ph	**228a**, **229a**	30	700	92	N/A
2	p-MeC$_6$H$_4$	**228b**, **229b**	120	55.8	66	56
3	m-MeC$_6$H$_4$	**228c**, **229c**	36	66.5	73	65
4	o-MeC$_6$H$_4$	**228d**, **229d**	48	42.7	93	53
5	p-(^{t}Bu)C$_6$H$_4$	**228e**, **229e**	24	45.0	ND	72
6	p-ClC$_6$H$_4$	**228f**, **229f**	24	19.0	ND	91
7	o-ClC$_6$H$_4$	**228g**, **229g**	48	20.0	ND	74
8	p-CF$_3$C$_6$H$_4$	**228h**, **229h**	216	29.2	75	58
9	1-Naphthyl	**228i**, **229i**	72	28.4	66	61
10	p-FC$_6$H$_4$	**228j**, **229j**	48	56.4	86	71
11	p-MeOC$_6$H$_4$	**228k**, **229k**	48	61.3	86	79
12	o-MeOC$_6$H$_4$	**228l**, **229l**	48	49.3	70	55

[a] Yield over 2 steps starting from acetophenones **234**

3.2.5. Partial reduction of dibromocyclopropanes.

Reduction of dibromocyclopropanes (Table 13) was performed according to the previously reported protocol,[37b] with a few practical modifications that became essential during scale up. First, since the reaction is accompanied by evolution of gaseous flammable byproducts, including ethylene and ethane, it should be set up in a well ventilated fumehood. The reaction flask should not be more than one third full and must be equipped with an efficient reflux condenser. This extra space is used as a damper against uneven boiling and sudden splashes, and also proves indispensable during the quench, when a lot of heat and a large volume of gases are evolved. Second, the reaction has a certain initiation period, during which the first 20 mol % of the Grignard reagent, added dropwise, is being used to reduce the Ti(IV) complex into the Ti(II) species. Complete formation of the catalytically active complex can be judged by the color change from pale-yellow to very dark-brown. This, however, does not always indicate the completion of the activation period, which may take longer, in case the initial addition of the Grignard reagent was carried out too quickly (i.e., much faster than the rate of the Ti(IV)→Ti(II) reduction). In the latter case the risk of violent boiling off and splashing of the reaction mixture dramatically increases. Accordingly, at the initial stages of the reaction it is crucial to maintain a reasonably slow dropwise addition of the Grignard reagent, such as to allow relatively slow boiling of the solvent and evolution of the gaseous byproducts.

Table 13. Ti-catalyzed partial reduction of dibromocyclopropanes **229** *en route* to bromocyclopropanes **230**.
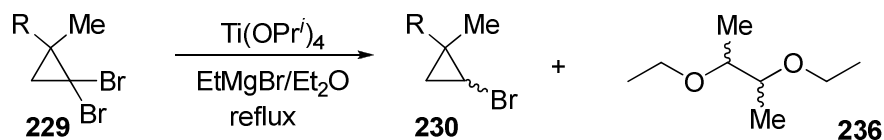
#	R		scale, mmol	trans/cis ratio[a]	Yield **230**, %[b]
1	Ph	**229a, 230a**	644	1.2:1	85
2	$p\text{-MeC}_6\text{H}_4$	**229b, 230b**	30.8	2.0:1	68
3	$m\text{-MeC}_6\text{H}_4$	**229c, 230c**	28.9	2.4:1	64
4	$o\text{-MeC}_6\text{H}_4$	**229d, 230d**	39.5	trans only	71
5	$p\text{-}(^t\text{Bu})\text{C}_6\text{H}_4$	**229e, 230e**	34.3	2.6:1	82
6	$p\text{-ClC}_6\text{H}_4$	**229f, 230f**	17.4	1.8:1	72
7	$o\text{-ClC}_6\text{H}_4$	**229g, 230g**	14.7	5.9:1	84
8	$p\text{-CF}_3\text{C}_6\text{H}_4$	**229h, 230h**	21.5	1.7:1	76
9	1-Naphthyl	**229i, 230i**	17.3	trans only	80
10	$p\text{-FC}_6\text{H}_4$	**229j, 230j**	47.8	1.9:1	75
11	$p\text{-MeOC}_6\text{H}_4$	**229k, 230k**	52.8	2.3:1	60
12	$o\text{-MeOC}_6\text{H}_4$	**229l, 230l**	34.3	2.5:1	84

[a] Determined by 1H NMR. [b] Isolated yields of mixtures of *trans*-**230** and *cis*-**230**.

Finally, the reaction should be carefully monitored by GC analysis to avoid overreduction of the target monobromide **230** into cyclopropane **232** (Scheme 43, Method **B**). The possibility of this side process occurring increases when the exact concentration of the employed Grignard reagent batch is unknown (i.e., it was not titrated prior to use, or moisture was present in the reaction mixture). We found it convenient to add ca. 1.1 equiv of EtMgBr using a graduated addition funnel, then allow the reaction mixture to stir for 15 minutes, and analyze it by GC. An additional amount of Grignard reagent, if needed, could be accurately estimated based on GC conversion. In a typical reaction run, the crude reaction mixture would consist of 98-99 % of bromocyclopropane **230**, and no more than 1 % of the starting material **229** and cyclopropane **232** (Scheme 43, Method **B**). In the perspective of the next step, it is better to leave behind some dibromide **229** rather than allow overreduction into **232**, since **229** will eventually be destroyed upon treatment with ^{t}BuOK during the 1,2-elimination step, while separation of cyclopropene **231** and cyclopropane **232** is essentially impossible. Therefore, if notable amounts of the overreduced product **232** were obtained, monobromide **230** must be purified by vacuum distillation, which also allows for removal of the by-product **236**, resulting from radical dimerization of diethyl ether (Table 13). Purification by column chromatography can be an option, if the reaction is performed in a relatively small scale and side product **232** is present in insignificant amounts. In the latter case it is essential to completely remove any remaining ethereal solvent from the crude product by evaporation in vacuum, as even a small amount of diethyl ether in the mixture affects the polarity of the system and

complicates separation. The yields of monobromides **230** were generally high, while the diastereoselectivity depended on the nature of aromatic substituent at C3. Generally, substrates possessing bulky aryl groups, such as *ortho*-substituted phenyls (Table 13, entries 4,7), or 1-naphthyl (entry 9) provided higher diastereoselectivities, than those bearing less bulky *para*- or *meta*-substituted arenes. In contrast, both *para*- (**230k**) and *ortho*-(**230l**) anisyl cyclopropanes were obtained as mixtures of *trans*- and *cis*-isomers with almost the same ratios (entries 11,12). In the context of cyclopropene synthesis, however, the diastereoselectivity is not an issue since both diastereomers of **230** are reactive toward dehydrohalogenation.

3.2.6. Dehydrohalogenation of monobromocyclopropanes.

Synthesis of cyclopropenes **231** from monobromocyclopropanes **230** was carried out in anhydrous DMSO in the presence of slight excess of *ᵗ*BuOK (Table 14).[155] It should be mentioned that the reaction is very sensitive to both traces of moisture and oxygen, and must be set up with appropriate precautions. In all our experiments potassium *tert*-butoxide was stored and handled in the nitrogen-filled glovebox, while Schlenk techniques were used for operations with all other reagents and solvents. The level of oxygen and moisture in the system could be visually monitored by the color of the reaction mixture which, depending on the substitution pattern, ranged from a baltic blue to dark spruce. The correctly set up reaction develops color very quickly and retains it until completion; however, in the presence of even small amounts of moisture and oxygen the mixture rapidly turns dark brown.

The product should be extracted and purified as quickly as possible after completion of the reaction to avoid decomposition. We found that extraction can be carried out under ambient atmosphere, as the product is reasonably stable in solution towards aqueous work up. Removal of solvents after extraction can be carried out using a rotovap; however, upon completion, the rotovap should be filled with inert gas in order to avoid exposure of the concentrated crude product to air. Final purification by distillation should be carried out in vacuum at the highest possible rate, at temperatures below 65 °C. The purified product should be stored in a freezer and handled under inert atmosphere, if prolonged storage is planned. We noticed that accidental brief exposure of arylcyclopropenes to air causes their slow decomposition, potentially, via a free radical-catalyzed polymerization. Thus, when a sample of cyclopropene **231a** was exposed to air for one hour at room temperature, and then was sealed under nitrogen, it completely decomposed within two weeks. Generally, cyclopropenes possessing electron-donating groups (**231b-d,k,l**) were more susceptible to decomposition, while more electron-deficient compounds **231f-h,j** were significantly more stable. However, with all the above-mentioned precautions the shelf life of arylcyclopropenes can be extended to more than a year.

Table 14. Synthesis of cyclopropenes **231**
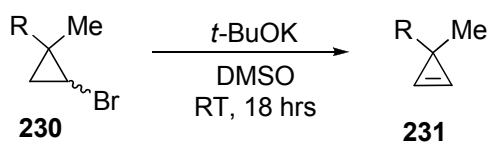
#	R		scale, mmol	bp, $^{\circ}$C(torr)	Yield **231**, %[a]
1	Ph[151]	**230a, 231a**	540	61-62(10)	79
2	p-MeC$_6$H$_4$	**230b, 231b**	17.8	30-35 (0.4)	77
3	m-MeC$_6$H$_4$	**230c, 231c**	18.4	60-61(5)	76
4	o-MeC$_6$H$_4$	**230d, 231d**	27.9	25-29 (0.4)	68
5	p-(^{t}Bu)C$_6$H$_4$	**230e, 231e**	34.3	ND[b]	86
6	p-ClC$_6$H$_4$	**230f, 231f**	12.5	ND[b]	79
7	o-ClC$_6$H$_4$	**230g, 231g**	12.3	ND[b]	86
8	p-CF$_3$C$_6$H$_4$	**230h, 231h**	16.3	49-52 (5)	69
9	1-Naphthyl	**230i, 231i**	17.3	ND[b]	66
10	p-FC$_6$H$_4$	**230j, 231j**	47.8	58-61(10)	76
11	p-MeOC$_6$H$_4$	**230k, 231k**	25.2	64-65(5)	82
12	o-MeOC$_6$H$_4$	**230l, 231l**	28.9	64-65(5)	92

[a] Isolated yields. [b] Boiling points were not determined; compounds were isolated by flash column chromatography.

3.2.7. Synthetic Studies toward 3-Methyl-3-(4-nitrophenyl)cyclopropene

In order to investigate the scope and limitations of the developed method, we also attempted synthesis of cyclopropene **231m** possessing a strongly electron-withdrawing *para*-nitro substituent. Our initial approach involved the Wittig olefination of acetophenone **234m**, followed by cyclopropanation of the resulting olefin **228m** with a dibromocarbene generated under the optimized PTC conditions (Scheme 46). These two transformations proceeded uneventfully, efficiently providing dibromocyclopropane **229m**. However, all our attempts to perform partial reduction of **229m** into bromocyclopropane **230m** were unproductive. The most efficient reduction protocols, such as Ti(IV)-catalyzed reduction with EtMgBr,[28] Mg- or Zn-assisted reductions,[172] and radical reduction with tributyltin hydride[27] produced no reaction, while an attempt to carry out the reduction in the presence of methyllithium[173] lead to complete decomposition of the starting material.

Scheme 46.
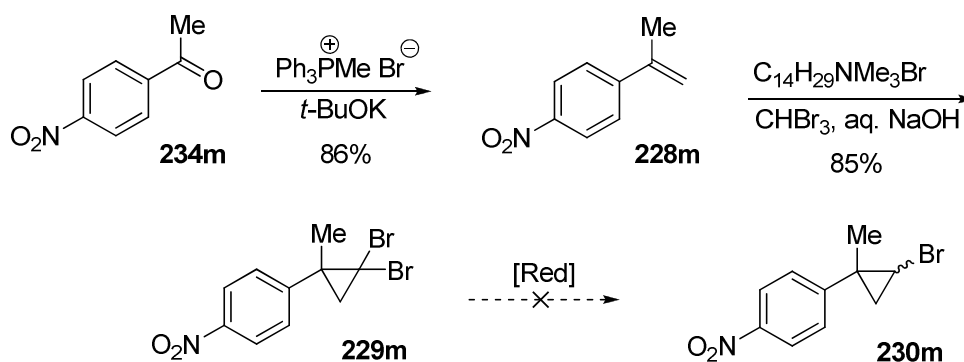
Accordingly, alternative approaches to monobromide **230m** were explored (Scheme 47).   First, we attempted cyclopropanation of **228m** with a monohalocarbene generated from dibromomethane and MeLi;[174] however, this reaction did not provide the desired product. In contrast, the electrophilic nitration[175] of bromocyclopropane **230a** provided *para*-nitro-derivative **230m** along with small amounts of an *ortho*-isomer (Scheme 47). However, all our attempts to carry out 1,2-dehydrobromination of **230m** in the presence of ^{t}BuOK in DMSO at various temperatures failed, leading to complete decomposition of the starting material (Scheme 47).

Scheme 47.
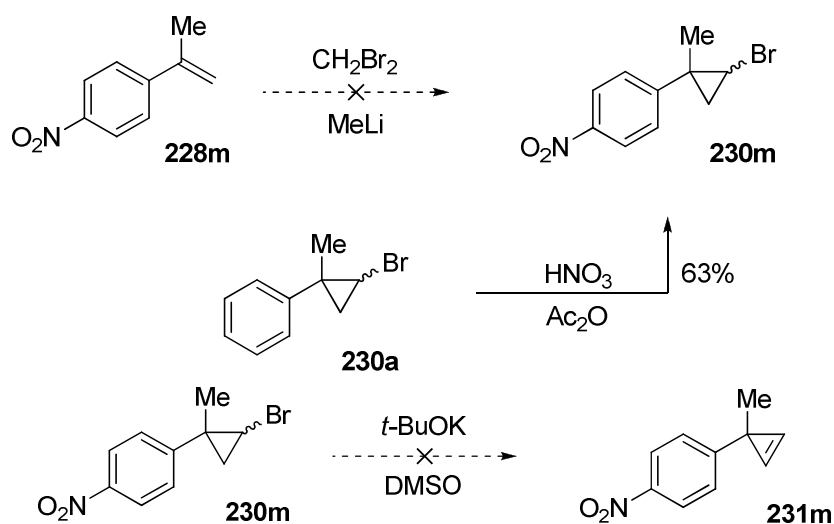
3.2.8. Conclusions

In conclusion, an efficient preparative protocol for synthesis of various 3-arylcyclopropenes in a multigram-scale was designed. Optimization of the reaction conditions and isolation procedures allowed for significant improvement of the

chemical yields of these strained products. The described protocol was used for efficient preparation of a series of 3-methyl-3-arylcyclopropenes possessing different substituents in the aromatic ring. Further work to expand the scope of this method to 3-alkyl-3-aryl- and 3-alkyl-3-hetarylcyclopropenes is currently underway in our laboratories.

3.3. Synthesis of Cyclopropenes via 1,2-Elimination of Bromocyclopropanes Catalyzed by Crown Ether

3.3.1. Introduction

As it was described in section 3.1 of this chapter, two general methods have largely been used for the synthesis of cyclopropenes **237.** These include the transition metal-catalyzed addition of carbenoids **238** to alkynes **239** (Scheme 48, Path **A**)[113,114,140a,141, 176] and a protocol involving 1,2-elimination of H-Hal[36a,39b,156,163d,174b] or Hal-Hal[130,142c,143, 177] entities from cyclopropyl halide precursors **240** (Scheme 48, Path **B**). The former method has been receiving much attention from the synthetic community, resulting in substantial expansion of its scope, thereby making available a range of cyclopropenes,[116,117a] including optically active compounds.[113,114,115,140a] In contrast, the second approach has not undergone any significant development in decades[178] since the first report on the synthesis of 3,3-disubstituted cyclopropenes via the 1,2-elimination of a hydrogen halide in the presence of ^{t}BuONa and DMSO.[179] At the same time, the requisite use of DMSO as a reaction medium significantly limits the potential of the method for scale up and its

appeal for process development. Furthermore, it becomes a major liability when the target cyclopropene is relatively hydrophilic. In this case, repetitive washing of the organic phase with water, necessary for complete removal of DMSO (Chapter 3.5.6),[178] leads to substantial loss of the product. Alternative approaches involving removal of DMSO by distillation or column chromatography usually do not provide satisfactory results, particularly in multigram scale syntheses. In an attempt to overcome this issue, we considered the possibility of replacing DMSO with alternative, more practical solvents. We rationalized that employment of chelating agents, such as crown ethers,[180] could potentially help enhance the basicity of ^{t}BuOK and enable an efficient elimination reaction in less polar media. It should be mentioned that preparative methods for 1,2-dehydrohalogenation in non-polar media employing 18-crown-6 ether as phase-transfer catalyst have been previously reported;[180] however, they have never been used for the preparation of strained olefins. Herein we wish to report a new protocol for the synthesis of cyclopropenes via a base-assisted 1,2-elimination in ethereal solvents in the presence of catalytic amounts of 18-crown-6 ether. We also demonstrate the application of the new method for the efficient synthesis of cyclopropenyl-3-carboxamides, an important class of functionalized cyclopropenes.[142b,150b.181]

Scheme 48. Two most important retro-synthetic approaches to cyclopropene core
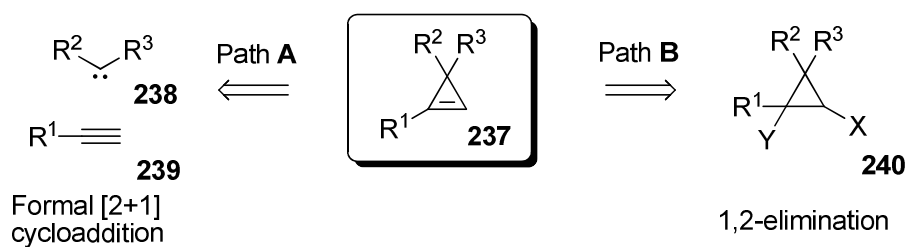
3.3.2. Results and Discussion

First, we tested dehydrobromination of 2-bromo-1-methyl-1-phenylcyclopropane (**230a**) with potassium *tert*-butoxide in THF in the presence of various amounts of 18-crown-6 ether (Table 15, entries 1-3). It was found that addition of stoichiometric amounts of crown ether facilitated a rapid dehydrohalogenation; however, notable decomposition of product **231a** was observed leading to moderate overall yields. Decreasing the amount of crown ether was beneficial for the reaction yield (Table 15, entries 2,3), and with additional optimization we discovered yields can be further improved by lowering the reaction temperature to 30 ^{o}C (Table 15, entry 4). Screening of various ethereal solvents demonstrated that THF and diethyl ether appear to be the most suitable media for this transformation. In contrast, reactions in dibutyl ether and diglyme did not produce any product at all (Table 15, entries 6,9), while employing other ethers resulted in a much slower and less efficient reaction. Although both THF and diethyl ether provided essentially the same results, we chose THF as a more practical solvent.

Table 15. Optimization of 1,2-Elimination Reaction
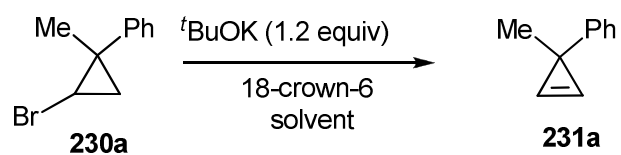
entry	18-crown-6 (equiv)	Solvent	Time (h)	T (^{o}C)	GC yield (%)
1	1.2	THF	1	50	40
2	0.3	THF	3	50	65
3	0.1	THF	3	50	70
4	0.1	THF	14	30	93
5	0.1	1,4-dioxane	48	30	86
6	0.1	Bu$_2$O	48	30	0
7	0.1	TBDME	48	30	76
8	0.1	DME	48	30	21
9	0.1	Diglyme	48	30	0
10	0.1	Et$_2$O	14	30	84

Table 16. Preparative Syntheses of Cyclopropenes
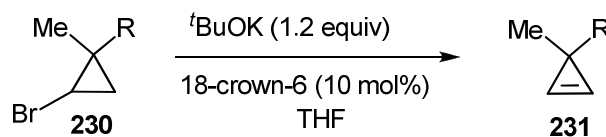
entry	R	Time (h)	T (^{o}C)	Yield (%)[a]
1	Ph (**230a**, **231a**)	18	30	85[b] (79)
2	2-Naphthyl (**230n**, **231n**)	18	30	84
3	2-FC$_6$H$_4$ (**230o**, **231o**)	18	40	75
4	C(O)NEt$_2$ (**230p**, **231p**)	3	30	90[c] (60)
5	C(O)N(i-Pr)$_2$ (**230q**, **231q**)	2	30	85 (69)
6	C(O)N(CH$_2$CH$_2$)$_2$O (**230r**, **231r**)	1	30	81 (30)
7	C(O)N(CH$_2$CH$_2$)$_2$CH$_2$ (**230s**, **231s**)	1	30	85 (61)
8	C(O)N(CH$_2$CH$_2$)$_2$NMe (**230t**, **231t**)	1	30	75 (50)
9	C(O)N(n-Hex)Me (**230u**, **231u**)	2	30	95
10	C(O)NPh$_2$ (**230v**, **231v**)	2	30	0
11	C(O)N(C$_6$H$_4$NO$_2$-4)Et (**230w**, **231w**)	18	40	0
12	C(O)NPhEt (**230x**, **231x**)	2	30	30
13	C(O)N(C$_6$H$_4$OMe-4)Et (**230y**, **231y**)	24	30	53

[a] Isolated yields (250 mg scale); isolated yields obtained in DMSO are provided in parentheses. [b] The reaction was performed on a 10.0 g scale. [c] The reaction performed on a 15.0 g scale afforded **230o** in 89 % yield.

Preparative scale synthesis under the optimized conditions provided 3-methyl-3-phenylcyclopropene (**231a**) in high yield, which slightly exceeded that obtained in DMSO (Table 16, entry 1).[178] Similarly, other 3-methyl-3-arylcyclopropenes (**231n,o**) were efficiently synthesized using the THF protocol (Table 16, entries 2,3). The major advantage of the new method was revealed in the synthesis of significantly more polar cyclopropenylcarboxamides **231p-u,x,y** (Table 16, entries 4-9, 12, 13). Thus, in contrast to the reactions performed in DMSO, which suffered from substantial product loss due to high hydrophilicity of the compounds, the new conditions allowed for high isolated yields for all alkyl-substituted amides tested.

Scheme 49. Decomposition of cyclopropene-3-carboxamides upon nucleophilic attack by *tert*-butoxide species
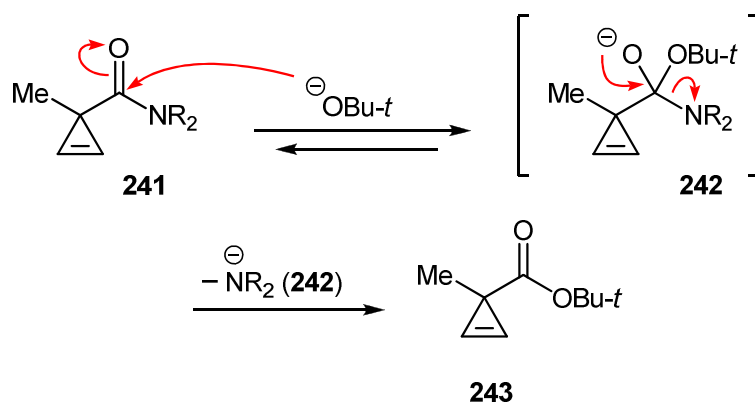
On the other hand, an attempted reaction employing *N,N*-diphenyl-carboxamide **230v** did not lead to the formation of a cyclopropene (Table 16, entry 10). The only product detected by GC/MS analysis of the crude reaction mixture was diphenylamine, suggesting this type of substrate has increased carbonyl activity.[182]

Apparently, the less electron rich nitrogen in diphenylamide **230v** as compared to dialkylamide analogs (Scheme 49), results in a greater positive charge on the carbon atom of carbonyl group. Furthermore, diphenylamide species **241** (R = Ph) makes a much better nucleofuge then dialkylamide equivalents, altogether making arylamides much more sensitive towards nucleophilic substitution by an alkoxide. To prove this rationale, we tested the dehydrobromination reaction on a series of *N*-ethyl-*N*-arylamides **230w-y**. Expectedly, the reaction of monobromide **230w** possessing the electron-poor *p*-NO$_2$C$_6$H$_4$ group resulted in rapid alcoholysis, affording *N*-ethyl-*p*-nitroaniline as the sole reaction product. It should be mentioned that formation of *tert*-butyl ester **243** was observed in this case at early stages of the reaction[183] (Table 16, entry 11). Similar results were obtained with phenyl-substituted amide **230x**; however, product decomposition proceeded much slower, permitting isolation of the corresponding cyclopropene **231x** in poor yield (Table 16, entry 12). Finally, more electron-rich anisidine-derived amide **230y** afforded cyclopropene **231y** in moderate yield (Table 16, entry 13). Overall, these results demonstrated a clear-cut trend between the electronic nature of the carboxamide and the stability of the corresponding product towards nucleophilic attack under the described reaction conditions.

3.3.3. Conclusions

In conclusion, a convenient, general protocol for the synthesis of cyclopropenes via dehydrobromination of bromocyclopropanes has been developed. The new optimized conditions significantly improved the scale-up compatibility of the method and allowed for expanding the scope of available cyclopropenes, particularly those possessing polar functionalities. Application of the new protocol for the efficient preparation of cyclopropene-3-carboxamides has been demonstrated. While all the cyclopropenes used in this work have a methyl group at C3, there is no indication that the presented synthetic method is limited to this particular type of substrates. The latter were chosen for this studies as the most readily available model compounds.

3.4. Rhodium-Catalyzed Hydroformylation of Cyclopropenes

3.4.1. Introduction

Cyclopropylcarboxaldehydes are arguably some of the most sought after compounds in the chemistry of small cycles. Not only are they themselves important biologically active targets,[184] but also are extremely versatile synthons as the aldehyde moiety can be readily transformed into a number of useful functionalities.[185] Established synthetic approaches towards these important targets include various

modes of [2 + 1] cycloadditions (Scheme 50, path **a**), such as Michael-initiated ring-closure reaction (MIRC)[186] the cyclization of conjugated aldehydes with carbenoid equivalents derived from dihalomethanes, [187 , 188] diazocompounds, [189] nitrogen ylides,[190] sulphur ylides,[191] or arsonium ylides;[192] as well as functional group transformations in pre-existing cyclopropyl rings, such as oxidation of cyclopropylmethanols (Scheme 50, path **b**),[193] reduction of cyclopropylcarboxylic acid derivatives (Scheme 50, path **c**),[194] and oxidative cleavage of the double bond in vinylcyclopropanes (Scheme 50, path **d**). [195] In light of the recent advances in chemistry of cyclopropenes,[138,143e-g, 196] we envisioned an alternative approach to cyclopropylcarboxaldehydes via catalytic hydroformylation[197] of the cyclopropene double bond (Scheme 50, path **e**). We hoped to develop a practical, atom economic, and mild protocol for the stereoselective installation of a new carbon-carbon bond in the three-membered cycle, while avoiding the use of reactive organometallic reagents invoked in most C-C bond forming reactions involving cyclopropenes. [138,142c,146, 198,199]

Scheme 50. Synthetic Approaches toward Formylcyclopropanes
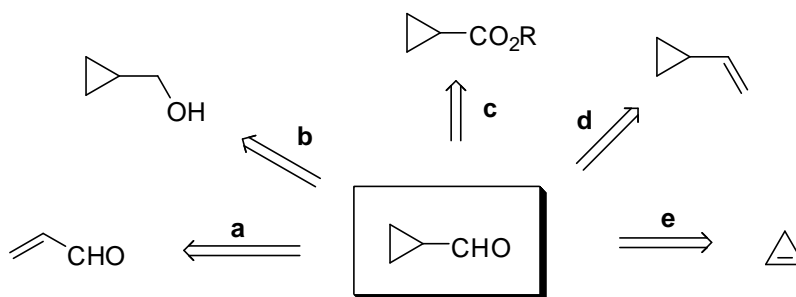
To date, hydroformylation of cyclopropenes is represented by a few stoichio-metric reactions mediated by $HMn(CO)_5$ or $HCo(CO)_4$, reported by Orchin and Noyori.[200,201] Orchin first demonstrated that 1,2-substituted cyclopropenes undergo hydroformylation in the presence of Mn- and Co-complexes to afford low yields of aldehyde **246**, accompanied by large amounts of the reduction product **245** (Scheme 51). Application of micellar catalysis allowed for improved yields of aldehydes (up to 93%); however, this reaction produced mixtures of *syn-* and *anti-*addition products.[200c] Later, Noyori investigated the hydroformylation reaction using a stoichiometric $HMn(CO)_5$ complex in various solvents, including $scCO_2$, yet was unsuccessful in obtaining an aldehyde yield above 40%.[201]

Scheme 51.
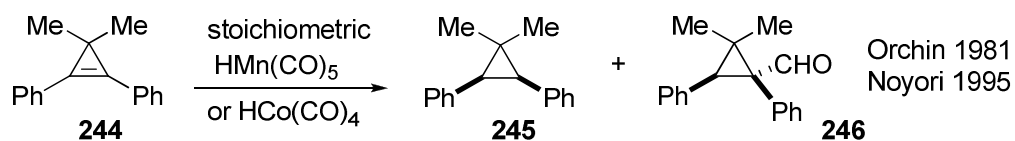
Herein we report the first examples of catalytic diastereo- and enantioselective hydroformylation of prochiral cyclopropenes to produce tri- and tetrasubstituted cyclopropylcarboxaldehydes, proceeding under mild conditions and very low catalyst loading (Scheme 52).

3.4.2. Results and Discussion

Scheme 52.
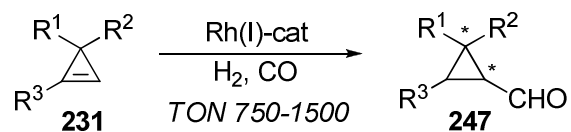
The long-standing challenge associated with the use of coordinatively unsaturated electron-deficient transition metal catalysts derived from metal carbonyl complexes in cyclopropene chemistry lies in the significantly more facile migratory insertion of cyclopropene into a metal-carbon bond (Scheme 53, Path **II**) as compared to the CO insertion step (Path **I**). Another commonly encountered problem is a very fast formal [2 + 2] dimerization of cyclopropenes occurring in the presence of electron-poor transition metal reagents (Scheme 53, Path III).[202, 203] These two dominating side processes do not allow efficient incorporation of the carbonyl functionality into the final product, leading instead to the formation of polymers and mixtures of oligocarbocyclic hydrocarbons and ketones.[204] To date, only one highly selective carbonylative transformation involving cyclopropenes, the Pauson-Khand reaction, has been reported; however, this process requires use of at least stoichiometric amounts of metal carbonyl complexes.[143d,205]

Scheme 53. Mechanistic Pathways for Different Processes Occurring in the Rh(I)-Catalyzed Hydroformylation of Cyclopropenes
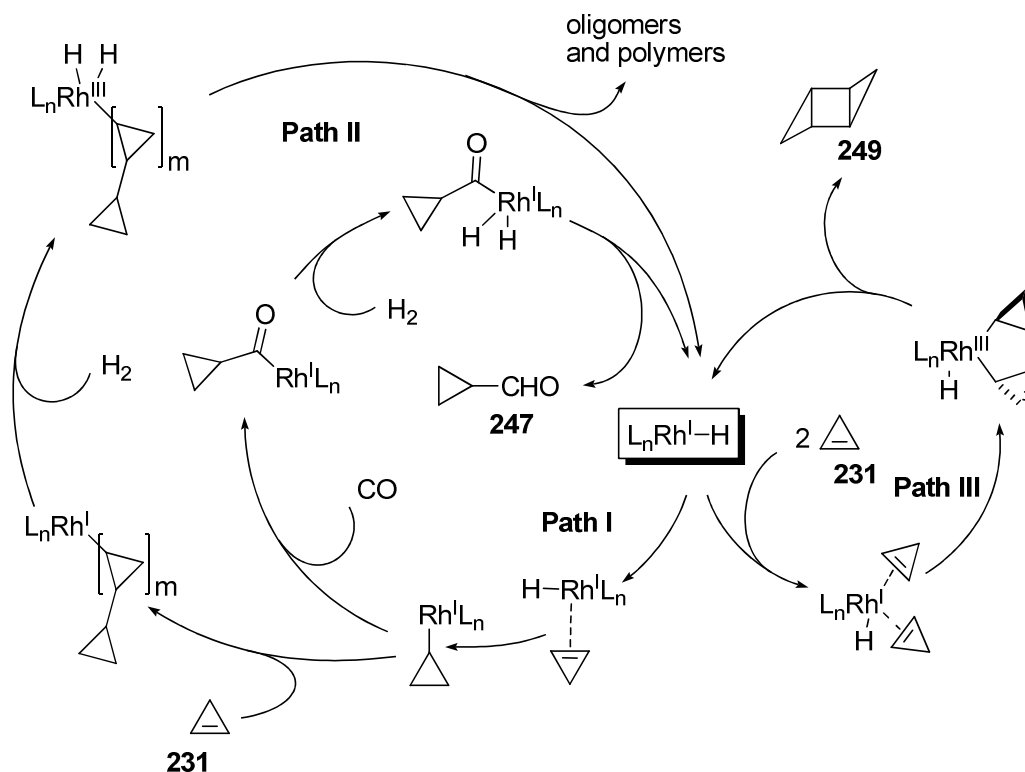
In line with the reasoning mentioned above, our initial experiments demonstrated that treatment of 3-methyl-3-phenylcyclopropene (**231a**) with syngas in the presence of standard hydroformylation catalyst, Rh(acac)(CO)$_2$, afforded quantitatively dimeric product **249** (Scheme 54). Attempts to suppress the unwanted cyclization by saturating the coordination sphere of the transition metal with monodentate phosphine ligands[206a,b] were unsuccessful (Scheme 54). Next, we tested several bidentate diphosphine ligands,[206c,d] anticipating their chelating effect would help stabilize the catalytically active Rh(I) species in a more saturated form. It was found that employment of dppm, dppp, and dppb in combination with Rh(acac)(CO)$_2$

allowed for suppressing of the redundant cyclization, however, it did not promote the hydroformylation reaction, leading instead to complete recovery of cyclopropene **231a** (Scheme 54). In contrast, the Rh(acac)(CO)$_2$/dppe combination produced desired product **247a** in low yield, whereas the analogous complex with a more rigid ferrocenyl backbone (dppf) provided complete conversion of **231a** into formylcyclopropanes **247a** and **248a** (Scheme 54). The hydroformylation reaction proceeded very diastereoselectively affording less sterically hindered aldehyde **247a** as a major product. Remarkably, no products of ring-opening were detected in this reaction. Based on the ligand effect observed, it would be reasonable to propose the reaction is very sensitive to the ligand bite angle; however, the enhanced catalytic activity of the dppf complex might also be explained by the increased electronic density provided by the ferrocenyl backbone.

