University of Alberta

Synthesis of 1,8-disubstituted fluorene ligand. Metal-mediated carbonylative ring expansion of cyclobutane-containing natural products.

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

Edmonton, Alberta
Fall 2007

Your file Votre référence
ISBN: 978-0-494-33216-0
Our file Notre référence
ISBN: 978-0-494-33216-0

Abstract

Two syntheses of 1,8-disubstituted fluorene/fluorenone derivatives have been developed. The first one is based on a 4e-electrocyclization reaction. Compound **14**, 1,8-dibromofluorene, was prepared in 53% yield over 5 steps and the final diimine ligand **17** was prepared in about 10% yield over 8 steps. The second one is based on directed *peri*-metallation. The diamine ligand **27** was prepared over 5 steps.

Low valent cobalt complexes with labile ligands can be used to open the strained four-membered ring of pinene and related compounds under reasonably mild reaction conditions. Using the cyclopentadienyl ligand, the ring-opened products were unreactive toward carbonylation, although indenyl ligand analogues were more promising. Furthermore, the addition of conjugated carbonyl functionality enhances the selectivity of the carbonylation step, giving a ring-expanded product amenable for use in taxinine synthesis. Using the cyclobutanone substrate afforded similar result and treatment of the intermediate with the Meerwein salt give a Fisher carbene.

Acknowledgements

First of all, I would like to thank my supervisor and mentor, Dr. Jeffrey M. Stryker, for his instructions and inspirations during my three years' learning and exploration in the world of organometallic chemistry.

I would also like to thank all the past and current members of the Stryker group for their knowledge and help: Dr. Meekyung Chung, Dr. Masaki Morita, Dr. Dave Norman, Ross Witherell, Jason Norman, Bryan Chan, Rick Bauer, Paul Fancy, Owen Lightbody, Kai Ylijoki, Andrew Kirk, Jeremy Gauthier and Jeff Quesnel. In particular, I would like to thank Owen for sharing the fume hood at the beginning and teaching me the inert atmosphere technique, the later collaboration on the ligand project and the final proofreading of my thesis. My life in Canada will be much less interesting without your help. Also thank Bryan very much for the help on the thesis proofreading.

Many thanks to the technical staff at University of Alberta for their help in the structure characterization of my products, especially thanks the NMR staff for their help on obtaining high quality spectra for those organometallic compounds and the X-ray crystallographer for solving the crystal structures.

And finally, thanks to my family for their never ending support and love throughout my life.

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List of Schemes

List of Abbreviations

Ac-d_6	perdeuteroacetone
Anth	anthracenyl
aq.	aqueous
Bu	butyl
BuLi	butyl lithium
CAN	cerium(IV) ammonium nitrate
CGC	constrained geometry catalyst
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
DMG	directed metallation group
E^+	electrophile
ee	enantiomeric excess
Et	ethyl
FTIR	Fourier transform infrared
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coorelation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Ind	indenyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
Me	methyl
NIS	N-iodosuccimide
NMR	nuclear magnetic resonance
PDI	polydispersity index
Ph	phenyl
PPA	polyphosphoric aicd
Pr	propyl
Rf	retention factor
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N'N'-tetramethylethylenediamine
TsN_3	*p*-toluenesulfonyl azide

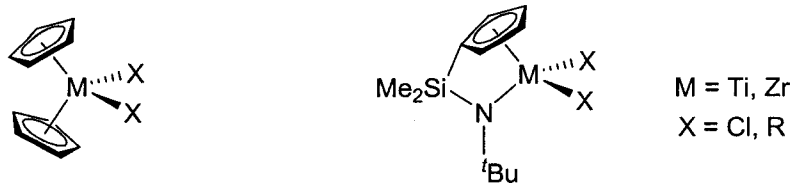
Part I. Synthesis of 1,8-Disubstituted Fluorene Ligand

1. Introduction

1.1. Single-site Olefin Polymerization Catalysts

Ziegler and Natta discovered new catalysts (a combination of titanium and aluminum complexes) for the stereoselective polymerization of α-olefins in the 1950s.[1] The scientific and practical significance of their work earned Ziegler and Natta the joint award of the 1963 Nobel Prize in Chemistry. However, their original discovery was based on heterogeneous systems that are ill-defined. These systems' mode and mechanism of action still remain a topic of current research.

Since the mid-1980s, there has been another revolution, the discovery and development of homogenous Group 4 metallocene precatalysts **1** and related half-sandwich amide ("constrained geometry") precatalysts **2**. These well-defined single site catalysts, when activated with alkylaluminum cocatalysts, found use as homogeneous olefin polymerization catalysts.[2]

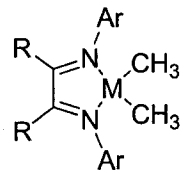


1 **2**

Fig. 1.1. Group 4 metallocenes 1 and constrained geometry catalysts 2

During this period, studies on the Group 4 metallocenes afforded much needed insight into the nature of the active species, a coordinately unsaturated and highly electrophilic cationic metal center.[3-6] Industrial interest was not sparked, however, until discoveries demonstrated that metallocenes combined with aluminoxanes (partial hydrolysis products of trialkylaluminium) led to long-lived catalysts with very high activity.[7, 8]

During the first half of the 1990s, interest grew in developing a new generation of "non-metallocene" catalysts.[9-11] The discovery of highly active (α-diimine)nickel and palladium catalysts **3** for polymerizing ethylene expanded the possible commercially useful metals beyond the first half of the transition series.[12, 13] The steric and electronic properties of the α-diimine ligand can be readily adjusted by modifying the imino carbon and nitrogen substituents.



3

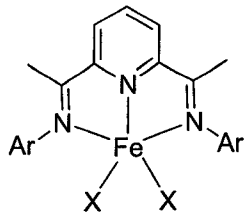
Ar = 2,6-$C_6H_3(Me)_2$, 2,6-C_6H_3(i-Pr)$_2$

R = H, Me, 1,8-naphthyl

M = Ni, Pd

Fig. 1.2. (α-Diimine) nickel and palladium catalysts 3

Continuous exploration of the late transition metals led to the discovery of highly active ethylene polymerization catalysts **4** based on iron in the late 1990s, a metal with no previous track record in olefin polymerization.[14, 15]



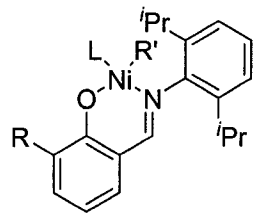
4

Ar = 2,6-$C_6H_3(Me)_2$, 2,6-$C_6H_3(i\text{-}Pr)_2$
2-$C_6H_4(t\text{-}Bu)$

X = Cl^-, Br^-, NO_3^-

Fig. 1.3. Iron catalysts 4 for olefin polymerization

As the active species is coordinatively unsaturated and highly electrophilic, both traditional catalysts for Ziegler-Natta polymerization and cationic metallocenes require rigorous exclusion of air and moisture, and hyperpurification of the starting monomers, because heteroatoms poison the precatalysts and cocatalysts. A family of neutral, single component nickel polyolefin catalysts **5** that tolerate heteroatoms was developed by Grubbs in 2000.[16] These heteroatom-tolerant neutral nickel complexes can produce high molecular weight polyethylene, polymerize functionalized olefins, require no cocatalyst, and tolerate less pure starting materials.



5

R	R'	L
Anth	Ph	PPh_3
Anth	CH_3	CH_3CN

Fig. 1.4. Neutral, single component nickel catalysts 5

1.2. Binuclear Catalysts and Cooperative Effect

Group 4 "constrained geometry" catalysts (CGCs) are well known single-site polymerization agents[17, 18] that produce unusual branched, and hence far more processable, polyethylenes with high productivity and selectivity. When two of these units are connected by a bridge, with the activation of a binuclear bisborate cocatalyst, novel macromolecular structures and significantly improved polymer properties can be obtained by means of such binuclear catalyst-cocatalyst design strategies.[19-21]

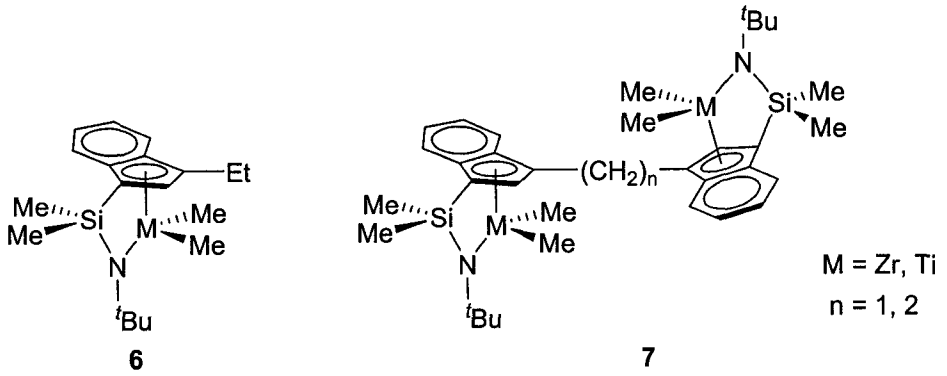
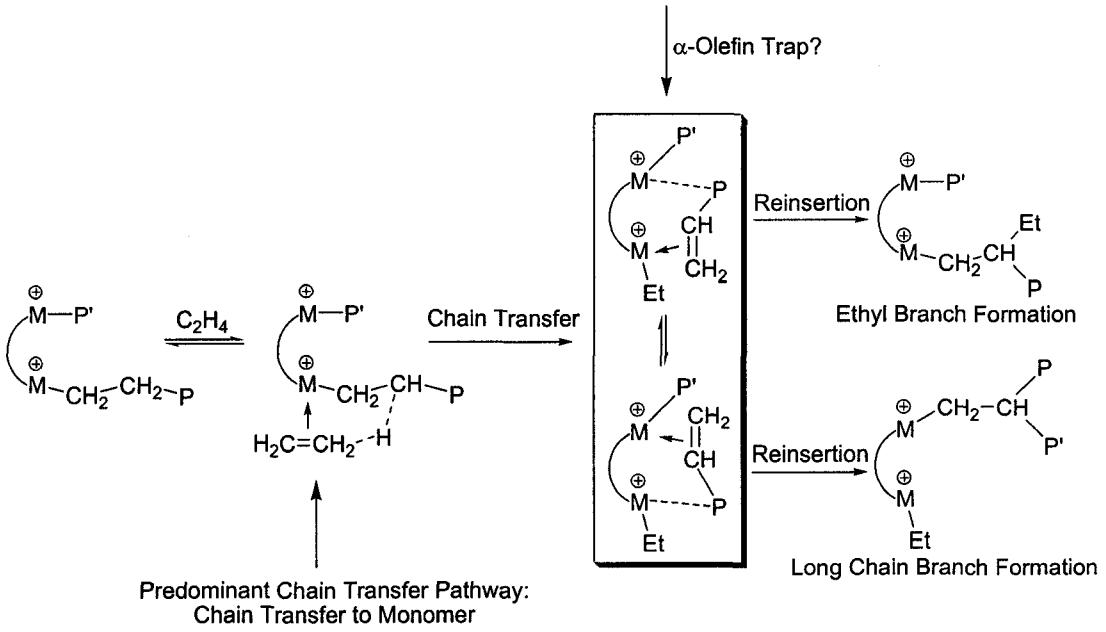


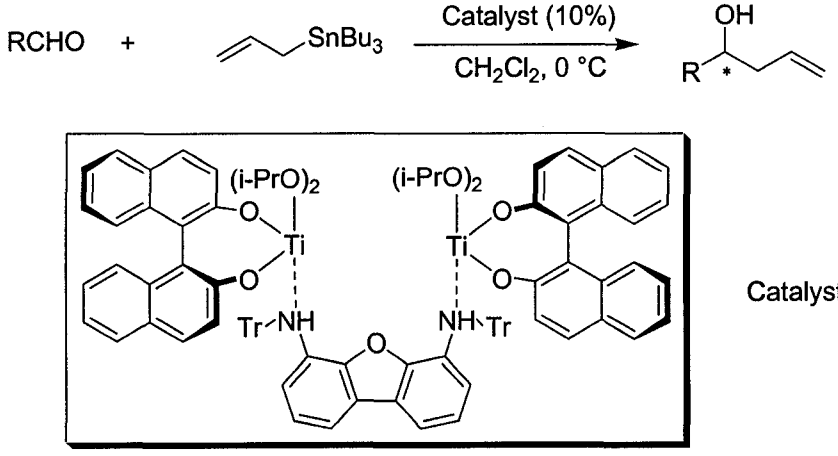
Fig. 1.5. Mononuclear 6 and binuclear 7 constrained geometry catalysts

For ethylene homopolymerization at constant conversion, the branch content of the polyolefin products, primarily ethyl branches, is significantly enhanced as the catalyst or cocatalyst nuclearity is increased. Compared with the mononuclear zirconium catalyst **6** (M = Zr), the bimetallic zirconium catalyst **7** (M = Zr, n = 2) produces 11 times more ethyl branches (predominant type of branch) in ethylene homopolymerization via a process that is predominantly intradimer in character, as shown in Sch. 1.1[19, 21]



Sch. 1.1. Proposed pathways for branch formation facilitated by binuclear group 4 CGCs

Binuclear catalysts not only play an important role in olefin polymerization catalysis, but also have been used as efficient catalysts in organic synthesis. For example, a bidentate ligand with a dibenzofuran spacer was successfully applied to the asymmetric tin allylation of aldehyde in high yields and excellent *ee*.[22]



Eq. 1.1. Catalytic asymmetric allylation of aldehyde with the chiral bimetallic catalyst

1.3. Surface Model Catalyst

The chemistry at the active site of heterogeneous Ziegler-Natta catalysts is not well understood despite extensive study. Fig. 1.6 Shows a hypothetical active site model when propylene is polymerized into isotactic polypropylene by a slurry of violet crystalline $3TiCl_3 \cdot AlCl_3$ and Et_2AlCl in heptane.[23] The surface titanium sites are alkylated when treated with Et_2AlCl, and the active site is assumed to be a monoalkylated Ti(III) ion attached to the crystal by Ti-Cl-M (M = Mg or Ti) bridges. The growing polymer chain attached to the crystal by a Ti-C bond, and the polymer grows by insertion of the coordinated propylene into the Ti-C bond with great regularity with respect to head-to-tail orientation and tacticity.

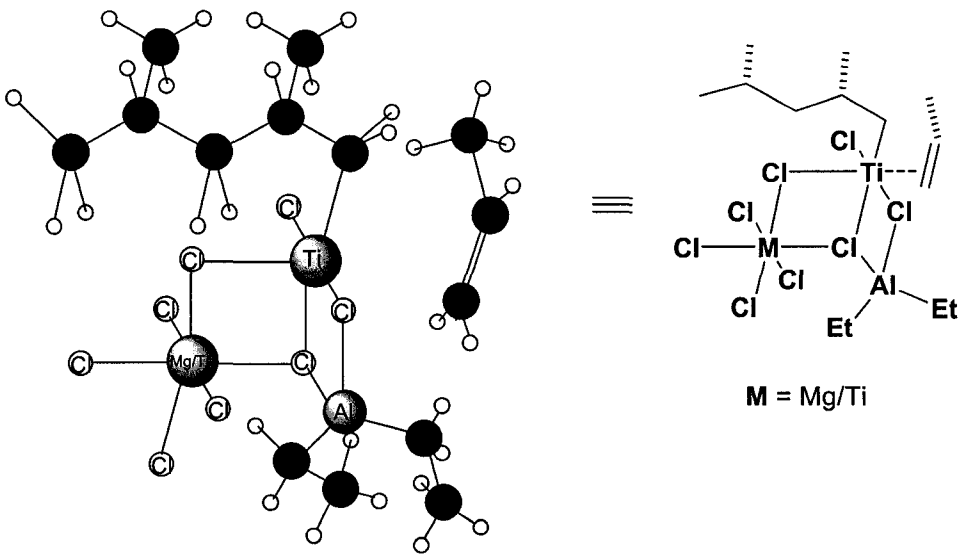


Fig. 1.6. Active site of Ziegler-Natta catalysts

To understand the chemistry and the active site of Ziegle-Natta catalysts better, it is necessary to develop rigid ligand systems that can hold metals into close proximity, functioning as a homogeneous model of heterogeneous Ziegle-Natta catalysts.

2. Goal of the Project

Efforts in our group have been devoted to designing preorganized ligands for surface model catalysts in olefin polymerization. Three types of ligand systems that are being investigated are shown in Fig.1.6: *ortho*-substituted tetraphenylethylene **8**, dibenzofuran **9** and fluorene **10**.[24-29]

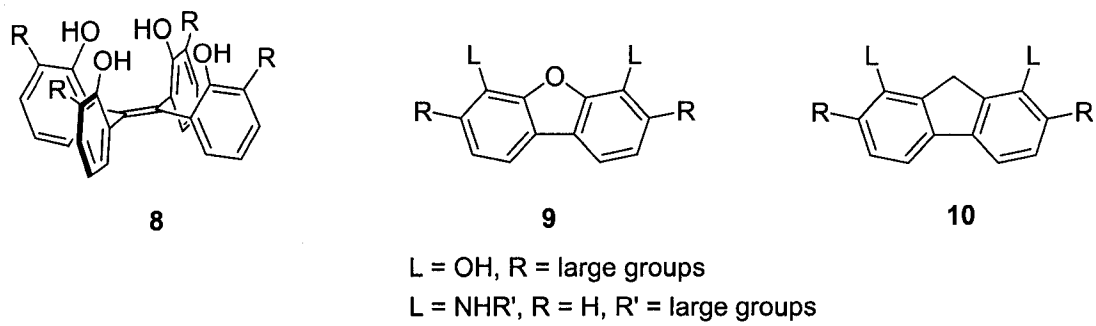


Fig. 1.7. Three types of ligand system

The last two ligands are designed to have the following two properties: (1) the two substitutents (L) are disposed distant enough so that each can bind to one metal (M) instead of chelation to a single metal, but on the other hand, (2) they are close enough so that the two metals can interact via single atom ligand bridges (X) with the ligands (L), which creates a cooperative environment for catalyst function in alkene polymerization (Fig.1.7).

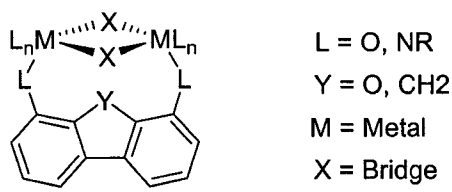
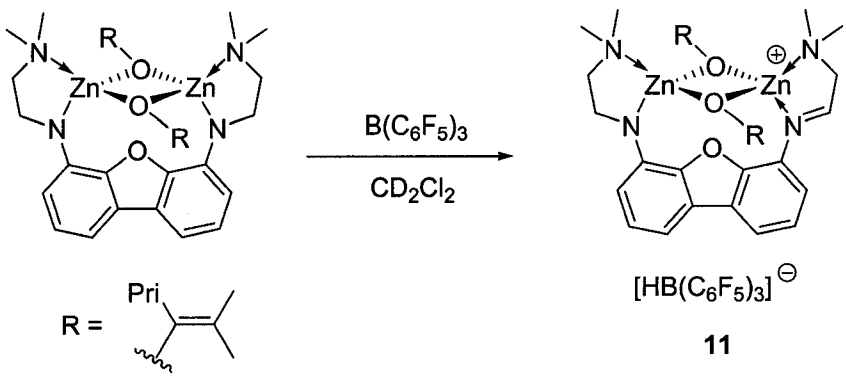


Fig. 1.8. Disubstituted fluorene/benzofuran-supported bimetallic catalyst compositions

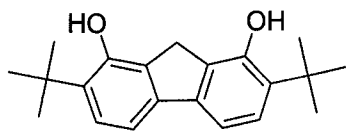
During the course of this investigation, it has been reported that cationic zinc enolate **11** supported by the dibenzofuran bis-(amidoamine) ligand is a highly active catalyst for acrylate polymerization, for which Group 4 metallocene enolates are poor catalysts.[30] High molecular weight (M_n = 5.40×10^5 g/mol; polydispersity index, PDI = 2.15) poly(*n*-butyl acrylate) with a catalyst loading as low as 0.02 mol % can be obtained at room temperature.



11

Eq. 1.2. Dibenzofuran ligand for acrylate polymerization

Previously, Fujita in the Stryker group found that 2,7-di-*tert*-butyl-1,8-dihydroxyfluorene **12** is a good ligand for supporting bimetallic olefin polymerization catalysts. However, the preparation of ligand **12** was inconvenient in length and proceeded in low overall yield (Sch. 1.3).[27]

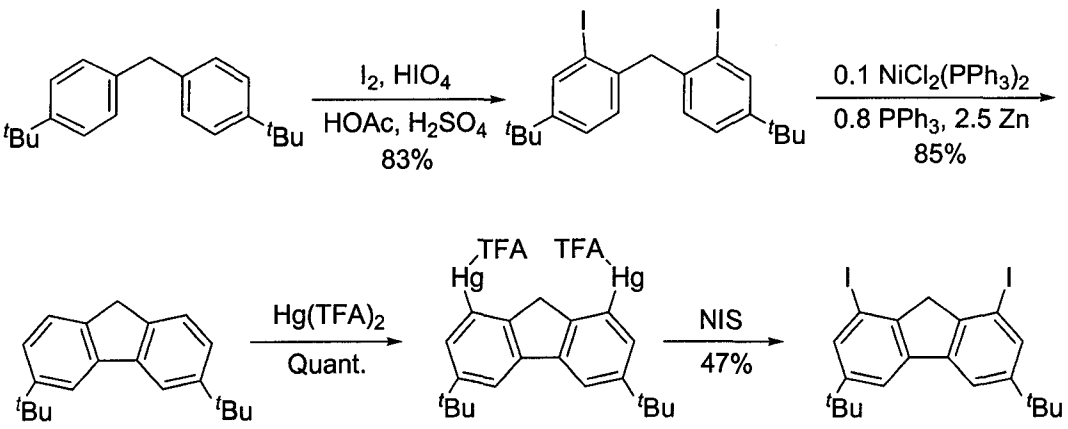


12

Fig. 1.9. 2,7-Di-*tert*-butyl-1,8-dihydroxyfluorene

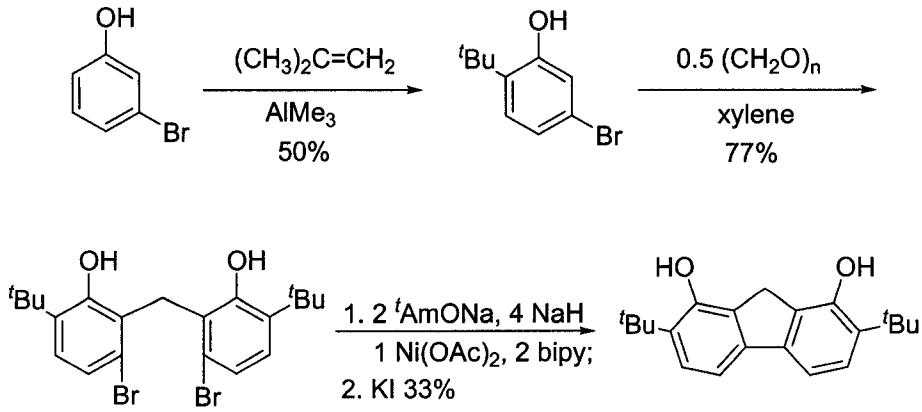
Electrophilic substitution is the most direct way to introduce substituents into the aromatic ring system, but regioselectivity is usually a serious problem, which is certainly the case for fluorene. Direct aromatic electrophilic substitution takes place much more readily at the 2,7-positions, which makes the preparation of 1,8-disubstituted fluorene derivatives challenging.[31-34]

Two recently reported syntheses of 1,8-disubstituted fluorenes provide an illustration of the problem and are shown below. In the first example, the large *tert*-butyl groups on the 3,6-positions block the adjacent 2,7-positions, and the large electrophilic mercury(II) ions are forced to metallate the 1,8-positions (Sch. 1.2).[35, 36]



Sch. 1.2. Synthesis of 3,6-di-*t*-butyl-1,8-diiodofluorene

The second example shows Fujita's modification of the original synthesis of 1,8-dihydroxyfluorene, reported by Wuest and coworkers. The substituents are incorporated into the substrate first and the ligand **12** is constructed subsequently by closing the central five-membered ring via a nickel-catalysed coupling reaction (Sch. 1.3).[27, 37]



Sch. 1.3. Fujita's modified synthesis of 2,7-di-*t*-butyl-1,8-dihydroxyfluorene

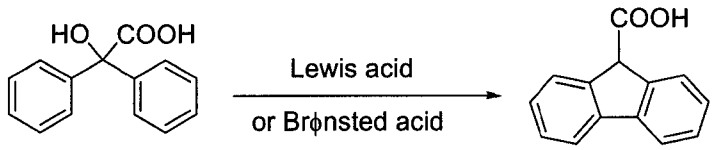
Neither of these two synthetic pathways is general and the overall yields are not satisfactory. The goal of this project, therefore, was to develop a new and general process to prepare this kind of sterically buttressed 1,8-disubstituted fluorene ligands for our ongoing investigation of coordination chemistry and olefin polymerization catalysis.

3. Synthetic Strategies, Results and Discussions

3.1. Four-Electron Electrocyclization

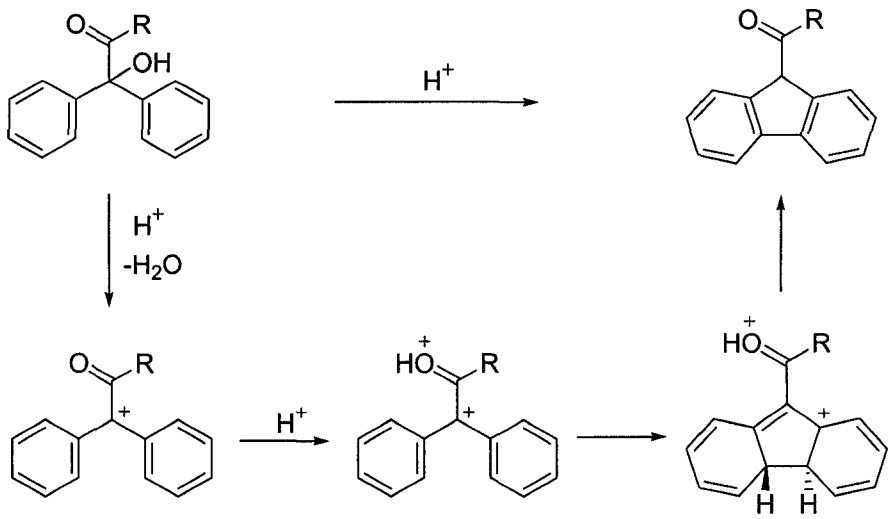
3.1.1. Backgound

Fluorene-9-carboxylic acid can be prepared in high yield by treating benzilic acid with a strong Lewis acid or Brϕnsted acid (Eq. 1.2). [38, 39]



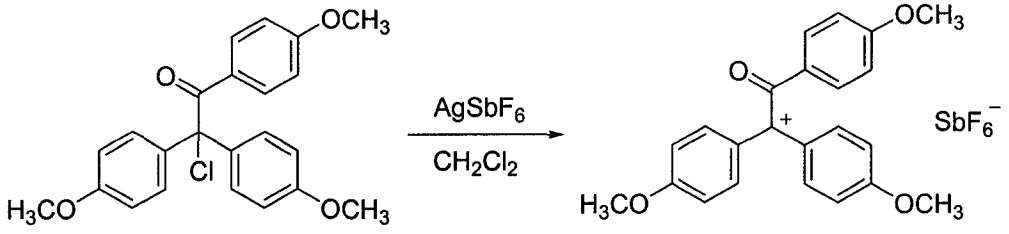
Eq. 1.3. 4e-Electrocyclization reaction of benzilic acid

This important historical reaction has been used recently for the synthesis of many fluorene derivatives.[40-42] The mechanism of this reaction has been investigated extensively and a dicationic four-electron electrocyclization mechanism has been proposed (Sch. 1.4).[43-45] Under strongly acidic conditions, the hydroxy group is protonated and the monocation produced after losing water. Further protonation of the carbonyl oxygen generates the dication, which undergoes the electrocyclization reaction to form the central five-membered ring. Rearomaticization via rearrangement and loss of protons produces the observed product.



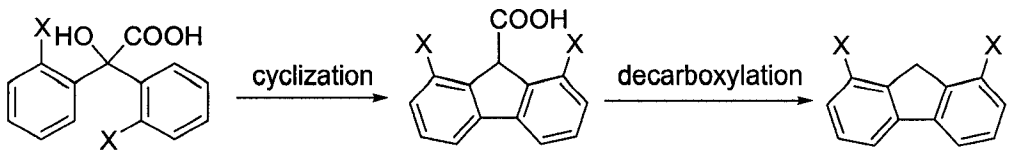
Sch. 1.4. Proposed mechanism of the 4e-electrocyclization reaction

One strong piece of evidence for the above mechanism is the isolation of the relevant di-*p*-anisyl(*p*-methoxybenzoyl)methyl monocarbocation as a stable, crystalline hexafluoroantimonate salt, which does not cyclize into a fluorene derivative under the nominally neutral reaction conditions (Eq. 1.3).[46]



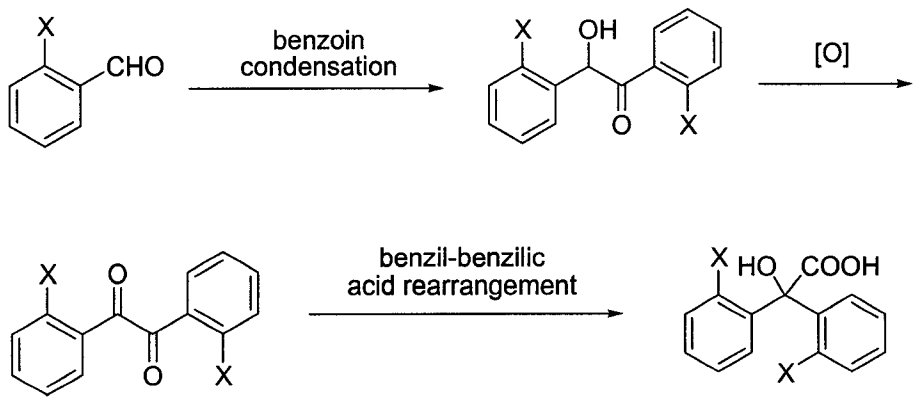
Eq. 1.4. Preparation of the monocation

Based on this reaction, if substitutents are initially introduced at the *ortho* positions of the starting benzilic acid, the 1,8-disubstituted fluorene-9-carboxylic acid could, we propose, be obtained upon treatment with strong acid. Subsequent decarboxylation, well-established for fluorene-9-carboxylic acids, will give the desired 1,8-disubstitutedfluorene (Sch. 1.5).



Sch. 1.5. Proposed synthesis of the 1,8-disubstitutedfluorene

The required *ortho*-substituted benzilic acid can be prepared by benzil-benzilic acid rearrangement from the corresponding benzil derivative, which in turn could be made from *ortho*-substituted benzaldehyde by benzoin condensation and subsequent oxidation, as shown below (Sch. 1.6).

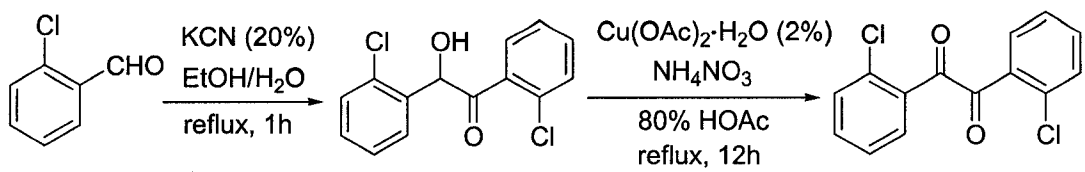


Sch. 1.6. Preparation of the *ortho*-substituted benzilic acid

3.1.2. Results and Discussion

A. 1,8-Dichlorofluorene Synthesis

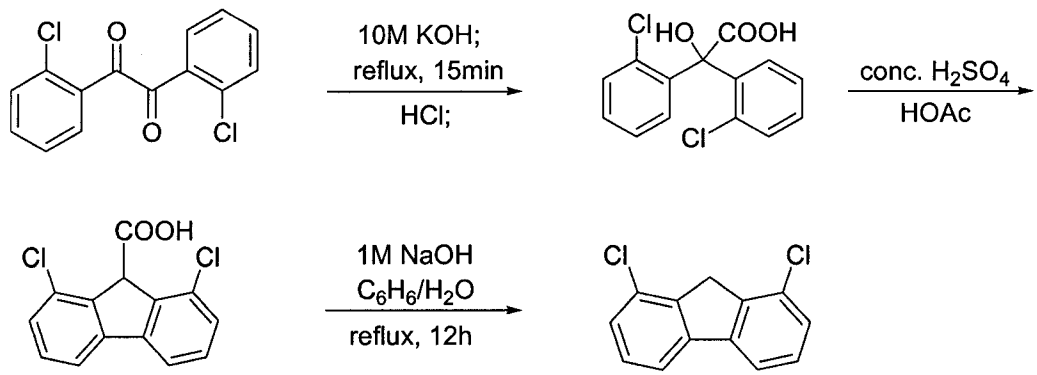
Starting with commercially available 2-chlorobenzaldehyde (Cdn $ 14.40/250 g, Alfa Aesar), the benzoin condensation mediated by cyanide ion catalyst in ethanol/water afforded 2,2'-chlorobenzoin, a known compound in the literature.[47] After extraction and removal of the solvent, oxidation of the benzoin to the benzil was achieved by using ammonium nitrate with a catalytic amount of cupric acetate in 80% acetic acid.[48] The oxidized product crystallized from the reaction mixture when it was slowly cooled to room temperature and was collected by vacuum filtration in 78% yield over two steps. This material could be further purified by recrystallization from ethanol (Sch. 1.7).



Sch. 1.7. Preparation of 2,2'-dichlorobenzil

The benzil-benzilic acid rearrangement took place as anticipated in concentrated KOH solution; acid work-up gave the crude benzilic acid (Sch 1.8). After extraction and removal of the solvent, the crude benzilic acid was treated with concentrated H_2SO_4 dropwise in acetic acid.[43] After additional stirring for 2h, ice was added into the reaction mixture and the product was collected by vacuum filtration. Subsequent

decarboxylation was carried out in NaOH(aq.)/benzene solution at reflux overnight. After extraction and concentration, the solution was passed through a short column of silica gel and eluted with hexanes. Further purification by recrystallization from hexanes afforded 1,8-dichlorofluorene **13** as a white crystalline solid in 32% yield over three steps (Sch. 1.8). This compound was characterized by NMR spectroscopy and mass spectrometry.



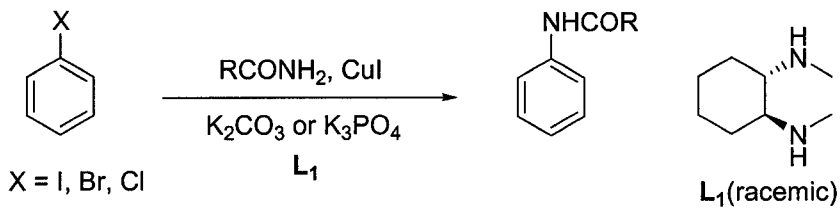
Sch. 1.8. Preparation of 1,8-dichlorofluorene 13

B. Amidation Reactions

With the 1,8-dichlorofluorene in hand, introduction of the two nitrogen substitutents was the next goal. Transition metal-catalysed C-N bond and C-O bond formation under mild conditions has seen extensive development in recent years.[49-52] However, direct synthesis of primary anilines and phenols by using ammonia and

water as coupling partners in these reactions is difficult and it was not until very recently that breakthroughs were made in ligand design from two groups, respectively.[53, 54]

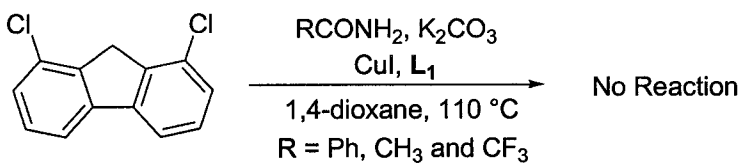
Since this project was carried out prior to these two reports, an alternative method was used instead. Buchwald and coworkers reported an efficient copper-diamine catalysed aryl amidation reaction, in which aryl iodides, bromides, and in some cases even aryl chlorides can be efficiently amidated (Eq. 1.4).[55]



Eq. 1.5. Buchwald's copper catalysed amide coupling reaction

The resulting amide could be hydrolysed to give the free amine for further manipulation, provided an appropriate amide is chosen.