Scheme 54.

L	Product
none, PPh$_3$, (o-Tol$_3$)P, TTMPP	**249** only
dppm, dppp, dppb	No reaction
dppe	**247a, 248a** (conv. 30%, **247a:248a** = 20:1)
dppf	**247a, 248a** (conv. >99%, **247a:248a** = 11:1)
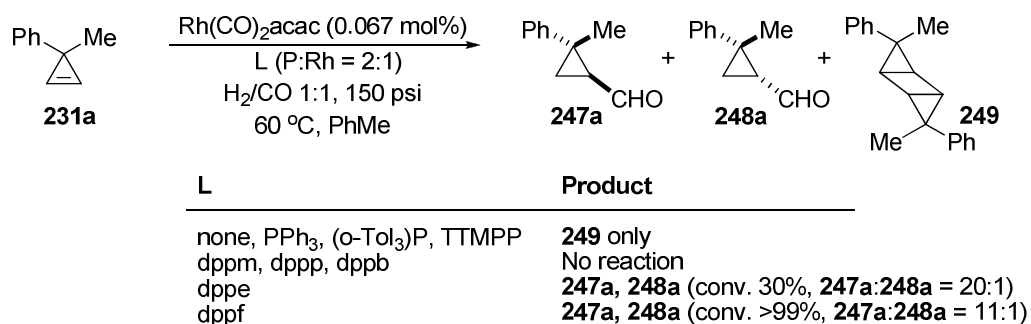
Preparative scale hydroformylation of **231a** also proceeded smoothly under these conditions providing aldehyde **247a** in high isolated yield. It was found that as little as 0.067 mol % of Rh(I) was enough to drive this reaction to completion under very mild conditions (Table 17, entry 1). Efficient isolation of products could be achieved either by column chromatography or by direct vacuum distillation of the reaction mixtures. The scope of this novel transformation was examined on a series of 3,3-disubstituted cyclopropenes (Table 17). Cyclopropenes **231f,j** bearing substituted aryl groups at C3 reacted uneventfully to provide the corresponding aldehydes **247f,j** (entries 1-3). Both acetal (entry 4) and ester (entry 5) protecting groups for a primary alcohol function were perfectly compatible with the reaction conditions: the corresponding aldehydes **247z** and **247aa** were obtained in high yield and good selectivity.   The diastereoselectivity of this transformation is largely controlled by steric factors. Thus, the reaction of electron-deficient cyclopropene **231ab** provided a nearly equimolar mixture of two diastereomeric cyclopropyl-carboxaldehydes **247ab** and **248ab** due to the similar effective size of the substituents at C3 (entry 6). At the same time, the analogous ester derivative bearing a small Me-group at C3 (**231ac**) reacted very selectively (entry 7). Finally, the substrate possessing a very bulky Bn-protected tertiary alcohol function (**231ad**) provided a single diastereomer of formylcyclopropane **247ad** (entry 8).   We also tested hydroformylation reaction of 1,3,3-trisubstituted cyclopropene **231ae**, which represents a more challenging model, as it can potentially produce four different products in the *syn*-specific addition and, therefore, requires simultaneous control of

facial and regioselectivity. It was found that standard reaction conditions using 0.067 mol % of Rh-catalyst did not produce any reaction with **231ae**, presumably, due to the increased steric demand in the substrate. However, increasing catalyst loading to 1 mol % provided tetrasubstituted cyclopropane **247ae** in good yield and high regio- and diastereoselectivity (entry 9).

Table 17. Rh(I)-Catalyzed Hydroformylation of 3,3-Disubstituted Cyclopropenes
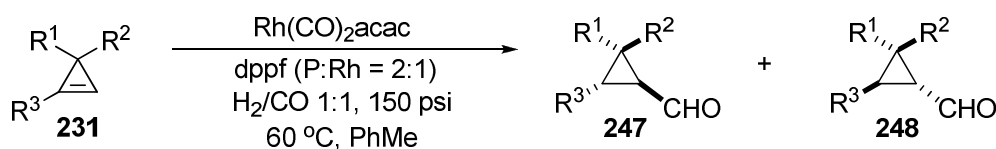
Entry	R^1	R^2	R^3		Rxn time, hrs (246:Rh ratio)[a]	Yield of 247, %[c]	dr (247:248)[b]
1	Ph	Me	H	**231a**	18 (1500:1)	**247a** 87	11:1
2	p-Cl-C$_6$H$_4$	Me	H	**231f**	18 (1500:1)	**247f** 71[d]	8:1
3	p-F-C$_6$H$_4$	Me	H	**231j**	18 (100:1)	**247j** 91[d]	12:1
4	Ph	CH$_2$OMOM	H	**231z**	36 (1500:1)	**247z** 72	10:1
5	Ph	CH$_2$OAc	H	**231aa**	36 (1500:1)	**247aa** 75	7:1
6	Ph	CO$_2$Me	H	**231ab**	18 (1500:1)	**247ab** 90[d]	1:1
7	CO$_2$Me	Me	H	**231ac**	36 (1500:1)	**247ac** 64	24:1
8	CMe$_2$OBn	Me	H	**231ad**	72 (1500:1)	**247ad** 91	-[e]
9	Ph	Me	Me	**231ae**	18 (100:1)	**247ae** 80[d]	7:1[f]

[a] dppf:Rh molar ratio of 2:1 was employed. [b] Determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Isolated yields of a major diastereomer. [d] Combined isolated yields of two diastereomers. [e] A single diastereomer **247ad** was obtained. [f] Regioselectivity of >10:1 was observed.

Naturally, having in hand efficient conditions for the diastereoselective hydroformylation, we were very intrigued by the possibility of performing an asymmetric hydroformylation of prochiral cyclopropenes (Table 18). We began our optimization[207] by testing several commercially available ligands, which were shown to produce high enantioselectivities in the asymmetric hydroformylation (AHF) of styrene.[42,80,81,82,84,85,208] However, all of these ligands provided unsatisfactory results in the hydroformylation of cyclopropene **231a**. Thus, Ph-BPE (**83**),[86] reported by Klosin as one of the best-performing ligands for the AHF of terminal olefins, provided **247a** with 42% ee only (Table 18, entry 1). Another highly reputed AHF ligand BINAPINE (**121**) afforded 18% ee in the reaction with **231a** (entry 2). Further optimization demonstrated that, generally, all C_2-symmetric phospholane ligands provided significantly lower enantioselectivities than those observed in the AHF of styrenes (entries 3-7). Next, we screened a series of C_1-symmetric ligands with planarly chiral ferrocene backbone (entries 8 - 19). This family of ligands[209] possesses great structural diversity and a wide spectrum of electronic properties. Here again, it was found that several ligands showing respectable selectivities in hydroformylation of styrenes, demonstrated less than satisfying results in the reaction with **231a** (entries 10,11). And *vice versa*, the "obvious outsiders" unexpectedly produced promising enantioselectivities (entry 19). While not comprehensive, this screening clearly demonstrated that the existing immense experience in ligand optimization acquired

Table 18. Ligand Screening in the Asymmetric Hydroformylation of 3-Methyl-3-phenylcyclopropene (**231a**).
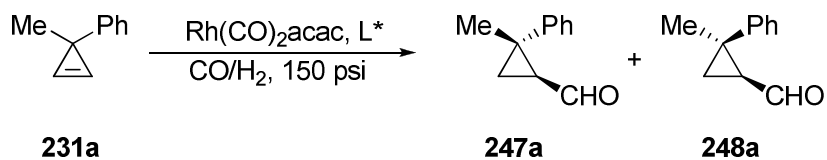
#	Ligand	conv, % (NMR)	dr[c] 247a:248a	ee[d] % 247a	ee % 248a
1	(*R,R,R,R*)-Ph-BPE (**83**)	100	12:1	-42	-3
2	(*R*)-BINAPINE (**121**)	49	13:1	+18	+1
3	(*R,R,S,S*)-Tangphos (**127**)	100	2.9:1	+31	-24
4	(*R,R,S,S*)-DUANPHOS (**126**)	100	14:1	+8	-3
5	(*S,S,S,S*)-Me-DUPHOS (**101**)	6	4:1	-10	N/D
6	(*R,R,R,R*)-*i*Pr-DUPHOS (**104**)	100	13:1	-18	+43
7	CatASium m(R) (**86**)	0	-	-	-
8	Josiphos J001-1 (**89**)	82	14:1	+14	-6
9	Josiphos J002-1 (**90**)	80	10.6:1	+56	-41
10	Josiphos J003-1 (**91**)	95	18.5:1	+24	-7
11	Josiphos- J008-1 (**249**)	100	14:1	+16	-20

Table 18. Continued

12	Josiphos- J010-1 (**250**)	23	27:1	-19	-4
13	Walphos W001-1 (**93**)	100	5.4:1	+50	+33
14	Walphos W002-1 (**94**)	100	10.3:1	+42	+28
15	Taniaphos T001-1 (**95**)	96	7:1	-43	-34
16	Taniaphos T003-1 (**251**)	100	12:1	-47	-36
17	Taniaphos T021-1 (**252**)	<1	-	N/D	N/D
18	Mandyphos M001-1 (**87**)	<1	-	N/D	N/D
19	Mandyphos M004-1 (**88**)	100	27:1	-73	+23
20	(*R*)-BINAP (**80**)	84	12:1	-13	+28
21	(*R*)-Tol-BINAP (**81**)	72	13:1	-1	+19
22	(*R*)-Xyl-BINAP (**82**)	52	20:1	+14	-10
23	CTH-(*R*)-BINAM (**110**)	0	-	-	-
24	(R)-SYNPHOS (**111**)	86	15:1	-64	+77
25	(R)-SOLPHOS (**112**)	70	22:1	-68	+78
26	(R)-Xyl-SOLPHOS (**113**)	50	31:1	-53	N/D

Table 18. Continued

27	(R)-C₃-TUNEPHOS (**118**)	100	25:1	-74	+78
28	(R)-DIFLUOROPHOS (**114**)	86	12:1	-36	+64
29	BIPHEP SL-A101 (**115**)	4	13:1	-8	-3
30	BIPHEP SL-A109 (**116**)	36	34:1	-45	+10
31	(*R*)-Cl-MeO-BIPHEP (**117**)	64	13:1	-41	+47
32	CTH-R-P-PHOS (**99**)	100	15:1	-27	+55
33	CTH-R-Xyl-P-PHOS (**100**)	100	36:1	-13	+22
34	(*R,R*)-NORPHOS (**105**)	2	9:1	N/D	N/D
35	(*R,R*)-DIOP (**123**)	100	10:1	-16	+27
36	(*S,S*)-CHIRAPHOS (**107**)	91	16:1	-5	+10
37	(*S*)-PHANEPHOS (**97**)	0	-	-	-
38	(*S*)-Xyl-PHANEPHOS (**98**)	0	-	-	-
39	CARBOPHOS (**108**)	30	11:1	+13	0
40	(*R,R*)-BINAPHANE (**122**)	8	6:1	+2	+20
41	(*R*)-SDP (**120**)	0	-	-	-

Table 18. Continued

42	CTH-R-SpiroP (**119**)	90	5:1	+36	-50
43	CatASium I (**125**)	<1		N/D	N/D
44	CatASium T2 (**106**)	7	4.4:1	+2	0
45	CatASium DR (**124**)	50	13:1	+12	-6
46	Rhophos P001-2 (**253**)	0	-	-	-

[a] A Rh:L ratio of 1:1.2 was employed.[86] [b] In the cited literature the opposite enantiomers of these ligands were employed; accordingly, the opposite enantiomers of the products were obtained. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Negative values of ee are provided when the levorotatory (*R,R*)-enantiomer was obtained as major product. Positive values of ee indicate the predominant formation of the dextrorotatory (*S,S*)-product.

through the AHF of terminal olefins cannot be directly applied to the hydroformylation of small cycles. Such a discrepancy is not surprising, considering the significant difference in geometry, electronic properties, and reactivity of the two types of substrates.

Accordingly, we performed an independent search for the best catalytic system. To this end, we performed screening of a few more sets of commercially available chiral diphosphine ligands, which included a group of C_2-symmetric ligands with a flexible axially chiral backbone (entries 20-33), and several other types of chiral ligands featuring both flexible and rigid scaffolds (entries 34-46). Although no promising results were obtained in the latter case, the screening of the former group appeared to be more rewarding. Thus, promising results were obtained for

SYNPHOS (**111,** entry 24), SOLPHOS (**112,** entry 25), and DIFLUOROPHOS (**114,** entry 28), while the best conversion and enantioselectivity were attained in the presence of C3-TUNEPHOS (**118,** entry 27). Notably, C3-TUNEPHOS was previously reported to be a marginal ligand for the AHF of styrene.[86]

3.4.3. Stereochemical Rational

The following rationale, based on molecular mechanics modeling (UUF), was used to account for the origins of diastereo- and enantioselectivity in the asymmetric hydroformylation reaction (stereomodels **A1** and **A2**, Figure 22).[210] As mentioned above, the facial selectivity of the reaction is controlled by sterics, as the approach of the rhodium hydride species predominantly occurs from the less hindered face of the cyclopropene (*i.e.*, *syn-* to a smaller substituent, Figure 22). The absolute stereochemistry of the process is determined by the relative orientation of the cyclopropene in the resulting rhodium complex (**A1** vs **A2**). Molecular modeling suggests the two pseudo-equatorial phenyl rings at the phosphorus atoms of (*R*)-C3-TUNEPHOS obstruct quadrants **II** and **IV** (shaded in gray in Figure 22), while quadrants **I** and **III**, with the pseudo-axial phenyl groups slightly tilted back, remain relatively unhindered.[211] Accordingly, the orientation of the cyclopropene in the trigonal bipyramidal rhodium complex **A1** is such that it minimizes the unfavorable interaction of the small substituent "S" with the phenyl groups of the ligand, favoring complex **A1** vs **A2**, which explains the absolute stereochemistry of the obtained products **247a** (Figure 22).[212]
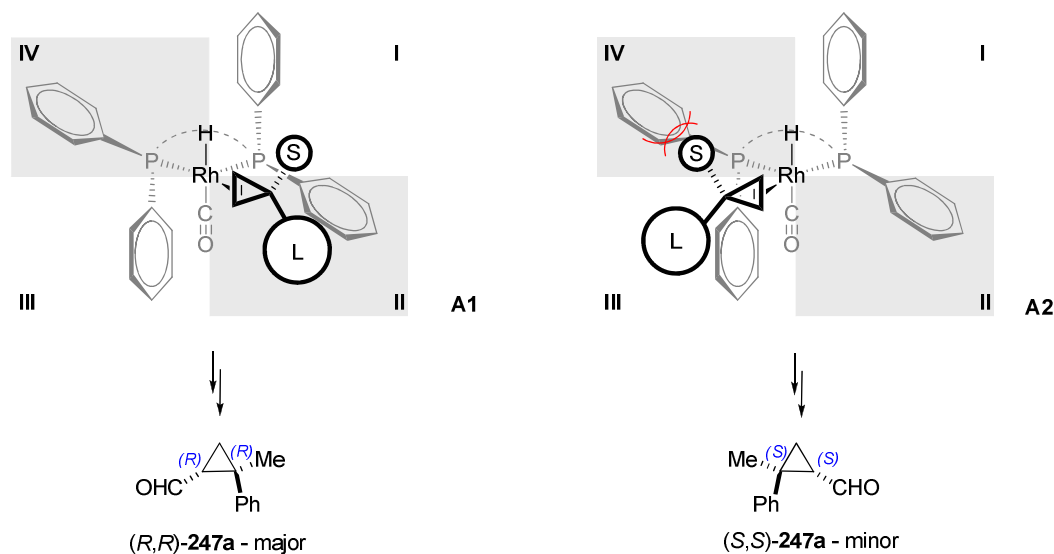
Figure 22. Proposed stereomodels for the Rh/(*R*)-C3-TUNEPHOS-catalyzed hydroformylation.

3.4.4. Scope and Limitation Studies

To investigate the scope of the asymmetric hydroformylation reaction, we tested a series of cyclopropenes possessing different substituents at C3 in the presence of Rh/C3-TUNEPHOS catalyst (Table 19). It was found that the enantioselectivity of this reaction depended significantly on the substrate nature. Thus, phenyl- and ester-substituted cyclopropenes **231ac** and **231a** provided the corresponding formylcyclopropanes with 74 % ee (entries 1,3), while hydroformylation of cyclopropene **231ad** possessing a benzyl-protected tertiary alcohol function afforded aldehyde **247ad** with only moderate ee of 57 % (entry 2). Remarkably, in the hydroformylation of the 3-arylcyclopropene series (Table 19, entries 3-5),

introduction of an electron-withdrawing substituent in the *para*-position of the aryl ring led to a notable improvement of enantioselectivity (entry 4), whereas installation of an electron-donating group resulted in deterioration of ee (entry 5). The reasons for this unusual electronic effect are not yet completely understood. Further work to improve the enantioselectivity of this asymmetric transformation, and to understand the origins of the observed significant electronic effect on the enantioinduction of hydroformylation, is currently underway in our laboratories.

Table 19. Rh-Catalyzed Asymmetric Hydroformylation of 3,3-Disubstituted Cyclopropenes

conversion (NMR) >99%

(*R*)-C3-TUNEPHOS

#	R^1		**246**: [Rh] ratio	dr (**247:248**)	ee % **247**	Yield, %	$[\alpha]_D$ (conc., CH_2Cl_2)
1	CO_2Me	**231ac**	750:1	22:1	74	63	-109.8 (c 1.17)
2	CMe_2OBn	**231ad**	375:1	**247** only	57	82	-24.6 (c 1.25)
3	Ph	**231a**	750:1	25:1	74	86	-114.3 (c 1.42)
4	p-Cl-C_6H_4	**231f**	375:1	17:1	83	54	-137.8 (c 0.64)
5	p-Me-C_6H_4	**231b**	750:1	17:1	68	78	-128.1 (c 1.56)

3.4.5. Conclusions

In conclusion, we demonstrated the first catalytic diastereo- and enantioselective hydroformylation of prochiral cyclopropenes proceeding under very mild conditions and low loadings of the Rh(I)-catalyst. Optimization of the reaction protocol allowed for complete suppression of the dominating side processes, and

permitted design of a novel, efficient catalytic carbonylative transformation amenable for scale-up production. This methodology opens new avenues toward efficient preparation of optically active cyclopropylcarboxaldehydes, valuable building blocks for synthetic chemistry.

3.5. Experimental Section

3.5.1 Improved Preparative Route toward 3-Arylcyclopropenes (DMSO Method)

3.5.2. General Information

See Chapter 1.4.1. for instrumentation details.

Anhydrous dimethylsulfoxide was purchased form Acros Organics and used as received. Anhydrous diethyl ether and tetrahydrofuran were obtained by passing degassed HPLC-grade commercially available solvents consecutively through two columns with activated alumina (Innovative Technology). All other chemicals were purchased from Sigma-Aldrich or Acros Organics, and used as received.

3.5.3. Preparation of dibromocyclopropanes

Typical procedure:
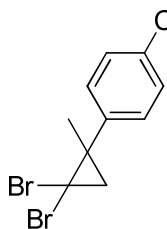
229f: Magnesium turnings (1.44 g, 60 mmol) were stirred in anhydrous ether (60 mL) and methyl iodide (3.7 mL) was added dropwise maintaining moderate reflux of the reaction mixture. Then the mixture was stirred for 30 min and ethyl *p*-chlorobenzoate (3.50 g, 19 mmol) in ether (10 mL) was added dropwise. The resulting mixture was stirred for 2 hrs, then quenched with saturated aqueous NH_4Cl and extracted with ether. Combined ethereal layers were washed consecutively with 5% aqueous HCl, 10% $NaHCO_3$, and brine, dried with $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (50 mL), *p*-toluenesulfonic acid (100 mg) was added, and the mixture was stirred at reflux for 2 hrs. When GC analysis showed the reaction complete, the mixture was cooled to room temperature, and quenched with aqueous $NaHCO_3$. The organic phase was separated, aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. To the vigorously stirred solution of the resulting residue, bromoform (61 mmol, 4.9 mL) and cetrimide (100 mg) in dichloromethane (20 mL), 50 % aqueous solution of NaOH (5 mL) was added dropwise. The stirring at room temperature was continued for 24 hrs, when GC analysis showed the reaction complete. Then the mixture was quenched with water (100 mL) and extracted with dichloromethane (3 x 50 mL). Combined organic phases were washed consecutively with dilute aqueous HCl, water, and brine, then dried with $MgSO_4$, filtered and

concentrated in vacuum. Flash column chromatography of the residual oil on Silica gel (eluent - hexane) gave dibromocyclopropane **229f** as colorless oil. Overall yield 5.63 g (17.4 mmol, 91 %).

^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.15 (d, *J* = 7.6 Hz, 1H), 1.81 (d, *J* = 7.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 140.8, 133.0, 129.9 (+, 2C), 128.6 (+, 2C), 36.0, 35.2, 33.8 (-), 27.5 (+). GC/MS (EI 70 eV) 12.01 min, m/z 324 (M+, <1%), 309 (M-Me, 1%)+, 245 (34%), 163 (55%), 129 (100%); HRMS (TOF ES) Found 242.9578, Calculated for C$_{10}$H$_9$BrCl (M-Br) 242.9576 (0.1 ppm).
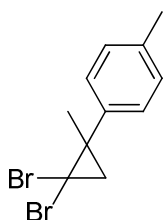
229b:[213] ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 2.40 (s, 3H), 2.19 (d, *J* = 7.6 Hz, 1H), 1.81 (d, *J* = 7.6 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 139.3, 136.9, 129.1 (+, 2C), 128.3 (+, 2C), 37.1, 35.4, 33.7 (+), 27.7 (-), 21.2 (+); HRMS (TOF ES) Found 223.0122, Calculated for C$_{11}$H$_{12}$Br (M-Br) 223.0122 (0.0 ppm).
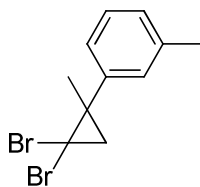
229c: ^{1}H NMR (400.13 MHz, CDCl3) δ 7.28 (t, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 2.41 (s, 3H), 2.19 (d, *J* = 7.6 Hz, 1H), 1.80 (d, *J* = 7.6 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 142.2, 138.0, 129.2 (+), 128.2 (+), 128.0 (+), 125.5 (+), 36.9, 35.7, 33.7 (-), 27.8 (+), 21.5 (+); HRMS (TOF ES) Found 223.0114, Calculated for C$_{11}$H$_{12}$Br (M-Br) 223.0122 (3.6 ppm).
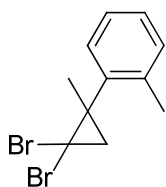
229d:[214] ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.29 (d, J = 7.6 Hz, 1H), 7.25 (ps.-t, J = 7.6 Hz, 7.1 Hz, 1H), 7.19 (ps.-t, J = 7.3 Hz, 7.1 Hz, 1H), 7.13 (d, J = 7.3 Hz, 1H), 2.58 (s, 3H), 2.14 (d, J = 7.3 Hz, 1H), 1.84 (d, J = 7.3 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 140.9, 137.6, 130.8 (+), 128.4 (+), 127.3 (+), 126.0 (+), 37.7, 35.8, 34.4 (-), 25.7 (+), 20.0 (+);
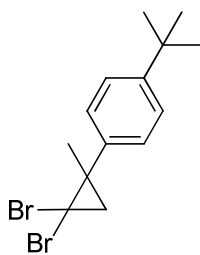
229e: ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.40 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 2.19 (d, J = 7.6 Hz, 1H), 1.80 (d, J = 7.6 Hz, 1H), 1.74 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 150.0, 139.2, 128.0 (+, 2C), 125.2 (+, 2C), 37.1, 35.3, 34.5, 33.7 (+), 31.4 (+, 3C), 27.7 (-); HRMS (TOF ES) Found 265.0588, Calculated for C$_{14}$H$_{18}$Br (M-Br) 265.0592 (1.5 ppm).
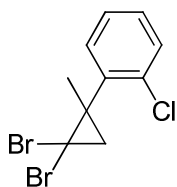
229g: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major atropomer: 7.47 (m, 1H), 7.28-7.24 (m, 2H), 7.20 (m, 1H), 2.11 (d, J = 7.6 Hz, 1H), 1.84 (d, J = 7.6 Hz, 1H), 1.75 (s, 3H); minor atropomer: 7.59 (dd, J = 7.6 Hz, 1.8 Hz, 1H), 7.38 (dd, J = 7.7 Hz, 1.3 Hz, 1H), 7.33 (td, J = 7.6 Hz, 1.3 Hz, 1H), 7.28 (m, 1H), 2.21 (d, J = 8.1 Hz, 1H), 2.05 (d, J = 8.1 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major atropomer: 140.4, 135.2, 130.2 (+), 130.0 (+), 128.7 (+), 127.0 (+), 36.2, 35.6, 34.3 (-), 24.5 (+); minor atropomer: 138.8, 134.1,

132.7 (+), 130.1 (+), 128.5 (+), 126.4 (+), 37.5 (-), 36.2, 34.1, 27.1 (+); GC/MS (EI 70 eV) 11.75 min, m/z 324 (M+, <1%), 309 (M-Me, 3%)+, 245 (35%), 163 (58%), 129 (100%); HRMS (TOF ES) Found 242.9576, Calculated for $C_{10}H_9BrCl$ (M-Br) 242.9576 (0.0 ppm).
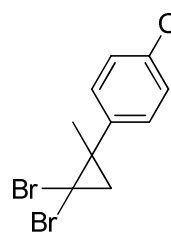
229h: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 2.21 (d, J = 7.6 Hz, 1H), 1.87 (d, J = 7.6 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 146.2, 129.5 (q, $^2J_{CF}$ = 32.9 Hz), 129.0 (+, 2C), 125.4 (q, $^3J_{CF}$ = 3.7 Hz, +, 2C), 124.1 (q, $^1J_{CF}$ = 272.3 Hz), 35.5, 35.2, 33.8 (-), 27.5 (+); ^{19}F NMR (376.50 MHz, $CDCl_3$) δ -62.4; HRMS (TOF ES) Found 276.9843, Calculated for $C_{11}H_9BrF_3$ (M-Br) 276.9840 (1.1 ppm).
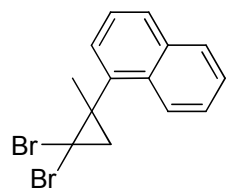
229i: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.71 (ps.t, J = 7.3 Hz, 7.1 Hz, 1H), 7.59 (t, J = 7.3 Hz, 1H), 7.46 (ps.t, J = 7.8 Hz, 7.3 Hz, 1H), 7.36 (d, J = 7.1 Hz, 1H), 2.31 (d, J = 7.6 Hz, 1H), 2.01 (d, J = 7.6 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 139.7, 134.0, 131.4, 128.6 (+), 128.0 (+), 126.2 (+), 126.0 (+), 125.9 (+, 2C), 125.4 (+), 37.3, 35.4, 34.4 (-), 27.0 (+); HRMS (TOF ES) Found 259.0130, Calculated for $C_{14}H_{12}Br$ (M-Br) 259.0122 (3.1 ppm).

3.5.4. Preparation of dibromocyclopropanes from acid-sensitive styrenes

Alternative procedure:

Scheme 55.

229j: Ar = 4-FC$_6$H$_5$
229k: Ar = 4-OMeC$_6$H$_5$
229l: Ar = 2-OMeC$_6$H$_5$
229n: Ar = 2-naphthyl
229o: Ar = 2-FC$_6$H$_4$
229m Ar = 4-NO$_2$C$_6$H$_5$
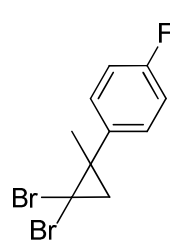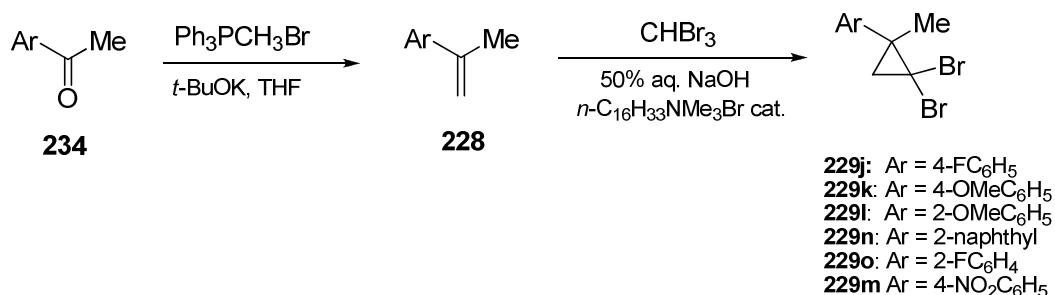
229j: To a stirred at 0 °C suspension of methyltriphenylphosphonium bromide (41.37 g, 115.8 mmol, 1.6 equiv.) in anhydrous THF (175 mL) was added dropwise solution of potassium *tert*-butoxide (7.76 g, 69.13 mmol, 0.955 equiv.)   The resulting yellow suspension was stirred for 1 hr at 0 °C, then *p*-fluoroacetophenone (10.0 g, 8.7 mL, 72.39 mmol) was added dropwise.   The mixture was stirred overnight, then quenched with aqueous NH$_4$Cl, and partitioned between water and diethyl ether.   The ethereal extract was dried with Na$_2$SO$_4$, filtered, and concentrated.   The residue was purified by short column chromatography (eluent - hexane) to afford *p*-fluoro-α-methylstyrene (10e) as a colorless oil.   Yield 7.68 g (56.4 mmol, 82%).   This material without further purification was mixed with bromoform (25.22 g, 8.7 mL, 99.8 mmol, 1.66 equiv.), benzyltriethylammonium chloride (TEBAC) (117 mg, 0.51 mmol, 0.85 mol%), and dichloromethane (20 mL).   The mixture was vigorously stirred, and 50% aqueous solution of sodium hydroxide was added dropwise.   The mixture was stirred (900-

1100 rpm) overnight at 30-35 °C, when GC/MS analysis indicated full conversion of the olefin. Then, the mixture was quenched with water (100 mL) and extracted with dichloromethane (3 x 50 mL). Combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with hexane. Yield 14.63 g (50.97 mmol, 86%).