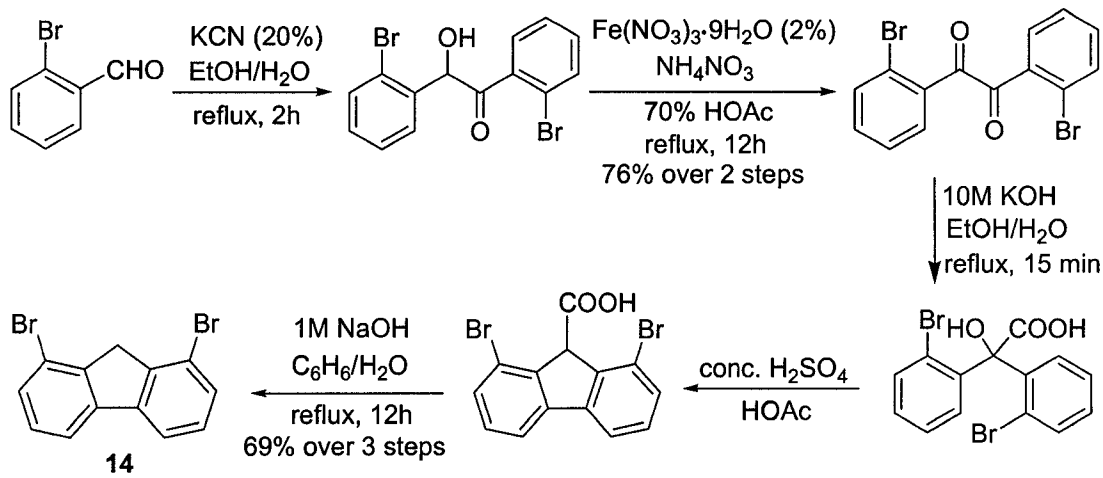
Unfortunately, 1,8-dichlorofluorene was not reactive toward various amides under these coupling conditions (Eq. 1.5). Based on this result, the synthesis of a more reactive bromo analogue was investigated to accomplish the necessary transformation.



Eq. 1.6. Attempted reaction of 1,8-dicholorofluorene with amides

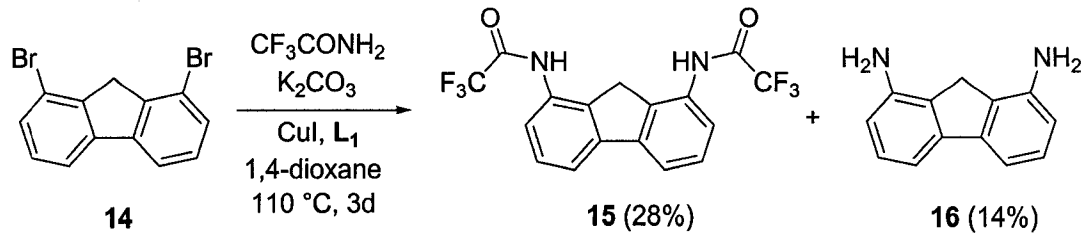
C. 1,8-Dibromofluorene Synthesis

1,8-dibromofluorene **14** was prepared in a similar way to the chloro analogue, starting from 2-bromobenzaldehyde (Cdn $ 136.00/100 g, Alfa Aesar). One exception was in the benzoin oxidation: $Cu(OAc)_2$ did not work; instead, $Fe(NO_3)_3$ was used as the catalyst to oxidize the benzoin. One plausible explanation is that Cu(II) is reduced by benzoin into Cu(I) and the latter reacts with the bromide under the reaction conditions and shut down the catalytic oxidation cycle.



Sch. 1.9. Preparation of 1,8-dibromofluorene 14

After obtaining 1,8-dibromofluorene, the compound was subjected to the copper-catalysed amide coupling reaction, this time producing the desired amide, albeit in low yield (Eq. 1.7). The free bisamine was also obtained, which was probably formed by hydrolysis by adventitious water or the amine ligand $\mathbf{L_1}$. Increasing the reactivity of the substrate by using iodo-substituted starting material might increase the yield; but unfortunately, 2-iodobenzaldehyde is too expensive (Cdn $ 263.00/5 g, Alfa Aesar) for this investigation and thus was not adopted.



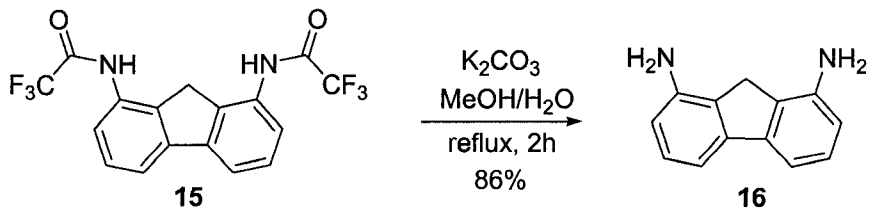
Eq. 1.7. Copper catalysed amide coupling with 1,8-dibromofluorene

The product bisamide **15** was fully characterized by NMR and IR spectroscopy (Table 1.1). The major absorptions in IR spectroscopy are at 3252 cm^{-1} for N-H stretch and 1706 cm^{-1} for C=O stretch; in the ^{1}H NMR spectrum, the amide protons appear at 10.27 ppm, the CH_2 protons appear at 4.02 ppm and the aromatic protons appear between 7.88 - 7.49 ppm. In the ^{13}C NMR spectrum, the C=O carbon appears as a quartet at 160.46 ppm due to ^{13}C-^{19}F coupling (J = 38 Hz); the CF_3 carbon also appears as a quartet at 121.72 ppm (J = 288 Hz); the CH_2 carbon appears at 39.10 ppm as a singlet and the rest aromatic carbons appear between 147.98 - 124.47 ppm.

Table 1.1. Characterization data for compound 15

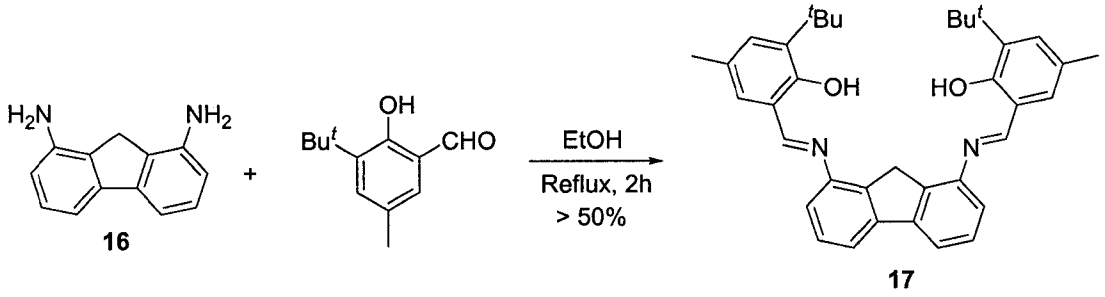
IR	1706, 3252 cm^{-1}
^{1}H NMR (Ac-d_6, 400 MHz)	10.27 (bs, 2H), 7.88 (d, J = 7.6 Hz, 2H), 7.56 (dd, J = 7.6, 1.0 Hz, 2H), 7.49 (dd, J = 7.6, 1.0 Hz, 2H), 4.02 (s, 2H)
^{13}C NMR (Ac-d_6, 100 MHz)	160.46 (q), 147.98, 142.36, 137.38, 133.39, 128.69, 124.47, 121.72 (q), 39.10
HRMS (EI)	Calculated for $C_{17}H_{10}O_2N_2F_6$: 388.0646; Found 388.0646;
Elemental analysis	Calculated: C, 52.59; H, 2.60; N 7.22; Found C, 52.36; H, 2.55; N, 7.33.

Hydrolysis of the amide **15** with K_2CO_3 in methanol/water at reflux proceeded without problems, giving the free 1,8-bisaminofluorene **16** in good yield.



Eq. 1.8. Hydrolysis of the amide 15 into free amine 16

In order to create a sterically hindered coordination environment for binding both early and late transition metals, bulky substitutents on the nitrogen donor sites were introduced. Although many amine derivatives are also targeted, in this case, a chelating aryloxy imine binding site was constructed. Thus, 1,8-bis(amino) fluorene was heated to reflux with the aldehyde in anhydrous ethanol. The crystalline product was collected after concentration of the solution and slow cooling, providing the desired system **17** in good yield.



Eq. 1.9. Preparation of diimine ligand 17.

Given the low yield in the amidation reaction, an alternative synthetic strategy was developed, as discussed in the next section.

3.2. Directed Metallation

3.2.1. Background

Directed *ortho* metallation is another powerful method to introduce functionality into the aromatic ring system.[56, 57] In contrast, directed *peri-* metallation has little practical use in organic synthesis since regioselectivity is usually a big problem.[57]

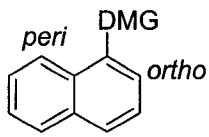
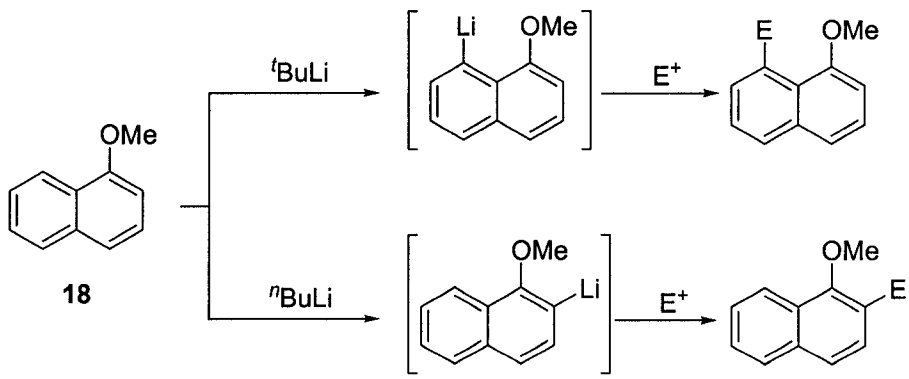


Fig. 1.10. Directed *ortho* and *peri* metallation

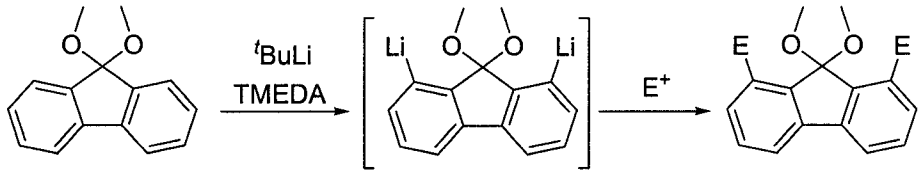
One exception for directed *peri* metallation is 1-methoxynaphthalene **18**. It has been reported that good selectivity with this compound can be achieved by choosing a proper base. ^{t}BuLi afforded the thermodynamic *peri* deprotonated product while ^{n}BuLi afforded the kinetic *ortho* deprotonated product (Sch. 1.9).[58, 59]



Sch. 1.10. Regioselective deprotonation of 1-methoxynaphthalene

Previous research in the Stryker group has shown that 9,9-dimethoxyfluorene **19** can be metallated at the 1,8-positions by ^{t}BuLi/TMEDA. Reaction of the resulting

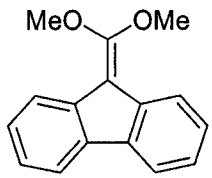
lithium salt with various electrophiles and removal of the methoxy groups generated the 1,8-disubstituted fluorenone derivatives.[60] This reaction is general in scope, but the deprotonation step requires prolonged reaction time at low temperatures, and the overall yields were not satisfactory (Sch. 1.11).



19

Sch. 1.11. Directed metallation of 9,9-dimethoxyfluorene

We proposed that the difficulties in deprotonation arise from the out-of-plane location of the two methoxy directing groups in compound **19**. Therefore, two compounds, 9-(dimethoxymethylene)-9H-fluorene **20** and 9,10-dimethoxy phenanthrene **21**, with in-plane directing groups came into our sight for investigation.



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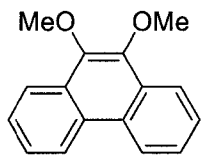
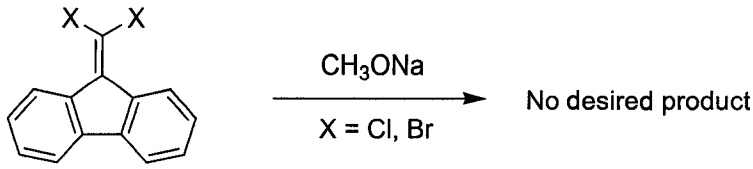


21

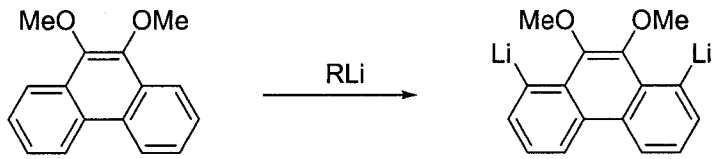
Fig. 1.11. Compounds 20 and 21 with in-plane directing groups

Compound **20** is unknown in literature and synthesis from the corresponding dihalogen precursors[61] by nucleophilic substitution was attempted, but in vain (Eq. 1.10). Reaction of the halogen precursors with sodium methoxide afforded a complex mixture and no desired product was obtained.



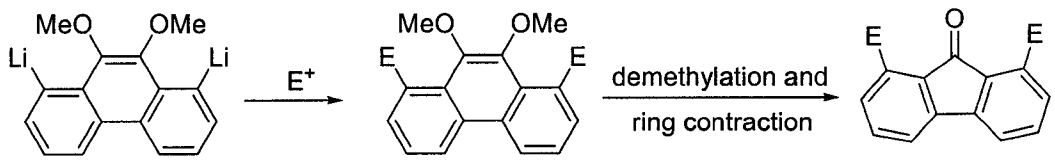
Eq. 1.10. Attempted synthesis of compound 20

Compound **21** is known in literature and can be prepared by reductive methylation of 9,10-phenanthrenequinone in high yield. Regioselective metallation should not be a problem for this compound since only the *peri* positions are available for directed metallation (Eq. 1.11).



Eq. 1.11. Directed metallation of compound 21

After introducing the substitutents at the *peri* positions by quenching the lithium salt with electrophiles, the central six-membered ring can be demethylated and contracted to the five-membered ring, which constitutes a new pathway to the desired 1,8-disubstituted fluorene derivatives (Sch.1.11).

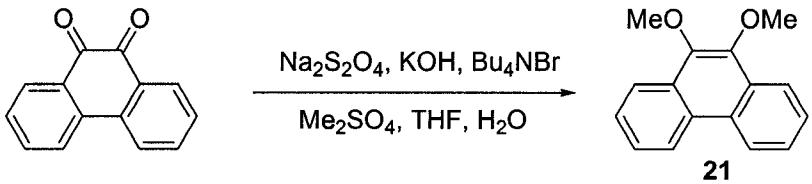


Sch. 1.12. Planned synthesis of the 1,8-disubstitutedfluorene derivatives

3.2.2. Results and Discussion

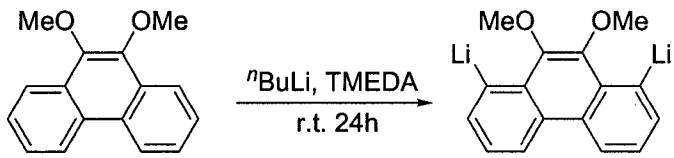
A. Metallation

Compound **21**, 9,10-dimethoxyphenanthrene, was made by reductive methylation of 9,10-phenanthrenequinone (Cdn $ 117.00/100 g, Alfa Aesar) in high yield following a literature procedure.[62, 63] It is a white solid with a low melting point after purification by recrystallization from hexanes.



Eq. 1.12. Preparation of compound 21

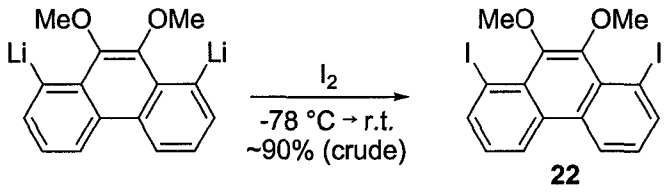
Deprotonation of 9,10-dimethoxyphenanthrene was first tried using ^{t}BuLi. After stirring at room temperature in hexanes for 36h, the reaction mixture was quenched with CH_3I, a complex mixture was observed by ^{1}H NMR spectroscopy. Next, the use of ^{n}BuLi was investigated; no reaction occurred after stirring at room temperature in hexanes overnight. TMEDA was therefore added, whereupon the color of the reaction mixture changed from colorless to slightly red over several minutes and a reddish brown precipitate formed after several hours. The reaction mixture was stirred for 24h before introducing any quenching steps.



Eq. 1.13. Directed metallation of compound 21

B. Iodonation

The suspension of the dilithium salt was cooled to -78 °C and a solution of I_2 in THF was added via canula. The reaction mixture was then warmed to room temperature and stirred for another 1h. Excess I_2 was removed by stirring the solution over aqueous $Na_2S_2O_3$; extraction with ethyl acetate and removal of the solvent afforded the crude 1,8-diiodo-9,10-dimethoxyphenanthrene **22**, along with small amount of 1-iodo-9,10-dimethoxyphenanthrene, in good yield.



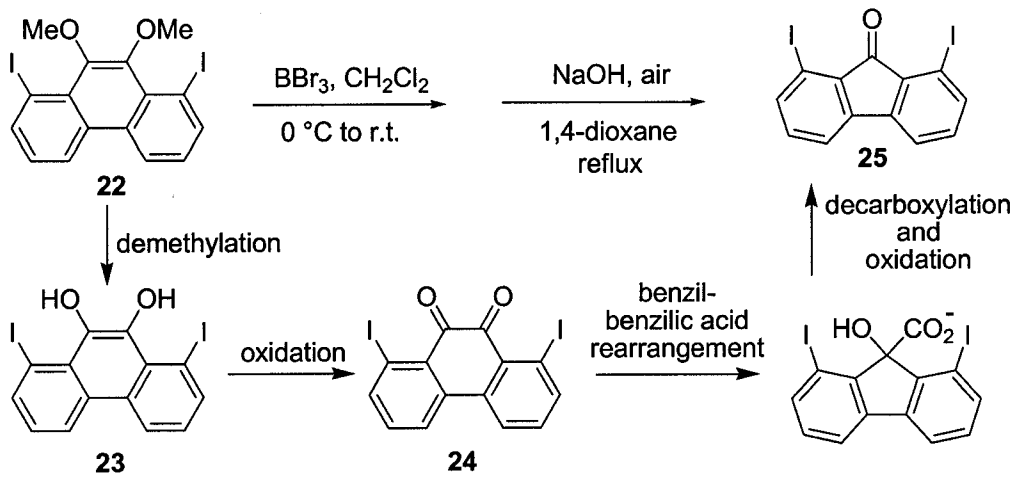
22

Eq. 1.14. Preparation of compound 22

Compound **22** was next treated with CAN, a reagent that can convert methyl ether of hydroquinones into quinones directly.[64] A precipitate which was insoluble in common organic solvents was formed very quickly. The product was collected by vacuum filtration and subsequent treatment with concentrated NaOH solution at reflux returned the starting material **22**. Only a trace amount of desired product 1,8-diiodofluorenone **25** was obtained as determined by ^1H NMR analysis. The reason for the failed demethylation is not clear at present. Plausibly, compound **22** was oxidised to hypervalent iodine compound when treated with CAN,[65, 66] which made the aromatic ring less electron rich and caused the demethylation step to fail, or the

ceric ion just coordinated to the iodo atom (halocarbon metal complexes: Ir[67], Ru[68], Pt[69], review[70]), oxygen atom, or the aromatic ring and, once base was added, free **22** was released.

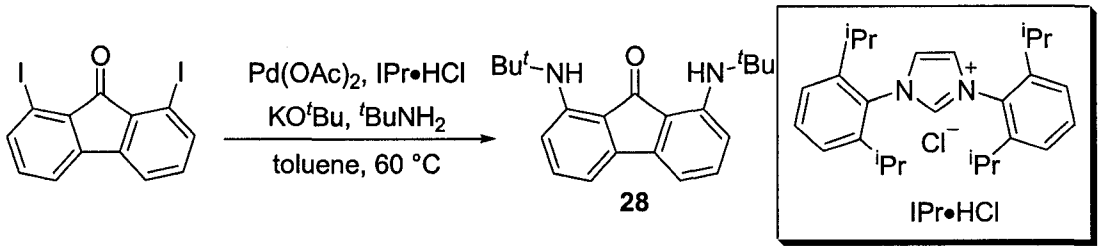
The desired deprotection was ultimately achieved by using BBr_3 in dichloromethane. After removal of the volatiles under vacuum, the residue was heated to reflux in concentrated NaOH solution under air; after work up and separation by flash chromatography, the desired 1,8-diiodofluorenone **25** was obtained in low yield (~20%). This compound has been fully characterized by IR and NMR spectroscopy and elemental analysis. The detailed process mediated in this reaction sequence is proposed as follows: compound **22** was demethylated to give compound **23**, which was oxidized in air to generate 1,8-diiodophenanthrenequinone **24**; NaOH-mediated benzil/benzilic acid rearrangement formed the benzilic acid; subsequent decarboxylation in basic solution followed by air oxidation formed the final product, 1,8-diiodofluorenone **25** (Sch. 1.12).



Sch. 1.13. Preparation of compound 25

Although the desired product **25** was obtained very efficiently, it was formed in low yield; other by-products included 1-iodofluorenone **26** and other unidentified materials. Since oxidation of the hydroquinones involves reactive aryloxy radicals, many other reaction processes could intervene, including the dehalogenation process that accounts for the formation of compound **26**. The use of other oxidants instead of air, such as $KBrO_3$ or $FeCl_3$, afforded similar results.

With compound **25** in hand, various amine cross-coupling reactions could be evaluated. For example, the bulky ^{t}BuNH- group was introduced into the compound under palladium catalysis[71] to afford diaminated fluorenone **27** (Eq.1.13).

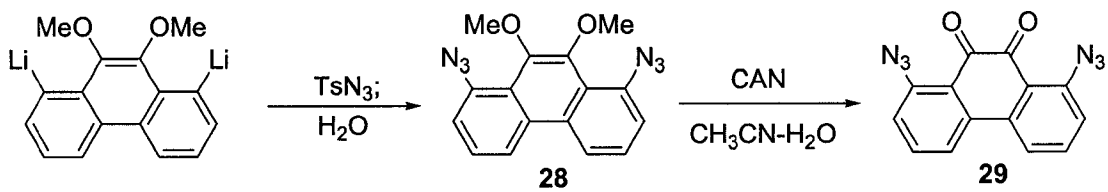


Eq. 1.15. Pd catalysed amination of compound 25

Further investigation and optimisation of this synthetic pathway remains ongoing.

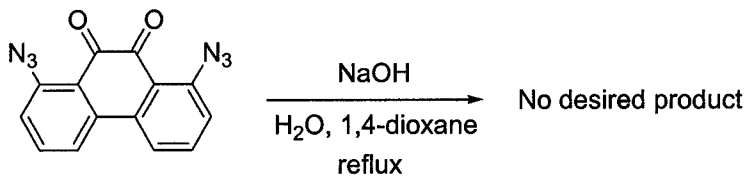
C. Azide transfer

Quenching of the lithium salt with tosyl azide and hydrolysis of the intermediate with water generated the 1,8-diazido-9,10-dimethoxyphenanthrene **28**. Removal of the methoxy directing groups proceeded smoothly using CAN in aqueous CH_3CN solution at 0 °C to afford 1,8-diazidophenanthrenequinone **29** (Sch. 1.13).



Sch. 1.13. Preparation of 1,8-bis(azido) phenanthrenequinone

However, all attempts to contract the central ring of compound **29** were in vain. Compound **29** was heated to reflux in concentrated NaOH solution; the solution turned into dark red, and work up of the reaction mixture afforded no desired product. Possibly, side reactions involving reactive nitrene intermediates dominate under the reaction conditions.

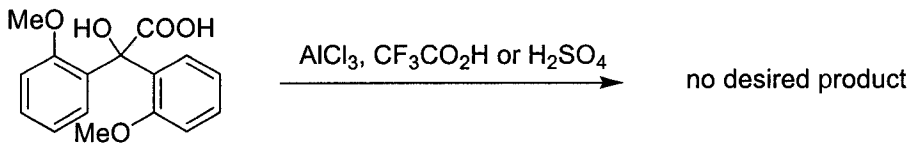


Eq. 1.16. Attempted ring contraction of compound 29

3.3. Other Attempted Syntheses

3.3.1. 1,8-Dimethoxyfluorene

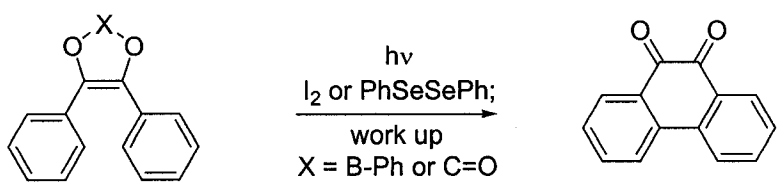
When methoxy substitutents were used instead of halogen in the electrocyclization strategy, all attempts to close the central five-membered ring from the corresponding benzilic acid did not succeed, despite using a variety of Lewis acids ($AlCl_3$, $BF_3 \cdot Et_2O$) and Brφnsted acids (TFA, PPA, H_2SO_4). Only unidentified dark materials were obtained in all cases. One possible reason is that when the cation is generated, an intermolecular Fridel-Crafts reaction was faster, resulting in the oligormerization of the starting material.



Eq. 1.17. Attempted ring closure of the 2,2'-dimethoxybenizlic acid

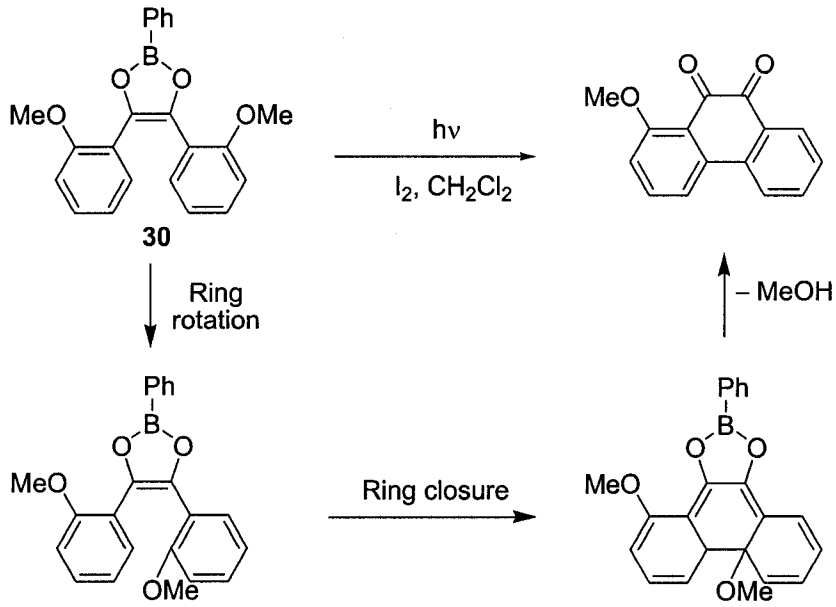
3.3.2. Tethered Stilbene

It is well-known that 9,10-phenanthrenequinone can be prepared by photocyclization of the tethered stilbene derivatives.[72-74]



Eq. 1.18. Preparation of 9,10-phenanthrenequinone via photocyclization

Therefore, the dimethoxy-substituted substrate **30** was made by following a similar literature procedure. When subjected to photolysis, however, only trace amounts of the desired 1,8-dimethoxy-9,10-phenanthrenequinone were obtained; the major by-products being 1-methoxyphenanthrenequinone and 2,2'-dimethoxy benzil. A mechanism rationalizing the loss of one methoxy group is suggested below (Sch. 1.14).



Sch. 1.14. Proposed mechanism for the loss of the methoxy group

4. Conclusion and Outlook

In summary, two novel synthetic pathways to make the 1,8-disubstituted fluorene/fluorenone derivatives have been developed, but not optimised.

The first synthesis is based on a 4e-electrocyclization reaction, related to the Nazarov cyclization. Compound **14**, 1,8-dibromofluorene, was prepared in 53% yield over 5 steps and the final diimine ligand **17** was prepared in about 10% yield over 8 steps. The advantage of this synthesis is that all the reagents used in the syntheses are inexpensive. However, there are still some disadvantages: highly toxic cyanide was used in the synthesis, the amidation step proceeded in low yield, and finally, the synthesis remains excessively long.

The second synthesis is based on directed *peri*-metallation. The diamine ligand **27** was prepared over 5 steps. Due to the limitation of time, the reaction conditions and yields have not been optimised. The synthesis is very promising, provided the oxidative demethylation step can be optimised. Potential solutions include using a milder oxidant (i.e. Fremy's salt[75]) to oxidize the hydroquinone after demethylation with BBr_3. It would also be interesting and helpful to find out what happened in the reaction of compound **22** and CAN. Solving this problem will make this syntheses a good candidate for making the necessary 1,8-disubstituted fluorene/fluorenone derivatives for use in coordination chemistry and catalysis.

Part II. Metal-mediated Carbonylative Ring Expansion of Cyclobutane-containing Natural Products.

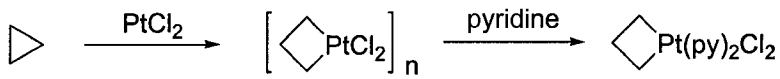
1. Introduction

Selective activation and subsequent functionalization of unreactive chemical bonds is a useful and challenging process in chemistry.[76] The use of abundant and cheap raw materials such as hydrocarbons as synthetic precursors is very attractive because these substances represent the most inexpensive sources of carbon, the most common element in organic compounds. On the other hand, direct usage of these compounds under mild conditions is difficult because of their chemical inertness and the nonselectivity of conventional chemical transformations.

The past 30 years has seen great strides towards the goal of selectively activating C-H bonds, mainly using organometallic catalysts that work by forming transient bonds between carbon and a metal.[77-80] Breaking the C–C bonds of alkanes is thermodynamically and kinetically more difficult than breaking the C–H bonds because two relatively weak M–C bonds (together worth ~70 kcal/mol) are formed for the loss of a C–C bond (~85 kcal/mol), and a C–C bond is sterically less accessible than a C–H bond from a kinetic perspective.[81] In order to overcome these problems, a number of strategies have been developed for C-C bond activation processes, among which the most common methods include the use of small ring

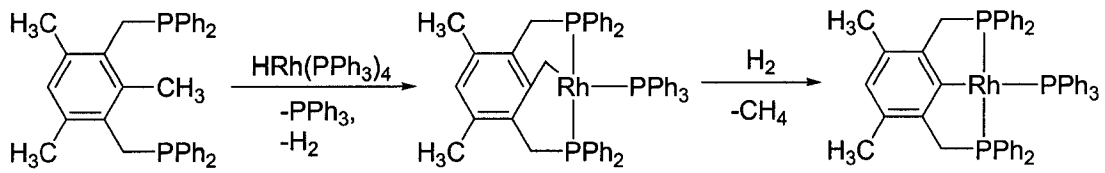
strain, pincer-type chelating ligands, and ring aromatization, as illustrated below.[82]

The first example of C-C bond activation dates from 1955, when Tipper observed the reaction between cyclopropane and $PtCl_2$;[83] the correct metalacyclobutane structure of the product was suggested by Chatt in 1961 (Sch. 2.1).[84]



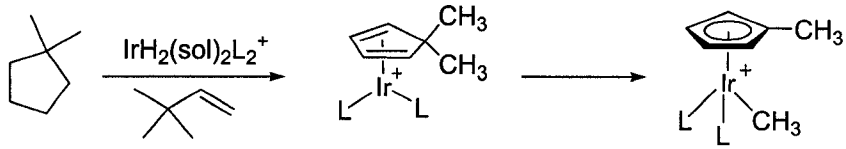
Sch. 2.1. Three-membered ring opening by $PtCl_2$

Milstein has devised a series of pincer-type chelating ligands, in which a strong C_{aryl}–C bond is favorably oriented toward the transition metal center. A rhodium metal complex inserts readily into the carbon-carbon bond and breaks it (Sch. 2.2).[85, 86]



Sch. 2.2. C-C bond activation with pincer type ligand

Crabtree showed that an unsaturated iridium complex can transform 1,1-dimethylcyclopentane into a 1-methylcyclopentadienyl ligand by a C–C bond-breaking process. Isolation of the intermediate cyclopentadiene complex showed that the reaction proceeds via prior C–H bond breaking. The system is set up so that the unfavorable C–C bond cleavage is accompanied by concomitant formation of a thermodynamically very stable Cp'–M(Cp' = methylcyclopentadienyl) bond (Sch. 2.3).[87]

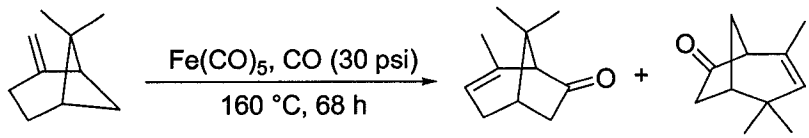


Sch. 2.3. C-C bond activation by aromatization

Many other types of C-C bond activation reactions are known, including several developed in this research group;[88-91] several reviews have been published.[76, 82, 92]

2. Goal of the Project

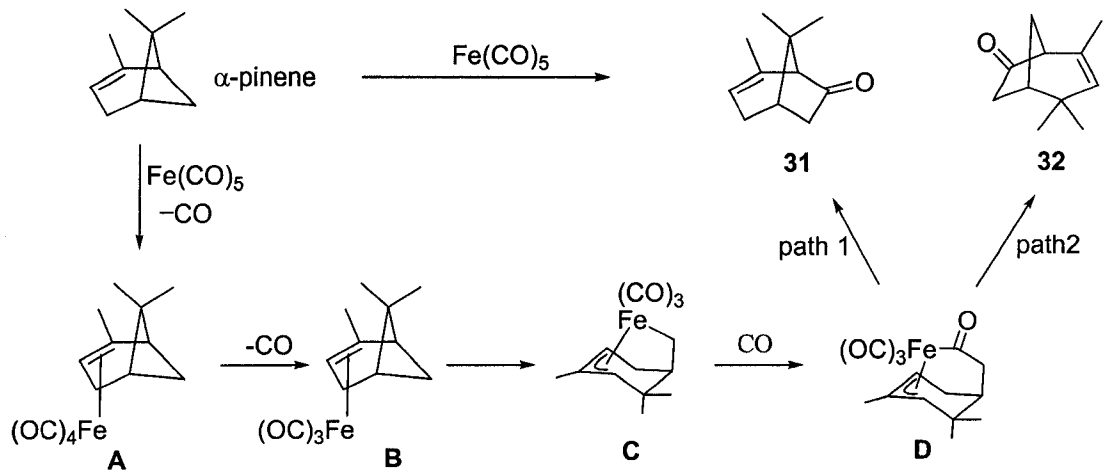
One early example of carbon-carbon bond activation with a soluble transition metal complex was reported by Stockis and Weissberger in 1975, utilizing both a neighbouring coordination site and small ring strain to promote the reaction.[93] Iron pentacarbonyl induced carbonyl insertions into the cyclobutane rings of both α- and β-pinene at elevated temperature and prolonged reaction time, giving two isomeric ketonic products (**31** and **32**) in near random distribution (Eq. 2.1).