^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.31 (dd, J = 8.3 Hz, $^4J_{HF}$ = 5.3 Hz, 2H), 7.07 (ps.-t, J = $^3J_{HF}$ = 8.3 Hz, 2H), 2.16 (d, J = 7.6 Hz, 1H), 1.82 (d, J = 7.6 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 161.8 (d, $^1J_{CF}$ = 245.9 Hz), 138.1 (d, $^4J_{CF}$ = 3.7 Hz), 130.1 (d, $^3J_{CF}$ = 8.1 Hz, +, 2C), 115.3 (d, $^2J_{CF}$ = 21.2 Hz, +, 2C), 36.4, 35.1, 33.8 (-), 27.7 (+); HRMS (TOF ES) Found 226.9872, Calculated for C$_{10}$H$_9$BrF (M-Br) 226.9872 (1.3 ppm).
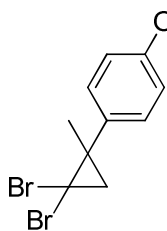
229k:[155] ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.84 (s, 3H), 2.15 (d, J = 7.6 Hz, 1H), 1.78 (d, J = 7.6 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 158.6, 134.5, 129.5 (+, 2C), 113.7 (+, 2C), 55.2 (+), 37.4, 35.1, 33.7 (-), 27.7 (+);
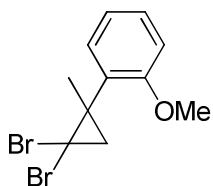
229l: ^{1}H NMR (CDCl$_3$, 400.13 MHz) □ 7.32 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.09 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.95 (ps.-t, J = 8.3 Hz, 7.6 Hz, 1H), 3.99 (s, 3H), 2.05 (d, *J* = 7.6 Hz, 1H), 1.77 (d, *J* = 7.6 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 158.1, 131.2, 128.9 (+), 128.6 (+), 120.4 (+), 110.8 (+), 55.6 (+), 37.5, 34.1 (-), 34.0, 24.6 (+); HRMS (TOF ES) Found 239.0072, Calculated for C$_{11}$H$_{12}$BrO (M-Br) 239.0072 (0.0 ppm).
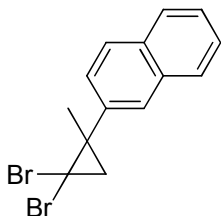
229n: Flash column chromatography on silica gel (eluent - hexane) gave clear oil, yield 10.31 g (30.3 mmol, 66%).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.90 (m, 4H), 7.76 (s, 1H), 7.56 (m, 2H), 2.36 (d, *J* = 7.6 Hz, 1H), 1.91 (d, *J* = 7.6 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 140.0, 133.3, 132.6, 128.2 (+), 127.9 (+), 127.8 (+), 127.0 (+), 126.9 (+), 126.3 (+), 126.1 (+), 36.7, 36.0, 33.9 (-), 27.7 (+).
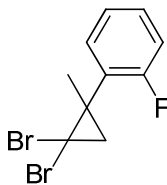
229o: Quick filtration through a short plug of silica gel (eluent: hexane) afforded clear oil, yield 10.14 g (32.9 mmol, 88%).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.31 (m, 2H), 7.15 (m, 2H), 2.14 (br. d, *J* = 7.6 Hz, 1H), 1.84 (br. s, 1H), 1.72 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 160.2 (d, $^1J_{CF}$ = 250.3 Hz), 130.0 (br.), 129.7 (+, br.), 129.2 (+, d, J = 8.0 Hz), 124.2 (+), 115.8 (+, d,

$^2J_{CF}$ = 21.2 Hz), 35.5 (br.), 33.8 (-, br.), 25.1 (br.), 14.1 (+, br.); ^{19}F NMR (376.50

MHz, CDCl$_3$) δ -113.6.
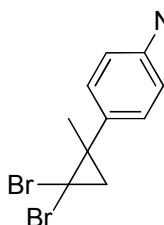
229m: [2 + 1] cycloaddition of dibromocarbene to olefin **228m** was carried out according to the typical procedure described above. The reaction was performed in 2.37 mmol scale, and afforded 674.8 mg (2.01 mmol, 85%) of dibromocyclopropane **229m**.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H),

2.23 (d, J = 7.8 Hz, 2H), 1.92 (d, J = 7.8 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (100.67

MHz, CDCl$_3$) δ 149.5, 145.0, 129.6 (+, 2C), 123.7 (+, 2C), 35.5, 34.5, 33.9 (-), 27.3

(+).

3.5.5. Partial reduction of dibromocyclopropanes:

Typical procedure:
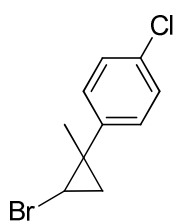
230f: To a stirred solution of dibromocyclopropane **229f** (5.63 g, 17.4 mmol) and titanium (IV) isopropoxide (10 mol%, 1.7 mmol, 490 µL) in anhydrous diethyl ether (50 mL) was added dropwise 3M solution of ethylmagnesium bromide (21 mmol, 7.0 mL). When

intensive gas evolution had ceased, the mixture was stirred at room temperature for 2

hrs, then cooled in an ice bath and quenched by consecutive addition of water (10

mL) and 10 % aqueous sulfuric acid (20 mL). Organic phase was separated; aqueous layer was extracted with ether (3 x 25 mL). Combined ethereal phases were washed consecutively with 10% aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on Silica gel (eluent – hexane) to afford bromocyclopropane **230f** as colorless oil (mixture of two diastereomers 1.8:1).[215] Yield 3.08 g (12.5 mmol, 72%). ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.29 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 3.20 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 1.64 (ps.t, *J* = 8.0 Hz, 7.2 Hz, 1H), 1.62 (s, 3H), 3.20 (dd, *J* = 7.2 Hz, 4.8 Hz, 1H); minor: 7.35 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 3.11 (dd, *J* = 7.4 Hz, 4.5 Hz, 1H), 1.46 (s, 3H), 1.41 (ps.t, *J* = 7.4 Hz, 6.8 Hz, 1H), 1.37 (dd, *J* = 6.8 Hz, 4.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major: 142.9, 132.2, 128.6 (+, 2C), 128.4 (+, 2C), 30.1 (+), 25.3, 23.8 (+), 23.3 (-); minor: 140.7, 132.5, 130.7 (+, 2C), 128.3 (+, 2C), 27.9 (+), 27.0, 26.8 (+), 22.2; GC/MS (EI 70 eV) major: 10.80 min, m/z 246 (M[+],<1%), 165 (M-Br, 100%); minor: 10.65 min, m/z 246 (M[+], <1%), 165 (M-Br, 100%), HRMS (TOF ES) Found 165.0047, Calculated for $C_{10}H_{10}Cl$ (M-Br) 165.0470 (0.6 ppm).
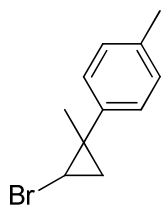
230b: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.17 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.23 (dd, *J* = 7.8 hz, 4.3 Hz, 1H), 2.35 (s, 3H), 1.65 (ps.-t, *J* = 7.8 Hz, 6.5 Hz, 1H), 1.62 (s, 3H), 1.07 (dd, *J* = 6.5 Hz, 4.6 Hz, 1H); minor: 7.25 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 3.11 (dd, J = 7.2 Hz, 4.6 Hz, 1H), 2.38 (s, 3H), 1.47 (s, 3H), 1.40-1.37 (m, 2H); ^{13}C NMR

(CDCl$_3$, 100.61 MHz) δ major 141.5, 136.1, 129.2 (+, 2C), 126.9 (+, 2C), 30.6 (+),

25.4, 24.0 (+), 23.2 (-), 21.0 (+); minor 139.2, 136.3, 129.2 (+, 2C), 128.9 (+, 2C),

28.4 (+), 27.2, 27.0 (+), 22.1 (-), 21.1 (+); HRMS (TOF ES) Found 223.0121,

Calculated for C$_{11}$H$_{12}$Br (M-H) 223.0122 (0.4 ppm).
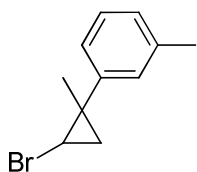
230c: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.36-7.11 (m, 4H), 3.31 (dd, J = 8.1 Hz, 4.8 Hz, 1H), 2.43 (s, 3H), 1.72 (ps.-t, J = 8.1 Hz, 6.3 Hz, 1H), 1.70 (s, 3H), 1.14 (dd, J = 6.3 Hz, 4.8 Hz, 1H);

minor: 7.36-7.11 (m, 4H), 3.15 (dd, J = 7.6 Hz, 4.3 Hz, 1H), 2.47 (s, 3H), 1.53 (s, 3H), 1.48-1.41 (m, 2H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major: 144.4, 138.1, 128.4 (+), 127.8 (+), 127.2 (+), 124.0 (+), 30.6 (+), 27.0 (+), 25.7, 24.0 (+), 23.2 (-); minor: 142.0, 137.6, 130.1 (+), 128.0 (+), 127.6 (+), 126.4 (+), 28.3 (+), 27.5 (+), 22.0 (-), 21.5, 21.4 (+); HRMS (TOF ES) Found 223.0123, Calculated for C$_{11}$H$_{12}$Br (M-H) 223.0122 (0.4 ppm).
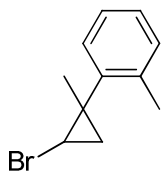
230d: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.24-7.21 (m, 1H), 7.18-7.14 (m, 3H), 3.22 (dd, J = 8.1 Hz, 4.6 Hz, 1H), 2.43 (s, 3H), 1.57 (ps.-t, J = 8.1 Hz, 6.3 Hz, 1H), 1.52 (s, 3H), 1.09 (dd, J = 6.3 Hz, 4.6 Hz, 1H);

^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 142.7, 137.2, 130.6 (+), 128.9 (+), 126.9 (+), 126.0 (+), 30.8 (+), 26.1, 23.3 (+), 23.2 (-), 19.3 (+); HRMS (TOF ES) Found 208.9958, Calculated for C$_{10}$H$_{10}$Br (M-Me) 208.9966 (3.8 ppm).
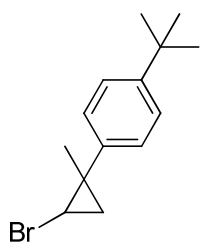
230e: ¹H NMR (CDCl₃, 400.13 MHz) δ major: 7.41 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 3.30 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 1.73 (dd, *J* = 7.8 Hz, 6.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 9H), 1.14 (dd, *J* = 6.3 Hz, 4.8 Hz, 1H); minor 7.45 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.16 (dd, *J* = 7.3 Hz, 4.3 Hz, 1H), 1.70 (s, 3H), 1.47-1.43 (m, 2H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 100.61 MHz) δ major: 149.3, 141.3, 126.5 (+, 2C), 125.4 (+, 2C), 34.4, 31.3 (+, 3C), 30.7 (+), 25.1, 23.8 (+), 23.4 (-); minor: 149.4, 139.0, 128.9 (+. 2C), 125.0 (+, 2C), 34.4, 31.4 (+, 3C), 28.5 (+), 27.1, 27.0 (+), 22.1 (-); HRMS (TOF ES) Found 187.1491, Calculated for C₁₄H₁₉ (M-Br) 187.1487 (2.1 ppm).
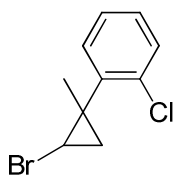
230g: ¹H NMR (CDCl₃, 400.13 MHz) δ major: 7.40-7.37 (m, 1H), 7.34-7.31 (m, 1H), 7.26-7.18 (m, 2H), 3.28 (dd, *J* = 8.3 Hz, 4.9 Hz, 1H), 1.61 (dd, *J* = 8.3 Hz, 6.2 Hz, 1H), 1.59 (s, 3H), 1.16 (dd, *J* = 6.2 Hz, 4.9 Hz, 1H); ¹³C NMR (CDCl₃, 100.61 MHz) δ major: 141.9, 135.0, 130.5 (+), 129.9 (+), 128.2 (+), 126.9 (+), 30.3 (+), 26.1, 23.4 (-), 22.6 (+); HRMS (TOF ES) Found 165.0478, Calculated for C₁₀H₁₀Cl (M-Br) 165.0471 (4.2 ppm).
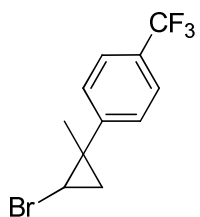
230h: ¹H NMR (400.13 MHz, CDCl₃) δ major: 7.59 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 3.24 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 1.71 (dd, *J* = 8.1 Hz, 6.6 Hz, 1H), 1.66 (s, 3H), 1.17 (dd, *J* = 6.6 Hz, 4.8 Hz, 1H); minor: 7.64 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 3.14 (dd, *J* =

7.5 Hz, 4.4 Hz, 1H), 1.50 (s, 3H), 1.47 (dd, J = 7.5 Hz, 6.6 Hz, 1H), 1.43 (dd, J = 6.6

Hz, 4.4 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ major: 148.4, 128.8 (q, $^2J_{CF}$ =

32.9 Hz), 127.4 (+, 2C), 125.5 (q, $^3J_{CF}$ = 3.7 Hz, +, 2C), 124.1 (q, $^1J_{CF}$ = 272.3 Hz),

30.0 (+), 25.6, 23.54 (+), 23.49 (-); minor: 146.2, 129.8 (+, 2C), 129.0 (q, $^2J_{CF}$ = 32.9

Hz), 125.2 (q, $^3J_{CF}$ = 3.7 Hz, +, 2C), 124.1 (q, $^1J_{CF}$ = 271.5 Hz), 27.5 (+), 26.6 (+),

25.6, 22.3 (-); ^{19}F NMR (376.50 MHz, CDCl$_3$) δ major: -62.44; minor: -62.37;

GC/MS: major (R$_t$ = 9.40 min) 278 (M$^+$, <1%), 259 (M$^+$ – F, 1%) , 209 (M$^+$ – CF$_3$,

1%), 199 (M$^+$ – Br, 100%); minor (R$_t$ = 9.22 min) 278 (M$^+$, <1%), 259 (M$^+$ – F, 1%) ,

209 (M$^+$ – CF$_3$, 1%), 199 (M$^+$ – Br, 100%). HRMS (TOF ES) Found 199.0734,

Calculated for C$_{11}$H$_{10}$F$_3$ (M-Br) 199.0735 (0.5 ppm).
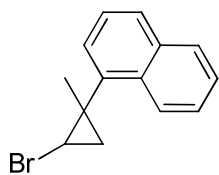
230i: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 8.24 (d, J = 8.3 Hz, 1H),

7.91 (d, J = 8.1 Hz, 1H), 7.79 (dd, J = 6.3 Hz, 3.3 Hz, 1H), 7.63

(td, J = 8.3 Hz, 1.7 Hz, 1H), 7.55 (td, J = 8.1 Hz, 1.0 Hz, 1H),

7.46-7.43 (m, 2H), 3.39 (d, J = 8.1 Hz, 4.5 Hz, 1H), 1.75 (s, 3H), 1.76 (m, 1H), 1.28

(dd, J = 6.3 Hz, 4.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 141.1, 134.0, 131.6,

128.8 (+), 127.6 (+), 126.3 (+), 126.0 (+), 125.7 (+), 125.5 (+), 124.8 (+), 30.8 (+),

25.6, 24.2 (+), 23.1 (-); HRMS (TOF ES) Found 181.1014, Calculated for C$_{14}$H$_{13}$ (M-

Br) 181.1017 (1.7 ppm).
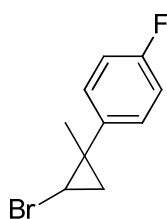
230j: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.25 (dd, J = 8.6 Hz, $^4J_{HF}$ = 5.3 Hz, 2H), 7.02 (ps.-t, J = $^3J_{HF}$ = 8.6 Hz, 2H), 3.22 (dd, J = 7.8 Hz, 4.8 Hz, 1H), 1.64 (dd, J = 7.8 Hz, 6.3 Hz, 1H), 1.62 (s, 3H), 1.10 (dd, J = 6.3 Hz, 4.8 Hz, 1H); minor: 7.31 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.6 Hz, 2H); 7.07 (ps.-t, J = $^3J_{HF}$ = 8.8 Hz, 2H), 3.11 (dd, J = 7.3 Hz, 4.3 Hz, 1H), 1.47 (s, 3H), 1.41 (dd, J = 7.3 Hz, 6.8 Hz, 1H), 1.37 (dd, J = 6.8 Hz, 4.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major: 161.4 (d, $^1J_{CF}$ = 245.2 Hz), 140.2 (d, $^4J_{CF}$ = 2.9 Hz), 128.7 (d, $^3J_{CF}$ = 8.1 Hz, +, 2C), 115.3 (d, $^2J_{CF}$ = 21.2 Hz, +, 2C), 30.1 (+), 25.3, 24.1 (+), 23.2 (-); minor: 161.6 (d, $^1J_{CF}$ = 245.2 Hz), 138.0 (d, $^4J_{CF}$ = 3.7 Hz), 130.9 (d, $^3J_{CF}$ = 8.1 Hz, +, 2C), 115.0 (d, $^2J_{CF}$ = 21.2 Hz, +, 2C), 28.1 (+), 26.97 (+), 26.94, 22.3 (-); HRMS (TOF ES) Found 149.0767, Calculated for C$_{10}$H$_{10}$F (M-Br) 149.0767 (0.7 ppm).
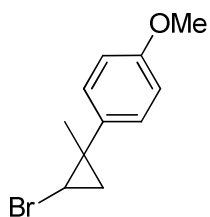
230k:[155] ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.20 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.22 (dd, J = 8.3 Hz, 4.8 Hz, 1H), 1.63 (dd, J = 8.7 Hz, 4.1 Hz, 1H), 1.62 (s, 3H), 1.07 (dd, J = 6.1 Hz, 4.8 Hz, 1H); minor: 7.28 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.11 (ps.-t), 1.46 (s, 3H), 1.37 (d, J = 5.8 Hz, 2H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major: 158.2, 136.6, 128.1 (+, 2C), 113.9 (+, 2C), 55.3 (+), 30.5 (+), 25.2, 24.2 (+), 23.2 (-); minor: 158.3, 134.4, 130.4 (+, 2C), 113.5 (+, 2C), 55.1 (+), 28.7 (+), 27.1 (+), 26.9, 22.2 (-);
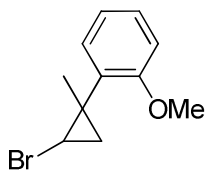
230l: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ major: 7.29-7.23 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 3.92 (s, 3H), 3.25 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 1.57 (s, 3H), 1.54 (ps.-t, *J* = 7.8 Hz, 6.1 Hz, 1H), 1.07 (dd, *J* = 6.1 Hz, 4.8 Hz, 1H); minor: 7.35-7.26 (m, 2H), 7.01-6.96, m, 2H), 3.93 (s, 3H), 3.17 (dd, *J* = 7.6 Hz, 4.3 Hz, 1H), 1.46 (s, 3H), 1.39 (dd, J = 7.6 Hz, 6.3 Hz, 1H), 1.31 (dd, *J* = 6.3 Hz, 4.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ major: 158.3, 132.6, 129.4 (+), 128.0 (+), 120.3 (+), 110.6 (+), 55.29 (+), 30.6 (+), 23.6, 22.84 (+), 22.78 (-); minor: 158.6, 130.7 (+), 130.5, 128.2 (+), 120.2 (+), 110.7 (+), 55.32 (+), 28.4 (+), 25.4, 24.3 (+), 22.6 (-); HRMS (TOF ES) Found 161.0968, Calculated for C$_{11}$H$_{13}$O (M-Br) 161.0966 (1.2 ppm).
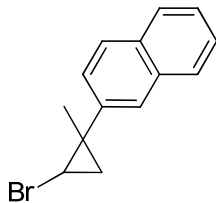
230n: was obtained as a mixture of diastereomers in a ratio of ~2:1 as determined by ^{1}H NMR. Isolated and purified via short column chromatography on silica gel (eluent - hexane) to afford an opaque, slowly crystallizing oil. Yield 5.185 g (30.3 mmol, 73%).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [7.84 (m), Σ4H], [7.72 (s), Σ1H], [7.50 – 7.42 (m), Σ2H], [3.35 (dd, *J* = 8.1 Hz, 4.5 Hz) & 3.19 (dd, *J* = 7.3 Hz, 4.3 Hz), Σ1H], [1.81 (ps.t, *J* = 6.6 Hz) & 1.57 (m), Σ1H], [1.74 (s) & 1.57 (s), Σ3H], [1.49 (ps.t, *J* = 7.3 Hz) & 1.02 (ps.t, *J* = 6.1 Hz), Σ1H], [1.19 (dd, *J* = 6.3 Hz, 4.6 Hz) & 0.85 (dd, *J* = 5.8 Hz, 4.0 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 141.9, 140.0, 139.9, 133.4, 132.5, 132.2, 128.4 (+), 128.0 (+), 127.9 (+), 127.8 (2C, +), 127.7 (2C, +), 127.6 (2C,

+), 126.3 (+), 125.9 (+), 125.7 (+), 125.6 (+), 125.5 (+), 30.4 (+), 28.3 (+), 27.9, 26.9

(+), 26.3, 24.1 (+), 23.3 (-), 22.3 (-); HRMS (TOF ES) Found 181.1022, Calculated

for $C_{14}H_{13}$ (M-Br) 181.1017 (2.8 ppm).
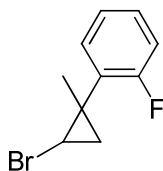
230o: was purified through flash chromatography on silica gel (eluent - hexane) to afford a mixture of diastereomers in a ratio of ~ 2:1 as a colorless oil. Yield 6.89 g (30.1 mmol, 91%).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [7.27 (m), & 7.09 (m) Σ 4H], [3.27 (dd, J = 8.3, 4.8

Hz) & 3.15 (dd, J = 7.6, 4.6 Hz), Σ1H], [1.58 (s) & 1.43 (s), Σ3H], [1.58 (m) & 1.43

(ps.t, J = 6.6 Hz), Σ1H], [1.35 (m) & 1.10 (dd, J = 6.3, 4.8 Hz), Σ1H]; ^{13}C NMR

(100.61 MHz, CDCl$_3$) δ 163.4 (d, $^1J_{CF}$ = 248.1 Hz), 163.0 (d, $^1J_{CF}$ = 248.8 Hz), 131.6,

131.4 (+, d, J = 4.3 Hz), 130.0 (+, d, J = 4.0 Hz), 129.6, 128.8 (+, d, J = 8.3 Hz),

128.6 (+, d, J = 7.9 Hz), 124.1 (+, d, J = 3.7 Hz), 123.9 (+, d, J = 3.7 Hz), 115.7 (+, d,

J = 21.2 Hz), 115.6 (+, d, J = 22.0 Hz), 29.2 (+), 27.3 (+), 24.9 (+), 24.4, 23.4 (+),

22.5, 22.4 (-), 22.3 (-); ^{19}F NMR (376.50 MHz, CDCl$_3$) δ -114.9, -115.8;   HRMS

(TOF ES) Found 149.0767, Calculated for $C_{10}H_{10}F$ (M-Br) 149.0767 (0.7 ppm).
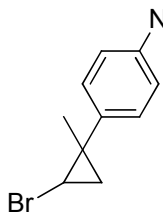
230m: Bromocyclopropane **230a** (5.00 g, 23.7 mmol) was stirred at 0 ^{o}C in acetic anhydride (22 mL), and nitric acid (9.9 mL) was added dropwise. The mixture was stirred at 0 ^{o}C for 10 min, then warmed up to RT and stirred overnight, then quenched with brine (20 mL),

neutralized with aqueous NaHCO$_3$ (50 mL), and extracted with EtOAc (3 x 100 mL). Combined organic phases were dried with MgSO$_4$, filtered, and concentrated. The residue was purified by vacuum distillation on Kugelröhr (ot 110-112 ^{o}C at 0.4 torr).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [8.24 (d, J = 8.5 Hz) & 7.82 (d, J = 8.5 Hz) & 8.18 (d, J = 7.8 Hz), & 7.41 (d, J = 7.8 Hz) Σ 2H], 7.53 (m, 2H), [3.23 (m) & 3.16 (dd, J = 7.6 Hz, 4.6 Hz), Σ 1H], [1.76 (ps. t, J = 7.3 Hz), & 1.45 (ps.t, 6.8 Hz), & 1.23 (dd, J = 6.7 Hz, 4.8 Hz), & 1.15 (dd, J = 11.6 Hz, 6.8 Hz, 4.8 Hz) Σ 1H], [1.71 (s), & 1.67 (s), & 1.62 (s), & 1.51 (s) Σ 3H], 1.53-1.43 (m, 4H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 152.0, 149.7, 139.1, 133.0 (+), 132.2 (+), 130.4 (+), 128.1 (+), 127.7 (+), 124.4 (+), 123.9 (+), 123.6 (+), 31.9 (+), 30.0 (+), 29.7 (+), 27.6, 27.3 (+), 26.4 (+), 25.7, 25.4, 24.4, 24.2 (-), 23.3 (+), 23.1 (-), 22.6 (-).

3.5.6. Synthesis of Amido-monobromocyclopropanes

Scheme 56.
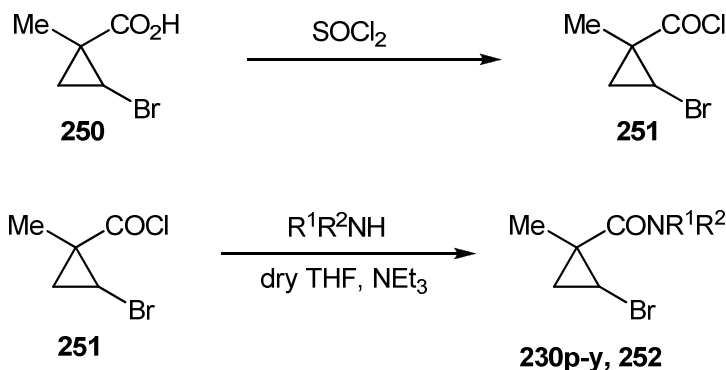
230p: $R^1 = R^2 = $ Et
230q: $R^1 = R^2 = $ *i*-Pr
230r: $R^1R^2 = (CH_2CH_2)_2O$
230s: $R^1R^2 = (CH_2CH_2)_2CH_2$
230t: $R^1R^2 = (CH_2CH_2)_2NMe$

230v: $R^1 = R^2 = $ Ph
230w: $R^1 = p\text{-}NO_2C_6H_4$, $R^2 = $ Et
230x: $R^1 = $ Ph, $R^2 = $ Et
230y: $R^1 = p\text{-}MeOC_6H_4$, $R^2 = $ Et
252: $R^1 = n\text{-}Hexyl$, $R^2 = $ H
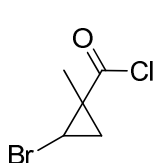
251: 2-Bromo-1-methylcyclopropanecarboxylic acid (**250**)[37b] (25.9 g, 200 mmol, mixture of diastereomers, 1:1) and freshly distilled thionyl chloride (50 mL) were stirred at room temperature overnight. Excess of thionyl chloride was distilled off at ambient pressure. The residue was distilled in vacuum, b.p. 50-53 °C (10 mm Hg) to obtain a mixture of diastereomeric acylchlorides 1:1 as a colorless oil. Yield 37.9 g (192 mmol, 96%). This material was used as is in further acylations of primary and secondary amines as described below.
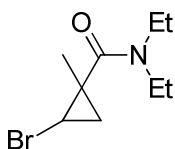
230p: (Typical Procedure) To a stirred solution of freshly distilled diethyl amine (5.56 g, 7.94 mL, 76 mmol) under an atmosphere of N_2

in anhydrous THF (20 mL) was added the acid chloride **251** (5 g, 25.3 mmol) in dry THF (35 mL) dropwise. After ~ 1 hr of stirring at room temperature the starting materials was consumed as judged by GCMS analysis; then the precipitate formed in the reaction mixture was removed by suction filtration and the filter cake was rinsed with THF (2 x 20 mL). Then, the precipitate was dissolved in water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried with Mg_2SO_4, combined with the THF filtrate and condensed in vacuum. Vacuum distillation in a Kugelröhr at 90 °C at 0.6 mm Hg gave the product as a pale-yellow oil. Overall yield 5.64 g (24.1 mmol, 95 %).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ [3.71 (m) & 3.57 (m), & 3.32 (m), & 3.19 (m), Σ4H], [3.13 (dd, J = 7.3 Hz, 4.6 Hz) & 2.96 (dd, J = 7.3 Hz, 4.6 Hz), Σ1H], [1.67 (dd, J = 6.7 Hz, 4.8 Hz) & 1.59 (dd, J = 6.7 Hz, 4.8 Hz), Σ1H], [1.25 (t, J = 14.3 Hz, 7.1 Hz) & 1.10 (t, J = 14.0 Hz, 7.0 Hz), Σ3H], [1.43 (s) & 1.35 (s), Σ3H], [1.11-1.06 (m) & 0.86 (dd, J = 6.7 Hz, 5.0 Hz), Σ4H]; ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 171.1, 169.6, 41.2 (-), 41.1(-), 39.0 (-), 38.9 (-), 27.9, 27.4 (+), 25.9 (+), 22.2 (-), 22.0, 21.6 (+), 21.4 (-), 20.6, 13.9 (+), 13.7 (+), 12.4 (+), 12.2 (+); HRMS (TOF ES): found 234.0490, calculated for $C_9H_{17}BrNO$ (M+H) 234.0493 (1.3 ppm).
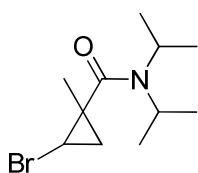
230q: This material was prepared according to the typical procedure starting from 2.00 g (10.1 mmol) of acyl chloride **251** and freshly distilled diisopropylamine (4.50 mL, 3.13 g, 30.3 mmol). Yield 2.31 g (8.79 mmol, 87 %). The physical and spectral properties of this substance were identical to those reported in literature.[216]
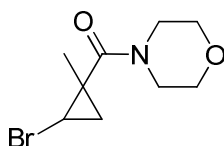
230r: This compound was obtained starting from 5.00 g (25.3 mmol) of acyl chloride **251**, and freshly distilled morpholine (6.6 mL, 6.62 g, 76 mmol) according to a typical procedure. Vacuum distillation in a Kugelröhr (oven temperature 133 °C at 0.6 torr) of the resulting residue afforded 5.52 g (22.3 mmol 88 % yield) of the title compound (mixture of trans- and cis-isomers 1:1) as a colorless oil.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 3.68 (m, 8H), [3.15 (dd, J = 8.3 Hz, 5.1 Hz) & 2.98 (dd, J = 7.6 Hz, 4.8 Hz), Σ1H], [1.70 (ps.t, J = 8.1) & 1.58 (dd, J = 6.8 Hz, 4.8 Hz), Σ1H], [1.45 (s) & 1.37 (s), Σ3H], [1.20 (ps.t, J = 7.3 Hz) & 0.91 (dd, J = 6.6 Hz, 4.8 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 170.6, 168.9, 67.1 (-), 66.9 (-), 66 .7 (-, 2C), 46.4 (-), 42.6 (-), 27.5 (+), 27.1, 25.6, 25.4 (+), 21.6 (-), 21.4 (+), 21.2 (-), 19.4 (+); HRMS (TOF ES): found 168.1026, calculated for C$_9$H$_{14}$NO$_2$ (M-Br) 168.1025 (0.6 ppm).
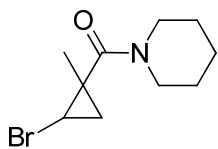
230s: This compound was obtained starting from 5.10 g (25.8 mmol) of acyl chloride **251**, and freshly distilled piperidine (7.7 mL, 6.60 g, 85 mmol). Vacuum distillation in a Kugelröhr (oven temperature 150 °C at 0.4 torr) of the resulting residue afforded 6.26 g (25.4 mmol, 98 % yield) of the compound (mixture of *trans-* and *cis*-isomers 1:1) as a colorless oil.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [3.70-3.57 (m) & 3.49-3.35 (m), Σ4H], [3.11 (dd, *J* = 8.1 Hz, 4.8 Hz) & 2.94 (dd, *J* = 8.1 Hz, 4.8 Hz), Σ1H], 1.65-1.45 (m, 7H), [1.38 (s) & 1.30 (s), Σ3H], [1.10 (ps. t, *J* = 8.6 Hz, 5.3 Hz) & 0.82 (ps.t, *J* = 6.8 Hz, 4.8 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 170.1, 168.8, 46.9 (-), 43.2 (-), 27.9, 27.5 (+), 26.5 (-), 26.1 (-), 26.0 (+), 25.7, 25.6 (-), 24.6 (-), 24.5 (-), 21.9 (-), 21.7 (+), 21.3 (-), 19.5 (+); HRMS (TOF ES): found 166.1233, calculated for C$_{10}$H$_{16}$NO (M-Br) 166.1232 (1.0 ppm).
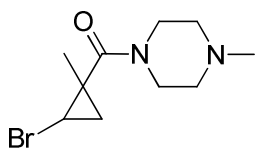
230t: This compound was obtained starting from 5.00 g (25.3 mmol) of acyl chloride **251**, and freshly distilled 1-methyl-piperazine (8.5 mL, 7.61 g, 76 mmol). Purification was performed by vacuum distillation in a Kugelröhr (oven temperature 150 °C at 0.6 torr), and afforded 5.72 g (21.9 mmol 87 % yield) of the compound (mixture of *trans-* and *cis*-isomers 1:1) as a colorless oil.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 3.75-3.45 (m, 4H), [3.09 (dd, J = 4.89 Hz, 4.12 Hz) & 2.92 (dd, J = 4.89 Hz, 4.12 Hz), Σ1H], 2.55-2.27 (m, 4H), [2.25 (s) & 2.24 (s), Σ3H], [1.60 (ps.t, J = 8.1 Hz, 7.1 Hz) & 1.48 (ps.t, J = 8.1 Hz, 7.1 Hz), Σ1H], [1.38 (s) & 1.30 (s), Σ3H], [1.11 (ps.t, J = 7.7 Hz, 6.8 Hz) & 0.82 (ps.t, J = 7.7 Hz, 6.8 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 170.2, 168.8, 55.4 (-), 54.6 (-), 46.1 (+), 46.0 (+), 45.8 (-), 42.1 (-), 28.3 (-), 27.7 (+), 27.3 (+), 25.6, 25.5, 21.7 (-), 21.6 (-), 19.5 (+); HRMS (TOF ES): found 261.0603, calculated for C$_{10}$H$_{18}$BrN$_2$O (M+H) 261.0603 (0.0 ppm)
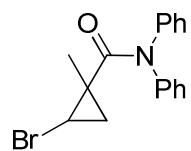
230u: To a stirred solution of diphenylamine (4.23 g, 25 mmol, 1eq.), DMAP (100 mg), and triethylamine (5 mL) in THF (30 mL) was added acid chloride **251** (4.94 g, 25 mmol, 1eq.) and the mixture was allowed to reflux overnight. It was worked up according to the above procedure and isolated via column chromatography on silica gel (eluent – 5:1 Hexane:EtOAc, R$_f$ = 0.4 and 0.23). The product was obtained as an off-white solid, yield 6.76 g (20.47 mmol, 82%).