β-pinene **31** (29%) **32** (34%)

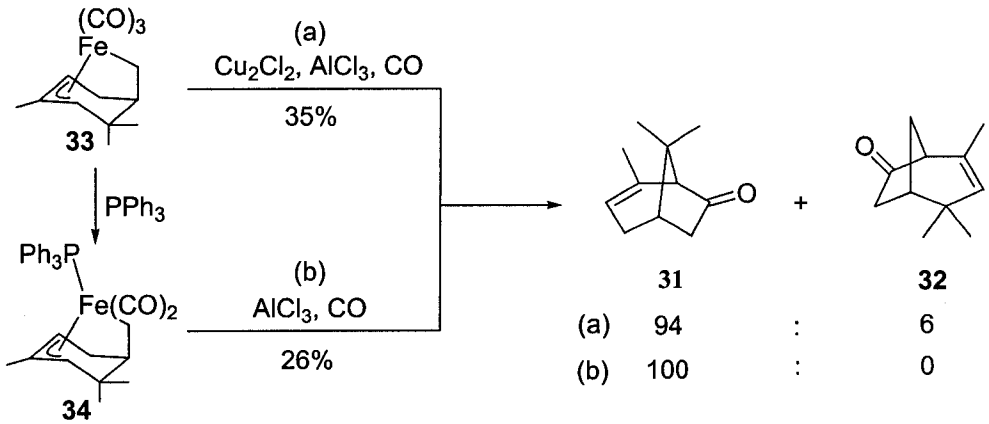
Eq. 2.1. Carbonylative ring expansion of pinene with $Fe(CO)_5$

The reaction mechanism proposed by Stockis and Weissberger is shown in Sch. 2.4. Loss of one carbon monoxide ligand from iron pentacarbonyl leaves a vacant coordination site, which is followed by coordination of the carbon-carbon double bond of pinene (**A**). Due to steric hindrance, the coordination occurs only from the opposite side of the ring from the *gem*-dimethyl group. After the loss of a second carbon monoxide ligand (**B**), oxidative addition opens the strained cyclobutane ring to give the σ-alkyl-π-allyl intermediate (**C**), followed by carbon monoxide migratory insertion (**D**) and reductive elimination to produce the carbonylative ring expansion products. During the last step, reductive elimination can take place on either side of the allyl fragment, affording the two isomers, as observed.



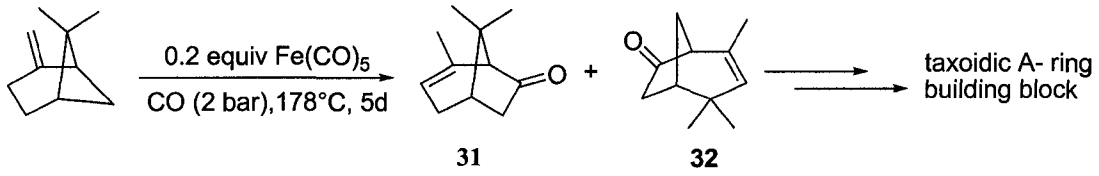
Sch. 2.4. Plausible mechanism of the carbonylation reaction

In 2002, Jenny and coworkers isolated the putative σ-alkyl-π-allyl intermediate **33** by conducting the reaction under milder conditions.[94] The structure was confirmed by single crystal X-ray crystallographic analysis of a triphenylphosphine derivative **34**. Both of these intermediates could be further transformed into the ketones under carbon monoxide. Additives can change the selectivity of the carbonylation step, but results in unacceptably poor yields.



Sch. 2.5. Carbonylation of compound 33 and 34

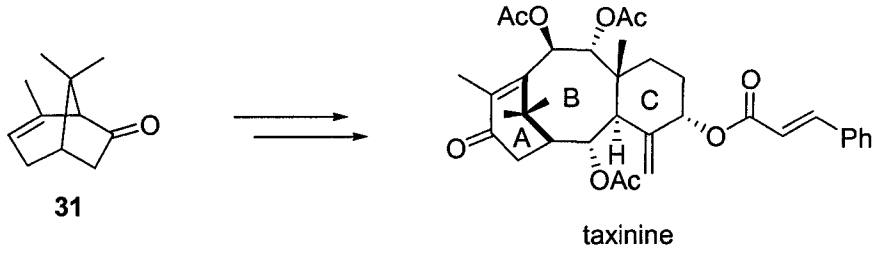
A semi-catalytic version of this reaction was reported by Blechert in 1999,[95] although only a few catalyst turnovers could be obtained prior to decomposition. Both ketones were subsequently transformed into the taxoidic A-ring building block.



Sch. 2.6. Catalytic carbonylation of pinene

Overall, this one pot carbonylative ring expansion of pinene proceeds in acceptable yield and can be done on a large scale. Unfortunately, the two ketones are very difficult to separate, due to very similar boiling points and R_f values on chromatographic supports. The separation requires HPLC or fractionation of the respective hydrazone derivatives, followed by hydrolysis to regenerate the free ketone.[96]

The West group at University of Alberta uses the stoichiometric carbonylation reaction to prepare the ketone **31** as the starting material for the total synthesis of taxinine, reporting similar difficulties and variable reaction yields.



Sch. 2.7. West' proposed synthesis of taxinine from ketone 31

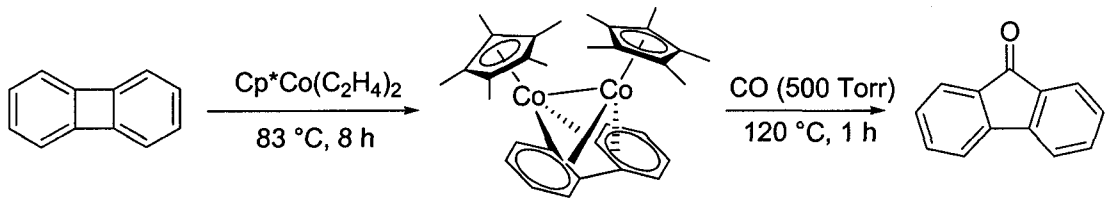
In order to efficiently utilize pinene for this transformation, we were interested in developing a more selective process and to investigate the possibility of a novel catalytic variant.

3. Results and Discussion

3.1. Cyclopentadienyl Cobalt Reactivity

Cyclopentadienylcobalt bis(ethylene) complex ($CpCo(C_2H_4)_2$) **35**, is an 18-electron cobalt(I) complex. The ethylene ligands are thermally labile slightly above room temperature and hence this compound is a good source of the reactive CpCo(I) synthon.[97] Previous research in the Stryker group has shown that the ethylene ligands in $CpCo(C_2H_4)_2$ can be readily substituted by a conjugated diene, including both acyclic and cyclic dienes.[91]

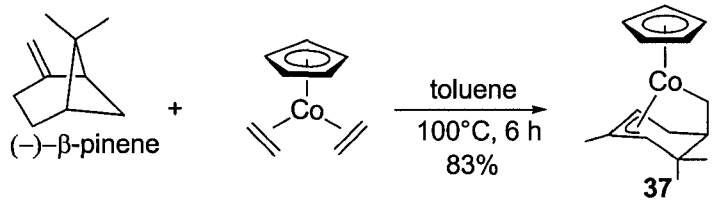
Relevant to the issue of oxidative insertion into the four-membered ring of pinene, Jones and coworkers have reported that $Cp^*Co(C_2H_4)_2$ **36** (Cp^* = pentamethylcyclopentadienyl) can insert into the C-C bond of biphenylene and the intermediate can be carbonylated to give fluorenone.[98]



Sch. 2.7. C-C bond activation of biphenylene

Thus, treatment of $CpCo(C_2H_4)_2$ **35** and β-pinene in benzene-d_6 solution led to the formation of a new compound by ^1H NMR spectroscopy. After evaporation of the solvent and separation by flash chromatography, a red oily product was obtained and characterized by NMR spectroscopy (^1H, ^{13}C, COSY, HMQC and HMBC) to be the

expected σ-alkyl-π-allyl cobalt complex **37**. The spectra data for this compound are summarized in Table 2.1.



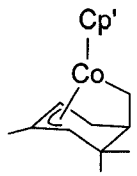
Eq. 2.2. Reaction of pinene with $CpCo(C_2H_4)_2$

The two signals at 4.32 and 3.88 ppm in ^1H NMR spectrum and the three signals at 64.6, 75.1 and 91.6 ppm in ^{13}C NMR spectrum, which are in the typical range for organometallic allyl complexes,[99] are assigned to the allyl fragment of compound **37**; The signals at 2.47 and 2.02 ppm in ^1H NMR spectrum and 25.6 ppm in ^{13}C NMR spectrum are assigned to the CH_2 group bonded to cobalt center; the three methyl signals are singlets at 1.65, 0.96 and 0.82 ppm in ^1H NMR spectrum.

Similar to the work previously reported with iron chemistry, both α- and β-pinene can be ring opened to give the same product **37** in similar yield. However, the reaction with β-pinene is slightly faster, making this the preferable conversion. A possible reason for this is that coordination of the C-C double bond to the cobalt metal may be the rate determining step for the reaction and β-pinene, by virtue of a less hindered, less substituted *exo*- double bond, coordinates faster.

The product was thoroughly characterized by NMR spectroscopy; however, all attempts to grow single crystals for X-ray crystallography analysis were unsuccessful. In addition, this compound was not reactive under 1 atm of CO at 80 °C.

Table 2.1. ^{1}H NMR and ^{13}C NMR data for compound 37 and 39



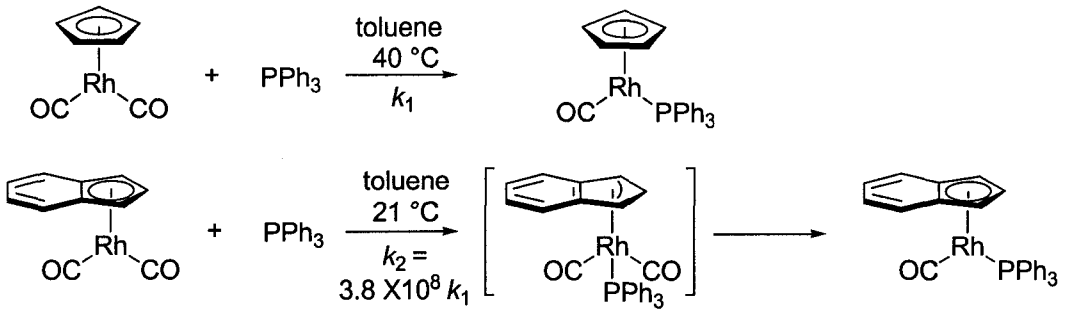
Cp' = Cp, **37**

Cp' = Ind, **39**

Functional Group	^{1}H NMR (ppm)		^{13}C NMR (ppm)	
	37	**39**	**37**	**39**
$\boldsymbol{C_5H_5}$ or $\boldsymbol{C_9H_7}$	4.37 (s, 5H)	7.30 - 4.62 (m, 7H)	84.3	125.0 - 78.4
CH_2-$\boldsymbol{CH}C(CH_3)CH$	4.32 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H)	3.92 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H)	64.6	65.5
CH_2-$CHC(CH_3)\boldsymbol{CH}$	3.88 (t, J = 1.8 Hz, 1H)	3.38 (t, J = 1.8 Hz, 1H)	75.1	76.5
Co-$\boldsymbol{CH_2}$-CH	2.47 (ddd, J = 6.8, 3.6, 2.8 Hz, 1H), 2.02 (dd, J = 6.8, 2.0 Hz, 1H)	2.50(ddd, J = 6.8, 4.8, 2.4 Hz, 1H) 2.11 (dd, J = 4.8, 2.0 Hz, 1H)	25.6	29.9
CH_2-$CHC(\boldsymbol{CH_3})CH$	1.65 (s, 3H)	1.78 (s, 3H)	27.9	27.4
$\boldsymbol{CH_2}$-$CHC(CH_3)CH$	1.16 (ddt, J = 13.2, 3.6, 2. 0 Hz, 1H), 0.92-0.98 (dt, J = 13.2, 4.0 Hz, 1H)	0.71 (app. q, J = 2.8 Hz, 2H)	33.8	33.0
$C(\boldsymbol{CH_3})_2$	0.96 (s, 3H), 0.82 (s, 3H)	0.75 (s, 3H), 0.63 (s, 3H)	26.7, 26.3	25.6, 25.2
Co-CH_2-$\boldsymbol{CH}$	0.90 (m, 1H)	0.67 (m, 1H)	51.4	51.7
CH_2-$CH\boldsymbol{C}(CH_3)CH$			91.6	91.3
$\boldsymbol{C}(CH_3)_2$			39.7	39.3

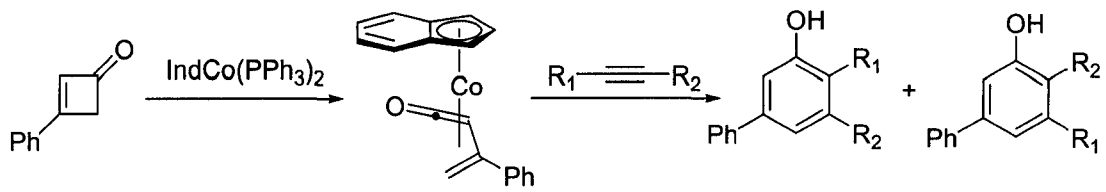
3.2. Indenyl Cobalt Reactivity

It is well understood that η^5-indenyl complexes undergo associative substitution reactions much faster than the corresponding cyclopentadienyl analogs. Substitution reactions of CO for PPh_3 in $CpRh(CO)_2$ and $IndRh(CO)_2$, for example, show that there is a 3.8×10^8 times increase in reaction rate for the indenyl complex, attributed generically to the "*indenyl effect*" (Sch. 2.8).[100] One explanation for this rate enhancement is that during the associative substitution, ring slippage (η^5-η^3) occurs in order to maintain an 18-electron configuration. Ring slippage is much more facile in the indenyl complex because the full aromatic stabilization of the annulated benzo-ring is restored in the slipped η^3-form. It is also possible that the use of indenyl in place of cyclopentadienyl allows for an associative exchange where only dissociative pathways were obtained for simple cyclopentadienyl systems.



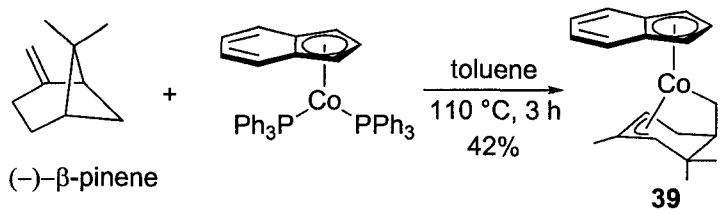
Sch. 2.8. Indenyl effect

Since $IndCo(C_2H_4)_2$ is not readily available,[101-103] we investigated the reactivity of the phosphine analogue $IndCo(PPh_3)_2$ **38** instead. Liebeskind and coworkers have used $IndCo(PPh_3)_2$ to open cyclobutenones and used the reactive intermediates to generate phenol derivatives upon reaction with various alkynes (Sch. 2.9).[104]



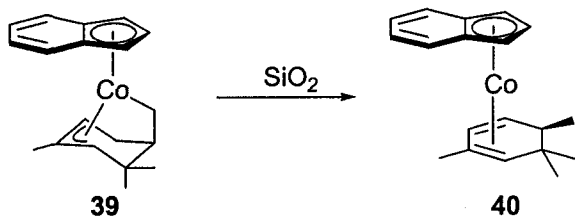
Sch. 2.9. Ring opening and alkyne insertion of cyclobutenone with $IndCo(PPh_3)_2$

Thus, a mixture of $IndCo(PPh_3)_2$ and β-pinene was heated in toluene and the reaction progress monitored by TLC. A red oily product was obtained after evaporation and purification of the residue by flash chromatography. The product was identified spectroscopically to be complex **39**, the indenyl analogue of compound **37**, as indicated by the closely analogous ^1H and ^{13}C NMR data (Table 2.1).



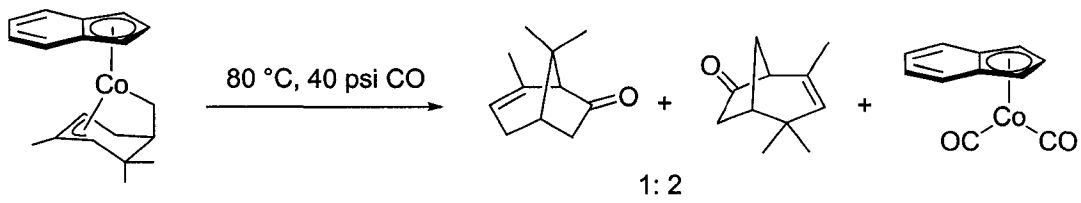
Eq. 2.3. Ring opening of pinene with complex $IndCo(PPh_3)_2$

Consistent with the "*indenyl effect,*" compound **39** is more reactive than complex **37** and partially rearranges to the diene complex **40** on silica gel column under air. The two compounds are inseparable and a pure sample of compound **39** was obtained by flash chromatography under inert atmosphere. Attempts to obtain a single crystal of this complex for X-ray analysis were also unsuccessful.



Eq. 2.4. Rearrangement of complex 39 into 40

When complex **39** was heated at 80 °C under 40 psi of CO for 24 hours, ^{1}H NMR analysis established that a mixture of the two ketone isomers was formed in the ratio of 1 : 2, by comparison with the spectroscopy of an authentic sample from the West group and the data previously reported in the literature.

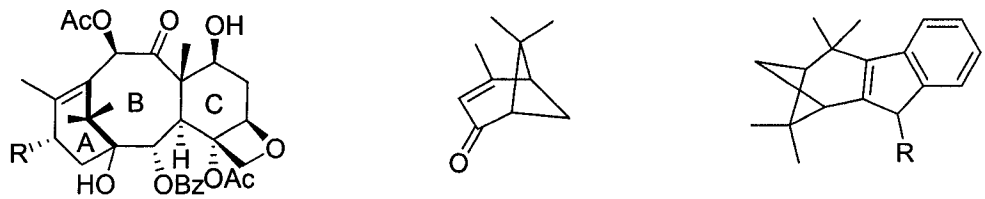


Eq. 2.5. Carbonylation of the compound 38

Other indenyl cobalt precursors, such as IndCo(1,5-COD) and $IndCo(CO)_2$ were also evaluated as starting materials for the ring opening reaction. Reaction of IndCo(1,5-COD) with β-pinene at 140 °C for 20 hours gave 20% conversion (^{1}H NMR analysis) based on the consumption of β-pinene; no reaction was observed between $IndCo(CO)_2$ and β-pinene under same thermal conditions. Further heating at higher temperatures resulted in degradation of the organometallic starting materials. Photolysis of $IndCo(CO)_2$ and β-pinene with N_2 purging for 40 hours also gave about 20% conversion. Due to the slow reaction rate, these processes were not further investigated.

3.3. Ring Opening and Carbonylation of Verbenone

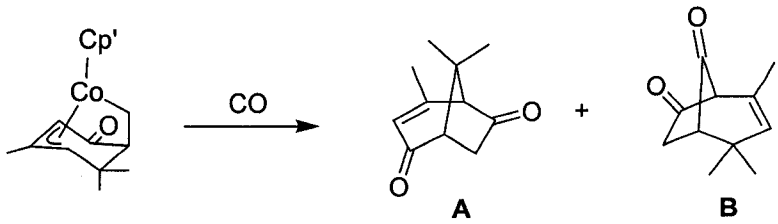
Verbenone is a versatile chiral precursor in organic synthesis. It is also a natural product and commercially available (Cdn $ 70.20/10 g, Aldrich), but can be obtained by oxidation of the more readily available natural product pinene ((-)-β-pinene, Cdn $ 135.50/1 L, Aldrich).[105, 106] Verbenone has been used as a chiral synthon in the total synthesis of taxol reported by Wender and coworkers;[105] also a new class of chiral indenyl ligands derived from verbenone was reported by Rupert and coworkers.[107]



taxol verbenone chiral indenes

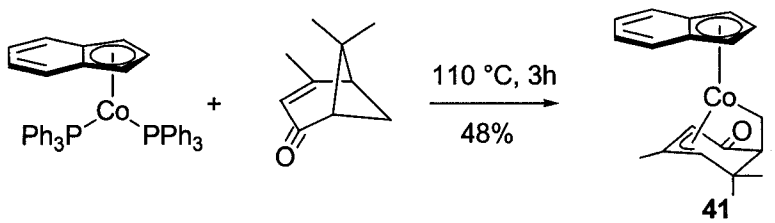
Sch. 2.10. Taxol, verbenone and chiral indene ligands

Previously, the poor selectivity of the carbonylation reaction of the ring-opened pinene derivatives was noted, a result of the non-regioselective reductive elimination of the carbonylation intermediate step. Verbenone is particularly attractive in that, during the carbonylation step, reductive elimination can potentially occur selectively at the γ-position (**A**) of the allylic system instead of the α-position (**B**) to maintain the conjugated enone structure and control the ratio of the two possible carbonylation products.



Eq. 2.6. Possible carbonylation products of verbenone

In the event, a mixture of verbenone and $IndCo(PPh_3)_2$ was heated at 110 °C for 3 hours, giving a dark red solid after purification by flash chromatography. The compound was exhaustively characterized by NMR and IR spectroscopy and found to be compound **41**, the oxo-analog of the pinene complexes isolated previously.



Eq. 2.7. Ring opening of verbenone with $IndCo(PPh_3)_2$

Moreover, a single crystal suitable for X-ray crystallography analysis was obtained from a cold solution in diethyl ether. This result definitively confirmed the structure anticipated from NMR analysis (Fig. 2.1). Complex **41** is an air and moisture stable dark red solid at room temperature, but decomposes upon prolonged heating in a benzene-d_6 solution under inert atmosphere at 110 °C. This is presumably the reason why no product was isolated when the reaction is run for longer time (20 hours).

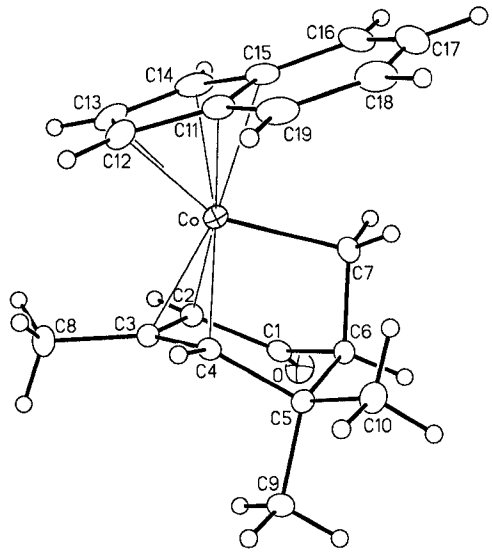
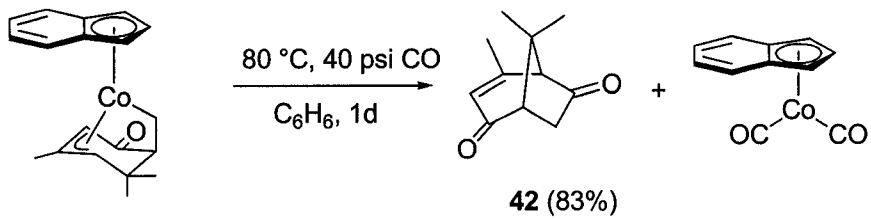


Fig. 2.1. X-ray structure of compound 41

Upon heating in benzene at 80 °C under 40 psi of CO for 24 hours, complex **41** produced only one carbonylation product, enone **42**, as determined by ^{1}H NMR spectroscopy of the reaction mixture.



42 (83%)

Eq. 2.8. Carbonylation of compound 41

The organic carbonylation product **42** was separated from the reaction mixture by the addition of stoichiometric I_2, which converts the metal complex, $IndCo(CO)_2$, into air stable $IndCo(CO)I_2$, followed by simple flash chromatography to afford the pure ketone product **42**. Recrystallization via slow evaporation of a solution of hexane and diethyl ether at room temperature afforded a single crystal suitable for X-ray diffraction analysis, confirming the identity of the product (Fig. 2.2).

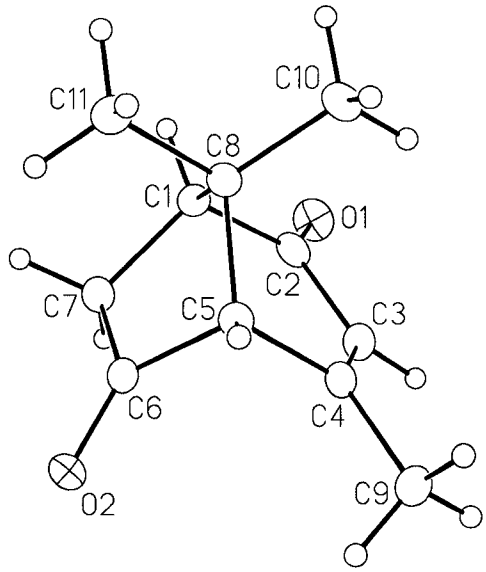
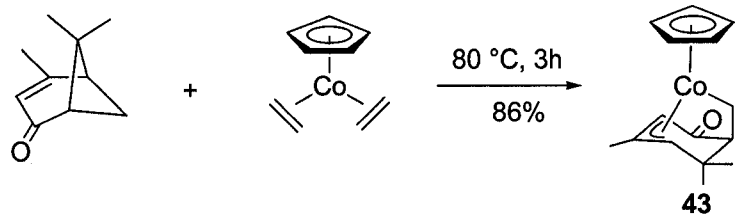


Fig. 2.2. X-ray structure of compound 42

The reaction gave excellent selectivity, but unfortunately the ring opening product **41** was obtained in disappointingly low yield. Using $CpCo(C_2H_4)_2$ instead of $IndCo(PPh_3)_2$ in the reaction increased the yield of the σ-alkyl-π-allyl intermediate from 50% to 86%. A single crystal of this product **43**, suitable for X-ray diffraction analysis, was obtained from a cold pentane solution.



43

Eq. 2.9. Ring opening of verbenone with $CpCo(C_2H_4)_2$

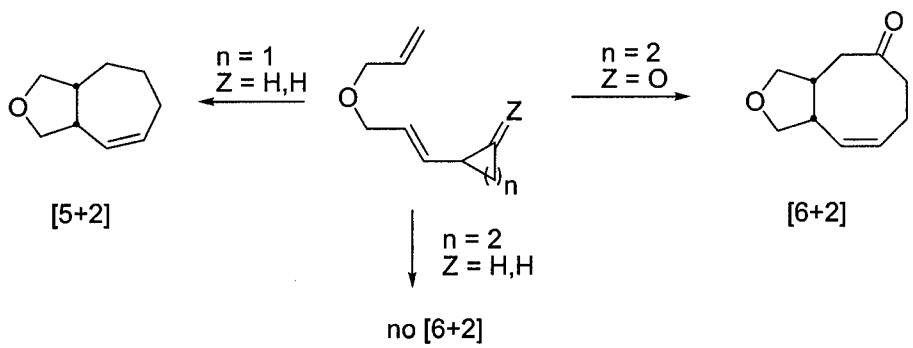
Complex **43** was subjected to carbonylation conditions, but found to be unreactive in toluene even under 1200 psi of CO and 120 °C for two days. The addition of potential promoters,[108, 81] such as reducing agents [Mg, Na(Hg), SmI_2] or oxidizing

agents [Cp_2FePF_6, $(NH4)_2Ce(NO_3)_6$, $AgNO_3$] returned only the starting material. Addition of Lewis acid accelerants, e.g., $AlMe_2Cl$, resulted in the decomposition of the starting cobalt complex.

3.4. Ring Opening of Cyclobutanone-containing Compound

3.4.1. Background

Wender's rhodium-catalysed cycloaddition of vinylcyclopropane with alkenes and alkynes is a good example of a carbon-carbon bond activation reaction that utilizes the small-ring strain strategy. This process has been successful in intra- and some intermolecular multi-component coupling reactions. Thus far, there have been no reports of successful vinylcyclobutane-type substrates, although such substrates were investigated. Exceptions to this chemistry with four-membered ring substrates were noted for vinyl cyclobutanone and allenyl cyclobutane substrates, both more reactive than simple vinyl cyclobutanes (Sch. 2.11).[109, 110]



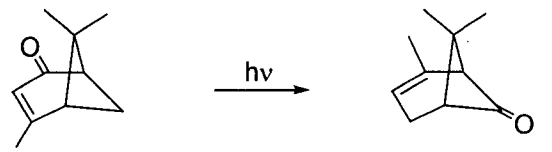
Sch. 2.11. Wender's rhodium-catalysed coupling chemistry

From the results of the cobalt-mediated ring-openning of pinene, it was proposed that introducing a carbonyl group into the four-membered ring could increase the strain of the ring and make the ring opening step easier. It is also possible that the carbonyl group would coordinate to the unsaturated metal center and promote the oxidative ring-opening.

44 **45**

Fig. 2.3. Chrysanthenone 44 and its *exo* isomer 45

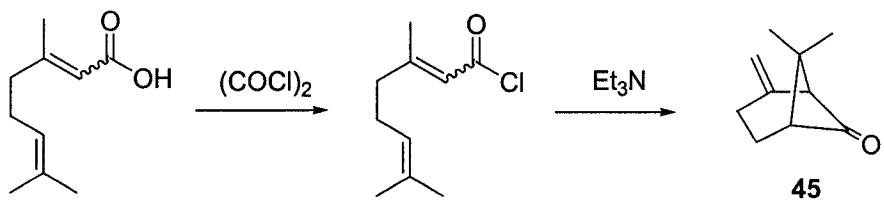
One corresponding natural compound containing a cyclobutanone structure is chrysanthenone **44**, which can be made by a photochemical 1,3-allylic rearrangement reaction starting from verbenone.[111]



verbenone chrysanthenone

Sch. 2.12. Photochemical 1,3-allylic rearrangement

The corresponding *exo*-isomer of chrysanthenone **45** is also a possible substrate for this reaction; this compound can be made by an intramolecular [2+2] cycloaddition reaction starting from the acid chloride of geranic acid.[112]

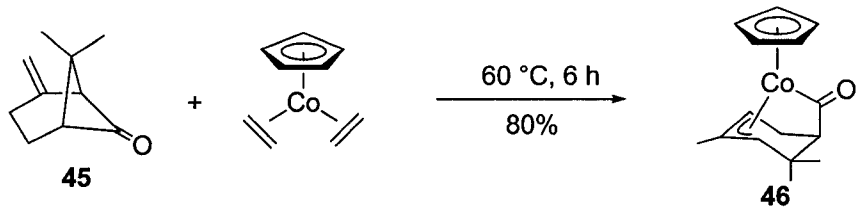


45

Sch. 2.13. Preparation of 45 by [2+2] cycloaddition

3.4.2. Results and Discussion

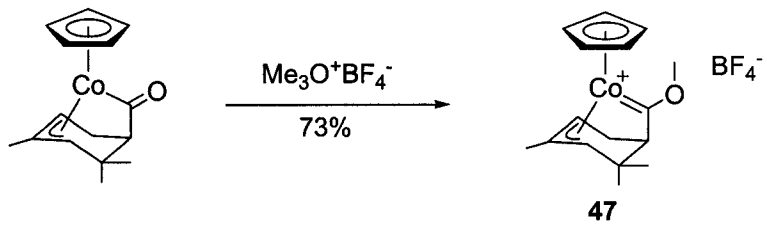
When the ketone **45** was heated with $CpCo(C_2H_4)_2$, a similar ring opening reaction occurs to afford the acyl complex **46**, isolated in 80% yield after purification by flash chromatography. The compound was further purified by recrystallization from toluene and obtained as an orange solid and characterized by IR and NMR spectroscopy and X-ray crystallography analysis.



45 **46**

Eq. 2.10. Ring-opening of compound 45

The intermediate, unfortunately, was not reactive under carbonylation conditions or toward alkyne insertion. Treatment of the compound with the Meerwein salt, however, results in the formation of the Fisher carbene complex **47** in 73% yield after purification by flash chromatography; single crystals were obtained by slow evaporation of a solution in toluene and CH_3CN. The complex was characterized by NMR spectroscopy and X-ray crystallography analysis (Fig. 2.4).



47

Eq. 2.11. Preparation of complex 47

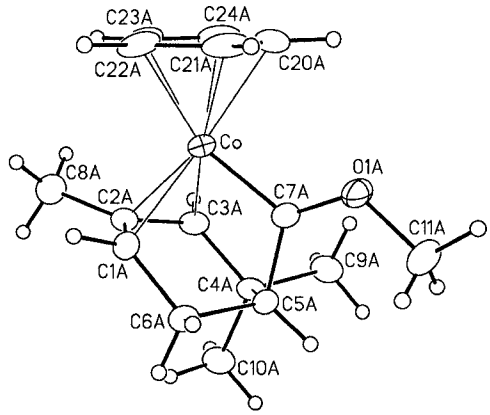
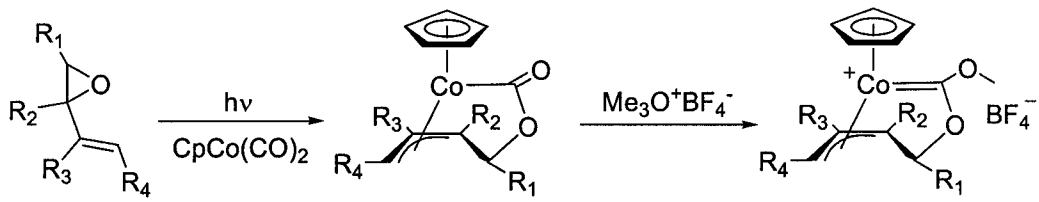


Fig. 2.4. X-ray structure of carbene complex 47

Similar complexes have been reported by Schobert and coworkers via the carbonylative ring opening of various vinyl epoxides and further treantment with the Meerwein salt (Sch. 2.14).[113]



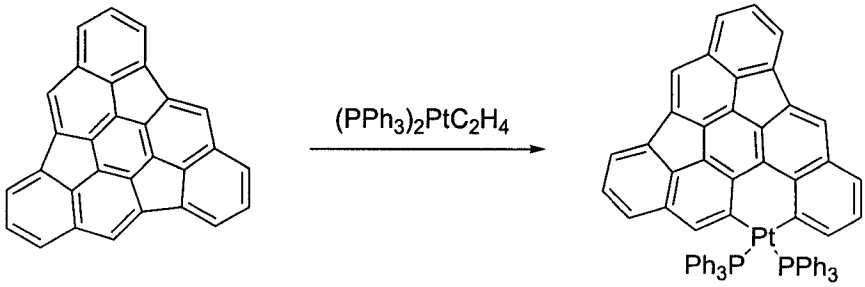
Sch. 2.14. Fisher carbene complexes from vinyl epoxides

No further conversion of the carbene complex could be induced and this line of investigation was thus abandoned.

4. Conclusion and Outlook

In conclusion, low valent cobalt complexes with labile ligands can be used to open the strained four-membered ring of pinene and related compounds under reasonably mild reaction conditions. Using the cyclopentadienyl ligand, the ring-opened products were unreactive toward carbonylation, although indenyl ligand analogues were more promising. Furthermore, the addition of conjugated carbonyl functionality enhances the selectivity of the carbonylation step, giving a ring-expanded product amenable for use in taxinine synthesis.

Unfortunately, there are still several hurdles to cross to optimize these processes. First, the carbonyl group must be removed to apply verbenone to the total synthesis of taxinine, which reduces the overall efficiency of the synthesis. Secondly, the reaction is both stepwise and stoichiometric in cobalt and has been done only on a laboratory scale. A catalytic version of this process is highly desirable and potential possibilities exist by using rhodium and possibly, other metal complexes. For example, $PtCl_2$ opens the cyclopropane rings even without a pre-coordination site (Sch. 2.1). It has also been shown by Rabideau and coworkers that $(PR_3)_2Pt(C_2H_4)$ can be used to open the five-membered ring of a fullerene subunit (Eq. 2.11).[114] The coordination abilities of alkene and carbon monoxide to platinum are comparable,[115, 116] which makes a catalytic cycle possible with platinum. Such pathways remain under investigation.

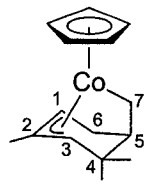


Eq. 2.12. C-C bond activation in a five-membered ring with Pt(0) complex

Part III. Experimental Part

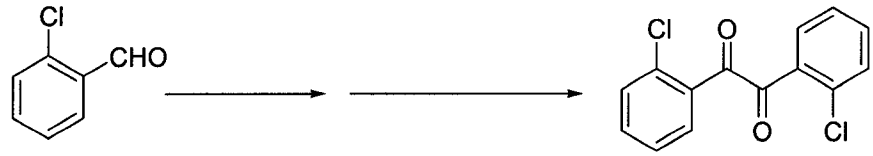
General Procedures. Manipulations of air sensitive compounds were performed under an argon atmosphere using standard Schlenk techniques or in a nitrogen-filled drybox. Toluene was distilled over sodium; 1,4-dioxane, benzene, diethyl ether and THF were distilled over Na/benzophenone; hexanes and pentane were distilled over K/benzophenone; CH_3CN and CH_2Cl_2 were distilled over CaH_2. 2-chlorobenzaldehyde and 2-bromobenzaldehyde were distilled under vacuum and stored under inert atmosphere; TMEDA was distilled over KOH pellets before use and stored under inert atmosphere. Fisher-Porter bottle and steel autoclave were used for carbonylation reactions. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Inova 300 MHz, 400 MHz, 500 MHz or Varian Mercury 400 MHz spectrometers. Chemical shifts are reported using the δ scale, referenced to residual protium in deuterated NMR solvents. High resolution mass spectrometry data were recorded on a Kratos MS-50 spectrometer by University of Alberta Mass Spectroscopy Laboratory, infrared spectroscopy were recorded on a Nicolet Magna 750 FTIR spectrometer and elemental analyses were performed by the University of Alberta Analytical and Instrumentation Laboratory. Compounds **21**,[62, 63] **35**,[117, 97] **38**,[118] **45**[112] were prepared according to literature procedures. Full X-ray structure reports for compounds **41**, **42**, **43**, **46,** and **47** are available from University of Alberta Department of Chemistry Structure Determination Laboratory (report numbers: jms0620, jms0621, jms0622,

jms0631 and jms0633). The numbering scheme for compounds **37**, **39**, **41**, **43**, **46**, and **47** follows the example shown below.