^{1}H NMR (400.13 MHz, CDCl$_3$); [7.38 – 7.24 (m, Σ10H], [3.42 (dd, J = 8.5 Hz, 5.3 Hz) & 2.90 (dd, J = 7.6 Hz, 5.0 Hz), Σ1H], [2.07 (dd, J = 8.5 Hz, 6.4 Hz) & 1.53 (dd, J = 7.0 Hz, 5.0Hz), Σ1H], [1.17 (s) & 1.09 (s), Σ3H], [1.26 (ps.t, J = 7.0 Hz) & 0.86 (dd, J = 6.4 Hz, 5.3 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 173.0, 171.2,

144.0 (2C, +) 143.5 (2C,+), 129.8 (4C, +), 129.7 (4C,+), 128.0 (4C, +), 127.8 (4C, +),

127.4 (2C,+), 127.3 (2C, +), 30.9 (+), 29.0 (+), 28.4, 26.8, 25.2 (-), 24.5 (-), 22.8 (+),

19.8 (+); HRMS (TOF ES): Found 330.0485, Calculated for $C_{17}H_{17}BrNO$ (M+H)

330.0493 (2.4 ppm).
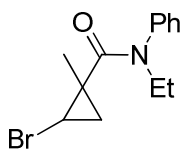
230t: was prepared according to the typical procedure starting from 2.0 g (10.1 mmol) of acyl chloride **251** and *N*-ethylaniline (3.81 mL, 3.68 g, 30.3 mmol). Purification involved partitioning between a saturated aqueous solution of citric acid (75 mL) and EtOAc (2 x 50 mL). Combined organic phases were washed with brine, dried with MgSO$_4$, filtered, and concentrated in vacuum. The residue was distilled twice in a Kugelröhr apparatus (oven temperature 155 °C at 0.2 torr) yielding 1.45 g (5.13 mmol, 51 %) of the compound as colorless oil.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [7.46 - 7.15 (m), Σ5H], [4.18 (m) & 3.44 (br. s),

Σ1H], [3.81 (m) & 3.64 (m), Σ1H], [3.21 (dd, *J* = 8.3 Hz, 5.1 Hz) & 2.75 (br. s),

Σ1H], [1.85 (ps.t, *J* = 6.6 Hz) & 1.61 (ps.t, *J* = 5.6 Hz), Σ1H], [1.13 (t, *J* = 7.1 Hz) &

1.08 (t, *J* = 7.3 Hz), Σ3H], [1.03 (br. s) & 0.88 (br. s), Σ3H], [0.88 (br.s) & 0.71 (ps. t,

J = 5.6 Hz), Σ1H]; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 171.2, 169.1, 142.6, 141.6,

129.5 (2C, +), 129.4 (2C, +), 128.4 (2C, +), 127.9 (2C, +), 127.6 (2C, +), 127.5 (2C,

+), 46.6 (-), 45.9 (-), 29.8 (+), 28.2, 27.2 (+), 24.4, 24.2 (-), 23.4 (-), 19.9 (+), 12.8

(+); HRMS (TOF ES): found 202.1234, calculated for $C_{13}H_{16}NO$ (M-Br) 202.1232 (1.0 ppm).
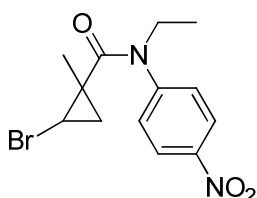
230w: This compound was prepared according to the protocol described above for amide **230t**, starting from acylchloride **251** (1.24 g, 6.25 mmol), *N*-ethyl-(4-nitroaniline) (0.99 g, 5.96 mmol), and triethylamine (1.68 g, 14.9 mmol). Crude material was purified via short column chromatography on a silica gel (eluent Hexane:EtOAc 3:1, R_f = 0.39 and 0.32).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [8.34 (d, *J* = 8.8 Hz) & 8.31 (d, *J* = 8.8 Hz), Σ2H], [7.55 (d, *J* = 8.8 Hz) & 7.37 (d, *J* = 8.8 Hz), Σ2H], [4.22 (sextet, *J* = 7.1 Hz) & 3.93 (sextet, *J* = 7.1 Hz), Σ1H], [3.74 (sextet, *J* = 7.1 Hz) & 3.66 (sextet, *J* = 7.1 Hz), Σ1H], [3.26 (dd, *J* = 8.3 Hz, 5.1 Hz) & 2.94 (dd, *J* = 7.3 Hz, 4.8 Hz), Σ1H], [1.96 (dd, *J* = 8.3 Hz, 6.6 Hz) & 1.80 (ps.-t, *J* = 6.3 Hz), Σ1H], [1.30 (dd, *J* = 7.6 Hz, 6.6 Hz) & 0.83 (dd, *J* = 6.6 Hz, 5.3 Hz), Σ1H], [1.18 (t, *J* = 7.1 Hz) & 1.12 (t, *J* = 7.1 Hz), Σ3H], 1.10 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 178.9, 171.4, 147.5, 146.2, 128.4 (+, 2C), 128.1 (+, 2C), 125.0 (+, 2C), 124.8 (+, 2C), 46.0 (-), 45.9 (-), 29.3 (+), 28.9 (+), 26.8, 25.9, 23.6 (-), 23.2 (-), 21.6 (+), 19.6 (+), 13.4 (+), 13.0 (+); HRMS (TOF ES): Found 327.0345, Calculated for $C_{13}H_{16}BrN_2O_3$ (M+H) 327.0344 (0.3 ppm).
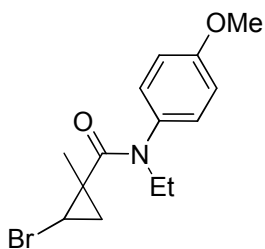
230y: This compound was obtained according to procedure described above for **230t**, starting from acyl chloride **251** (1.24 g, 6.29 mmol), *N*-ethylanisidine (0.99 g, 6.47 mmol), and triethylamine (1.68 g, 14.9 mmol). Acid-base extraction followed by Kugelröhr vacuum distillation (oven temperature 200 °C at 0.1 torr) afforded the title compound. Yield 2.025 g (6.48 mmol, 99 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ [7.33 (d, *J* = 8.8 Hz) & 6.95 (d, *J* = 8.8 Hz), Σ2H], [7.07 (d, *J* = 8.8 Hz) & 6.97 (d, *J* = 9.1 Hz), Σ2H], [4.17 (m) & 3.79 (m), Σ1H], [3.87 (s) & 3.85 (s), Σ3H], [3.60 (m) & 3.38 (m), Σ1H], [3.22 (dd, *J* = 8.3 Hz, 5.1 Hz) & 2.75 (dd, *J* = 7.1 Hz, 4.8 Hz), Σ1H], [1.85 (dd, *J* = 8.1 Hz, 6.6 Hz) & 1.66 (dd, *J* = 6.3 Hz, 5.1 Hz), Σ1H], [1.14 (t, *J* = 7.1 Hz) & 1.08 (t, *J* = 7.1 Hz), Σ3H], [1.05 (br.s) & 0.89 (br.s), Σ3H], [0.95 (ps.t, *J* = 7.1 Hz) & 0.72 (br.s), Σ1H] ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 171.4, 169.2, 158.7 (2C), 135.3 (2C), 129.6 (2C, +), 129.2 (2C, +), 114.6 (2C, +), 114.5 (2C, +), 55.5 (+), 55.4 (+), 46.5 (-), 45.9 (-), 29.7 (+), 28.2, 27.1 (+), 26.2, 24.1 (-), 23.4 (-), 22.1 (+), 20.0 (+), 12.9 (+), 12.7 (+); HRMS (TOF ES): Found 312.0593, Calculated for C$_{14}$H$_{19}$BrNO$_2$ (M+H) 312.0599 (1.9 ppm).
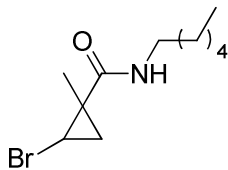
252: A solution of 4.01 mL (3 eq., 30.4 mmol) of *N*-hexylamine in 10 mL of THF was added dropwise to a solution of acid chloride **251** (2 g, 10.13 mmol) in THF (7 mL). After the amine

addition was complete, the mixture was allowed to stir at room temperature until GCMS analysis showed no remaining starting materials (1 hr). The precipitate was filtered off through a fritted funnel, and the filtrate was washed with EtOAc (15 mL), then dissolved in water (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. All the organics phases were combined together and condensed under vacuum. The residue was purified by Kugelröhr distillation (oven temp of 175 °C at 0.6 torr) to afford the mixture of diastereomers (~ 1:1) as a clear oil. Yield 2.16 g (8.25 mmol, 81 %).

^{1}H NMR (500.13 MHz, CDCl$_3$) δ [5.99 (s) & 5.87 (s), Σ1H], [3.59 (dd, J = 8.2 Hz, 5.4 Hz) & 2.98 (dd, J = 7.6 Hz, 5.0 Hz), Σ1H], [3.44-3.31 (m) & 3.08 (m), Σ2H], [1.95 (dd, J = 7.6 Hz, 5.7 Hz) & 1.75 (ps.t, J = 5.7 Hz), Σ1H], 1.62 (m, 2H), [1.58 (s) & 1.48 (s), Σ3H], 1.39 (m, 6H), 1.27 (ps.t, J = 6.9 Hz, 1H), 0.98 (br. t, J = 5.7 Hz, 3H); ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 172.1, 169.9, 40.3 (-), 40.2 (-), 31.5 (-), 31.2 (-), 29.7 (-), 29.6 (-), 29.2 (+), 27.9, 27.6 (-), 26.7 (-), 26.3 (-), 25.3 (+), 24.3 (-), 24.0, 22.6 (-), 22.5 (-), 21.6 (+), 21.1 (+), 17.3 (+), 14.1 (+).
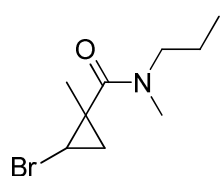
230u: Flame-dried flask was charged with NaH (60 weight % suspension in mineral oil) (183 mg, 4.77 mmol, 2.5 eq) under nitrogen atmosphere. This was suspended in 25 mL of anhydrous THF, and amide **252** (500.0 mg, 1.91 mmol) was added. The mixture was stirred at

50 °C for 10 min before methyl iodide (325.0 mg, 143 μL, 2.29 mmol, 1.2 eq.) was added. The reaction was complete after 4 hrs at 50 °C as shown by the disappearance of the starting material. The reaction was quenched by pouring into brine, and extracting with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (~ 15 mL) and condensed under vacuum. The crude product was purified via column chromatography on silica gel (eluting with hexane to remove the mineral oil, and then with Hexane:EtOAc (3:1)) to obtain a mixture of diastereomers (~ 2:1, R_f = 0.34 and 0.27) as colorless oil. Yield 328.9 mg (1.19 mmol, 62 %).

^{1}H NMR (500.13 MHz, CDCl$_3$) δ [3.43 (m) & 3.30 (m), Σ2H], [3.18 (dd, J = 8.2 Hz, 5.0 Hz) & 2.99 (dd, J = 7.6 Hz, 4.7 Hz), Σ1H], [3.15 (s) & 2.94 (s), Σ3H], 1.71 (ps.t, J = 7.3 Hz) & 1.59 (m), Σ1H], [1.59 (m) & 1.17 (dd, J = 14.9 Hz, 7.3 Hz), Σ1H], [1.47 (s) & 1.39 (s), Σ3H], [1.30-0.88 m, 11H]; ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 169.8, 169.7, 49.8 (-), 48.2 (-), 47.8 (-), 47.7 (-), 35.6 (+), 35.3 (+), 32.8 (+), 31.6 (-), 31.5 (-), 28.6 (-), 27.9, 26.7 (-), 26.5 (-), 25.9 (+), 22.6 (-), 22.5, 21.8 (-), 20.9 (+), 19.8 (-), 18.9 (+), 14.0 (+), 13.9 (+); HRMS (TOF ES): Found 276.0960, Calculated for C$_{12}$H$_{23}$BrNO (M+H) 276.0963 (1.1 ppm).

3.5.7. Synthesis of cyclopropenes DMSO Method

Typical procedure:
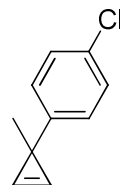
231f: Bromocyclopropane **8f** (3.08 g, 12.5 mmol) was added dropwise to a stirred solution of ^{t}BuOK (1.68 g, 15 mmol) in anhydrous DMSO (20 mL). The resulting mixture was stirred at room temperature overnight, then quenched with water (150 mL) and extracted with ether (3 x 50 mL). Combined organic phases were washed consecutively with water (3 x 50 mL) and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography of a residue[217] (eluent - hexane) afforded cyclopropene **9f** as colorless oil. Yield 1.62 g (9.8 mmol, 79 %). ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.28 (d, J = 8.6 Hz, 2H), 7.28 (s, 2H), 7.17 (d, J = 8.6 Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 148.5, 130.7, 127.7 (+, 2C), 127.4 (+, 2C), 115.3 (+, 2C), 25.2 (+), 21.4; HRMS (TOF ES) Found 165.0480, Calculated for $C_{10}H_{10}{}^{35}Cl$ (M+H) 165.0471 (5.5 ppm).
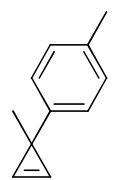
231b: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.37 (s, 2H), 7.23 (s, 4H), 2.45 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 146.9, 134.4, 128.5 (+, 2C), 125.9 (+, 2C), 115.7 (+, 2C), 25.5 (+), 21.5, 20.8 (+); HRMS (TOF ES) Found 145.1023, Calculated for $C_{11}H_{13}$ (M+H) 145.1017 (4.1 ppm).
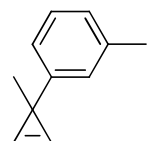
231c: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.31 (s, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.11-7.09 (m, 2H), 7.05 (d, J = 7.6 Hz, 1H), 2.41 (s, 3H), 1.69 (s,

3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 149.9, 137.3, 127.7 (+), 126.8 (+), 125.8 (+), 123.1 (+), 115.5 (+, 2C), 25.5 (+), 21.7, 21.5 (+); HRMS (TOF ES) Found 143.0866, Calculated for C$_{11}$H$_{11}$ (M-H) 143.0861 (3.5 ppm).
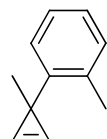
231d: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.77 (s, 2H), 7.30-7.19 (m, 4H), 2.56 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 147.6, 135.6, 130.3 (+), 127.5 (+), 126.2 (+), 125.9 (+), 121.4 (+, 2C), 28.2 (+), 23.5, 19.1 (+); HRMS (TOF ES) Found 145.1019, Calculated for C$_{11}$H$_{13}$ (M+H) 145.1017 (1.4 ppm).
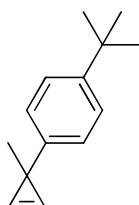
231e: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.46 (d, J = 8.6 Hz, 2H), 7.36 (s, 2H), 7.30 (d, J = 8.6 Hz, 2H), 1.76 (s, 3H), 1,45 (s, 9H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 147.7, 146.9, 125.7 (+, 2C), 124.7 (+, 2C), 115.5 (+, 2C), 34.3, 31.4 (+, 3C), 25.4 (+), 21.4; HRMS (TOF ES) Found 159.1179, Calculated for C$_{12}$H$_{15}$ (M-Me) 159.1174 (3.1 ppm).
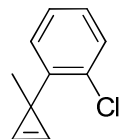
231g: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.70 (s, 2H), 7.34 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.30 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.22 (td, J = 7.4 Hz, 1.3 Hz, 1H), 7.15 (td, J = 7.8 Hz, 1.8 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 146.6, 133.6, 129.6 (+), 129.3 (+), 127.2 (+), 127.1 (+), 120.6 (+, 2C), 27.3 (+), 23.7; HRMS (TOF ES) Found 165.0476, Calculated for C$_{10}$H$_{10}$^{35}Cl (M+H) 165.0471 (3.0 ppm).
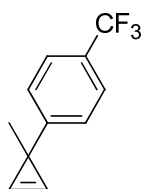
231h: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.56 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.28 (s, 2H), 1.68 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 154.1, 127.2 (q, $^2J_{CF}$ = 32.2 Hz), 126.3 (+, 2C), 124.7 (q, $^3J_{CF}$ = 3.7 Hz, +, 2C), 124.5 (q, $^1J_{CF}$ = 271.5 Hz), 114.9 (+, 2C), 25.01 (+), 21.9; ^{19}F NMR (376.50 MHz, CDCl$_3$) δ major: -62.1; HRMS (TOF ES) Found 179.0677, Calculated for C$_{11}$H$_9$F$_2$ (M-F) 179.0672 (2.8 ppm).
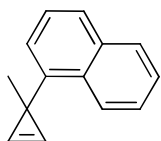
231i: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 8.47 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.91 (s, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.63 (ps.-t, J = 7.8 Hz, 7.1 Hz, 1H), 7.56 (ps.-t, J = 7.6 Hz, 7.3 Hz, 1H), 7.50-7.44 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 146.3, 134.0, 130.1, 128.8 (+), 126.4 (+), 126.0 (+), 125.5 (+), 125.4 (+), 124.8 (+), 124.0 (+), 121.2 (+, 2C), 29.1 (+), 23.0; HRMS (TOF ES) Found 147.0609, Calculated for C$_{10}$H$_8$F (M-H) 147.0610 (0.7 ppm).
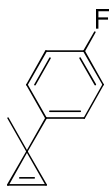
231j: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.31 (s, 2H), 7.22 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.3 Hz, 2H), 7.02 (ps.-t, J = $^3J_{HF}$ = 8.8 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 160.8 (d, $^1J_{CF}$ = 243.0 Hz), 145.6 (d, $^4J_{CF}$ = 2.9 Hz), 127.4 (d, $^3J_{CF}$ = 8.1 Hz, +, 2C), 115.7 (+, 2C), 114.4 (d, $^2J_{CF}$ = 21.2 Hz, +, 2C), 25.5 (+), 21.4; ^{19}F NMR (CDCl$_3$, 376.50 MHz) δ -119.0; HRMS (TOF ES) Found 180.0931, Calculated for C$_{14}$H$_{12}$ (M$^+$) 180.0939 (4.4 ppm).
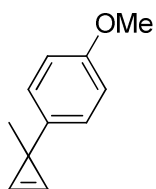
OMe **231k**:[155] ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.33 (s, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 157.2, 142.1, 126.9 (+, 2C), 116.0 (+, 2C), 113.2 (+, 2C), 55.2 (+), 25.6 (+), 21.2; HRMS (TOF ES) Found 161.0968, Calculated for C$_{11}$H$_{13}$O (M+H) 161.0966 (1.2 ppm).
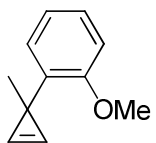
231l: ^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.70 (s, 2H), 7.22 (td, J = 8.1 Hz, 2.0 Hz, 1H), 7.19 (dd, J = 7.1 Hz, 1.8 Hz, 1H), 6.94 (td, J = 7.3 HZ, 1.0 HZ, 1H), 6.90 (d, J = 8.1 HZ, 1H), 3.93 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 157.8, 137.6, 128.3 (+), 126.9 (+), 121.0 (+, 2C), 120.6 (+), 110.8 (+), 55.2 (+), 27.7 (+), 21.3; HRMS (TOF ES) Found 161.0970, Calculated for C$_{11}$H$_{13}$O (M+H) 161.0966 (2.5 ppm).

3.5.8. Preparation of Cyclopropenes 18-Crown-6 Method
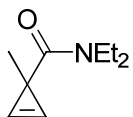
231p: (Typical procedure): An oven-dried 10 mL Wheaton vial equipped with a mininert cap was charged with ^{t}BuOK (160 mg, 1.43 mmol, 1.5 eq), 18-crown-6 (25.2 mg 0.095 mmol, 0.1 eq), and dry THF (5 mL). To this solution was added 2-bromo-*N*,*N*-diethyl-1-methylcyclopropanecarboxamide (**5d**) (250 mg, 0.954 mmol) and the reaction mixture was stirred at 30 ^{o}C until the GCMS showed the disappearance of the starting materials (3 hours). Then the reaction was quenched by pouring the mixture into brine (50 mL). The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with brine (25 mL), dried with MgSO$_4$, and concentrated under vacuum. The residue was purified by Kugelröhr distillation (oven temperature of 60 °C at 0.2 torr) to afford the title cyclopropene as a colorless liquid, yield 146.7 mg (0.957 mmol, 90 %). A scale-up synthesis was performed according to the same procedure starting from bromocyclopropane **5d** (15.0 g, 61.7 mmol), ^{t}BuOK (10.38 g, 92.5 mmol), and 18-crown-6 ether (1.63 g, 6.17 mmol, 10 mol%) in THF (290 mL) to afford 8.74 g (54.91 mmol, 89 %) of cyclopropene **231p**.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.28 (s, 2H), 3.54 (br. s, 2H), 3.29 (br. s, 2H), 1.31 (s, 3H), 1.18 (br. s, 3H), 1.06 (br. s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 175.5, 115.8 (+, 2C), 41.3 (-), 38.7 (-), 23.9 (+), 23.2, 14.3 (+), 12.6 (+); HRMS (TOF ES):

Found 154.1231, Calculated for $C_9H_{16}NO$ (M+H) 154.1232 (0.6 ppm). HRMS (TOF ES): m/z $[M+H]^+$ calcd for $C_9H_{16}NO$ 154.1232; found 154.1231.
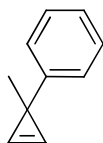
231a: This compound was obtained from bromocyclopropane **230a** (10.00 g, 47.18 mmol) according to the typical procedure. The crude material was purified by Kugelröhr vacuum distillation (oven temperature 75 °C at 5 torr) to afford a clear oil, yield 5.22 g (40.1 mmol, 85 %). All physical and spectral properties of this material were identical to those, described in literature.[151]
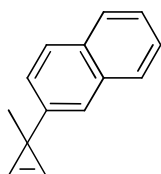
231n: was prepared from bromocyclopropane **230n** (250 mg, 0.95 mmol) according to the typical procedure. Purification by Kugelröhr vacuum distillation (oven temperature of 120 °C at 0.2 torr) afforded 144.1 mg (0.80 mmol, 84 %) of a colorless oil.

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.80 (m, 3H), 7.46 (m, 3H), 7.38 (s, 2H), 7.35 (dd, J = 8.6, 1.7, 1H), 1.78 (s) 3H; ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 147.4, 133.4, 131.5, 127.6 (+), 127.5 (+), 127.2 (+), 125.9 (+), 125.0 (+), 124.7 (+), 124.5 (+), 115.8 (+, 2C), 25.6 (+), 22.2; HRMS (TOF ES): Found 179.0859, Calculated for $C_{14}H_{11}$ (M-H) 179.0861 (1.1 ppm).
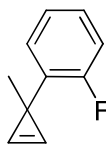
231o: was obtained from bromocyclopropane **230o** (250 mg, 1.09 mmol), and purified via Kugelröhr vacuum distillation (oven temperature of 75 °C at 10 torr) to afford a clear oil, yield 120.9 mg (0.816 mmol, 75 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.63 (s, 2H), 7.09 (m, 4H), 1.59 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 162.9 (d, $^1J_{CF}$ = 245.9 Hz), 136.1 (d, $^2J_{CF}$ = 15.4 Hz), 129.1 (d, $^3J_{CF}$ = 5.1 Hz, +), 127.4 (d, $^3J_{CF}$ = 8.1 Hz, +), 123.9 (d, $^4J_{CF}$ = 3.7 Hz, +), 119.8 (+, 2C), 115.8 (d, $^2J_{CF}$ = 22.7 Hz, +), 27.6 (d, $^4J_{CF}$ = 2.2 Hz, +), 20.2; ^{19}F NMR (376.50 MHz, CDCl$_3$) δ -117.5; HRMS (TOF ES) Found 129.0707, Calculated for C$_{10}$H$_9$ (M-F) 129.0704 (2.3 ppm).
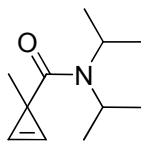
231q: was obtained according to the typical procedure from bromocyclopropane **230q** (250 mg, 0.96 mmol) and was purified by Kugelröhr distillation (oven temperature of 55 °C at 0.2 torr) to afford a colorless liquid, yield 147.6 mg (0.81 mmol, 85 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.31 (s, 2H), 4.57 (br. s, 1H), 3.30 (br. s, 1H), 1.38 (br. s, 6H), 1.31 (s, 3H), 1.24 (br. s, 6H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 175.2, 115.6 (+, 2C), 48.9 (+), 45.3 (+), 28.0, 23.7 (+), 20.9 (+, 2C), 20.6 (+, 2C); HRMS (TOF ES): Found 182.1543, Calculated for C$_{11}$H$_{20}$NO (M+H) 182.1545 (1.1 ppm).
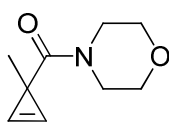
231r: was obtained from cyclopropane **230r** (250 mg, 1.01 mmol) using the same protocol as described above. The reaction mixture was quenched by pouring into brine and extracting the aqueous layer with THF (2 x 25 mL). The combined organic layers were washed once with brine (15 mL), dried with $MgSO_4$, concentrated in vacuum. The residue was purified by Kugelröhr vacuum distillation (oven temperature of 95 °C at 0.2 torr) to afford cyclopropene as a clear liquid, yield 136.7 mg (0.82 mmol, 81 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.32 (s, 2H), 3.62 (br. s, 8H), 1.35 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 174.8, 115.4 (+, 2C), 66.9 (-, 2C), 23.6 (+), 22.49 (Due to the restricted rotation about the amide bond, the peak at 3.62 in the ^{1}H is broad, and the CH$_2$ groups alpha to the N are not observed in the ^{13}C NMR); HRMS (TOF ES): Found 168.1024, Calculated for C$_9$H$_{14}$NO$_2$ (M+H) 168.1025 (0.6 ppm).
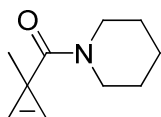
231s: was obtained from cyclopropane **230s** (250 mg, 1.02 mmol) using the same protocol as described above. The product was isolated by Kugelröhr vacuum distillation (oven temperature of 75 °C at 0.2 torr) as a colorless oil, yield 142.7 mg (0.86 mmol, 85 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.28 (s, 2H), 3.61 (br. s, 2H), 3.46 (br. s 2H), 1.61 (br. s 2H), 1.53 (br. s 4H), 1.31 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 174.5,

115.7 (+, 2C), 46.7 (-), 42.5 (-), 26.6 (-), 25.6 (-), 24.6 (-), 23.7 (+), 22.9; HRMS (TOF ES): Found 150.0917, Calculated for $C_9H_{12}NO$ (M-Me) 150.0919 (1.3 ppm).
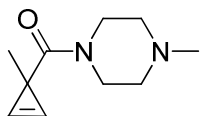
231t: was obtained from bromocyclopropane **230t** (250 mg, 0.96 mmol) according to the typical procedure. The product was isolated by Kugelröhr vacuum distillation (oven temperature of 85 °C at 0.2 torr) as a colorless oil, yield 128.0 mg (0.71 mmol, 75 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.28 (s, 2H), 3.70 (br. s, 2H), 3.56 (br. s 2H), 2.39 (br. s, 4H), 2.29 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 174.6, 115.5 (+, 2C), 55.3 (-), 54.6 (-), 46.0 (+), 45.5 (-), 41.3 (-), 23.7 (+), 22.7; HRMS (TOF ES): Found 181.1343, Calculated for $C_{10}H_{17}N_2O$ (M+H) 181.1341 (1.1 ppm).
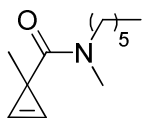
231u: Purified via column chromatography Hex: EtOAc 3:1 Rf = 0.31;

^{1}H NMR (500.13 MHz, C$_6$D$_6$) δ 7.27 (s, 2H), 3.35-3.25 (br.s, 2H), 2.76 (br.s, 3H), 1.37 (s, 3H), 1.47-1.16 (m, 8H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.67 MHz, C$_6$D$_6$) δ 174.8, 116.1 (+, 2C), 53.4 (-), 47.1 (+), 34.2, 31.9 (-), 26.7 (-, 2C), 23.2 (+), 22.9 (-), 14.2 (+); HRMS (TOF ES): Found 180.1388, Calculated for $C_{11}H_{18}NO$ (M-Me) 180.1388 (2.2 ppm).
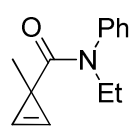
231x: was obtained from bromocyclopropane **230x** (250 mg, 0.89 mmol) according to the typical procedure. The product was isolated as a yellow oil by column chromatography on silica gel (eluent hexane-EtOAc 2:1, Rf = 0.35). Yield 51.9 mg (0.26 mmol, 30 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.41 (m, 2H), 7.32 (m, 1H), 7.15 (m, 2H), 6.56 (s, 2H) 3.70 (q, J = 14.1 Hz, 7.1 Hz, 2H), 1.14 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.61 MHz, CDCl$_3$) δ 176.4, 142.1, 129.1 (2C, +), 128.1 (2C, +), 127.2 (+), 114.37 (2C, +), 44.9 (-), 24.0 (+), 23.9, 12.9 (+). HRMS (TOF ES): Found 202.1231, Calculated for C$_{13}$H$_{16}$NO (M+H) 202.1232 (0.5 ppm)**.**
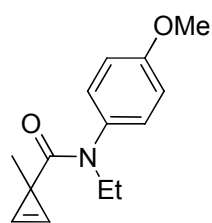
231y: was obtained from bromocyclopropane **230y** (110 mg, 0.353 mmol) according to a typical procedure. Purified via column chromatography on silica gel (eluent – hexane:EtOAc 2:1, R$_f$ = 0.32) to afford a yellow oil, yield 37.6 mg (0.187 mmol, 53 %).

^{1}H NMR (500.13 MHz, CDCl$_3$) δ 7.05 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 6.62 (s, 2H), 3.65 (q, J = 7.3 Hz, 2H), 1.15 (s, 3H), 1.07 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125.67 MHz, CDCl$_3$) δ 176.3, 158.5, 134.8, 129.2 (2C, +), 114.5 (2C, +), 114.2 (2C,+), 55.5 (+), 44.9 (-), 24.1 (+), 23.7, 12.8 (+); HRMS (TOF ES): Found 230.1180, Calculated for C$_{14}$H$_{16}$NO$_2$ (M-H) 230.1181 (0.4 ppm).

3.5.9. Rhodium-Catalyzed Hydroformylation of Cyclopropenes

3.5.10. General Information

See Chapter 1.4.1. for instrumentation details.

Anhydrous toluene, diethyl ether, and tetrahydrofuran were obtained by passing degassed HPLC-grade commercially available solvents consecutively through two columns with activated alumina (Innovative Technology). Anhydrous dimethylsulfoxide was purchased form Acros Organics and used as received. The Rh(CO)$_2$(acac) complex was purchased from Sigma-Aldrich, and phosphine ligands were obtained from Strem Chemicals. Starting materials: 3-methyl-3-phenylcyclopropene (**231a**),[151 ,178] 1-chloro-4-(1-methylcycloprop-2-en-1-yl)benzene (**231f**),[178] 1-fluoro-4-(1-methylcycloprop-2-en-1-yl)-benzene (**231j**), [178] [1-[(methoxymethoxy)methyl]-2-cyclopropen-1-yl]-benzene (**231l**),[148a] (1-phenylcycloprop-2-en-1-yl)methyl acetate (**231aa**),[148a] methyl 1-phenylcycloprop-2-ene-1-carboxylate (**231ab**),[148b] and 1-methylcycloprop-2-ene-1-carboxylate (**231ac**) [148b, 161] 1,3-dimethyl-3-phenylcyclopropene (**231ae**),[159] 1-methyl-4-(1-methylcycloprop-2-en-1-yl)benzene (**231b**)[178] were prepared according to the published procedures. Preparative procedures for synthesis cyclopropene **231ac** are provided below. Syngas (equimolar mixture of hydrogen and carbon monoxide, certified Standard Spec.) was purchased from Airgas and used as received. All other

chemicals were purchased from Sigma-Aldrich or Acros Organics, and used as received.

3.5.11. Special Equipment
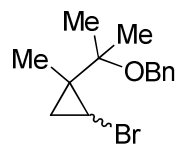
See Chapter 2.4.2. for this information.

3.5.12. Construction of the Synthesis Gas Manifold

See Chapter 2.4.3. for this information

3.5.13. Synthesis of a Cyclopropene Containing a Benzyl Protected Tertiary Alcohol
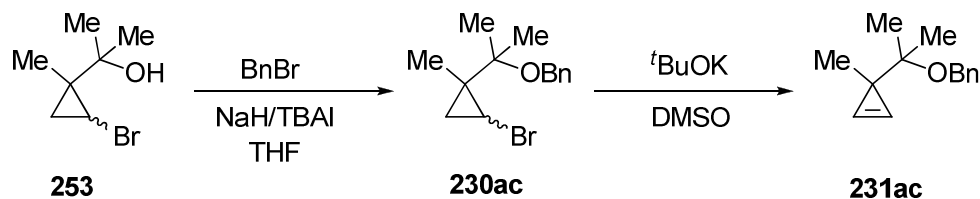
230ac: To a stirred suspension of sodium hydride (suspension in mineral oil, 60 %) (979 mg, 24.47 mmol, 1.05 equiv.) in anhydrous THF (45 mL) was added 2-(2-bromo-1-methyl-cyclopropyl)propan-2-ol [218] (**253**) (4.50 g, 23.31 mmol) dropwise at room temperature. The mixture was stirred for 1 hr, then cooled to 0 °C and cannulated into a solution of benzyl bromide (4.78 g, 28.00

mmol, 1.2 equiv.) and tetrabutylammonium iodide (517 mg, 1.40 mmol, 6 mol %) in dry THF (25 mL). The resulting mixture was warmed up to room temperature and stirred overnight. Then, the mixture was quenched with water and partitioned between water and diethyl ether. Combined ethereal extracts were washed with brine, dried with MgSO$_4$, filtered and concentrated to afford 7.54 g of crude material in a mixture with residual mineral oil. This was used in the following transformation without further purification.
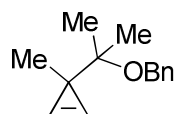
231ac: Crude bromocyclopropane **230ac** (7.54 g) was added dropwise to a stirred solution of ^{t}BuOK (3.57 g, 31.8 mmol) in anhydrous DMSO (20 mL). The resulting mixture was stirred at room temperature for 5 hrs, when GC/MS analysis indicated full consumption of both diastereomeric bromocyclopropanes. Then the mixture was quenched with water (150 mL) and extracted with hexane (3 x 50 mL). Combined organic phases were washed consecutively with water (3 x 50 mL) and brine (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated. Flash column chromatography of the residue (eluent – hexane/EtOAc 7:1) afforded cyclopropene **231ac** as colorless oil. Yield 3.42 g (16.9 mmol, 73 % over two steps).