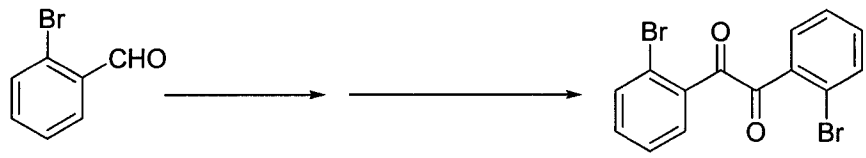
37

2,2'-Dichlorobenzil



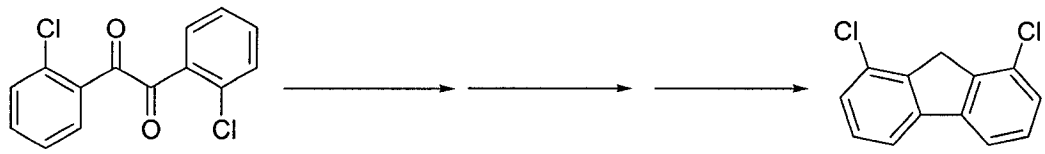
2-Chlorobenzaldehyde 23.03 g (164 mmol) was heated to reflux with KCN 2.07 g (31.8 mmol, ~20%) in a mixture of 30 mL EtOH and 20 mL H_2O for 1 h. The orange to dark red solution was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 three times. The combined extracts were washed with water and brine, dried over $MgSO_4$, and the solvent was removed under vacuum. The dark red oil residue was dissolved in 50 mL 80% acetic acid, then 8.10 g (101 mmol) NH_4NO_3 and 0.32 g (1.6 mmol, 2%) $Cu(OAc)_2 \cdot H_2O$ were added. The mixture was heated to reflux overnight, and then slowly cooled to room temperature to crystallize the product from the reaction mixture. More water was added and the mixture was cooled in an ice bath; the solid yellow product[47] was collected by vacuum filtration, washed with water and air dried. The yield was 17.80 g (63.8 mmol, 78%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (m, 2H), 7.58 (m, 2H), 7.47 (m, 4H).

2,2'-Dibromobenzil



2-Bromobenzaldehyde 30.67 g (168 mmol) was heated to reflux with KCN 2.20 g (33.8 mmol, 20%) in a mixture of 30 mL EtOH and 20 mL H_2O for 2 h. The orange to dark red solution was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 three times. The combined extracts were washed with water and brine, dried over $MgSO_4$, and the solvent was removed under vacuum after filtration. The dark red oil residue was dissolved in 30 mL 80% acetic acid, then 7.96 g (99.5 mmol) NH_4NO_3 and 0.67 g (1.66 mmol, 2%) $Fe(NO_3)_3 \cdot 9H_2O$ were added. The mixture was heated to reflux overnight, and then cooled to room temperature to crystallize the product. More water was added, and the mixture was cooled in an ice bath. The solid yellow product was collected by vacuum filtration, washed with water and air dried. The yield was 23.50 g (63.9 mmol, 76%) and the product[119] could be further purified by recrystallization from ethanol. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (m, 2H), 7.68 (m, 2H), 7.46 (m, 4H).

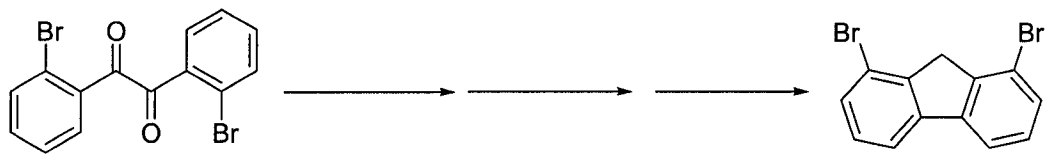
1,8-Dichlorofluorene



2,2'-Dichlorobenzil 4.37 g (15.7 mmol) was heated to reflux with 3.68 g KOH in 6 mL H_2O (~11 M) and 6 mL EtOH on a steam bath for 15 min. The dark red solution was cooled to room temperature, diluted with ice and acidified to pH 1-2 with concentrated HCl. The resulting oily product was extracted three times with diethyl ether and the combined extracts washed with water and brine, and then dried over $MgSO_4$. The solvent was removed under vacuum. Acetic acid (15 mL) was added into the sticky crude product, which was cooled in an ice bath, after which 45 mL concentrated H_2SO_4 was added dropwise. The resultant viscous solution was stirred for 3 h and then ice was added into the reaction mixture. The product precipitated out and was collected by vacuum filtration, washed with water, air dried. The filtrate was extracted with diethyl ether and the solvent was removed *in vacuo*. The residue was combined with the solid and analysed by ^{1}H NMR spectroscopy (Ac-d_6, 400 MHz): δ 7.89 (dd, J = 7.6, 1.0 Hz, 2H), 7.51 (td, J = 8.0, 0.4 Hz, 2H), 7.25 (dd, J = 8.0, 1.0 Hz, 2H), 5.01 (s, 1H). Without further purification, the crude acid was heated to reflux in a mixture of 1M NaOH and benzene overnight. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried and concentrated, diluted with hexane, and then filtered through a short silica

gel column eluted with hexane. 1.20 g (5.13 mmol, 32%) solid white product was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz) (ABC system) δ 7.66 (m, 2H), 7.46 (m, 2H), 7.32 (m, 2H), 3.93 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.86, 140.63, 131.23, 128.68, 127.33, 118.69, 36.34; HRMS (EI): calculated for $C_{13}H_8Cl_2$, 234.0003; found 234.0005.

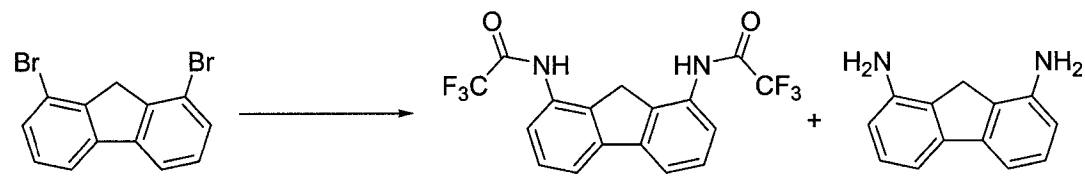
1,8-Dibromofluorene



2,2'-Dibromobenzil 3.04 g (8.26 mmol) was heated to reflux with 1.53 g KOH in 3 mL H_2O (~9 M) and 4.5 mL EtOH on a steam bath for 15 min. The dark red solution was cooled to room temperature, diluted with ice and acidified to pH 1-2 with concentrated HCl. The resulting oily product was extracted three times with diethyl ether and the combined extracts were washed with water and brine, dried over $MgSO_4$, the solvent was removed under vacuum. Acetic acid (15 mL) was added into the sticky product and, after cooling in an ice bath, 45 mL concentrated H_2SO_4 was added dropwise. The viscous solution was stirred for 3 h, after which ice was added into the reaction mixture and the precipitated product collected by vacuum filtration,

washed with water and air dried. The filtrate was extracted with diethyl ether and combined with the solid after evaporation of the solvent. The crude acid was heated to reflux in a mixture of 1M NaOH and benzene overnight. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried, concentrated, and filtered through a short silica gel column eluted with hexane. 1.85 g (5.7 mmol, 69%) solid white product was obtained. Further purification by recrystallization from hexane afforded a white crystalline compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 7.6 Hz, 2H), 7.46 (dd, J = 8.0, 0.8 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 3.76 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.87, 142.83, 130.50, 128.99, 120.33, 119.48, 40.57. HRMS (EI): calculated for $C_{13}H_8Br_2$, 323.8972; found 323.8975. Elemental analysis: calculated for $C_{13}H_8Br_2$, C, 48.19; H, 2.49; found C, 48.28; H, 2.44.

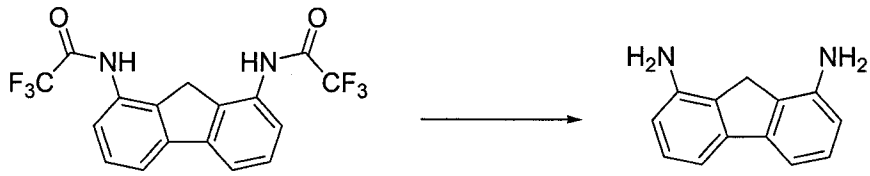
1,8-Bis(trifluoacetamido)fluorene



14 **15** (28%) **16** (14%)

1,8-Dibromofluorene **14** 1.00 g (3.09 mmol), CF_3CONH_2 2.96 g (26.1 mmol), K_2CO_3 4.26 g (30.8 mmol), and CuI 118 mg (0.62 mmol) were added into a resealable Schlenk tube, which was evacuated and back filled with argon. To this mixture was added ligand $\mathbf{L_1}$ ((±)-*trans*-1,2-N,N'-dimethylaminocyclohexane) 217 μL (~1.70 mmol) and 15 mL 1,4-dioxane via syringe. The mixture was heated at 110°C for 3 d, cooled to room temperature and the crude reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was washed with ethyl acetate, the combined organic layers were washed with water and brine, dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography eluted with hexane/ethyl acetate (10:1) to afford the white solid amide **15** (340 mg, 28%) and 1,8-diaminofluorene **16** (86 mg, 14%). Compound **15**: IR (microscope) 3252, 1706 cm^{-1}; ^1H NMR (Ac-d_6, 400 MHz) δ 10.27 (bs, 2 H), 7.88(d, J = 7.6 Hz, 2 H), 7.56 (dd, J = 7.6, 1.0 Hz, 2 H), 7.49 (dd, J = 7.6, 1.0 Hz, 2 H), 4.02 (s, 2 H); ^{13}C NMR (Ac-d_6, 100 MHz) δ 160.4 (q), 147.98, 142.36, 137.38, 133.39, 128.69, 124.47, 121.72 (q), 39.10; HRMS (EI): calculated for $C_{17}H_{10}O_2N_2F_6$, 388.0646; found 388.0646; Elemental analysis: calculated for $C_{17}H_{10}O_2N_2F_6$: C, 52.59; H, 2.60, N 7.22; found C, 52.36; H, 2.55; N, 7.33. Characterization data for compound **16** is given in the subsequent experimment.

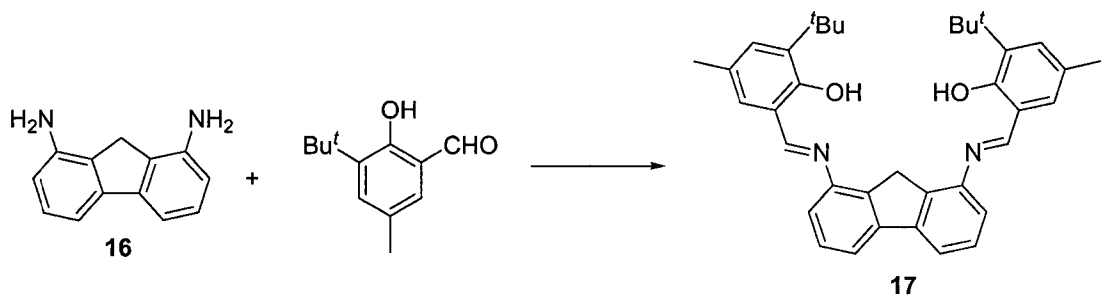
1,8-Diaminofluorene



15 **16**

Amide **15** 23 mg (0.059 mmol) was heated to reflux together with 62 mg K_2CO_3 in 2 mL MeOH and 2 mL H_2O for 2 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate; the organic layers were combined and washed with H_2O and brine, dried over $MgSO_4$, and the solvent was removed under vacuum to afford 10.0 mg of the solid product diamine **16** (0.051 mmol, 86%). IR (microscope) 3444, 3409, 3360, 3324. ^{1}H NMR ($CDCl_3$, 400M Hz) δ 7.25 (dd, J = 7.6, 1.2 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 6.67 (dd, J = 7.2, 1.2 Hz, 2H), 3.73 (bs, 4H), 3.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 100M Hz) δ 143.41, 142.81, 128.47, 127.15, 113.76, 111.51, 31.22. HRMS (EI): calculated for $C_{13}H_{12}N_2$ 196.1000; found 196.0997.

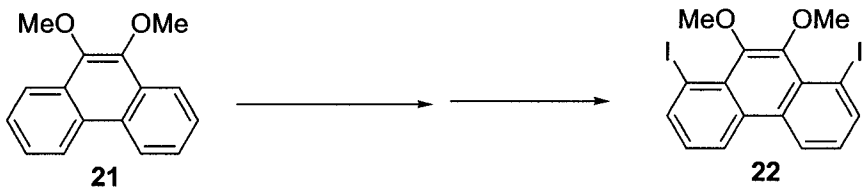
Diimine 17



16 **17**

In a Dean-Stark distillation apparatus, 10.0 mg (0.051 mmol) of amine **16** was heated to reflux with 30 mg aldehyde (3.1 equiv.) in 10 mL anhydrous EtOH for 2 h. Most of the solvent was removed in the Dean-Stark trap. The solution was further concentrated to 1-2 mL and cooled to room temperature to afford crystalline bisimine **17**, which was collected by vacuum filtration (14 mg, 50%). Extraction of the filtrate afforded additional, but less pure material. ^{1}H NMR ($CDCl_3$, 300M Hz) δ 13.79 (bs, 2H), 8.80 (s, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 1.8 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 1.5 Hz, 2H), 4.20 (s, 2H), 2.39 (s, 6H), 1.54 (s, 18H). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 163.73, 158.90, 145.54, 143.07, 137.88, 137.86, 131.96, 130.66, 128.61, 127.29, 119.03, 118.63, 116.28, 35.10, 33.70, 29.65, 20.92. HRMS (EI): calculated for $C_{37}H_{40}O_2N_2$ 544.3090; found 544.3077.

1,8-Diiodo-9,10-dimethoxyphenanthrene

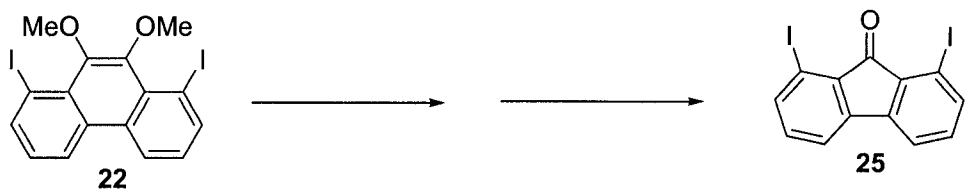


21 **22**

9,10-dimethoxyphenanthrene **21** 2.38 g (10 mmol) was dissolved in 30 mL dry hexanes and the solution was cooled in an ice bath. 9.6 mL ^{n}BuLi (2.5 M in hexanes, 24 mmol) followed by 3.0 mL TMEDA (20 mmol) were added slowly via syringe. The color of the reaction mixture changed over several minutes and a reddish-brown

precipitate formed after several hours. The reaction mixture was stirred for 24 h and then cooled in a dry ice-acetone bath and diluted with 30 mL anhydrous THF. A solution of 6.4 g (25.2 mmol) I_2 in 30 mL dry THF was added via canula over 10 minutes. The cooling bath was removed and the reaction mixture was warmed to room temperature and stirred for another 30 minutes. A solution of 2.0 g $Na_2S_2O_3$ in 20 mL H_2O was added and the mixture stirred for 1 h. The two layers were separated and the aqueous layer was extracted with ethyl acetate. All organic solutions were combined and washed with brine. The solution was dried over $MgSO_4$ and the solvents were removed after filtration to afford the crude product (4.80 g, 98% yield). Only the desired diiodide and monoiodide (~ 10 : 1 by integration of the CH_3O- in ^1H NMR spectrum) were observed as major products in the ^1H NMR spectrum. A pure sample of diiodide **22** was obtained by recrystallization from hexanes. ^1H NMR ($CDCl_3$, 400M Hz) δ 8.61 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 7.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 2H), 3.99 (s, 6H). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 145.46, 142.99, 130.10, 128.33, 126.79, 123.50, 85.31, 60.68. HRMS (EI): m/z calculated for $C_{16}H_{12}O_2I_2$, 489.8927, found 489.8927.

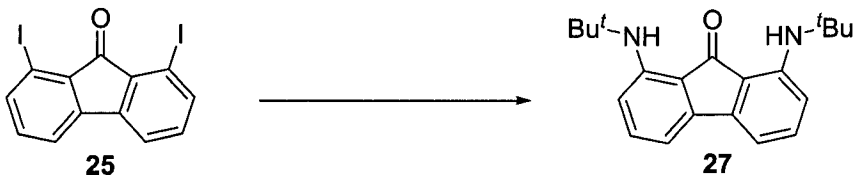
1,8-Diiodofluorenone



22 25

0.46 g Compound **22** was dissolved in 20 mL dry CH_2Cl_2, and cooled in an ice bath. BBr_3 (excess, 3 equiv.) was added via syringe and the reaction mixture was warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum. 10 mL 1,4-Dioxane and 10M NaOH was added. The reaction mixture was refluxed for 6 hours and the color of the solution turned dark and finally became yellow. Water was added into the reaction mixture and the solution was extacted with ethyl acetate, the organic layers were combined and washed with water, brine and dried over $MgSO_4$. Flash column chromatography with hexane/ethyl acetate (20 : 1) afforded the solid orange yellow product 1,8-diiodfluorenone **25** in low yield (~20%). IR(microscope) 1713.8 cm^{-1}. ^1H NMR ($CDCl_3$, 400M Hz) δ 7.76 (dd, J = 8.0, 0.8 Hz, 2H), 7.54 (dd, J = 7.2, 0.8 Hz, 2H), 7.19 (dd, J = 7.6, 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 189.72, 144.76, 141.17, 135.18, 133.39, 119.69, 91.93. HRMS (EI): calculated for $C_{13}H_6OI_2$ 431.8508, found 431.8506. Elemental analysis: calculated for $C_{13}H_6OI_2$ C, 36.14; H, 1.40; found C, 36.23; H, 1.42.