^{1}H NMR (CDCl$_3$, 400.13 MHz) δ 7.42 (d, J = 7.6 Hz, 2H), 7.37 (ps.-t, J = 7.6 Hz, 7.3 Hz, 2H), 7.32 (s, 2H), 7.28 (t, J = 7.3 Hz, 1H), 4.53 (s, 2H), 1.28 (s, 3H), 1.13 (s, 6H);

^{13}C NMR (CDCl$_3$, 100.61 MHz) δ 140.0, 128.2 (+, 2C), 127.4 (+, 2C), 127.0 (+), 118.4 (+, 2C), 79.5, 64.1 (-), 25.7 (+, 2C), 25.5, 22.0 (+).

3.5.14. Optimization Procedure

All loading operations were performed in a nitrogen-filled glovebox. To an oven-dried 8 mL glass liners was added 2.91 μmol of chiral diphosphine ligand and 1.46 μmol of the Rh source (29 μL of a 0.05 molar Rh(acac)(CO)$_2$ stock solution in toluene) followed by 1.75 mL of dry toluene. 3-methyl-3-phenyl cyclopropene (250 mg, 1.92 mmol) was then added to give a total vessel volume of ~ 2 mL and a substrate to catalyst ratio of 1500:1. Then the liner was placed in 10 mL stainless steel Parr reactor, which was sealed, removed from the glove box and placed in the RS10 unit. The reaction mixture was stirred at 800 rpm and heated to 60 °C for 15 hours. A constant supply of syn gas (1:1 H$_2$:CO) was provided at a pressure of 150 psi. Then the vessel was vented to a well ventilated fume-hood and opened (after this point all the operations were performed in air). The reaction mixture was transferred into 50 mL round bottomed flask and concentrated in vacuum. The residual oil was dissolved in carbon tetrachloride (1 mL) and dibromomethane (77 μL) was added via microsyringe. Then the flask was capped, and the content was stirred for 10 minutes at room temperature. An aliquot (50 μL) of the mixture was placed in NMR tube and diluted with chloroform-*d* for measurement of ^{1}H NMR spectra. An aliquot (30 μL)

of solution form NMR tube was dissolved in dichloromethane (1 mL) for GC/MS and

chiral GC analysis.

Table 20. Optimization of diastereoselective hydroformylation of 3-methyl-3-phenylcyclopropene **231a.**
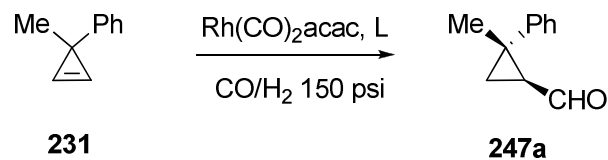
#	Ligand	Yield of **247a**, % (NMR)	**247a**:**248a** ratio
1	None	0	N/D
2	PPh$_3$	0	N/D
3	o-Tol$_3$P	0	N/D
4	TTMPP	0	N/D
5	dppm	0	N/D
6	dppe	50	21:1
7	dppp	0	N/D
8	dppb	0	N/D
9	dppf	100	11:1

3.5.15. Preparative Procedures
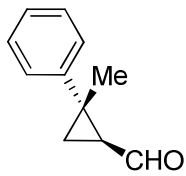
247a: Typical procedure. All loading operations were performed in nitrogen-filled glovebox. To oven-dried 8 mL glass liners was added dppf (2.84 mg, 5.1 μmol, 0.13 mol %) and 0.05M solution of Rh(acac)(CO)2 in anhydrous toluene[219] (51 μL, 2.56 μmol, 0.07 mol%) followed by 3.08 mL of dry toluene. 3-methyl-3-phenylcyclopropene (**5a**) (500 mg, 3.84 mmol) was then added to give a total vessel volume of ~ 4 mL and a substrate to catalyst ratio of 1500:1. Then the reaction and the post-reaction work up were carried out as described in the previous section. The residue was purified by bulb-to-bulb distillation (oven temperature 70 °C at 0.4 torr). Yield 419 mg (3.23 mmol, 84 %). Alternatively, purification by flash column chromatography on silica gel can be performed, affording the same product (eluent hexane/EtOAc 10:1, Rf 0.40). Yield 533 mg (3.33 mmol, 87 %). Relative configuration was assigned by comparison of ^{1}H NMR spectra with known literature data.[220]

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.63 (d, J = 4.8 Hz, 1H), 7.38-7.32 (m, 4H), 7.29-7.25 (m, 1H), 2.20 (ddd, J = 8.3 Hz, 5.8 Hz, 4.8 Hz, 1H), 1.74 (ps.-t, J = 5.8 Hz, 4.8 Hz, 1H), 1.68 (dd, J = 8.3 Hz, 4.8 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 200.6 (+), 144.9, 128.5 (+, 2C), 127.1 (+, 2C), 126.7 (+), 36.7 (+), 33.9, 21.9 (-), 20.9 (+); HRMS (TOF ES) Found 159.0813, Calculated for C$_{11}$H$_{11}$O (M-H) 159.0810 (1.9 ppm).
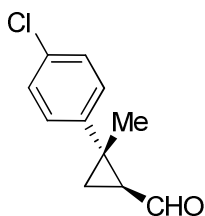
247f: This compound was obtained in a similar manner starting from 250 mg (1.52 mmol) of cyclopropene **4b**. A substrate to rhodium ratio of 1500:1 was employed. Isolation was performed using column chromatography on silica gel (eluent hexane/EtOAc 20:1. Rf 0.30). Yield 210 mg (1.08 mmol, 71 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.61 (d, J = 4.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 2.14 (ddd, J = 8.4 Hz, 5.3 Hz, 4.8 Hz, 1H), 1.72 (ps.-t, J = 5.3 Hz, 5.1 Hz, 1H), 1.62 (dd, J = 8.4 Hz, 5.1 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 200.2 (+), 143.5, 132.6, 128.6 (+, 4C), 36.6 (+), 33.3, 21.9 (-), 20.7 (+); HRMS (TOF ES) Found 165.0468, Calculated for C$_{10}$H$_{10}$Cl (M-CHO) 165.0471 (1.8 ppm).
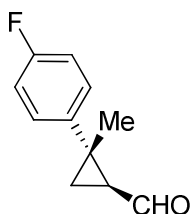
247jc: This compound was prepared in a similar manner, starting from 250 mg (1.69 mmol) of cyclopropene **4c**. 4.36 mg (17 μmol) of Rh(acac)(CO)$_2$ and 19 mg (34 μmol) of dppf were employed to maintain a substrate to rhodium ratio of 100:1. The reaction was carried out at 60 °C for 18 hrs. Isolation was performed using column chromatography on silica gel (eluent hexane/EtOAc 7:1, Rf 0.31). Yield 275 mg (1.54 mmol, 91 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.60 (d, J = 5.1 Hz, 1H), 7.28 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.3 Hz, 2H), 7.02 (ps.-t, J = $^3J_{HF}$ = 8.8 Hz, 2H), 2.15 (ddd, J = 8.3 Hz, 5.6 Hz, 5.1

Hz,1H), 1.71 (dd, J = 5.6 Hz, 4.8 Hz, 1H), 1.62 (dd, J = 8.3 Hz, 4.8 Hz); ^{19}F NMR (CDCl3, 376.50 MHz) δ -115.6; HRMS (TOF ES) Found 179.0877, Calculated for $C_{11}H_{12}OF$ (M+H) 179.0872 (2.8 ppm).
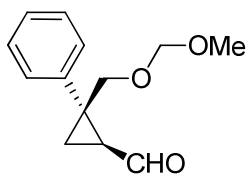
247z: This compound was prepared according to the typical procedure starting from 500 mg (2.63 mmol) of cyclopropene **4f**, maintaining a substrate to rhodium ratio of 1500:1. The reaction was carried out at 60 °C for 36 hrs. The product was isolated by column chromatography on silica gel (eluent hexane/EtOAc 10:1, Rf 0.26). Yield 414 mg (1.88 mmol, 72 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.68 (d, J = 4.6 Hz, 1H), 7.41 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 4.50 (s, 2H), 4.03 (d, J = 10.5 Hz, 1H), 3.74 (d, J = 10.5 Hz, 1H), 3.19 (s, 3H), 2.31 (ddd, J = 8.1 Hz, 5.8 Hz, 4.6 Hz, 1H), 1.86 (ps.-t, J = 5.8 Hz, 4.8 Hz , 1H), 1.59 (dd, J = 8.1 Hz, 4.8 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 199.4 (+), 141.8, 128.6 (+, 2C), 128.3 (+, 2C), 127.2 (+), 96.1 (-), 69.6 (-), 55.2 (+), 38.2, 34.6 (+), 19.1 (-); HRMS (TOF ES) Found 220.1093, Calculated for $C_{13}H_{16}O_3$ (M+) 220.1099 (2.7 ppm).
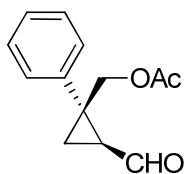
247aa: This compound was prepared according to the typical procedure starting from 500 mg (2.66 mmol) of cyclopropene **4g**,

maintaining a substrate to rhodium ratio of 1500:1. The reaction was carried out at 60 °C for 36 hrs. The product was isolated by column chromatography on silica gel (eluent hexane/EtOAc 4:1, Rf 0.26). Yield 435 mg (1.99 mmol, 75 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.70 (d, J = 4.3 Hz, 1H), 7.37-7.34 (m, 4H), 7.30 (m, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.25 (d, J = 11.9 Hz, 1H), 2.37 (ddd, J = 8.1 Hz, 5.8 Hz, 4.3 Hz, 1H), 1.98 (s, 3H), 1.88 (ps.-t, J = 5.8 Hz, 5.1 Hz , 1H), 1.59 (dd, J = 8.1 Hz, 5.1 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 198.9 (+), 170.4, 140.9, 128.6 (+, 2C), 128.5 (+, 2C), 127.5 (+), 66.3 (-), 37.1, 34.5 (+), 20.6 (+), 19.5 (-); HRMS (TOF ES) Found 189.0923, Calculated for C$_{12}$H$_{13}$O$_2$ (M-CHO) 189.0916 (3.7 ppm).
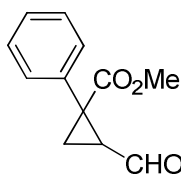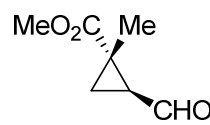
247ab+248ab: This compound was prepared according to the typical procedure starting from 250 mg (1.44 mmol) of cyclopropene **231ab**, maintaining a substrate to rhodium ratio of 1500:1. The reaction was carried out at 60 °C for 18 hrs. The product was isolated by column chromatography on silica gel as mixture of diastereomers 1.12:1 (eluent hexane/EtOAc 7:1, Rf 0.37, 0.28). Yield 262 mg (1.29 mmol, 90 %). The material was identical to the one described in literature.[221]
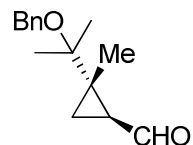
(major): ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 8.59 (d, J = 6.3 Hz, 1H), 7.40-7.32 (m, 5H), 3.68 (s, 3H), 2.76 (ddd, J = 8.8 Hz, 6.3 Hz, 6.1 Hz, 1H), 2.17 (dd, J = 8.8 Hz, 4.8 Hz, 1H), 2.10 (dd, J = 6.1 Hz, 4.8 Hz, 1H); HRMS (TOF ES) Found 205.0862, Calculated for C$_{12}$H$_{13}$O$_3$ (M+H) 205.0865 (1.5 ppm).

(**minor**): ^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.48 (d, J = 5.8 Hz, 1H), 7.40-7.32 (m, 5H), 3.69 (s, 3H), 2.45 (dd, J = 6.6 Hz, 4.8 Hz, 1H), 2.36 (ddd, J = 8.4 Hz, 6.6 Hz, 5.8 Hz), 1.82 (dd, J = 8.4 Hz, 4.8 Hz, 1H).

247ac: This compound was prepared according to the typical procedure starting from 250 mg (2.23 mmol) of cyclopropene **231ac**, maintaining a substrate to rhodium ratio of 1500:1. The reaction was carried out at 60 °C for 36 hrs. The product was purified by short filtration through silica gel (eluent Et$_2$O). Yield 202 mg (1.42 mmol, 62 %). The material was identical to the one described in literature.[222]

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.57 (d, J = 4.3 Hz, 1H), 3.75 (s, 3H), 2.57 (ddd, J = 8.6 Hz, 6.6 Hz, 4.3 Hz, 1H), 2.39 (s, 3H), 1.76 (dd, J = 8.6 Hz, 4.6 Hz, 1H), 1.55 (dd, J = 6.6 Hz, 4.6 Hz, 1H); HRMS (TOF ES) Found 141.0556, Calculated for C$_7$H$_9$O$_3$ (M-H) 141.0552 (2.8 ppm).

247ad: This compound was prepared according to the typical procedure starting from 500 mg (2.47 mmol) of cyclopropene **231ad**, maintaining a substrate to rhodium ratio of 1500:1. The reaction was carried out at 60 °C for 72 hrs. The product was purified by short filtration through silica gel (eluent EtOAc). Yield 524 mg (2.26 mmol, 91 %).
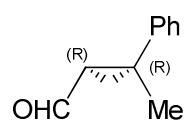
^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.50 (d, J = 5.3 Hz, 1H), 7.37-7.26 (m, 5H), 4.47 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 2.26 (ddd, J = 8.3 Hz, 5.6 Hz, 5.3 Hz, 1H), 1.56 (dd, J = 8.3 Hz, 4.6 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.29 (dd, J = 5.6 Hz, 4.6 Hz, 1H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 202.4 (+), 139.3, 128.2 (+, 2C), 127.1 (+), 126.9 (+, 2C), 75.6, 63.7 (-), 36.7, 31.8 (+), 22.6 (+), 22.2 (+), 19.1 (-), 15.6 (+); HRMS (TOF ES) Found 233.1547, Calculated for C$_{15}$H$_{21}$O$_2$ (M+H) 233.1542 (2.1 ppm).
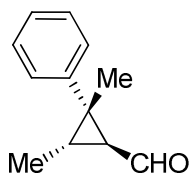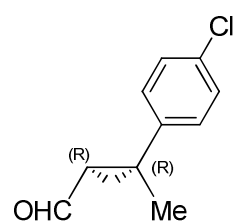
247ae: This compound was prepared according to the typical procedure starting from 250 mg (1.73 mmol) of cyclopropene **231ae**, maintaining a substrate to rhodium ratio of 100:1. The reaction was carried out at 60 °C for 18 hrs. The product was purified by short filtration through silica gel (eluent EtOAc). Yield 242 mg (1.39 mmol, 80 %).

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 9.60 (d, J = 5.3 Hz, 1H), 7.38-7.25 (m, 5H), 2.05-1.95 (m, 2H), 1.59 (s, 3H), 0.95 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100.67 MHz, CDCl$_3$) δ 201.3 (+), 142.2, 129.1 (+, 2C), 128.6 (+, 2C), 126.8 (+), 42.1 (+), 40.3, 29.4 (+), 24.0 (+), 15.2 (+); HRMS (TOF ES) Found 145.1017, Calculated for C$_{11}$H$_{13}$ (M-CHO) 145.1016 (0.7 ppm).

3.5.16. Preparative Procedure for Asymmetric Hydroformylation

(-)-(_R,R_)-247a: All loading operations were performed in a nitrogen-filled glovebox. To oven-dried 8 mL glass liners was added C3-TunePHOS (3.04 mg, 2.56 μmol, 0.13 mol %) and 0.05M solution of Rh(acac)(CO)$_2$ in anhydrous toluene[219] (51 μL, 2.56 μmol, 0.13 mol %) followed by 3.08 mL of dry toluene. 3-methyl-3-phenylcyclopropene (**231a**) (250 mg, 1.92 mmol) was then added to give a total vessel volume of ~ 4 mL and a substrate to catalyst ratio of 750:1. Then the liner was placed in 10 mL stainless steel Parr reactor, which was sealed, removed from the glove box and placed in the RS10 unit. The reaction mixture was stirred at 800 rpm and heated to 60 °C for 18 hours. A constant supply of synthesis gas (1:1 H$_2$:CO) was provided at a pressure of 150 psi. Then the vessel was vented to a well ventilated fume-hood and opened. The reaction mixture was transferred into 50 mL round bottomed flask and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel, affording the enantiomerically enriched aldehyde (_R,R_)-**5a**. Yield 265 mg (1.65 mmol, 86%). Enantiomeric excess[223] 74%; R$_t$: 42.59 min - (_S,S_)-**5a**, minor; 43.07 min – (_R,R_)-**5a**, major. NMR spectra of this material were identical to spectra provided for the above racemic product. [α]D^{25} -114.3° (c 1.42, CH$_2$Cl$_2$).

(-)-(_R,R_)-247f: Was obtained in a similar manner starting from cyclopropene **231f** (250 mg, 1.52 mmol). Yield 159 mg (0.82

mmol, 54 %). Enantiomeric excess[223] 83 %; R_t: 79.40 min - (*S,S*)-**247f**, minor; 81.16 min – (*R,R*)-**247f**, major. NMR spectra of this material were identical to spectra provided for the above racemic product. [α]D^{25} -137.8° (c 0.64, CH$_2$Cl$_2$).

(-)-(*R,R*)-**247j**: Was obtained in a similar manner starting from cyclopropene **231j** (250 mg, 1.69 mmol). Yield 187 mg (1.05 mmol, 62 %). Enantiomeric excess[223] 69 %; R_t: 45.62 min - (*S,S*)-**247j**, minor; 46.25 min – (*R,R*)-**247j**, major. NMR spectra of this material were identical to spectra provided for the above racemic product. [α]D^{25} -137.8° (c 0.64, CH$_2$Cl$_2$).

(-)-(*R,R*)-**247ac**: Was obtained in a similar manner starting from cyclopropene **231ac** (250 mg, 2.23 mmol). Yield 198.2 mg (1.39 mmol, 63 %). Enantiomeric excess[223] 74 %; R_t: 21.06 min - (*S,S*)-**247ac**, minor; 21.38 min – (*R,R*)-**231ac**, major. NMR spectra of this material were identical to spectra provided for the above racemic product. [α]D^{25} -109.8° (c 1.17, CH$_2$Cl$_2$).
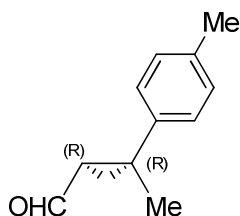
(-)-(*R,R*)-**247b**: Was obtained in a similar manner starting from cyclopropene **231b** (250 mg, 1.73 mmol). Yield 236 mg (1.35 mmol, 78 %). Enantiomeric excess[224] 68 %; R_t: 38.98 min -

(*S*,*S*)-**247b**, minor; 39.41 min – (*R*,*R*)-**247b**, major. NMR spectra of this material were identical to spectra provided for the above racemic product. $[\alpha]D^{25}$ -137.8° (c 0.64, CH_2Cl_2).

[^1]H NMR (400.13 MHz, CDCl_3) δ 9.61 (d, *J* = 5.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 2.36 (s, 3H), 2.17 (ddd, *J* = 8.3 Hz, 5.8 Hz, 5.1 Hz, 1H), 1.71 (dd, *J* = 5.8 Hz, 4.8 Hz, 1H), 1.66 (dd, *J* = 8.3 Hz, 4.8 Hz, 1H), 1.61 (s, 3H); [^13]C NMR (100.67 MHz, CDCl_3) δ 200.8 (+), 142.1, 136.5, 129.2 (+, 2C), 127.1 (+, 2C), 36.9 (+), 33.7, 22.1 (-), 20.9 (+), 15.4 (+); HRMS (TOF ES) Found 175.1123, Calculated for $C_{12}H_{15}O$ (M+H) 175.1123 (0.0 ppm).
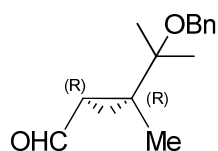
(-)-(*R*,*R*)-**247ad**: Was obtained in a similar manner starting from cyclopropene **231ad** (250 mg, 1.73 mmol). Yield 236 mg (1.35 mmol, 78 %). Enantiomeric excess 57 % (was determined as described below); NMR spectra of this material were identical to spectra provided for the above racemic product. αD^{25} -24.6° (c 1.25, CH_2Cl_2).
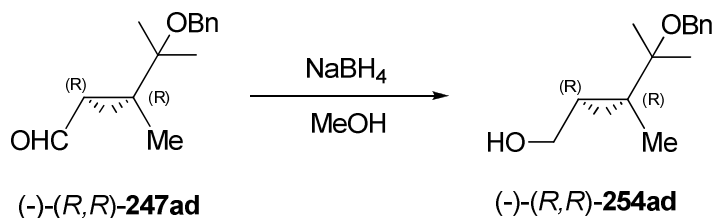
To determine optical purity the sample of compound **247ad** was converted into primary alcohol **254ad**. Aldehyde **247ad** (100 mg, 0.43 mmol) was added to a stirred suspension of $NaBH_4$ (33 mg, 0.86 mmol, 2 equiv) in methanol (1.0 mL). The mixture was stirred for 30 min at room temperature, then quenched with brine (10 mL) and extracted with EtOAc (2 x 5 mL). Combined organic phases were washed with brine, dried with Na_2SO_4, filtered and concentrated. The residue was purified by preparative flash column chromatography on Silica gel (R_f 0.35, eluent hexane-EtOAc 2:1). Yield 56 mg (0.24 mmol, 55 %).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.41-7.33 (m, 4H), 7.29-7.26 (m, 1H), 4.50 (s, 2H), 3.79 (dd, J = 11.4 Hz, 6.8 Hz, 1H), 3.61 (dd, J = 11.4 Hz, 8.3 Hz, 1H), 1.35-1.28 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 0.96 (dd, J = 9.1 Hz, 4.8 Hz, 1H), 0.19 (dd, J = 5.8 Hz, 4.8 Hz, 1H); ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 139.8, 128.2 (+, 2C), 127.1 (+, 2C), 127.0 (+), 76.6, 63.7 (-), 63.5 (-), 26.1, 23.1 (+), 22.5 (+), 21.6 (+), 15.2 (-), 15.0 (+); $[\alpha]D^{25}$ -9.2° (c 0.62, CH_2Cl_2); HRMS (TOF ES) Found 217.1591, Calculated for $C_{15}H_{21}O$ (M-OH) 217.1592 (0.5 ppm).

Acylation of **254** with (S)-Mosher acid chloride produced a diastereomeric mixture of esters, which was analyzed by ^{19}F NMR.

3.5.17. Assignment of Absolute Configuration
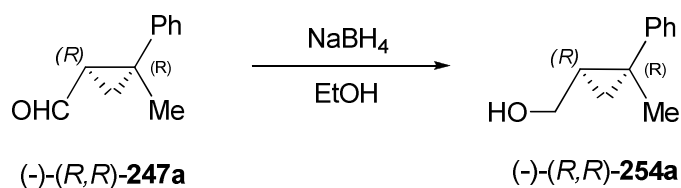
(-)-(R,R)-**247a** → (-)-(R,R)-**254a**

(NaBH$_4$, EtOH)

Assignment of absolute configuration for non-racemic compound **247a** was performed by chemical transformation of this product into 2-methyl-2-phenylcyclopropylmethanol **254a** with known absolute configuration. To a stirred at 0 °C solution of enantiomerically enriched sample of **247a** (265 mg, 1.65 mmol) in ethanol (5 mL) was added dropwise a solution of sodium borohydride (75 mg, 1.99 mmol, 1.2 equiv.) in ethanol (2 mL). The mixture was stirred for 10 min at 0 °C, and then quenched by 3N aqueous NaOH (10 mL) and stirred for 2.5 hrs at RT. The mixture was extracted by ether (3 x 15 mL), the combined organic phases were washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated. Purification of the crude residue by flash column chromatography on Silica gel afforded (-)-(R,R)-alcohol **254a** (253 mg, 1.56 mmol, 94%), which had ^{1}H NMR spectra identical to those reported in literature.[225]

^{1}H NMR (400.13 MHz, CDCl$_3$) δ 7.33-7.30 (m, 4H), 7.23-7.30 (m, 1H), 3.93 (dd, J = 11.4 Hz, 6.3 Hz, 1H), 3.73 (dd, J = 11.4 Hz, 8.3 Hz, 1H), 1.49 (s, 3H), 1.45 (m, 1H),

1.17 (dd, J = 8.8 Hz, 4.6 Hz, 1H), 1.17 (dd, J = 6.6 Hz, 4.6 Hz, 1H); $[\alpha]D^{20}$ = -26.4°

(c = 1.00, CH_2Cl_2);

The sign of optical rotation found for the synthesized sample of alcohol **254a** was opposite to that reported by Charette for (+)-(*S,S*)-**254a**, obtained in the asymmetric cyclopropanation of (2*E*)-3-phenyl-2-butene-1-ol in the presence of titanium (4*R*,5*R*)-TADDOLate.[225]   Based on this comparison, the absolute configuration of the obtained in our experiments levorotatory product **254a**, and also the absolute configuration of the parent aldehyde **247a**, was assigned as (1*R*,2*R*).

The absolute configurations of compounds **247b,f,ac,ad** were assigned by analogy with **247a** using the following considerations. The difference between cyclopropenes **231b,f,ac,ad** employed in the asymmetric hydroformylation is the large substituent "L", which is turned outward in the trigonal bipyramidal rhodium complex **I1** (Figure 22). Analysis of the corresponding stereomodels suggests the nature of the large substituent "L" should not dramatically affect the mode of enantioinduction. Accordingly, we assigned the configurations of products **247b,f,ac,ad** to be the same as that for aldehyde **247a**.

Appendix Crystallographic Studies on Pd-Ligand Complexes

A.1. Preparation of Palladium Complexes and Single Crystal X-Ray Studies

A mixture of $(MeCN)_2PdCl_2$ (30 mg, 0.116 mmol) and **L1** (40 mg, 0.116 mmol) in degassed methylene chloride (3 mL) was stirred in a 10 mL round-bottomed flask in a nitrogen-filled glove box for 30 min at room temperature. Then, degassed hexane was added (ca. 4 mL); the flask was closed with a cotton ball to allow slow evaporation of the solvent, and left overnight. The obtained yellow crystalline material was analyzed using single crystal X-ray crystallography. Analogously, a sample of the palladium complex $(\mathbf{L4})PdCl_2$ was obtained from $(MeCN)_2PdCl_2$ (40 mg, 0.154 mmol) and **L4** (54 mg, 0.156 mmol). It should be mentioned that crystallization of $(\mathbf{L4})PdCl_2$ complex produced a crystallosolvate with water and dichloromethane. We failed to obtain suitable quality crystals by crystallization from anhydrous solvents, which suggested that incorporation of solvent was essential for efficient packing of molecules in the crystalline lattice.

A.2. Single Crystal X-ray Studies for $(\mathbf{L4})PdCl_2 \cdot 0.25\ CH_2Cl_2 \cdot 0.50\ H_2O$ and $(\mathbf{L1})PdCl_2$.

Crystals of $(\mathbf{L4})PdCl_2 \cdot 0.25\ CH_2Cl_2 \cdot 0.50\ H_2O$, (**1**) were analyzed at 100(2) K, orthorhombic, space group $P2_12_12_1 - D_2^4$ (No. 19)] (**1**)[226] with **a** = 17.117(1) **b** = 17.473(1) Å, **c** = 33.072(2) Å, V = 9891(1) Å^3 and Z = 16 formula units {d_{calcd} =

1.485 g/cm^3; μ_a(MoKα) = 1.100 mm^{-1}}. Crystals of (**L4**)PdCl$_2$ (**2**), were analyzed at 100(2) K, monoclinic, space group P2$_1$ – C$_2^2$ (No. 4) (1) with **a** = 7.2466(4), **b** = 19.576(1) Å, **c** = 7.9997(4) Å, **β** = 104.296(1)°, V = 1110(1) Å^3 and Z = 2 molecules {d$_{calcd}$ = 1.579 g/cm^3; μ_a(MoKα) = 1.171 mm^{-1}} . Full hemispheres of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) were measured for single-domain specimens of both compounds using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System[227]. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 9554 (**1**) and 8994 (**2**) reflections. Totals of 117245 (**1**) and 13156 (**2**) integrated reflection intensities having 2θ(MoKα)< 61.15 (**1**) or 61.02º (**2**) were produced using the Bruker program SAINT;[228] 29017 (**1**) and 6415 (**2**) of these were unique and gave R$_{int}$ = 0.092 (**1**) and R$_{int}$ = 0.036 (**2**) with a coverage that was at least 98.4% complete for both compounds. The data were corrected empirically[229] for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.742 to 1.000 for **1** and 0.803 to 1.000 for **2**. The Bruker software package SHELXTL was used to solve both structures using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F$_o^2$ data with the SHELXTL Version 6.10 software package.[229]

All methyl groups in both compounds were incorporated into the structural model as rigid groups (using idealized sp^3-hybridized geometry and a C-H bond

length of 0.98 Å) which were allowed to rotate about their C-C bonds in least-squares refinement cycles. Hydrogen atoms for the water molecules of crystallization present in **1** were not included in the structural model. The remaining hydrogen atoms were incorporated into the structural model as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C-H bond lengths of 0.95 – 1.00 Å). The isotropic thermal parameters of all included hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded.

The CH_2Cl_2 solvent molecule and one of the two crystallographically-independent water molecules in **1** adopt three different arrangements in the crystal. Dichloromethane chlorine atom Cl(1) and the oxygen atom of the first water molecule [O(1w)], both share the same two sites in the crystal part of the time. The first site is 80 % Cl(1) and 20 % O(1w′) and the second site is 80 % O(1w) and 20 % Cl(1′). The other dichloromethane chlorine atom [Cl(2)] has two alternate positions [Cl(2) occupied 80 % of the time and Cl(2′) occupied 20 % of the time] separated by 1.44 Å. The dichloromethane methylene group is disordered with three orientations in the crystal. The methylene carbon occupies three different sites with the following occupancy factors: 0.45, 0.35 and 0.20 for C(1s), C(1s′) and C(1s″), respectively. The first orientation of the dichloromethane molecule is occupied 45 % of the time and specified by atoms Cl(1), C(1s) and Cl(2). The second orientation is occupied 35 % of the time and specified by atoms Cl(1), C(1s′) and Cl(2) and the third orientation is occupied 20 % of the time and specified by atoms Cl(1′), C(1s″) and

Cl(2′). A free variable representing the length of a C-Cl single bond was included in the refinement to restrain the disordered dichloromethane molecule. The values of all C-Cl bond lengths and tetrahedral Cl-C-Cl angles for the three different orientations of this disordered molecule were restrained by requiring pairs of non-hydrogen atoms to have separations near idealized multiples of this free variable. This free variable refined to a final value of 1.623(6) Å.

The final structural model for both compounds incorporated anisotropic thermal parameters for all ordered non-hydrogen atoms and isotropic thermal parameters for all included hydrogen atoms and the remaining non-hydrogen atoms.

A total of 1049 parameters were refined for *1* using 8 restraints, 29017 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0557\ P)^2 + (21.277\ P)]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.075 for 24699 independent absorption-corrected "observed" reflections having 2θ(MoKα)< 61.15° and I>2σ(I); R_1(unweighted, based on F) = 0.090 and wR_2(weighted, based on F^2) = 0.155 for all 29017 independent absorption-corrected reflections having 2θ(MoKα)< 61.15°. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference Fourier had maxima and minima of 1.90 e$^-$/Å^3 and –2.01 e$^-$/Å^3, respectively, that were within 1.02 Å of a Pd or disordered Cl atom. The absolute configuration was established experimentally for *1* using anomalous dispersion of the X-rays; the Flack "absolute structure parameter" refined to a final value of 0.06(3).

A total of 251 parameters were refined for *2* using 1 restraint, 6415 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0273\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement

factors at convergence are: R_1(unweighted, based on F) = 0.025 for 6226 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 61.02°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.025 and wR_2(weighted, based on F^2) = 0.058 for all 6415 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 61.02°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference Fourier had maxima and minima of 1.33 $e^-/\mathring{A}^3$ and –0.40 $e^-/\mathring{A}^3$, respectively, that were within $1.27\mathring{A}$ of the Pd atom. The absolute configuration was established experimentally for *2* using anomalous dispersion of the X-rays; the Flack "absolute structure parameter" refined to a final value of -0.03(2).

A.3. Crystallographic Data
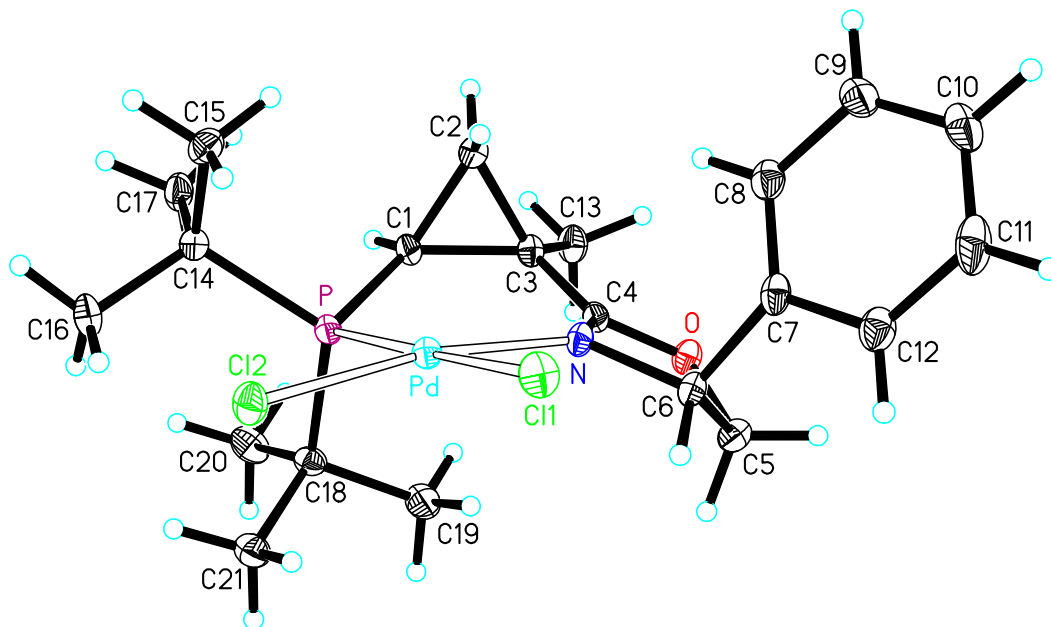
Figure 23. ORTEP drawing of (**L1**)PdCl$_2$ complex, showing the atom-numbering scheme; 50 % probability amplitude displacement ellipsoids are shown.
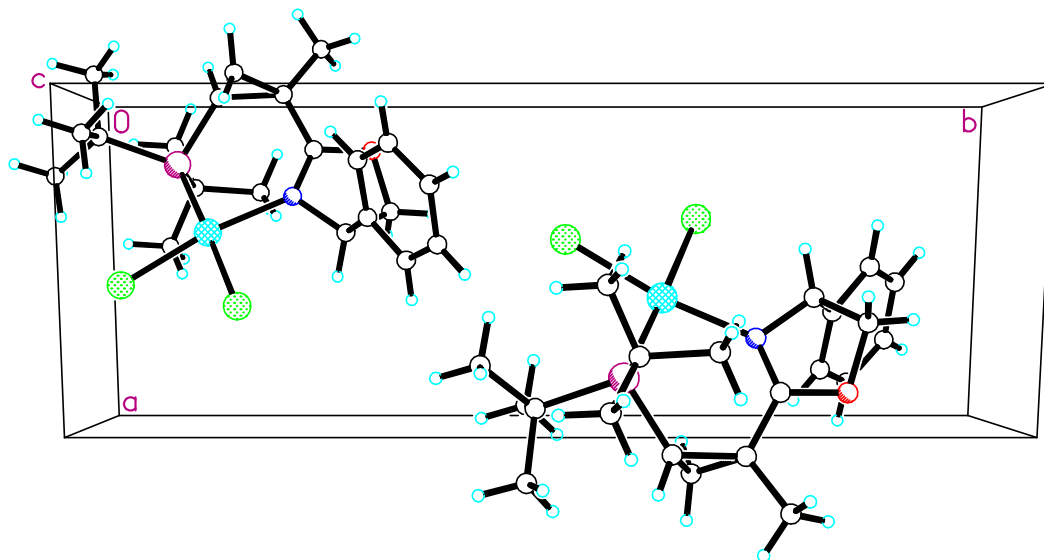
Figure 24. Packing of (**L1**)PdCl$_2$ complex in the crystalline lattice cell.

Table 21. Crystal data and structure refinement for (**L1**)PdCl$_2$.

Identification code	k13f
Empirical formula	$C_{21}H_{32}Cl_2NOPPd$
Formula weight	522.75
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2$_1$
Unit cell dimensions	a = 7.2466(4) Å α= 90°.
	b = 19.5763(10) Å β= 104.2960(10)°.
	c = 7.9997(4) Å γ= 90°.
Volume	1099.71(10) Å^3
Z	2
Density (calculated)	1.579 g/cm^3
Absorption coefficient	1.171 mm^{-1}
F(000)	536
Crystal size	0.36 x 0.24 x 0.10 mm^3
Theta range for data collection	2.63 to 30.51°.
Index ranges	$-10 \leq h \leq 10, -27 \leq k \leq 27, -11 \leq l \leq 11$
Reflections collected	13156
Independent reflections	6415 [R(int) = 0.0358]

Table 21. Continued

Completeness to theta = 30.51°	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.803
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6415 / 1 / 251
Goodness-of-fit on F^2	1.011
Final R indices [I>2sigma(I)]	$R_1 = 0.0246$, $\omega R_2 = 0.0573$
R indices (all data)	$R_1 = 0.0254$, $\omega R_2 = 0.0576$
Absolute structure parameter	-0.027(16)
Largest diff. peak and hole	1.327 and -0.403 $e\text{Å}^{-3}$

Table 22. Atomic coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (**L1**)PdCl$_2$

	x	y	z	U(eq)
Pd	4010(1)	1153(1)	1177(1)	12(1)
Cl(1)	6319(1)	1561(1)	3616(1)	19(1)
Cl(2)	5693(1)	153(1)	1449(1)	19(1)
P	1784(1)	724(1)	-1095(1)	12(1)
O	1350(2)	2999(1)	-743(2)	16(1)
N	2856(3)	2115(1)	772(2)	14(1)
C(1)	-389(3)	1215(1)	-1391(3)	14(1)
C(2)	-1063(3)	1455(1)	147(3)	16(1)
C(3)	-463(3)	1977(1)	-1010(3)	14(1)
C(4)	1333(3)	2338(1)	-293(3)	14(1)
C(5)	3325(3)	3218(1)	-88(3)	17(1)
C(6)	4024(3)	2732(1)	1427(3)	15(1)
C(7)	3568(3)	3011(1)	3053(3)	16(1)
C(8)	1825(4)	2916(1)	3425(3)	19(1)
C(9)	1369(4)	3275(1)	4784(3)	22(1)
C(10)	2649(4)	3727(1)	5759(3)	24(1)
C(11)	4426(4)	3805(1)	5436(3)	27(1)
C(12)	4900(4)	3451(1)	4097(3)	21(1)
C(13)	-2000(3)	2392(1)	-2217(3)	19(1)

Table 22. Continued

C(14)	898(3)	-167(1)	-801(3)	16(1)
C(15)	883(3)	-251(1)	1107(3)	19(1)
C(16)	2146(4)	-724(1)	-1309(3)	21(1)
C(17)	-1158(3)	-259(1)	-1881(3)	20(1)
C(18)	2472(3)	832(1)	-3190(3)	15(1)
C(19)	2609(4)	1602(1)	-3504(3)	22(1)
C(20)	1014(4)	528(1)	-4744(3)	23(1)
C(21)	4424(3)	517(1)	-3071(3)	19(1)

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U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table 23. Bond lengths [Å] and angles [°] for (**L1**)PdCl$_2$.

Pd-N	2.0538(19)	C(4)-O-C(5)	105.07(17)
Pd-P	2.2728(6)	C(4)-N-C(6)	106.08(18)
Pd-Cl(2)	2.2885(6)	C(4)-N-Pd	131.39(16)
Pd-Cl(1)	2.3730(6)	C(6)-N-Pd	120.84(14)
P-C(1)	1.810(2)	C(2)-C(1)-C(3)	59.86(15)
P-C(18)	1.874(2)	C(2)-C(1)-P	120.41(15)
P-C(14)	1.892(3)	C(3)-C(1)-P	124.46(16)
O-C(4)	1.344(3)	C(1)-C(2)-C(3)	60.72(16)
O-C(5)	1.462(3)	C(4)-C(3)-C(2)	116.57(19)
N-C(4)	1.292(3)	C(4)-C(3)-C(13)	115.6(2)
N-C(6)	1.493(3)	C(2)-C(3)-C(13)	118.33(19)
C(1)-C(2)	1.506(3)	C(4)-C(3)-C(1)	118.49(19)
C(1)-C(3)	1.526(3)	C(2)-C(3)-C(1)	59.42(14)
C(2)-C(3)	1.513(3)	C(13)-C(3)-C(1)	116.95(19)
C(3)-C(4)	1.467(3)	N-C(4)-O	116.0(2)

Table 23. Continued

C(3)-C(13)	1.518(3)	N-C(4)-C(3)	128.8(2)
C(5)-C(6)	1.526(3)	O-C(4)-C(3)	115.1(2)
C(6)-C(7)	1.521(3)	O-C(5)-C(6)	101.81(17)
C(7)-C(8)	1.380(3)	N-C(6)-C(7)	111.50(18)
C(7)-C(12)	1.404(3)	N-C(6)-C(5)	100.25(17)
C(8)-C(9)	1.400(3)	C(7)-C(6)-C(5)	110.81(19)
C(9)-C(10)	1.376(4)	C(8)-C(7)-C(12)	119.1(2)
C(10)-C(11)	1.383(4)	C(8)-C(7)-C(6)	122.7(2)
C(11)-C(12)	1.389(4)	C(12)-C(7)-C(6)	117.8(2)
C(14)-C(16)	1.534(3)	C(7)-C(8)-C(9)	120.3(2)
C(14)-C(17)	1.537(3)	C(10)-C(9)-C(8)	120.5(2)
C(14)-C(15)	1.538(3)	C(9)-C(10)-C(11)	119.6(2)
C(18)-C(21)	1.524(3)	C(10)-C(11)-C(12)	120.5(3)
C(18)-C(19)	1.536(3)	C(11)-C(12)-C(7)	120.0(3)
C(18)-C(20)	1.538(3)	C(16)-C(14)-C(17)	108.7(2)

Table 23. Continued

N-Pd-P	91.84(5)	C(16)-C(14)-C(15)	109.6(2)
N-Pd-Cl(2)	170.53(5)	C(17)-C(14)-C(15)	107.58(19)
P-Pd-Cl(2)	90.92(2)	C(16)-C(14)-P	112.43(17)
N-Pd-Cl(1)	89.91(5)	C(17)-C(14)-P	110.44(17)
P-Pd-Cl(1)	177.60(2)	C(15)-C(14)-P	107.97(16)
Cl(2)-Pd-Cl(1)	87.61(2)	C(21)-C(18)-C(19)	108.1(2)
C(1)-P-C(18)	103.80(10)	C(21)-C(18)-C(20)	109.6(2)
C(1)-P-C(14)	101.25(11)	C(19)-C(18)-C(20)	107.8(2)
C(18)-P-C(14)	112.84(11)	C(21)-C(18)-P	110.28(17)
C(1)-P-Pd	109.31(8)	C(19)-C(18)-P	107.40(16)
C(18)-P-Pd	112.34(8)	C(20)-C(18)-P	113.44(17)
C(14)-P-Pd	115.90(8)		

Table 24. Anisotropic displacement parameters $(\text{Å}^2 \times 10^3)$ for (**L1**)PdCl$_2$ complex. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a*2U^{11} + ... + 2 h k a* b* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd	14(1)	12(1)	10(1)	1(1)	2(1)	1(1)
Cl(1)	19(1)	20(1)	14(1)	-1(1)	-1(1)	1(1)
Cl(2)	20(1)	14(1)	22(1)	3(1)	3(1)	4(1)
P	14(1)	11(1)	12(1)	-1(1)	3(1)	1(1)
O	18(1)	13(1)	16(1)	2(1)	2(1)	-1(1)
N	16(1)	11(1)	14(1)	-2(1)	2(1)	-3(1)
C(1)	15(1)	13(1)	14(1)	-3(1)	3(1)	1(1)
C(2)	18(1)	13(1)	19(1)	0(1)	6(1)	-1(1)
C(3)	16(1)	12(1)	14(1)	0(1)	3(1)	1(1)
C(4)	18(1)	11(1)	13(1)	-2(1)	6(1)	0(1)
C(5)	17(1)	17(1)	16(1)	1(1)	3(1)	-3(1)
C(6)	17(1)	11(1)	17(1)	-1(1)	3(1)	-3(1)
C(7)	23(1)	11(1)	12(1)	2(1)	0(1)	1(1)
C(8)	27(1)	15(1)	15(1)	1(1)	4(1)	0(1)
C(9)	34(1)	18(1)	17(1)	4(1)	10(1)	4(1)
C(10)	43(2)	18(1)	12(1)	2(1)	7(1)	5(1)
C(11)	42(2)	19(1)	14(1)	-3(1)	-5(1)	-4(1)
C(12)	26(1)	18(1)	16(1)	-1(1)	2(1)	-3(1)

Table 24. Continued

C(13)	19(1)	16(1)	21(1)	0(1)	1(1)	3(1)
C(14)	18(1)	13(1)	19(1)	-1(1)	7(1)	0(1)
C(15)	24(1)	16(1)	19(1)	2(1)	7(1)	-3(1)
C(16)	25(1)	13(1)	25(1)	-2(1)	5(1)	5(1)
C(17)	21(1)	14(1)	24(1)	-4(1)	4(1)	-2(1)
C(18)	15(1)	17(1)	13(1)	2(1)	5(1)	2(1)
C(19)	30(1)	19(1)	19(1)	5(1)	12(1)	5(1)
C(20)	26(1)	29(1)	13(1)	-4(1)	5(1)	2(1)
C(21)	20(1)	21(1)	18(1)	0(1)	7(1)	2(1)

Table 25. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (**L1**)PdCl$_2$ complex.

	x	y	z	U(eq)
H(1)	-1437	1056	-2376	16
H(2A)	-209	1380	1305	20
H(2B)	-2438	1415	91	20
H(5A)	3400	3700	299	20
H(5B)	4063	3163	-969	20
H(6)	5415	2635	1616	18
H(8)	930	2607	2756	23
H(9)	168	3205	5035	27
H(10)	2313	3983	6648	29
H(11)	5330	4104	6137	33
H(12)	6126	3506	3887	25
H(13A)	-2288	2799	-1613	29
H(13B)	-3152	2114	-2594	29
H(13C)	-1551	2533	-3225	29
H(15A)	484	-717	1303	29
H(15B)	-8	77	1400	29
H(15C)	2165	-168	1834	29
H(16A)	1768	-1171	-955	32

Table 25. Continued

H(16B)	3485	-637	-735	32
H(16C)	1983	-718	-2562	32
H(17A)	-1511	-742	-1893	29
H(17B)	-1251	-104	-3064	29
H(17C)	-2021	12	-1375	29
H(19A)	3160	1676	-4491	33
H(19B)	3419	1817	-2476	33
H(19C)	1333	1804	-3747	33
H(20A)	1407	629	-5805	34
H(20B)	-241	730	-4814	34
H(20C)	946	32	-4603	34
H(21A)	4846	632	-4110	29
H(21B)	4343	19	-2973	29
H(21C)	5339	697	-2053	29

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Table 26. Torsion angles [°] for (**L1**)PdCl$_2$ complex.

N-Pd-P-C(1)	-28.89(10)	C(13)-C(3)-C(4)-O	2.8(3)
Cl(2)-Pd-P-C(1)	160.17(8)	C(1)-C(3)-C(4)-O	149.01(19)
Cl(1)-Pd-P-C(1)	108.0(5)	C(4)-O-C(5)-C(6)	-26.8(2)
N-Pd-P-C(18)	85.77(10)	C(4)-N-C(6)-C(7)	90.7(2)
Cl(2)-Pd-P-C(18)	-85.17(9)	Pd-N-C(6)-C(7)	-102.51(18)
Cl(1)-Pd-P-C(18)	-137.3(5)	C(4)-N-C(6)-C(5)	-26.6(2)
N-Pd-P-C(14)	-142.47(10)	Pd-N-C(6)-C(5)	140.15(15)
Cl(2)-Pd-P-C(14)	46.59(8)	O-C(5)-C(6)-N	31.6(2)
Cl(1)-Pd-P-C(14)	-5.6(6)	O-C(5)-C(6)-C(7)	-86.2(2)
P-Pd-N-C(4)	5.6(2)	N-C(6)-C(7)-C(8)	-26.5(3)
Cl(2)-Pd-N-C(4)	112.4(3)	C(5)-C(6)-C(7)-C(8)	84.2(3)
Cl(1)-Pd-N-C(4)	-172.8(2)	N-C(6)-C(7)-C(12)	161.4(2)
P-Pd-N-C(6)	-157.38(15)	C(5)-C(6)-C(7)-C(12)	-87.8(2)
Cl(2)-Pd-N-C(6)	-50.5(4)	C(12)-C(7)-C(8)-C(9)	2.4(3)
Cl(1)-Pd-N-C(6)	24.26(15)	C(6)-C(7)-C(8)-C(9)	-169.6(2)

Table 26. Continued

C(18)-P-C(1)-C(2)	-159.73(19)	C(7)-C(8)-C(9)-C(10)	0.3(4)
C(14)-P-C(1)-C(2)	83.1(2)	C(8)-C(9)-C(10)-C(11)	-2.7(4)
Pd-P-C(1)-C(2)	-39.7(2)	C(9)-C(10)-C(11)-C(12)	2.4(4)
C(18)-P-C(1)-C(3)	-87.40(19)	C(10)-C(11)-C(12)-C(7)	0.2(4)
C(14)-P-C(1)-C(3)	155.45(18)	C(8)-C(7)-C(12)-C(11)	-2.7(4)
Pd-P-C(1)-C(3)	32.65(19)	C(6)-C(7)-C(12)-C(11)	169.7(2)
P-C(1)-C(2)-C(3)	114.7(2)	C(1)-P-C(14)-C(16)	154.65(17)
C(1)-C(2)-C(3)-C(4)	-108.9(2)	C(18)-P-C(14)-C(16)	44.3(2)
C(1)-C(2)-C(3)-C(13)	106.2(2)	Pd-P-C(14)-C(16)	-87.22(17)
C(2)-C(1)-C(3)-C(4)	105.7(2)	C(1)-P-C(14)-C(17)	33.06(18)
P-C(1)-C(3)-C(4)	-2.5(3)	C(18)-P-C(14)-C(17)	-77.29(19)
P-C(1)-C(3)-C(2)	-108.15(19)	Pd-P-C(14)-C(17)	151.18(14)
C(2)-C(1)-C(3)-C(13)	-108.5(2)	C(1)-P-C(14)-C(15)	-84.31(16)
P-C(1)-C(3)-C(13)	143.31(18)	C(18)-P-C(14)-C(15)	165.34(15)
C(6)-N-C(4)-O	11.0(3)	Pd-P-C(14)-C(15)	33.82(17)

Table 26. Continued

Pd-N-C(4)-O	-153.81(16)	C(1)-P-C(18)-C(21)	173.03(17)
C(6)-N-C(4)-C(3)	-165.2(2)	C(14)-P-C(18)-C(21)	-78.21(19)
Pd-N-C(4)-C(3)	30.0(4)	Pd-P-C(18)-C(21)	55.06(18)
C(5)-O-C(4)-N	10.8(3)	C(1)-P-C(18)-C(19)	55.5(2)
C(5)-O-C(4)-C(3)	-172.42(18)	C(14)-P-C(18)-C(19)	164.22(18)
C(2)-C(3)-C(4)-N	33.2(3)	Pd-P-C(18)-C(19)	-62.51(19)
C(13)-C(3)-C(4)-N	179.0(2)	C(1)-P-C(18)-C(20)	-63.5(2)
C(1)-C(3)-C(4)-N	-34.8(3)	C(14)-P-C(18)-C(20)	45.2(2)
C(2)-C(3)-C(4)-O	-143.1(2)	Pd-P-C(18)-C(20)	178.48(15)
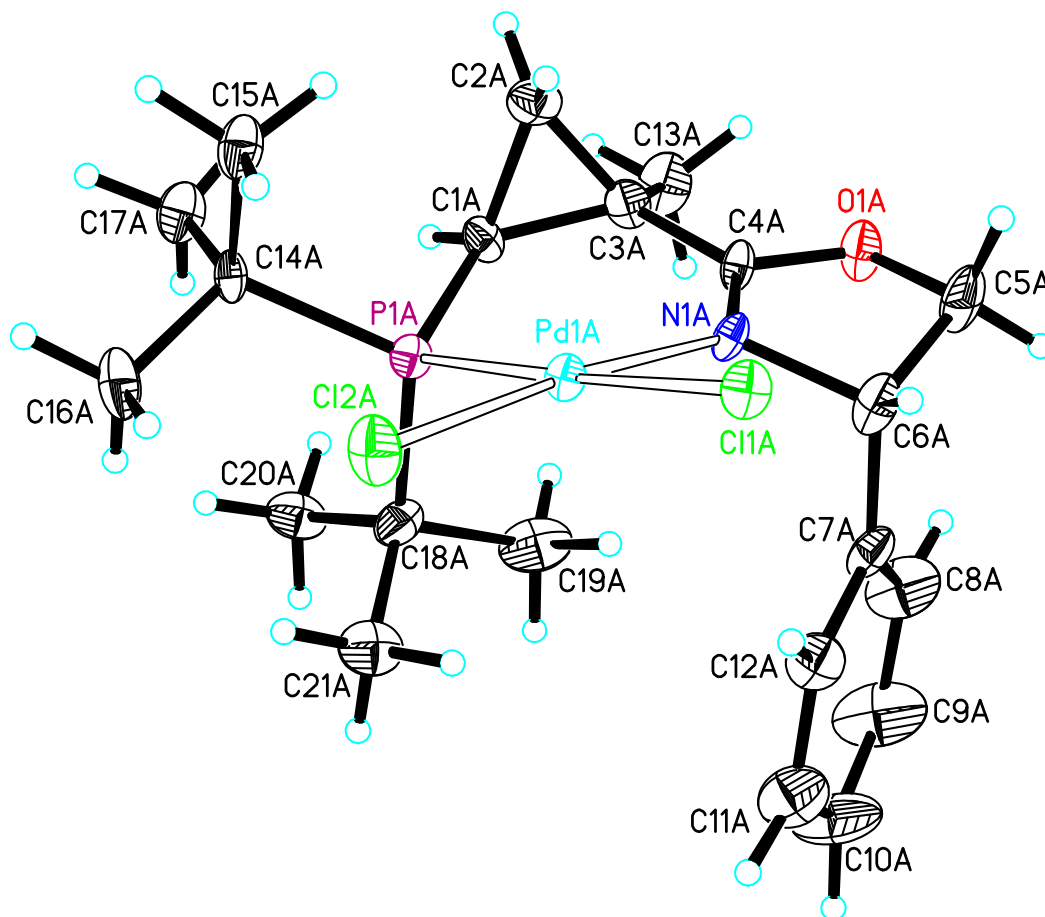
Figure 25. ORTEP drawing of complex (**L4**)PdCl$_2$ · 0.25 CH$_2$Cl$_2$ · 0.50 H$_2$O, (the first (A) of four crystallographically-independent molecules), showing the atom-numbering scheme; 50 % probability amplitude displacement ellipsoids are shown.

Four crystallographically-independent (**L4**)PdCl$_2$ molecules in a crystalline complex

(**L4**)PdCl$_2$ · 0.25 CH$_2$Cl$_2$ · 0.50 H$_2$O have nearly identical molecular conformations.

27 Non-hydrogen atoms for the second (B), third (C), and fourth (D) molecules can

be superimposed with the corresponding non-hydrogen atoms of the first molecule

(A) with a maximum rms deviation of 0.29 Å for any molecular pair. Furthermore,

the maximum deviation for any pair of atoms for these superimposed molecules is 0.90 Å.
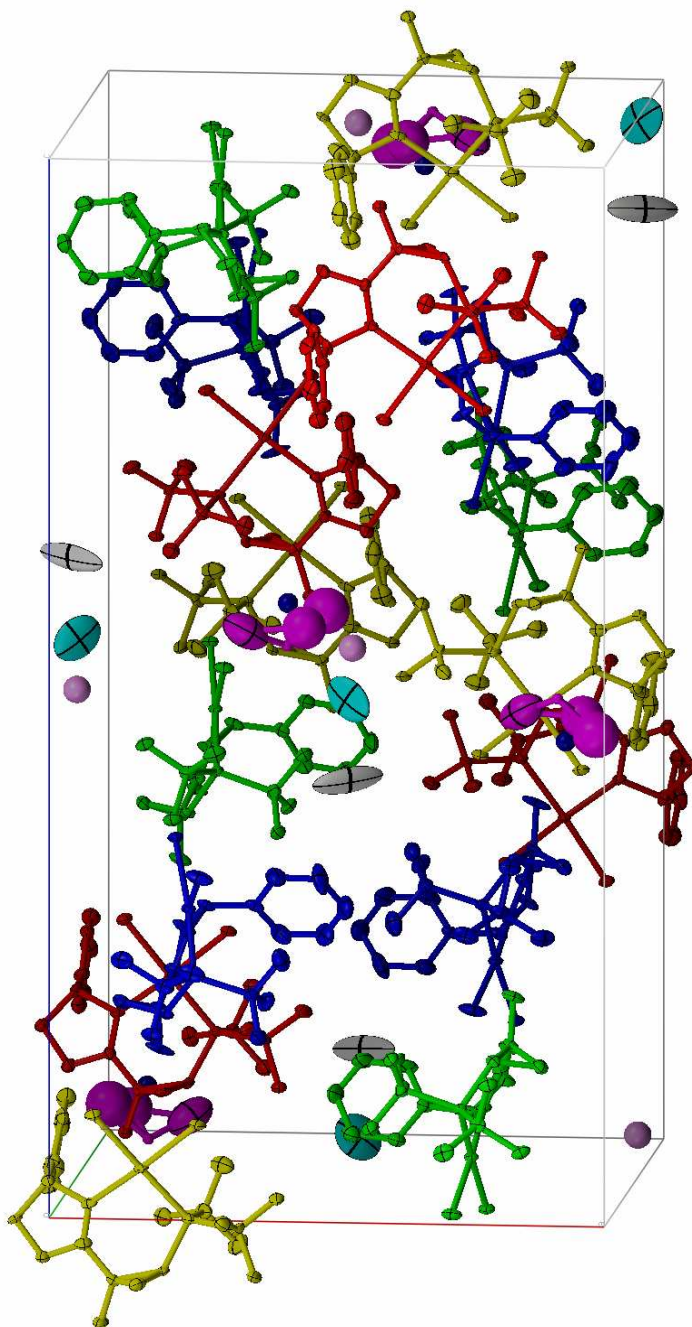
Figure 26. Packing of (**L4**)PdCl$_2$ complex in the crystalline lattice cell, showing four sets of crystallographically-independent molecules, colored by symmetry equivalence. Molecule A is shown in green, molecule B – in blue, molecule C – in red, molecule D – in yellow. Disordered water and dichloromethane molecules are shown in purple, violet, gray, and turquoise.

Table 27. Crystal data and structure refinement for (**L4**)PdCl$_2$.

Identification code	k12f
Empirical formula	C$_{21.25}$H$_{33.50}$Cl$_{2.50}$NO$_{1.50}$PPd
Formula weight	552.99
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2$_1$2$_1$2$_1$
Unit cell dimensions	a = 17.1172(12) Å α= 90°.
	b = 17.4726(12) Å β= 90°.
	c = 33.072(2) Å γ = 90°.
Volume	9891.1(12) Å^3
Z	16
Density (calculated)	1.485 g/cm^3
Absorption coefficient	1.100 mm^{-1}
F(000)	4536
Crystal size	0.40 x 0.30 x 0.09 mm^3
Theta range for data collection	1.67 to 30.57°
Index ranges	-23 $\leq$ h $\leq$ 24, -24 $\leq$ k $\leq$ 24, -46 $\leq$ l $\leq$ 46
Reflections collected	117245
Independent reflections	29017 [R(int) = 0.0918]

Table 27. Continued

Completeness to theta = 30.57°	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.742
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	29017 / 8 / 1049
Goodness-of-fit on F^2	1.121
Final R indices [I>2sigma(I)]	$R_1 = 0.0745$, $\omega R_2 = 0.1490$
R indices (all data)	$R_1 = 0.0898$, $\omega R_2 = 0.1549$
Absolute structure parameter	0.06(3)
Largest diff. peak and hole	1.901 and -2.012 eÅ^{-3}

Table 28. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for (**L4**)PdCl$_2$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1A)	7573(1)	308(1)	614(1)	14(1)
Cl(1A)	7757(1)	1170(1)	55(1)	20(1)
Cl(2A)	7318(1)	-622(1)	148(1)	26(1)
P(1A)	7459(1)	-524(1)	1135(1)	16(1)
O(1A)	8079(3)	1958(3)	1515(1)	25(1)
N(1A)	7706(3)	1193(3)	1005(2)	15(1)
C(1A)	8020(4)	-170(4)	1560(2)	18(1)
C(2A)	8841(4)	78(4)	1496(2)	25(2)
C(3A)	8246(4)	640(4)	1646(2)	22(1)
C(4A)	7998(4)	1251(4)	1361(2)	17(1)
C(5A)	7932(5)	2463(4)	1171(2)	30(2)
C(6A)	7412(5)	1980(4)	897(2)	25(2)
C(7A)	6559(4)	2019(4)	949(2)	23(2)
C(8A)	6205(5)	2287(5)	1292(2)	40(2)
C(9A)	5413(6)	2222(7)	1347(3)	54(3)
C(10A)	4948(5)	1960(7)	1053(3)	49(3)
C(11A)	5278(5)	1651(5)	704(2)	37(2)
C(12A)	6076(5)	1707(4)	649(2)	27(2)
C(13A)	8267(5)	877(5)	2086(2)	33(2)

Table 28. Continued

C(14A)	7879(4)	-1509(4)	1068(2)	19(1)
C(15A)	8653(4)	-1438(4)	811(2)	25(2)
C(16A)	7329(5)	-2043(4)	847(2)	31(2)
C(17A)	8106(5)	-1866(4)	1482(2)	27(2)
C(18A)	6425(4)	-563(4)	1319(2)	25(2)
C(19A)	6245(5)	214(5)	1515(2)	36(2)
C(20A)	6288(4)	-1179(5)	1646(2)	28(2)
C(21A)	5866(4)	-663(5)	954(2)	31(2)
Pd(1B)	7498(1)	5099(1)	2067(1)	18(1)
Cl(1B)	7803(1)	5739(1)	1448(1)	27(1)
Cl(2B)	7196(2)	4055(1)	1687(1)	42(1)
P(1B)	7329(1)	4445(1)	2650(1)	17(1)
O(1B)	7933(3)	7002(3)	2817(1)	29(1)
N(1B)	7627(3)	6098(3)	2375(2)	18(1)
C(1B)	7894(4)	4902(4)	3043(2)	18(1)
C(2B)	8714(4)	5150(4)	2959(2)	24(2)
C(3B)	8116(4)	5745(4)	3060(2)	23(2)
C(4B)	7881(4)	6255(4)	2732(2)	20(1)
C(5B)	7825(5)	7406(4)	2434(2)	32(2)
C(6B)	7367(4)	6826(4)	2178(2)	22(1)
C(7B)	6498(4)	6886(4)	2179(2)	22(2)

Table 28. Continued

C(8B)	6064(6)	7254(5)	2474(3)	45(2)
C(9B)	5275(6)	7249(6)	2472(3)	49(3)
C(10B)	4864(6)	6879(6)	2185(3)	49(3)
C(11B)	5274(6)	6510(7)	1887(4)	62(3)
C(12B)	6077(6)	6527(6)	1877(3)	45(2)
C(13B)	8123(6)	6111(5)	3479(2)	42(2)
C(14B)	7757(5)	3450(4)	2667(2)	29(2)
C(15B)	8519(5)	3453(5)	2426(2)	37(2)
C(16B)	7197(6)	2853(4)	2490(2)	38(2)
C(17B)	7954(5)	3216(4)	3107(2)	30(2)
C(18B)	6299(4)	4484(4)	2818(2)	25(2)
C(19B)	6126(5)	5318(5)	2952(3)	36(2)
C(20B)	6119(5)	3970(5)	3179(2)	37(2)
C(21B)	5749(5)	4286(5)	2470(3)	44(2)
Pd(1C)	1720(1)	4391(1)	1931(1)	17(1)
Cl(1C)	927(1)	4022(1)	2495(1)	23(1)
Cl(2C)	2763(1)	4399(1)	2366(1)	27(1)
P(1C)	2522(1)	4600(1)	1398(1)	19(1)
O(1C)	-122(3)	4427(3)	1070(1)	23(1)
N(1C)	752(3)	4499(3)	1571(2)	17(1)
C(1C)	2047(4)	4305(4)	935(2)	18(1)

Table 28. Continued

C(2C)	1670(4)	3528(4)	908(2)	20(1)
C(3C)	1178(4)	4231(4)	863(2)	16(1)
C(4C)	628(4)	4384(4)	1195(2)	18(1)
C(5C)	-605(4)	4457(4)	1444(2)	24(1)
C(6C)	-17(4)	4745(5)	1757(2)	25(2)
C(7C)	-14(4)	5602(4)	1830(2)	24(2)
C(8C)	-118(4)	6113(5)	1504(2)	29(2)
C(9C)	-140(5)	6892(6)	1566(3)	41(2)
C(10C)	-47(5)	7190(5)	1960(3)	37(2)
C(11C)	36(6)	6697(6)	2282(3)	44(2)
C(12C)	56(4)	5894(5)	2214(2)	26(2)
C(13C)	896(4)	4462(4)	446(2)	24(2)
C(14C)	3451(4)	4009(4)	1383(2)	23(2)
C(15C)	3248(5)	3207(5)	1549(2)	34(2)
C(16C)	4118(5)	4373(6)	1624(2)	39(2)
C(17C)	3723(4)	3901(4)	939(2)	23(2)
C(18C)	2694(4)	5653(5)	1319(2)	26(2)
C(19C)	1897(5)	6000(5)	1229(3)	32(2)
C(20C)	3253(5)	5811(5)	965(2)	34(2)
C(21C)	3027(5)	6021(5)	1715(2)	32(2)
Pd(1D)	6689(1)	5314(1)	-511(1)	19(1)

Table 28. Continued

Cl(1D)	5871(1)	5758(1)	-1047(1)	27(1)
Cl(2D)	7725(1)	5434(1)	-942(1)	34(1)
P(1D)	7517(1)	4986(1)	-11(1)	23(1)
O(1D)	4896(3)	5061(3)	363(1)	24(1)
N(1D)	5731(3)	5111(3)	-154(2)	18(1)
C(1D)	7069(4)	5204(4)	468(2)	21(1)
C(2D)	6693(4)	5960(4)	534(2)	25(2)
C(3D)	6187(4)	5261(4)	556(2)	22(1)
C(4D)	5630(4)	5151(4)	224(2)	23(1)
C(5D)	4395(4)	5065(4)	7(2)	22(1)
C(6D)	4968(4)	4889(4)	-343(2)	22(1)
C(7D)	4966(4)	4059(4)	-460(2)	23(1)
C(8D)	4853(5)	3467(5)	-179(2)	35(2)
C(9D)	4843(6)	2725(5)	-288(3)	39(2)
C(10D)	4968(5)	2521(5)	-688(3)	39(2)
C(11D)	5103(5)	3094(5)	-977(3)	39(2)
C(12D)	5111(4)	3859(5)	-864(2)	26(2)
C(13D)	5930(4)	4997(5)	976(2)	28(2)
C(14D)	8463(4)	5556(5)	34(2)	28(2)
C(15D)	8292(5)	6375(5)	-88(2)	37(2)
C(16D)	9120(5)	5212(7)	-233(2)	43(2)

Table 28. Continued

C(17D)	8756(5)	5559(6)	477(2)	42(2)
C(18D)	7673(5)	3929(5)	3(2)	31(2)
C(19D)	6900(5)	3562(5)	91(3)	35(2)
C(20D)	8262(6)	3675(5)	331(3)	42(2)
C(21D)	7972(6)	3637(5)	-411(3)	41(2)
Cl(1)	6738(5)	7557(4)	-354(2)	174(3)
O(1W')	6738(5)	7557(4)	-354(2)	174(3)
Cl(2)	5346(5)	8154(6)	-510(3)	219(4)
Cl(2')	5663(18)	7420(20)	-407(8)	188(15)
C(1S)	6044(5)	8098(7)	-180(3)	13(3)
C(1S')	5961(8)	7487(11)	-633(6)	41(6)
C(1S")	4783(13)	7340(40)	-230(9)	76(19)
O(1W)	4817(7)	6990(5)	225(4)	164(5)
Cl(1')	4817(7)	6990(5)	225(4)	164(5)
O(2W)	4876(13)	7391(8)	1022(3)	231(11)

Table 29. Bond lengths [Å] and angles [°] for (**L4**)PdCl$_2$.

Pd(1A)-N(1A)	2.029(5)	C(14B)-C(15B)	1.529(12)
Pd(1A)-P(1A)	2.2610(16)	C(14B)-C(16B)	1.532(11)
Pd(1A)-Cl(2A)	2.2818(17)	C(14B)-C(17B)	1.548(10)
Pd(1A)-Cl(1A)	2.4059(16)	C(18B)-C(20B)	1.525(10)
P(1A)-C(1A)	1.812(6)	C(18B)-C(21B)	1.528(11)
P(1A)-C(18A)	1.873(7)	C(18B)-C(19B)	1.552(11)
P(1A)-C(14A)	1.878(7)	Pd(1C)-N(1C)	2.049(5)
O(1A)-C(4A)	1.343(8)	Pd(1C)-P(1C)	2.2643(17)
O(1A)-C(5A)	1.462(8)	Pd(1C)-Cl(2C)	2.2921(17)
N(1A)-C(4A)	1.283(8)	Pd(1C)-Cl(1C)	2.3963(17)
N(1A)-C(6A)	1.508(8)	P(1C)-C(1C)	1.809(7)
C(1A)-C(2A)	1.488(10)	P(1C)-C(18C)	1.882(8)
C(1A)-C(3A)	1.494(9)	P(1C)-C(14C)	1.896(7)
C(2A)-C(3A)	1.501(10)	O(1C)-C(4C)	1.350(8)
C(3A)-C(4A)	1.487(9)	O(1C)-C(5C)	1.487(8)

Table 29. Continued

C(3A)-C(13A)	1.511(9)	N(1C)-C(4C)	1.280(8)
C(5A)-C(6A)	1.525(10)	N(1C)-C(6C)	1.514(8)
C(6A)-C(7A)	1.472(11)	C(1C)-C(2C)	1.506(10)
C(7A)-C(8A)	1.370(10)	C(1C)-C(3C)	1.512(9)
C(7A)-C(12A)	1.402(10)	C(2C)-C(3C)	1.496(9)
C(8A)-C(9A)	1.372(13)	C(3C)-C(4C)	1.469(9)
C(9A)-C(10A)	1.337(13)	C(3C)-C(13C)	1.517(9)
C(10A)-C(11A)	1.395(12)	C(5C)-C(6C)	1.531(10)
C(11A)-C(12A)	1.381(12)	C(6C)-C(7C)	1.516(11)
C(14A)-C(16A)	1.513(10)	C(7C)-C(12C)	1.372(9)
C(14A)-C(17A)	1.554(9)	C(7C)-C(8C)	1.413(10)
C(14A)-C(15A)	1.579(10)	C(8C)-C(9C)	1.379(12)
C(18A)-C(19A)	1.536(11)	C(9C)-C(10C)	1.412(12)
C(18A)-C(20A)	1.544(10)	C(10C)-C(11C)	1.375(13)
C(18A)-C(21A)	1.550(10)	C(11C)-C(12C)	1.422(12)

Table 29. Continued

Pd(1B)-N(1B)	2.032(5)	C(14C)-C(16C)	1.531(11)
Pd(1B)-P(1B)	2.2583(16)	C(14C)-C(15C)	1.545(11)
Pd(1B)-Cl(2B)	2.2753(19)	C(14C)-C(17C)	1.551(9)
Pd(1B)-Cl(1B)	2.3912(17)	C(18C)-C(19C)	1.523(10)
P(1B)-C(1B)	1.807(7)	C(18C)-C(20C)	1.537(10)
P(1B)-C(18B)	1.851(7)	C(18C)-C(21C)	1.567(10)
P(1B)-C(14B)	1.888(7)	Pd(1D)-N(1D)	2.053(6)
O(1B)-C(4B)	1.337(8)	Pd(1D)-P(1D)	2.2514(18)
O(1B)-C(5B)	1.462(8)	Pd(1D)-Cl(2D)	2.2844(18)
N(1B)-C(4B)	1.290(8)	Pd(1D)-Cl(1D)	2.3889(17)
N(1B)-C(6B)	1.498(8)	P(1D)-C(1D)	1.800(6)
C(1B)-C(2B)	1.496(10)	P(1D)-C(18D)	1.868(8)
C(1B)-C(3B)	1.523(9)	P(1D)-C(14D)	1.906(7)
C(2B)-C(3B)	1.497(10)	O(1D)-C(4D)	1.348(8)
C(3B)-C(4B)	1.458(9)	O(1D)-C(5D)	1.455(7)

Table 29. Continued

C(3B)-C(13B)	1.527(10)	N(1D)-C(4D)	1.263(8)
C(5B)-C(6B)	1.537(9)	N(1D)-C(6D)	1.498(9)
C(6B)-C(7B)	1.490(11)	C(1D)-C(2D)	1.486(10)
C(7B)-C(12B)	1.382(11)	C(1D)-C(3D)	1.542(9)
C(7B)-C(8B)	1.384(11)	C(2D)-C(3D)	1.499(10)
C(8B)-C(9B)	1.351(13)	C(3D)-C(4D)	1.467(9)
C(9B)-C(10B)	1.346(14)	C(3D)-C(13D)	1.528(9)
C(10B)-C(11B)	1.372(13)	C(5D)-C(6D)	1.550(9)
C(11B)-C(12B)	1.376(13)	C(6D)-C(7D)	1.501(10)
C(7D)-C(12D)	1.401(10)	C(18D)-C(21D)	1.549(11)
C(7D)-C(8D)	1.404(10)	Cl(1)-C(1S)	1.623(6)
C(8D)-C(9D)	1.345(12)	Cl(1)-Cl(2')	1.86(3)
C(9D)-C(10D)	1.388(13)	Cl(2)-Cl(2')	1.44(4)
C(10D)-C(11D)	1.402(13)	Cl(2)-C(1S)	1.623(6)
C(11D)-C(12D)	1.387(11)	Cl(2)-C(1S')	1.623(6)

Table 29. Continued

C(14D)-C(15D)	1.514(12)	Cl(2)-C(1S")	1.95(4)
C(14D)-C(16D)	1.550(11)	Cl(2')-C(1S')	0.91(3)
C(14D)-C(17D)	1.550(9)	Cl(2')-C(1S)	1.55(4)
C(18D)-C(19D)	1.499(12)	Cl(2')-C(1S")	1.623(6)
C(18D)-C(20D)	1.547(11)	C(16A)-C(14A)-C(17A)	109.5(5)
N(1A)-Pd(1A)-P(1A)	90.83(15)	C(16A)-C(14A)-C(15A)	108.0(6)
N(1A)-Pd(1A)-Cl(2A)	174.26(16)	C(17A)-C(14A)-C(15A)	107.3(6)
P(1A)-Pd(1A)-Cl(2A)	92.28(6)	C(16A)-C(14A)-P(1A)	112.5(5)
N(1A)-Pd(1A)-Cl(1A)	89.91(15)	C(17A)-C(14A)-P(1A)	111.2(5)
P(1A)-Pd(1A)-Cl(1A)	177.18(7)	C(15A)-C(14A)-P(1A)	108.1(4)
Cl(2A)-Pd(1A)-Cl(1A)	87.21(6)	C(19A)-C(18A)-C(20A)	106.8(6)
C(1A)-P(1A)-C(18A)	105.1(3)	C(19A)-C(18A)-C(21A)	107.7(6)
C(1A)-P(1A)-C(14A)	101.6(3)	C(20A)-C(18A)-C(21A)	111.9(6)
C(18A)-P(1A)-C(14A)	111.5(3)	C(19A)-C(18A)-P(1A)	107.2(5)
C(1A)-P(1A)-Pd(1A)	109.1(2)	C(20A)-C(18A)-P(1A)	113.3(5)

Table 29. Continued

C(18A)-P(1A)-Pd(1A)	110.6(2)	C(21A)-C(18A)-P(1A)	109.6(5)
C(14A)-P(1A)-Pd(1A)	117.9(2)	N(1B)-Pd(1B)-P(1B)	91.22(15)
C(4A)-O(1A)-C(5A)	104.0(5)	N(1B)-Pd(1B)-Cl(2B)	171.86(16)
C(4A)-N(1A)-C(6A)	106.0(5)	P(1B)-Pd(1B)-Cl(2B)	92.14(7)
C(4A)-N(1A)-Pd(1A)	133.6(4)	N(1B)-Pd(1B)-Cl(1B)	90.20(15)
C(6A)-N(1A)-Pd(1A)	120.4(4)	P(1B)-Pd(1B)-Cl(1B)	174.34(7)
C(2A)-C(1A)-C(3A)	60.4(5)	Cl(2B)-Pd(1B)-Cl(1B)	87.18(7)
C(2A)-C(1A)-P(1A)	119.2(5)	C(1B)-P(1B)-C(18B)	106.0(3)
C(3A)-C(1A)-P(1A)	127.4(5)	C(1B)-P(1B)-C(14B)	100.2(3)
C(1A)-C(2A)-C(3A)	60.0(5)	C(18B)-P(1B)-C(14B)	113.2(4)
C(4A)-C(3A)-C(1A)	119.1(5)	C(1B)-P(1B)-Pd(1B)	108.8(2)
C(4A)-C(3A)-C(2A)	117.0(6)	C(18B)-P(1B)-Pd(1B)	111.1(2)
C(1A)-C(3A)-C(2A)	59.6(5)	C(14B)-P(1B)-Pd(1B)	116.3(2)
C(4A)-C(3A)-C(13A)	114.7(6)	C(4B)-O(1B)-C(5B)	106.4(5)
C(1A)-C(3A)-C(13A)	116.7(6)	C(4B)-N(1B)-C(6B)	108.5(5)

Table 29. Continued

C(2A)-C(3A)-C(13A)	118.8(6)	C(4B)-N(1B)-Pd(1B)	132.8(5)
N(1A)-C(4A)-O(1A)	117.5(6)	C(6B)-N(1B)-Pd(1B)	118.7(4)
N(1A)-C(4A)-C(3A)	129.4(6)	C(2B)-C(1B)-C(3B)	59.5(5)
O(1A)-C(4A)-C(3A)	113.0(5)	C(2B)-C(1B)-P(1B)	119.7(5)
O(1A)-C(5A)-C(6A)	103.2(6)	C(3B)-C(1B)-P(1B)	125.9(5)
C(7A)-C(6A)-N(1A)	110.3(6)	C(1B)-C(2B)-C(3B)	61.2(5)
C(7A)-C(6A)-C(5A)	118.9(6)	C(4B)-C(3B)-C(2B)	116.7(6)
N(1A)-C(6A)-C(5A)	99.7(5)	C(4B)-C(3B)-C(1B)	119.8(6)
C(8A)-C(7A)-C(12A)	117.4(7)	C(2B)-C(3B)-C(1B)	59.4(4)
C(8A)-C(7A)-C(6A)	123.4(7)	C(4B)-C(3B)-C(13B)	114.8(6)
C(12A)-C(7A)-C(6A)	119.0(6)	C(2B)-C(3B)-C(13B)	119.1(6)
C(7A)-C(8A)-C(9A)	121.2(8)	C(1B)-C(3B)-C(13B)	116.0(6)
C(10A)-C(9A)-C(8A)	121.3(8)	N(1B)-C(4B)-O(1B)	115.0(6)
C(9A)-C(10A)-C(11A)	119.6(9)	N(1B)-C(4B)-C(3B)	130.0(6)
C(12A)-C(11A)-C(10A)	118.8(8)	O(1B)-C(4B)-C(3B)	115.0(6)

Table 29. Continued

C(11A)-C(12A)-C(7A)	121.1(7)	N(1C)-C(6C)-C(7C)	110.0(6)
O(1B)-C(5B)-C(6B)	102.9(5)	N(1C)-C(6C)-C(5C)	101.7(5)
C(7B)-C(6B)-N(1B)	110.8(5)	C(7C)-C(6C)-C(5C)	115.8(6)
C(7B)-C(6B)-C(5B)	117.6(6)	C(12C)-C(7C)-C(8C)	118.8(7)
N(1B)-C(6B)-C(5B)	99.7(5)	C(12C)-C(7C)-C(6C)	121.0(7)
C(12B)-C(7B)-C(8B)	116.1(8)	C(8C)-C(7C)-C(6C)	120.1(6)
C(12B)-C(7B)-C(6B)	119.1(7)	C(9C)-C(8C)-C(7C)	120.9(7)
C(8B)-C(7B)-C(6B)	124.7(7)	C(8C)-C(9C)-C(10C)	119.9(8)
C(9B)-C(8B)-C(7B)	122.0(8)	C(11C)-C(10C)-C(9C)	119.7(8)
C(10B)-C(9B)-C(8B)	122.0(8)	C(10C)-C(11C)-C(12C)	119.9(8)
C(9B)-C(10B)-C(11B)	117.7(9)	C(7C)-C(12C)-C(11C)	120.7(8)
C(10B)-C(11B)-C(12B)	121.2(9)	C(16C)-C(14C)-C(15C)	111.1(6)
C(11B)-C(12B)-C(7B)	121.0(9)	C(16C)-C(14C)-C(17C)	108.6(6)
C(15B)-C(14B)-C(16B)	109.7(7)	C(15C)-C(14C)-C(17C)	107.1(6)
C(15B)-C(14B)-C(17B)	107.7(6)	C(16C)-C(14C)-P(1C)	112.7(6)

Table 29. Continued

C(16B)-C(14B)-C(17B)	108.5(6)	C(15C)-C(14C)-P(1C)	107.2(5)
C(15B)-C(14B)-P(1B)	108.1(5)	C(17C)-C(14C)-P(1C)	110.0(4)
C(16B)-C(14B)-P(1B)	111.8(6)	C(19C)-C(18C)-C(20C)	109.7(6)
C(17B)-C(14B)-P(1B)	110.9(5)	C(19C)-C(18C)-C(21C)	109.0(6)
C(20B)-C(18B)-C(21B)	109.4(6)	C(20C)-C(18C)-C(21C)	109.6(6)
C(20B)-C(18B)-C(19B)	107.0(6)	C(19C)-C(18C)-P(1C)	106.0(5)
C(21B)-C(18B)-C(19B)	108.0(7)	C(20C)-C(18C)-P(1C)	112.3(5)
C(20B)-C(18B)-P(1B)	114.0(5)	C(21C)-C(18C)-P(1C)	110.1(5)
C(21B)-C(18B)-P(1B)	110.6(6)	N(1D)-Pd(1D)-P(1D)	92.08(15)
C(19B)-C(18B)-P(1B)	107.6(5)	N(1D)-Pd(1D)-Cl(2D)	174.46(17)
N(1C)-Pd(1C)-P(1C)	91.31(15)	P(1D)-Pd(1D)-Cl(2D)	89.65(7)
N(1C)-Pd(1C)-Cl(2C)	173.48(16)	N(1D)-Pd(1D)-Cl(1D)	90.80(15)
P(1C)-Pd(1C)-Cl(2C)	90.91(6)	P(1D)-Pd(1D)-Cl(1D)	175.21(7)
N(1C)-Pd(1C)-Cl(1C)	91.07(15)	Cl(2D)-Pd(1D)-Cl(1D)	87.84(7)
P(1C)-Pd(1C)-Cl(1C)	173.43(7)	C(1D)-P(1D)-C(18D)	104.4(3)

Table 29. Continued

Cl(2C)-Pd(1C)-Cl(1C)	87.39(6)	C(1D)-P(1D)-C(14D)	100.5(3)
C(1C)-P(1C)-C(18C)	103.4(3)	C(18D)-P(1D)-C(14D)	113.1(4)
C(1C)-P(1C)-C(14C)	101.6(3)	C(1D)-P(1D)-Pd(1D)	109.0(2)
C(18C)-P(1C)-C(14C)	113.4(3)	C(18D)-P(1D)-Pd(1D)	111.0(3)
C(1C)-P(1C)-Pd(1C)	110.0(2)	C(14D)-P(1D)-Pd(1D)	117.3(2)
C(18C)-P(1C)-Pd(1C)	111.1(2)	C(4D)-O(1D)-C(5D)	105.9(5)
C(14C)-P(1C)-Pd(1C)	116.1(2)	C(4D)-N(1D)-C(6D)	108.0(6)
C(4C)-O(1C)-C(5C)	106.1(5)	C(4D)-N(1D)-Pd(1D)	132.0(5)
C(4C)-N(1C)-C(6C)	107.2(5)	C(6D)-N(1D)-Pd(1D)	120.0(4)
C(4C)-N(1C)-Pd(1C)	133.2(5)	C(2D)-C(1D)-C(3D)	59.3(5)
C(6C)-N(1C)-Pd(1C)	119.5(4)	C(2D)-C(1D)-P(1D)	120.1(5)
C(2C)-C(1C)-C(3C)	59.4(4)	C(3D)-C(1D)-P(1D)	126.7(4)
C(2C)-C(1C)-P(1C)	120.0(5)	C(1D)-C(2D)-C(3D)	62.2(5)
C(3C)-C(1C)-P(1C)	126.8(4)	C(4D)-C(3D)-C(2D)	116.5(6)
C(3C)-C(2C)-C(1C)	60.5(4)	C(4D)-C(3D)-C(13D)	117.0(6)

Table 29. Continued

C(4C)-C(3C)-C(2C)	115.9(6)	C(2D)-C(3D)-C(13D)	117.2(6)
C(4C)-C(3C)-C(1C)	119.9(5)	C(4D)-C(3D)-C(1D)	119.1(5)
C(2C)-C(3C)-C(1C)	60.1(4)	C(2D)-C(3D)-C(1D)	58.5(5)
C(4C)-C(3C)-C(13C)	115.2(5)	C(13D)-C(3D)-C(1D)	115.7(6)
C(2C)-C(3C)-C(13C)	119.2(5)	N(1D)-C(4D)-O(1D)	117.3(6)
C(1C)-C(3C)-C(13C)	115.6(6)	N(1D)-C(4D)-C(3D)	131.3(7)
N(1C)-C(4C)-O(1C)	116.4(6)	O(1D)-C(4D)-C(3D)	111.4(6)
N(1C)-C(4C)-C(3C)	130.5(6)	O(1D)-C(5D)-C(6D)	103.3(5)
O(1C)-C(4C)-C(3C)	113.1(5)	N(1D)-C(6D)-C(7D)	111.1(5)
O(1C)-C(5C)-C(6C)	102.0(5)	C(1S)-Cl(1)-Cl(2')	52.3(12)
N(1D)-C(6D)-C(5D)	100.8(5)	Cl(2')-Cl(2)-C(1S)	60.5(16)
C(7D)-C(6D)-C(5D)	112.6(6)	Cl(2')-Cl(2)-C(1S')	34.0(12)
C(12D)-C(7D)-C(8D)	118.1(7)	C(1S)-Cl(2)-C(1S')	69.3(3)
C(12D)-C(7D)-C(6D)	119.1(6)	Cl(2')-Cl(2)-C(1S")	54.7(12)
C(8D)-C(7D)-C(6D)	122.8(7)	C(1S)-Cl(2)-C(1S")	89.9(10)

Table 29. Continued

C(9D)-C(8D)-C(7D)	122.4(8)	C(1S')-Cl(2)-C(1S")	85.1(18)
C(8D)-C(9D)-C(10D)	120.0(8)	C(1S')-Cl(2')-Cl(2)	84(3)
C(9D)-C(10D)-C(11D)	119.4(8)	C(1S')-Cl(2')-C(1S)	94(3)
C(12D)-C(11D)-C(10D)	120.4(8)	Cl(2)-Cl(2')-C(1S)	65.7(17)
C(11D)-C(12D)-C(7D)	119.7(8)	C(1S')-Cl(2')-C(1S")	146(3)
C(15D)-C(14D)-C(16D)	110.8(7)	Cl(2)-Cl(2')-C(1S")	79(2)
C(15D)-C(14D)-C(17D)	108.0(7)	C(1S)-Cl(2')-C(1S")	106(3)
C(16D)-C(14D)-C(17D)	107.7(6)	C(1S')-Cl(2')-Cl(1)	60.6(18)
C(15D)-C(14D)-P(1D)	108.0(5)	Cl(2)-Cl(2')-Cl(1)	106(2)
C(16D)-C(14D)-P(1D)	111.8(6)	C(1S)-Cl(2')-Cl(1)	55.9(12)
C(17D)-C(14D)-P(1D)	110.5(5)	C(1S")-Cl(2')-Cl(1)	153(2)
C(19D)-C(18D)-C(20D)	108.5(7)	Cl(2')-C(1S)-Cl(1)	71.9(12)
C(19D)-C(18D)-C(21D)	108.9(7)	Cl(2')-C(1S)-Cl(2)	53.8(13)
C(20D)-C(18D)-C(21D)	108.1(7)	Cl(1)-C(1S)-Cl(2)	109.55(9)
C(19D)-C(18D)-P(1D)	107.5(5)	Cl(2')-C(1S')-Cl(2)	62(2)

Table 29. Continued

C(20D)-C(18D)-P(1D)   113.2(6)   Cl(2')-C(1S")-Cl(2)   46.2(17)

C(21D)-C(18D)-P(1D)   110.6(6)

Table 30. Anisotropic displacement parameters $(\text{Å}^2 \times 10^3)$ for (**L4**)PdCl$_2$ complex. The anisotropic displacement factor exponent takes the form: $-2p^2[\, h^2 \, a^{*2}U^{11} + \ldots + 2\, h\, k\, a^* \, b^* \, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1A)	20(1)	14(1)	9(1)	-2(1)	1(1)	1(1)
Cl(1A)	27(1)	20(1)	12(1)	2(1)	1(1)	1(1)
Cl(2A)	41(1)	23(1)	15(1)	-4(1)	-3(1)	-2(1)
P(1A)	19(1)	17(1)	13(1)	2(1)	2(1)	0(1)
O(1A)	42(3)	16(2)	18(2)	-1(2)	-11(2)	0(2)
N(1A)	22(3)	12(2)	12(2)	-1(2)	1(2)	6(2)
C(1A)	22(3)	18(3)	15(3)	6(2)	-2(2)	-5(3)
C(2A)	23(3)	30(4)	22(3)	3(3)	-5(3)	0(3)
C(3A)	27(3)	22(3)	16(3)	3(3)	-8(3)	-3(3)
C(4A)	26(3)	11(3)	14(3)	-1(2)	3(2)	3(2)
C(5A)	49(5)	19(4)	21(3)	5(3)	-14(3)	7(3)
C(6A)	40(4)	18(3)	17(3)	-4(2)	-10(3)	8(3)
C(7A)	28(4)	19(3)	20(3)	-4(3)	-4(3)	11(3)
C(8A)	43(5)	49(5)	28(4)	-27(4)	-5(4)	16(4)
C(9A)	45(6)	86(8)	32(5)	-27(5)	1(4)	21(5)
C(10A)	26(4)	78(8)	43(5)	-17(5)	-1(4)	19(5)
C(11A)	40(5)	45(5)	26(4)	-1(4)	-5(4)	7(4)
C(12A)	33(4)	31(4)	19(3)	-1(3)	-4(3)	1(3)
C(13A)	50(5)	31(4)	17(3)	-5(3)	-13(4)	3(4)

Table 30. Continued

C(14A)	26(3)	9(3)	22(3)	7(2)	1(3)	-3(2)
C(15A)	35(4)	18(3)	21(3)	-1(3)	8(3)	3(3)
C(16A)	45(5)	16(3)	32(4)	2(3)	6(3)	-7(3)
C(17A)	38(5)	23(4)	22(3)	5(3)	3(3)	2(3)
C(18A)	22(3)	24(4)	28(4)	1(3)	2(3)	6(3)
C(19A)	26(4)	56(6)	26(4)	3(4)	12(3)	7(4)
C(20A)	23(4)	39(5)	22(3)	7(3)	2(3)	-6(3)
C(21A)	27(4)	40(5)	25(4)	7(3)	4(3)	-2(3)
Pd(1B)	22(1)	20(1)	10(1)	-3(1)	0(1)	6(1)
Cl(1B)	26(1)	45(1)	11(1)	3(1)	2(1)	6(1)
Cl(2B)	78(2)	26(1)	21(1)	-11(1)	-15(1)	15(1)
P(1B)	22(1)	14(1)	14(1)	-2(1)	1(1)	-1(1)
O(1B)	52(4)	16(2)	19(2)	4(2)	-15(2)	-11(2)
N(1B)	18(3)	20(3)	16(2)	3(2)	-1(2)	3(2)
C(1B)	28(3)	12(3)	14(3)	1(2)	-4(2)	4(3)
C(2B)	28(4)	18(3)	26(3)	8(3)	-7(3)	-5(3)
C(3B)	30(4)	23(4)	16(3)	2(3)	-6(3)	-7(3)
C(4B)	31(4)	12(3)	16(3)	7(2)	-6(3)	-7(3)
C(5B)	51(5)	19(4)	26(4)	2(3)	-25(4)	-8(3)
C(6B)	33(4)	14(3)	17(3)	5(2)	-8(3)	-2(3)
C(7B)	35(4)	14(3)	17(3)	1(2)	-8(3)	-1(3)

Table 30. Continued

C(8B)	51(6)	46(5)	37(5)	-22(4)	-15(4)	27(4)
C(9B)	45(6)	57(6)	46(5)	-18(5)	3(5)	30(5)
C(10B)	32(5)	60(7)	54(6)	-20(5)	0(4)	19(5)
C(11B)	31(5)	68(7)	87(8)	-42(7)	-23(5)	5(5)
C(12B)	45(6)	61(6)	31(5)	-19(4)	-7(4)	12(5)
C(13B)	84(7)	24(4)	18(3)	0(3)	-28(4)	-7(4)
C(14B)	40(5)	22(4)	24(4)	-4(3)	-4(3)	8(3)
C(15B)	57(6)	26(4)	30(4)	-5(3)	-1(4)	19(4)
C(16B)	67(6)	15(4)	32(4)	-3(3)	-11(4)	2(4)
C(17B)	48(5)	16(3)	24(4)	7(3)	-4(3)	3(3)
C(18B)	24(3)	30(4)	22(3)	7(3)	1(3)	-3(3)
C(19B)	34(4)	35(5)	38(4)	-2(4)	10(3)	12(4)
C(20B)	29(4)	48(5)	33(4)	15(4)	-2(3)	-10(4)
C(21B)	33(5)	39(5)	60(6)	18(5)	-8(4)	-10(4)
Pd(1C)	19(1)	24(1)	9(1)	-2(1)	1(1)	2(1)
Cl(1C)	27(1)	27(1)	15(1)	1(1)	4(1)	2(1)
Cl(2C)	26(1)	43(1)	12(1)	-1(1)	-3(1)	1(1)
P(1C)	19(1)	27(1)	11(1)	-2(1)	1(1)	4(1)
O(1C)	21(2)	24(3)	24(2)	-6(2)	3(2)	4(2)
N(1C)	22(3)	16(3)	12(2)	-1(2)	3(2)	4(2)
C(1C)	14(3)	26(4)	13(3)	1(3)	2(2)	12(3)

Table 30. Continued

C(2C)	29(4)	20(3)	11(3)	-5(2)	3(3)	10(3)
C(3C)	18(3)	10(3)	18(3)	-3(2)	-3(2)	7(2)
C(4C)	15(3)	20(3)	19(3)	2(3)	-3(2)	2(3)
C(5C)	20(3)	29(4)	22(3)	-7(3)	4(3)	1(3)
C(6C)	16(3)	34(4)	26(3)	-4(3)	5(3)	11(3)
C(7C)	24(3)	28(4)	20(3)	-5(3)	2(3)	9(3)
C(8C)	23(4)	31(4)	32(4)	0(3)	-1(3)	11(3)
C(9C)	32(5)	56(6)	34(5)	6(4)	-9(4)	17(4)
C(10C)	30(4)	28(4)	54(5)	-19(4)	-10(4)	10(3)
C(11C)	36(5)	55(6)	40(5)	-17(5)	0(4)	-4(4)
C(12C)	20(3)	33(4)	23(4)	-8(3)	1(3)	-2(3)
C(13C)	20(3)	35(4)	16(3)	0(3)	0(3)	2(3)
C(14C)	19(3)	38(4)	12(3)	2(3)	-3(2)	9(3)
C(15C)	37(4)	46(5)	19(3)	4(3)	9(3)	12(4)
C(16C)	31(4)	68(6)	18(3)	-3(4)	-6(3)	8(4)
C(17C)	24(4)	33(4)	12(3)	-1(3)	1(3)	-1(3)
C(18C)	22(4)	36(4)	21(3)	-1(3)	1(3)	3(3)
C(19C)	30(4)	24(4)	42(5)	0(3)	-5(3)	0(3)
C(20C)	33(4)	41(5)	28(4)	5(3)	-1(3)	-7(4)
C(21C)	43(5)	33(4)	20(4)	0(3)	-2(3)	-8(4)
Pd(1D)	22(1)	26(1)	8(1)	1(1)	-1(1)	2(1)

Table 30. Continued

Cl(1D)	29(1)	40(1)	12(1)	6(1)	-2(1)	4(1)
Cl(2D)	29(1)	64(1)	9(1)	-1(1)	3(1)	-4(1)
P(1D)	21(1)	36(1)	11(1)	0(1)	1(1)	6(1)
O(1D)	22(2)	37(3)	13(2)	3(2)	-1(2)	-3(2)
N(1D)	29(3)	15(3)	12(2)	3(2)	-5(2)	5(2)
C(1D)	17(3)	37(4)	9(3)	3(3)	-3(2)	2(3)
C(2D)	29(4)	31(4)	17(3)	2(3)	-4(3)	-11(3)
C(3D)	19(3)	31(4)	14(3)	-3(3)	3(2)	2(3)
C(4D)	31(4)	21(4)	17(3)	2(3)	-1(3)	-3(3)
C(5D)	21(3)	34(4)	11(3)	-2(3)	-8(2)	1(3)
C(6D)	19(3)	33(4)	16(3)	8(3)	1(2)	5(3)
C(7D)	25(3)	21(3)	22(3)	5(3)	-3(3)	6(3)
C(8D)	47(5)	30(4)	28(4)	12(3)	-12(4)	-5(4)
C(9D)	45(5)	26(4)	47(5)	8(4)	-1(4)	-1(4)
C(10D)	26(4)	27(4)	63(6)	0(4)	2(4)	-1(3)
C(11D)	37(5)	32(5)	47(5)	-15(4)	-4(4)	1(4)
C(12D)	18(3)	29(4)	31(4)	-1(3)	-1(3)	7(3)
C(13D)	24(3)	47(5)	13(3)	6(3)	0(3)	-9(3)
C(14D)	18(3)	47(5)	19(3)	-3(3)	-8(3)	-6(3)
C(15D)	34(4)	52(5)	26(4)	-8(4)	9(4)	-17(4)
C(16D)	25(4)	92(8)	12(3)	9(4)	0(3)	10(5)

Table 30. Continued

C(17D)	22(4)	88(8)	16(3)	-10(4)	3(3)	-3(4)
C(18D)	33(4)	36(4)	24(3)	-2(3)	-1(3)	18(3)
C(19D)	38(5)	33(4)	34(4)	3(3)	1(4)	16(4)
C(20D)	43(5)	44(5)	40(5)	14(4)	-12(4)	8(4)
C(21D)	59(6)	34(5)	31(4)	4(4)	5(4)	14(4)
Cl(1)	206(8)	170(6)	146(6)	35(5)	-62(6)	-31(6)
O(1W')	206(8)	170(6)	146(6)	35(5)	-62(6)	-31(6)
O(1W)	199(11)	74(6)	218(12)	7(7)	-55(9)	90(7)
Cl(1')	199(11)	74(6)	218(12)	7(7)	-55(9)	90(7)
O(2W)	440(30)	176(13)	75(8)	-16(8)	46(12)	-254(17)

Table 31. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (**L4**)PdCl$_2$ complex.

	x	y	z	U(eq)
H(1AA)	7949	-484	1811	22
H(2AA)	9026	133	1213	30
H(2AB)	9241	-105	1689	30
H(5AA)	8425	2603	1033	36
H(5AB)	7660	2936	1257	36
H(6AA)	7545	2091	608	30
H(8AA)	6513	2522	1496	48
H(9AA)	5190	2366	1599	65
H(10A)	4397	1985	1081	59
H(11A)	4960	1405	507	45
H(12A)	6301	1532	403	33
H(13A)	7743	1034	2171	49
H(13B)	8629	1307	2119	49
H(13C)	8442	445	2251	49
H(15A)	8936	-1925	818	37
H(15B)	8983	-1033	925	37
H(15C)	8520	-1310	531	37
H(16A)	7574	-2548	820	46
H(16B)	7217	-1836	578	46

Table 31. Continued

H(16C)	6842	-2091	1000	46
H(17A)	8301	-2388	1441	41
H(17B)	7645	-1881	1658	41
H(17C)	8514	-1555	1610	41
H(19A)	5691	235	1589	54
H(19B)	6362	626	1322	54
H(19C)	6566	278	1758	54
H(20A)	5746	-1153	1740	42
H(20B)	6642	-1088	1874	42
H(20C)	6391	-1686	1532	42
H(21A)	5329	-722	1052	46
H(21B)	6016	-1120	800	46
H(21C)	5898	-212	779	46
H(1BA)	7823	4663	3316	22
H(2BA)	8901	5122	2676	29
H(2BB)	9115	5034	3166	29
H(5BA)	8334	7531	2308	38
H(5BB)	7524	7884	2473	38
H(6BA)	7561	6841	1893	26
H(8BA)	6330	7519	2684	54
H(9BA)	5002	7514	2679	59

Table 31. Continued

H(10B)	4309	6874	2189	58
H(11B)	4998	6237	1683	74
H(12B)	6347	6288	1660	55
H(13D)	8461	6564	3476	63
H(13E)	8321	5741	3677	63
H(13F)	7590	6263	3553	63
H(15D)	8739	2935	2421	56
H(15E)	8892	3803	2554	56
H(15F)	8415	3623	2149	56
H(16D)	7380	2339	2560	57
H(16E)	7181	2907	2195	57
H(16F)	6673	2933	2601	57
H(17D)	8141	2685	3111	44
H(17E)	7485	3260	3275	44
H(17F)	8363	3554	3213	44
H(19D)	5567	5373	3010	53
H(19E)	6273	5671	2735	53
H(19F)	6428	5438	3196	53
H(20D)	5628	4133	3305	55
H(20E)	6543	4008	3377	55
H(20F)	6070	3439	3088	55

Table 31. Continued

H(21D)	5206	4354	2558	66
H(21E)	5831	3753	2388	66
H(21F)	5856	4625	2240	66
H(1CA)	2345	4448	686	22
H(2CA)	1771	3219	662	24
H(2CB)	1617	3229	1160	24
H(5CA)	-808	3945	1516	28
H(5CB)	-1048	4817	1413	28
H(6CA)	-98	4470	2019	30
H(8CA)	-173	5916	1237	34
H(9CA)	-218	7229	1344	49
H(10C)	-42	7727	2003	45
H(11C)	81	6893	2548	52
H(12C)	117	5555	2436	31
H(13G)	416	4183	381	36
H(13H)	1299	4340	245	36
H(13I)	791	5013	442	36
H(15G)	3721	2891	1556	51
H(15H)	2859	2965	1373	51
H(15I)	3035	3255	1823	51
H(16G)	4569	4027	1625	58

Table 31. Continued

H(16H)	3946	4464	1903	58
H(16I)	4266	4860	1499	58
H(17G)	4228	3637	936	34
H(17H)	3777	4403	810	34
H(17I)	3336	3596	792	34
H(19G)	1944	6558	1212	48
H(19H)	1532	5866	1446	48
H(19I)	1701	5800	971	48
H(20G)	3309	6365	928	51
H(20H)	3042	5583	717	51
H(20I)	3765	5587	1024	51
H(21G)	3195	6547	1659	48
H(21H)	3475	5722	1810	48
H(21I)	2621	6026	1924	48
H(1DA)	7382	5023	705	25
H(2DA)	6630	6299	296	30
H(2DB)	6810	6229	790	30
H(5DA)	4143	5570	-30	26
H(5DB)	3985	4667	28	26
H(6DA)	4853	5219	-583	27
H(8DA)	4782	3595	97	42

Table 31. Continued

H(9DA)	4749	2341	-91	47
H(10D)	4963	1997	-766	46
H(11D)	5190	2958	-1251	47
H(12D)	5213	4245	-1059	31
H(13J)	5524	5341	1078	42
H(13K)	6379	5005	1159	42
H(13L)	5722	4475	959	42
H(15J)	8766	6684	-56	56
H(15K)	7878	6581	85	56
H(15L)	8124	6388	-371	56
H(16J)	9600	5511	-197	65
H(16K)	8962	5228	-517	65
H(16L)	9215	4681	-152	65
H(17J)	9261	5822	491	63
H(17K)	8816	5031	572	63
H(17L)	8377	5826	648	63
H(19J)	6978	3018	150	52
H(19K)	6556	3616	-144	52
H(19L)	6660	3813	325	52
H(20J)	8263	3116	351	64
H(20K)	8111	3896	592	64

Table 31. Continued

H(20L)	8786	3854	258	64
H(21J)	7996	3077	-408	62
H(21K)	8495	3845	-463	62
H(21L)	7615	3805	-625	62
H(1SA)	6254	8596	-124	16
H(1SB)	5849	7892	70	16
H(1SC)	5702	7047	-522	50
H(1SD)	6029	7392	-917	50
H(1SE)	4570	6966	-412	91
H(1SF)	4467	7792	-245	91

Table 32. Torsion angles [°] for (**L4**)PdCl$_2$ complex.

N(1A)-Pd(1A)-P(1A)-C(1A)	C(7A)-C(8A)-C(9A)-C(10A) -6.3(17)
Cl(2A)-Pd(1A)-P(1A)-C(1A)	C(8A)-C(9A)-C(10A)-C(11A) 8.7(18)
Cl(1A)-Pd(1A)-P(1A)-C(1A)	C(9A)-C(10A)-C(11A)-C(12A)-7.9(16)
N(1A)-Pd(1A)-P(1A)-C(18A)	C(10A)-C(11A)-C(12A)-C(7A)4.6(13)
Cl(2A)-Pd(1A)-P(1A)-C(18A)	C(8A)-C(7A)-C(12A)-C(11A) -2.1(12)
Cl(1A)-Pd(1A)-P(1A)-C(18A)	C(6A)-C(7A)-C(12A)-C(11A) 172.5(7)
N(1A)-Pd(1A)-P(1A)-C(14A)	C(1A)-P(1A)-C(14A)-C(16A) 157.8(5)
Cl(2A)-Pd(1A)-P(1A)-C(14A)	C(18A)-P(1A)-C(14A)-C(16A) 46.3(6)
Cl(1A)-Pd(1A)-P(1A)-C(14A)	Pd(1A)-P(1A)-C(14A)-C(16A) -83.2(5)
P(1A)-Pd(1A)-N(1A)-C(4A)	C(1A)-P(1A)-C(14A)-C(17A) 34.6(5)
Cl(2A)-Pd(1A)-N(1A)-C(4A)	C(18A)-P(1A)-C(14A)-C(17A) -76.9(6)
Cl(1A)-Pd(1A)-N(1A)-C(4A)	Pd(1A)-P(1A)-C(14A)-C(17A) 153.6(4)
P(1A)-Pd(1A)-N(1A)-C(6A)	C(1A)-P(1A)-C(14A)-C(15A) -83.0(5)
Cl(2A)-Pd(1A)-N(1A)-C(6A)	C(18A)-P(1A)-C(14A)-C(15A) 165.6(5)
Cl(1A)-Pd(1A)-N(1A)-C(6A)	Pd(1A)-P(1A)-C(14A)-C(15A) 36.1(5)

Table 32. Continued

C(18A)-P(1A)-C(1A)-C(2A)	C(1A)-P(1A)-C(18A)-C(19A)	49.5(6)
C(14A)-P(1A)-C(1A)-C(2A)	C(14A)-P(1A)-C(18A)-C(19A)	158.7(5)
Pd(1A)-P(1A)-C(1A)-C(2A)	Pd(1A)-P(1A)-C(18A)-C(19A)	-68.1(5)
C(18A)-P(1A)-C(1A)-C(3A)	C(1A)-P(1A)-C(18A)-C(20A)	-68.1(6)
C(14A)-P(1A)-C(1A)-C(3A)	C(14A)-P(1A)-C(18A)-C(20A)	41.1(6)
Pd(1A)-P(1A)-C(1A)-C(3A)	Pd(1A)-P(1A)-C(18A)-C(20A)	174.3(5)
P(1A)-C(1A)-C(2A)-C(3A) 118.9(6)	C(1A)-P(1A)-C(18A)-C(21A)	166.1(5)
C(2A)-C(1A)-C(3A)-C(4A) 106.0(7)	C(14A)-P(1A)-C(18A)-C(21A)	-84.7(6)
P(1A)-C(1A)-C(3A)-C(4A) 0.2(10)	Pd(1A)-P(1A)-C(18A)-C(21A)	48.5(6)
P(1A)-C(1A)-C(3A)-C(2A) -105.8(7)	N(1B)-Pd(1B)-P(1B)-C(1B)	-31.7(3)
C(2A)-C(1A)-C(3A)-C(13A)	Cl(2B)-Pd(1B)-P(1B)-C(1B)	155.7(2)
P(1A)-C(1A)-C(3A)-C(13A)	Cl(1B)-Pd(1B)-P(1B)-C(1B)	72.7(7)
C(1A)-C(2A)-C(3A)-C(4A) -109.5(7)	N(1B)-Pd(1B)-P(1B)-C(18B)	84.7(3)
C(1A)-C(2A)-C(3A)-C(13A)	Cl(2B)-Pd(1B)-P(1B)-C(18B)	-87.9(3)
C(6A)-N(1A)-C(4A)-O(1A)	Cl(1B)-Pd(1B)-P(1B)-C(18B)	-170.9(7)

Table 32. Continued

Pd(1A)-N(1A)-C(4A)-O(1A)	N(1B)-Pd(1B)-P(1B)-C(14B)	-143.9(3)
C(6A)-N(1A)-C(4A)-C(3A)	Cl(2B)-Pd(1B)-P(1B)-C(14B)	43.5(3)
Pd(1A)-N(1A)-C(4A)-C(3A)	Cl(1B)-Pd(1B)-P(1B)-C(14B)	-39.5(8)
C(5A)-O(1A)-C(4A)-N(1A)	P(1B)-Pd(1B)-N(1B)-C(4B)	28.5(7)
C(5A)-O(1A)-C(4A)-C(3A)	Cl(2B)-Pd(1B)-N(1B)-C(4B)	142.8(10)
C(1A)-C(3A)-C(4A)-N(1A)	Cl(1B)-Pd(1B)-N(1B)-C(4B)	-146.0(7)
C(2A)-C(3A)-C(4A)-N(1A)	P(1B)-Pd(1B)-N(1B)-C(6B)	-149.1(5)
C(13A)-C(3A)-C(4A)-N(1A)	Cl(2B)-Pd(1B)-N(1B)-C(6B)	-34.8(15)
C(1A)-C(3A)-C(4A)-O(1A)	Cl(1B)-Pd(1B)-N(1B)-C(6B)	36.4(5)
C(2A)-C(3A)-C(4A)-O(1A)	C(18B)-P(1B)-C(1B)-C(2B)	-164.2(5)
C(13A)-C(3A)-C(4A)-O(1A)	C(14B)-P(1B)-C(1B)-C(2B)	77.9(6)
C(4A)-O(1A)-C(5A)-C(6A)	Pd(1B)-P(1B)-C(1B)-C(2B)	-44.6(5)
C(4A)-N(1A)-C(6A)-C(7A)	C(18B)-P(1B)-C(1B)-C(3B)	-92.2(6)
Pd(1A)-N(1A)-C(6A)-C(7A)	C(14B)-P(1B)-C(1B)-C(3B)	149.9(6)
C(4A)-N(1A)-C(6A)-C(5A)	Pd(1B)-P(1B)-C(1B)-C(3B)	27.4(7)

Table 32. Continued

Pd(1A)-N(1A)-C(6A)-C(5A)	P(1B)-C(1B)-C(2B)-C(3B)	116.6(6)
O(1A)-C(5A)-C(6A)-C(7A)	C(1B)-C(2B)-C(3B)-C(4B)	-110.4(7)
O(1A)-C(5A)-C(6A)-N(1A)	C(1B)-C(2B)-C(3B)-C(13B)	104.7(7)
N(1A)-C(6A)-C(7A)-C(8A)	C(2B)-C(1B)-C(3B)-C(4B)	105.2(7)
C(5A)-C(6A)-C(7A)-C(8A)-18.9(11)	P(1B)-C(1B)-C(3B)-C(4B)	-1.3(10)
N(1A)-C(6A)-C(7A)-C(12A)	P(1B)-C(1B)-C(3B)-C(2B)	-106.5(6)
C(5A)-C(6A)-C(7A)-C(12A)	C(2B)-C(1B)-C(3B)-C(13B)	-109.9(8)
C(12A)-C(7A)-C(8A)-C(9A)	P(1B)-C(1B)-C(3B)-C(13B)	143.6(6)
C(6A)-C(7A)-C(8A)-C(9A)-171.6(9)	C(6B)-N(1B)-C(4B)-O(1B)	-7.1(8)
Pd(1B)-N(1B)-C(4B)-O(1B)	N(1C)-Pd(1C)-P(1C)-C(14C)	-141.6(3)
C(6B)-N(1B)-C(4B)-C(3B) 172.3(7)	Cl(2C)-Pd(1C)-P(1C)-C(14C)	44.5(3)
Pd(1B)-N(1B)-C(4B)-C(3B)	Cl(1C)-Pd(1C)-P(1C)-C(14C)	-30.4(7)
C(5B)-O(1B)-C(4B)-N(1B) -11.4(9)	P(1C)-Pd(1C)-N(1C)-C(4C)	27.1(7)
C(5B)-O(1B)-C(4B)-C(3B) 169.1(6)	Cl(2C)-Pd(1C)-N(1C)-C(4C)	137.0(12)
C(2B)-C(3B)-C(4B)-N(1B) 53.3(11)	Cl(1C)-Pd(1C)-N(1C)-C(4C)	-146.7(7)

Table 32. Continued

C(1B)-C(3B)-C(4B)-N(1B)	-15.0(12)	P(1C)-Pd(1C)-N(1C)-C(6C)	-154.6(5)
C(13B)-C(3B)-C(4B)-N(1B)		Cl(2C)-Pd(1C)-N(1C)-C(6C)	-44.7(17)
C(2B)-C(3B)-C(4B)-O(1B)	-127.2(7)	Cl(1C)-Pd(1C)-N(1C)-C(6C)	31.5(5)
C(1B)-C(3B)-C(4B)-O(1B)	164.5(6)	C(18C)-P(1C)-C(1C)-C(2C)	-168.2(5)
C(13B)-C(3B)-C(4B)-O(1B)		C(14C)-P(1C)-C(1C)-C(2C)	74.1(5)
C(4B)-O(1B)-C(5B)-C(6B)	23.8(8)	Pd(1C)-P(1C)-C(1C)-C(2C)	-49.4(5)
C(4B)-N(1B)-C(6B)-C(7B)	-103.6(6)	C(18C)-P(1C)-C(1C)-C(3C)	-95.8(6)
Pd(1B)-N(1B)-C(6B)-C(7B)		C(14C)-P(1C)-C(1C)-C(3C)	146.5(6)
C(4B)-N(1B)-C(6B)-C(5B)	21.0(7)	Pd(1C)-P(1C)-C(1C)-C(3C)	23.0(7)
Pd(1B)-N(1B)-C(6B)-C(5B)		P(1C)-C(1C)-C(2C)-C(3C)	117.6(5)
O(1B)-C(5B)-C(6B)-C(7B)	93.7(7)	C(1C)-C(2C)-C(3C)-C(4C)	-111.0(6)
O(1B)-C(5B)-C(6B)-N(1B)	-26.1(7)	C(1C)-C(2C)-C(3C)-C(13C)	104.5(7)
N(1B)-C(6B)-C(7B)-C(12B)		C(2C)-C(1C)-C(3C)-C(4C)	104.5(7)
C(5B)-C(6B)-C(7B)-C(12B)		P(1C)-C(1C)-C(3C)-C(4C)	-1.9(9)
N(1B)-C(6B)-C(7B)-C(8B)	93.4(9)	P(1C)-C(1C)-C(3C)-C(2C)	-106.4(6)

Table 32. Continued

C(5B)-C(6B)-C(7B)-C(8B)	-20.4(10)	C(2C)-C(1C)-C(3C)-C(13C)	-110.3(6)
C(12B)-C(7B)-C(8B)-C(9B)		P(1C)-C(1C)-C(3C)-C(13C)	143.3(5)
C(6B)-C(7B)-C(8B)-C(9B)	-175.7(9)	C(6C)-N(1C)-C(4C)-O(1C)	-6.4(8)
C(7B)-C(8B)-C(9B)-C(10B)		Pd(1C)-N(1C)-C(4C)-O(1C)	171.9(4)
C(8B)-C(9B)-C(10B)-C(11B)		C(6C)-N(1C)-C(4C)-C(3C)	171.6(7)
C(9B)-C(10B)-C(11B)-C(12B)		Pd(1C)-N(1C)-C(4C)-C(3C)	-10.0(12)
C(10B)-C(11B)-C(12B)-C(7B)		C(5C)-O(1C)-C(4C)-N(1C)	-10.5(8)
C(8B)-C(7B)-C(12B)-C(11B)		C(5C)-O(1C)-C(4C)-C(3C)	171.2(6)
C(6B)-C(7B)-C(12B)-C(11B)		C(2C)-C(3C)-C(4C)-N(1C)	59.9(10)
C(1B)-P(1B)-C(14B)-C(15B)		C(1C)-C(3C)-C(4C)-N(1C)	-9.0(11)
C(18B)-P(1B)-C(14B)-C(15B)		C(13C)-C(3C)-C(4C)-N(1C)	-154.3(7)
Pd(1B)-P(1B)-C(14B)-C(15B)		C(2C)-C(3C)-C(4C)-O(1C)	-122.0(6)
C(1B)-P(1B)-C(14B)-C(16B)		C(1C)-C(3C)-C(4C)-O(1C)	169.1(6)
C(18B)-P(1B)-C(14B)-C(16B)		C(13C)-C(3C)-C(4C)-O(1C)	23.8(8)
Pd(1B)-P(1B)-C(14B)-C(16B)		C(4C)-O(1C)-C(5C)-C(6C)	21.8(7)

Table 32. Continued

C(1B)-P(1B)-C(14B)-C(17B)	C(4C)-N(1C)-C(6C)-C(7C)	-103.5(7)
C(18B)-P(1B)-C(14B)-C(17B)	Pd(1C)-N(1C)-C(6C)-C(7C)	77.8(6)
Pd(1B)-P(1B)-C(14B)-C(17B)	C(4C)-N(1C)-C(6C)-C(5C)	19.7(7)
C(1B)-P(1B)-C(18B)-C(20B)	Pd(1C)-N(1C)-C(6C)-C(5C)	-158.9(4)
C(14B)-P(1B)-C(18B)-C(20B)	O(1C)-C(5C)-C(6C)-N(1C)	-24.3(7)
Pd(1B)-P(1B)-C(18B)-C(20B)	O(1C)-C(5C)-C(6C)-C(7C)	94.9(7)
C(1B)-P(1B)-C(18B)-C(21B)	N(1C)-C(6C)-C(7C)-C(12C)	-106.5(7)
C(14B)-P(1B)-C(18B)-C(21B)	C(5C)-C(6C)-C(7C)-C(12C)	138.9(7)
Pd(1B)-P(1B)-C(18B)-C(21B)	N(1C)-C(6C)-C(7C)-C(8C)	76.2(8)
C(1B)-P(1B)-C(18B)-C(19B)	C(5C)-C(6C)-C(7C)-C(8C)	-38.4(9)
C(14B)-P(1B)-C(18B)-C(19B)	C(12C)-C(7C)-C(8C)-C(9C)	0.8(11)
Pd(1B)-P(1B)-C(18B)-C(19B)	C(6C)-C(7C)-C(8C)-C(9C)	178.1(7)
N(1C)-Pd(1C)-P(1C)-C(1C)	C(7C)-C(8C)-C(9C)-C(10C)	0.9(13)
Cl(2C)-Pd(1C)-P(1C)-C(1C)	C(8C)-C(9C)-C(10C)-C(11C)	-2.4(13)
Cl(1C)-Pd(1C)-P(1C)-C(1C)	C(9C)-C(10C)-C(11C)-C(12C)	2.2(13)

Table 32. Continued

N(1C)-Pd(1C)-P(1C)-C(18C)	C(8C)-C(7C)-C(12C)-C(11C) -1.0(11)
Cl(2C)-Pd(1C)-P(1C)-C(18C)	C(6C)-C(7C)-C(12C)-C(11C) -178.3(7)
Cl(1C)-Pd(1C)-P(1C)-C(18C)	C(10C)-C(11C)-C(12C)-C(7C) -0.5(13)
C(1C)-P(1C)-C(14C)-C(16C)	C(13D)-C(3D)-C(4D)-N(1D) -158.2(8)
C(18C)-P(1C)-C(14C)-C(16C)	C(1D)-C(3D)-C(4D)-N(1D) -11.0(12)
Pd(1C)-P(1C)-C(14C)-C(16C)	C(2D)-C(3D)-C(4D)-O(1D) -125.8(7)
C(1C)-P(1C)-C(14C)-C(15C)	C(13D)-C(3D)-C(4D)-O(1D) 20.0(9)
C(18C)-P(1C)-C(14C)-C(15C)	C(1D)-C(3D)-C(4D)-O(1D) 167.2(6)
Pd(1C)-P(1C)-C(14C)-C(15C)	C(4D)-O(1D)-C(5D)-C(6D) 18.8(7)
C(1C)-P(1C)-C(14C)-C(17C)	C(4D)-N(1D)-C(6D)-C(7D) -102.8(7)
C(18C)-P(1C)-C(14C)-C(17C)	Pd(1D)-N(1D)-C(6D)-C(7D) 78.5(6)
Pd(1C)-P(1C)-C(14C)-C(17C)	C(4D)-N(1D)-C(6D)-C(5D) 16.7(7)
C(1C)-P(1C)-C(18C)-C(19C)	Pd(1D)-N(1D)-C(6D)-C(5D) -162.0(4)
C(14C)-P(1C)-C(18C)-C(19C)	O(1D)-C(5D)-C(6D)-N(1D) -21.0(6)
Pd(1C)-P(1C)-C(18C)-C(19C)	O(1D)-C(5D)-C(6D)-C(7D) 97.5(6)

Table 32. Continued

C(1C)-P(1C)-C(18C)-C(20C)	N(1D)-C(6D)-C(7D)-C(12D)	-99.4(7)
C(14C)-P(1C)-C(18C)-C(20C)	C(5D)-C(6D)-C(7D)-C(12D)	148.3(6)
Pd(1C)-P(1C)-C(18C)-C(20C)	N(1D)-C(6D)-C(7D)-C(8D)	78.2(9)
C(1C)-P(1C)-C(18C)-C(21C)	C(5D)-C(6D)-C(7D)-C(8D)	-34.0(9)
C(14C)-P(1C)-C(18C)-C(21C)	C(12D)-C(7D)-C(8D)-C(9D)	-3.2(13)
Pd(1C)-P(1C)-C(18C)-C(21C)	C(6D)-C(7D)-C(8D)-C(9D)	179.1(8)
N(1D)-Pd(1D)-P(1D)-C(1D)	C(7D)-C(8D)-C(9D)-C(10D)	1.9(15)
Cl(2D)-Pd(1D)-P(1D)-C(1D)	C(8D)-C(9D)-C(10D)-C(11D)	-0.2(14)
Cl(1D)-Pd(1D)-P(1D)-C(1D)	C(9D)-C(10D)-C(11D)-C(12D)	-0.1(13)
N(1D)-Pd(1D)-P(1D)-C(18D)	C(10D)-C(11D)-C(12D)-C(7D)	-1.3(12)
Cl(2D)-Pd(1D)-P(1D)-C(18D)	C(8D)-C(7D)-C(12D)-C(11D)	2.9(11)
Cl(1D)-Pd(1D)-P(1D)-C(18D)	C(6D)-C(7D)-C(12D)-C(11D)	-179.4(7)
N(1D)-Pd(1D)-P(1D)-C(14D)	C(1D)-P(1D)-C(14D)-C(15D)	-83.6(5)
Cl(2D)-Pd(1D)-P(1D)-C(14D)	C(18D)-P(1D)-C(14D)-C(15D)	165.7(5)
Cl(1D)-Pd(1D)-P(1D)-C(14D)	Pd(1D)-P(1D)-C(14D)-C(15D)	34.4(6)

Table 32. Continued

P(1D)-Pd(1D)-N(1D)-C(4D)	C(1D)-P(1D)-C(14D)-C(16D) 154.3(5)
Cl(2D)-Pd(1D)-N(1D)-C(4D)	C(18D)-P(1D)-C(14D)-C(16D) 43.6(6)
Cl(1D)-Pd(1D)-N(1D)-C(4D)	Pd(1D)-P(1D)-C(14D)-C(16D) -87.7(6)
P(1D)-Pd(1D)-N(1D)-C(6D)	C(1D)-P(1D)-C(14D)-C(17D) 34.4(7)
Cl(2D)-Pd(1D)-N(1D)-C(6D)	C(18D)-P(1D)-C(14D)-C(17D) -76.3(6)
Cl(1D)-Pd(1D)-N(1D)-C(6D)	Pd(1D)-P(1D)-C(14D)-C(17D) 152.4(5)
C(18D)-P(1D)-C(1D)-C(2D)	C(1D)-P(1D)-C(18D)-C(19D) 54.8(6)
C(14D)-P(1D)-C(1D)-C(2D)	C(14D)-P(1D)-C(18D)-C(19D) 163.2(5)
Pd(1D)-P(1D)-C(1D)-C(2D)	Pd(1D)-P(1D)-C(18D)-C(19D) -62.5(5)
C(18D)-P(1D)-C(1D)-C(3D)	C(1D)-P(1D)-C(18D)-C(20D) -65.0(6)
C(14D)-P(1D)-C(1D)-C(3D)	C(14D)-P(1D)-C(18D)-C(20D) 43.4(7)
Pd(1D)-P(1D)-C(1D)-C(3D)	Pd(1D)-P(1D)-C(18D)-C(20D) 177.8(5)
P(1D)-C(1D)-C(2D)-C(3D) 117.3(6)	C(1D)-P(1D)-C(18D)-C(21D) 173.6(6)
C(1D)-C(2D)-C(3D)-C(4D) -109.3(6)	C(14D)-P(1D)-C(18D)-C(21D) -78.0(6)
C(1D)-C(2D)-C(3D)-C(13D)	Pd(1D)-P(1D)-C(18D)-C(21D) 56.4(6)

Table 32. Continued

C(2D)-C(1D)-C(3D)-C(4D)	105.0(7)	C(1S)-Cl(2)-Cl(2')-C(1S')	-97(2)
P(1D)-C(1D)-C(3D)-C(4D)	-1.6(11)	C(1S")-Cl(2)-Cl(2')-C(1S')	150(4)
P(1D)-C(1D)-C(3D)-C(2D)	-106.6(7)	C(1S')-Cl(2)-Cl(2')-C(1S)	97(2)
C(2D)-C(1D)-C(3D)-C(13D)		C(1S")-Cl(2)-Cl(2')-C(1S)	-114(2)
P(1D)-C(1D)-C(3D)-C(13D)		C(1S)-Cl(2)-Cl(2')-C(1S")	114(2)
C(6D)-N(1D)-C(4D)-O(1D)		C(1S')-Cl(2)-Cl(2')-C(1S")	-150(4)
Pd(1D)-N(1D)-C(4D)-O(1D)		C(1S)-Cl(2)-Cl(2')-Cl(1)	-39.4(12)
C(6D)-N(1D)-C(4D)-C(3D)		C(1S')-Cl(2)-Cl(2')-Cl(1)	57.1(15)
Pd(1D)-N(1D)-C(4D)-C(3D)		C(1S")-Cl(2)-Cl(2')-Cl(1)	-153(3)
C(5D)-O(1D)-C(4D)-N(1D)		C(1S)-Cl(1)-Cl(2')-C(1S')	118(3)
C(5D)-O(1D)-C(4D)-C(3D)		C(1S)-Cl(1)-Cl(2')-Cl(2)	44.4(14)
C(2D)-C(3D)-C(4D)-N(1D)		C(1S)-Cl(1)-Cl(2')-C(1S")	-54(7)
C(1S')-Cl(2')-C(1S)-Cl(1)	-50(2)		
Cl(2)-Cl(2')-C(1S)-Cl(1)	-132.5(9)		
C(1S")-Cl(2')-C(1S)-Cl(1)	157.8(18)		

Table 32. Continued

C(1S')-Cl(2')-C(1S)-Cl(2)   82(2)

C(1S'')-Cl(2')-C(1S)-Cl(2)   -69.7(18)

Cl(1)-Cl(2')-C(1S)-Cl(2)   132.5(9)

Cl(2')-Cl(1)-C(1S)-Cl(2)   -39.1(12)

C(1S')-Cl(2)-C(1S)-Cl(2')   -36.4(13)

C(1S'')-Cl(2)-C(1S)-Cl(2')   48.4(19)

Cl(2')-Cl(2)-C(1S)-Cl(1)   48.0(11)

C(1S')-Cl(2)-C(1S)-Cl(1)   11.6(13)

C(1S'')-Cl(2)-C(1S)-Cl(1)   96(2)

C(1S)-Cl(2')-C(1S')-Cl(2)   -65.1(16)

C(1S'')-Cl(2')-C(1S')-Cl(2) 61(8)

Cl(1)-Cl(2')-C(1S')-Cl(2)   -112.2(14)

C(1S)-Cl(2)-C(1S')-Cl(2')   68(3)

C(1S'')-Cl(2)-C(1S')-Cl(2') -24(3)

C(1S')-Cl(2')-C(1S'')-Cl(2) -62(8)

Table 32. Continued

C(1S)-Cl(2')-C(1S")-Cl(2)   60.5(17)

Cl(1)-Cl(2')-C(1S")-Cl(2)   104(7)

C(1S)-Cl(2)-C(1S")-Cl(2')   -53(2)

C(1S')-Cl(2)-C(1S")-Cl(2') 16.3(19)

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27. An overlay of X-ray structures obtained for (**L1**)PdCl$_2$ and (**L4**)PdCl$_2$ complexes demonstrated that all atoms of the palladacycle, cyclopropyl ring, and both *tert*-butyl substituents can be almost perfectly superimposed,

which for both ligand configurations, confirms the strong preference of a conformation in which the *syn-tert*-Bu-substituent (C14) and the *anti-tert*-Bu-substituent (C18) at phosphorus assume pseudo-equatorial and pseudo-axial positions, respectively. See Appendix for details.

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88. Asymmetric hydrogenation is closely related to AHF and involves the same stereodifferentiating step, the migratory insertion of an alkene into the Rh-H bond.

89. It should be noted the L:Rh ratio under our conditions was 2:1 as dictated by the optimum L:Rh ratio for ligand **83** the benchmark for this study. For ligands **84**, **85**, **101**, **102**, and **104** the optimum L:Rh ratio is known to be 1.2:1; this in addition to the removal of the vinylacetate and allylcyanide could contribute to diminished ee's for these ligands. See ref 43.

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