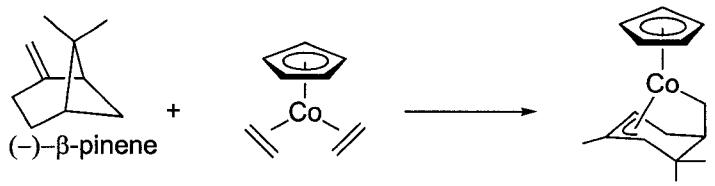
1,8-Di-tert-butylaminofluorenone



25 **27**

43.9 mg (0.1 mmol) 1,8-diiodofluorenone **25**, 2.7 mg (0.012 mmol) $Pd(OAc)_2$, 3.5 mg (0.008 mmol) IPr•HCl and 38 mg (0.34 mmol) KO^{t}Bu were added into a Schlenk flask. The flask was sealed, evacuated and then filled with argon. 30 μL ^{t}BuNH$_2$ and 1.5 mL toluene was added via syringe. The reaction mixture was heated at 60 °C for 2 hours, and then was cooled to room temperature. The reaction mixture was loaded on to the silica gel column directly and eluted with hexane/ ethyl acetate to afford 1,8-di-tert-butylaminofluorenone **27** as a solid red compound in modest yield. IR (CH_2Cl_2 microscope): 3346, 1644 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400M Hz) δ 7.21 (bs, 2H), 7.16 (dd, J = 8.4, 7.2 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.72 (dd, J = 7.2, 0.8 Hz, 2H), 1.49 (s, 18H). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 196.67, 147.14, 143.99, 134.53, 115.25, 114.69, 108.06, 50.75, 29.98. HRMS (EI): calculated for $C_{21}H_{26}ON_2$ 322.2045, found 322.2048.

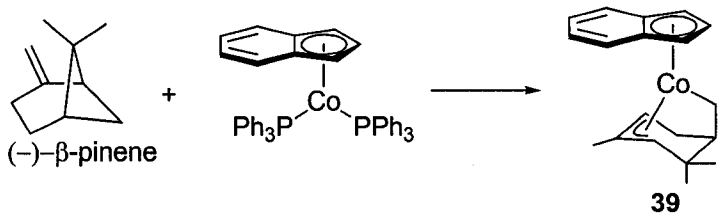
Complex 37



37

In the drybox, 106mg (0.78 mmol) (-)-β-pinene and 158 mg (0.88 mmol) $CpCo(C_2H_4)_2$ **35** were dissolved in 5 mL toluene in a Schlenk tube. The tube was sealed and heated at 100 °C for 6 h, then cooled to room temperature. The solution was exposed to the air and the solvent was removed under vacuum. The residue was purified by flash chromatography eluted with hexane to obtain a red oil compound 168 mg (0.65 mmol, 83%). ^{1}H NMR (C_6D_6, 400M Hz) δ 4.37 (s, 5H, C_5H_5), 4.32 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H, H_1), 3.88 (t, J = 1.8 Hz, 1H, H_3), 2.47 (ddd, J = 6.8, 3.6, 2.8 Hz, 1H, H_7), 2.02 (dd, J = 6.8, 2.0 Hz, 1H, H_7), 1.65 (s, 3H, CH_3), 1.16 (ddt, J = 13.2, 3.6, 2.0 Hz, 1H, H_6), 0.96 (s, 3H, CH_3), 0.95 (dt, J = 13.2, 4.0 Hz, 1H, H_6), 0.90 (m, 1H, H_7), 0.82 (s, 3H, CH_3). ^{13}C NMR (C_6D_6, 100M Hz) δ 91.6 (C_2), 84.3 (C_5H_5), 75.1 (C_3), 64.6 (C_1), 51.4 (C_5), 39.7 (C_4), 33.8 (C_6), 27.9 (CH_3), 26.7 (CH_3), 26.3 (CH_3), 25.6 (C_7). HRMS (EI): calculated for $C_{15}H_{21}Co$ 260.0975; found 260.0978.

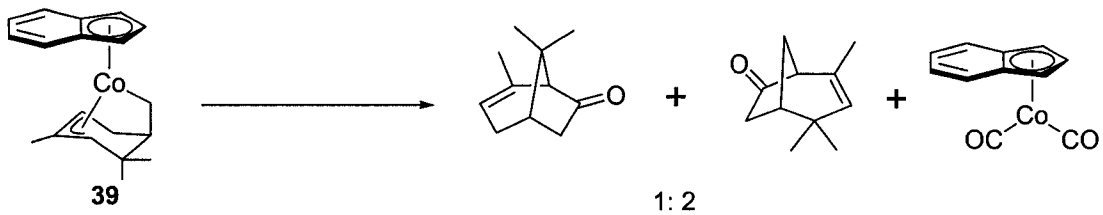
Complex 39



39

In the drybox, 100μL (0.64 mmol) (-)-β-pinene and 363 mg (0.52 mmol) $IndCo(PPh_3)_2$ **38** were dissolved in 10 mL toluene in a Schlenk tube. The tube was sealed and heated to 110 °C for 3 h, then cooled to room temperature. The solution was exposed to the air, the solvent was removed under vacuum, and the residue was purified by flash chromatography eluted with hexane to obtain a red oil compound 68 mg (0.22 mmol, 42%). ^1H NMR (C_6D_6, 400M Hz) δ 7.25-7.30 (m, 1H, Ar-H), 7.17-7.21 (m, 1H, Ar-H), 6.88-6.94 (m, 2H, Ar-H), 4.78 (ddd, J = 2.8, 1.6, 0.8 Hz, 1H, Ar-H), 4.74 (t, J = 3.0 Hz, 1H, Ar-H), 4.63 (ddd, J = 2.8, 1.6, 0.8 Hz, 1H, Ar-H), 3.92 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H, H_1), 3.38 (t, J = 1.8 Hz, 1H, H_3), 2.50 (ddd, J = 6.8, 4.8, 2.4 Hz, 1H, H_7), 2.11 (dd, J = 4.8, 2.0 Hz, 1H, H_7), 1.78 (s, 3H, CH_3), 0.75 (s, 3H, CH_3), 0.71 (app. q, J = 2.8 Hz, 2H, H_6), 0.67 (m, 1H, H_5), 0.63 (s, 3H, CH_3). ^{13}C NMR (C_6D_6, 100M Hz) δ 125.0, 124.5, 124.4, 124.3, 102.2, 101.7, 91.3 (C_2), 86.7, 78.5, 78.4, 76.5 (C_3), 65.5 (C_1), 51.7 (C_5), 39.3 (C_4), 33.0 (C_6), 29.9 (C_7), 27.4 (CH_3), 25.6 (CH_3), 25.2 (CH_3). HRMS (EI): calculated for $C_{19}H_{23}Co$ 310.1132; found 310.1129.

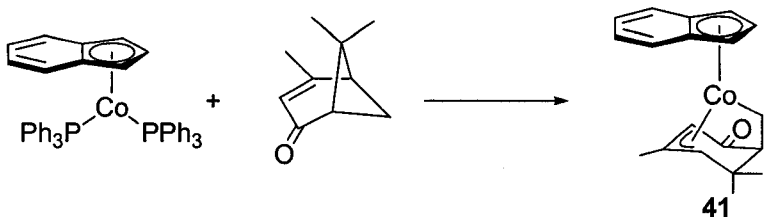
Carbonylation of 39



39 1: 2

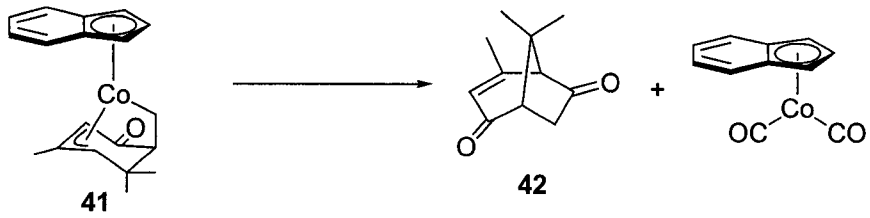
A sample of the complex **39** was dissolved in toluene in a Fisher-Porter pressure bottle in the drybox. The bottle was sealed and flushed with CO three times; then pressurized with CO to 40 psi. The bottle was heated at 80 °C for 1 d, cooled to room temperature, and the pressure was released. The bottle was brought into the drybox and the solvents were removed under vacuum; the residue was extracted with pentane and filtered through celite. The solvent was removed under vacuum. Analysis of the residue by ^{1}H NMR spectroscopy showed that the only products are the two organic ketone isomers **31** and **32** and $IndCo(CO)_2$. The two organic compounds were not isolated, but were compared to the ^{1}H NMR spectrum of an authentic sample mixture obtained from West group and the reported literature data. Ratio of the two organic products was about 1 : 2 by integration.

Complex 41



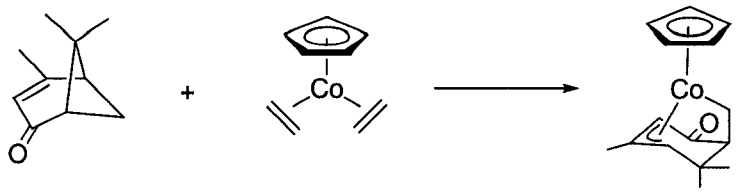
In the drybox, 29.5 mg (0.20 mmol) verbenone and 161 mg (0.23 mmol) $IndCo(PPh_3)_2$ were dissolved in about 10 mL toluene in a Schlenk tube. The tube was sealed and heated at 110 °C for about 3 h. The solution was cooled to room temperature. The solvent was removed under vacuum and the residue was purified by flash column chromatography eluted with 10:1 hexane/ethyl acetate to give 30.4 mg dark red product (0.094 mmol, 48%). An X-ray quality crystal was obtained from diethyl ether at -35 °C. IR (CH_2Cl_2 film): 1668 cm^{-1}. ^1H NMR (C_6D_6, 400M Hz) δ 7.00-7.02 (m, 1H), 6.93-6.96 (m, 1H), 6.77-6.81 (m, 2H), 4.76 (ddd, J = 2.8, 1.6, 1.2 Hz, 1H), 4.51 (ddd, J = 2.4, 1.4, 1.0 Hz, 1H), 4.34 (t, J = 2.8 Hz , 1H), 3.88 (t, J = 1.8 Hz, 1H, H_1), 3.44 (t, J = 1.8 Hz, 1H, H_3), 1.85 (dd, J = 6.4, 2.0 Hz, 1H, H_7), 1.66 (s, 3H, CH_3), 1.58 (dd, J = 6.4, 2.8 Hz, 1H, H_7), 1.09 (app. quint, J = 2.0 Hz, 1H, H_5), 0.66 (s, 3H, CH_3), 0.51 (s, 3H, CH_3). ^{13}C NMR (C_6D_6, 100M Hz) δ 202.7 (C=O), 126.2, 126.0, 125.1, 124.2, 102.1, 101.6, 98.6, 87.6, 77.8, 77.7, 76.0 (C_3), 63.7 (C_1), 61.9 (C_5), 42.0 (C_4), 28.0 (CH_3), 25.1 (CH_3), 23.7 (CH_3), 7.28 (C_7). HRMS (EI): calculated for $C_{19}H_{21}OCo$ 324.0924; found 324.0917. Elemental analysis: calculated for $C_{19}H_{21}OCo$, C% 70.37, H% 6.53; found C% 70.25, H% 6.58.

Compound 42



In the drybox, 127 mg (0.39 mmol) complex **41** was dissolved in 5 mL toluene and placed in a Fisher-Porter bottle. The bottle was sealed and taken out of the drybox, flushed with 40 psi CO, and pressurized with CO to 40 psi. The solution was heated at 80 °C for 1 day, then cooled to room temperature and the pressure was released. Still under inert atmosphere, 110 mg I_2 in 5 mL toluene was added quickly. The solution was stirred for another 30 min under inert atmosphere at room temperature. The solvent was removed under vacuum and the residue was purified by flash column chromatography eluting with CH_2Cl_2 and then 5 : 1 hexane/ethyl acetate, giving a white solid product, 58 mg (0.33 mmol, 83%). An X-ray crystal was obtained by slow evaporation of a hexane/diethyl ether solution at room temperature. IR (CH_2Cl_2): 1678, 1746 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400M Hz) δ 5.91 (m, 1H, H_2), 2.67 (ddd, J = 18.4, 7.2, 1.2 Hz, 1H, H_6), 2.67 (bs, 1H, H_4), 2.62 (dt, J = 7.2, 1.2 Hz, 1H, H_7), 2.25 (d, J = 18.8 Hz, 1H, H_6), 2.02 (d, J = 1.2 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 208.7 (C=O), 200.2 (C=O), 156.3 (C_3), 125.4 (C_2), 66.7 (C_4), 55.9 (C_7), 46.2 (C_8), 34.9 (C_6), 26.0 (CH_3), 23.5 (CH_3), 20.0 (CH_3). HRMS (EI): calculated for $C_{11}H_{14}O_2$ 178.0994; found: 178.0995.

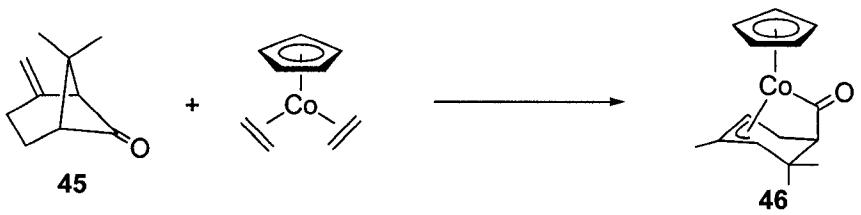
Complex 43



43

In the drybox, 120 mg (0.8 mmol) verbenone and 155 mg (0.86 mmol) $CpCo(C_2H_4)_2$ were dissolved in 5 mL toluene in a Schlenk tube. The tube was sealed and heated at 80 °C for 3 h. The solution was exposed to air and the solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting with 5 : 1 hexane /ethyl acetate to afford the red product, 189 mg (0.69 mmol, 86%). An X-ray crystal was obtained from pentane at -35 °C. IR (CH_2Cl_2 film): 1669 cm^{-1}. ^1H NMR ($CDCl_3$, 400M Hz) δ 4.77 (s, 5H, C_5H_5), 4.33 (t, J = 2.0 Hz, 1H, H_1), 4.22 (t, J = 1.6 Hz, 1H, H_3), 2.11 (dd, J = 6.4, 2.0 Hz, 1H, H_7), 1.46 (dd, J = 6.4, 2.8 Hz, 1H, H_7), 1.07 (app. quint., J = 2.0 Hz, H_5), 2.16 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.79 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100M Hz) δ 205.1 (C_6), 99.3 (C_2), 84.8 (C_5H_5), 75.1 (C_1), 62.5 (C_3), 60.6 (C_5), 41.9 (C_4), 28.0 (CH_3), 25.5 (CH_3), 25.0 (CH_3), 0.22 (C_7). HRMS (EI): calculated for $C_{15}H_{19}OCo$ 274.0768, found 274.0768. Elemental analysis: calculated for $C_{15}H_{19}OCo$, C% 65.56, H% 7.03; found C% 65.64, H% 6.88.

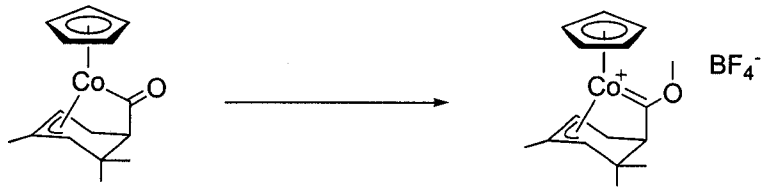
Complex 46



45 46

In the drybox, 340 mg (2.27 mmol) ketone **45** and 403 mg (2.24 mmol) $CpCo(C_2H_4)_2$ were dissolved in 10 mL toluene in a Schlenk tube. The tube was sealed and heated at 60 °C for 6 h. The solution was cooled to room temperature and exposed to air; the solvent was removed under vacuum. The residue was purified by flash chromatography eluting with hexane and then 10 : 1 hexane/ethyl acetate to give the oily lemon color product, 495 mg (1.80 mmol, 80%). An X-ray quality crystal was obtained from toluene at -35 °C. IR (microscope): 1672 cm^{-1}. ^1H NMR (C_6D_6, 400M Hz) δ 4.54 (s, 5H, C_5H_5), 4.37 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H, H_1), 4.03 (t, J = 1.8 Hz, 1H, H_3), 1.60 (s, 3H, CH_3), 1.55-1.57 (m, 1H, H_5), 1.03 (dt, J = 14.0, 4.4 Hz, 1H, H_6), 0.91 (s, 3H, CH_3), 0.63 (s, 3H, CH_3), 0.57 (d, J = 14.4 Hz, 1H, H_6). ^{13}C NMR (C_6D_6, 100M Hz) δ 250.6 (C_7), 93.1 (C_2), 88.2 (C_5H_5), 76.1 (C_3), 74.2 (C_5), 65.3 (C_1), 34.3 (C_4), 28.8, 27.3, 26.9, 23.2. HRMS (EI): calculated for $C_{15}H_{19}OCo$ 274.0768; found 274.0765. Elemental analysis: calculated for $C_{15}H_{19}OCo$, C% 65.59, H% 6.98; found C% 65.56, H% 7.03.

Compex 47



47

In the drybox, 168 mg (0.61 mmol) complex and 180 mg (1.2 mmol) of the Meerwein salt were added into a Schlenk flask. The flask was taken out of the drybox, 10 mL dry and degassed CH_2Cl_2 was added via cannula. The solution was stirred under argon at room temperature for 20 h and then loaded directly onto silica gel column and eluted with CH_2Cl_2, then 3 : 1 CH_2Cl_2/CH_3CN to obtain 168 mg (0.45 mmol, 73%) of the solid product **47**. An X-ray quality crystal was grown by slow evaporation of a toluene/acetonitrile solution under argon. ^1H NMR (Ac-d_6, 400M Hz) δ 5.61 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H, H_1), 5.40 (app. t, J = 1.8 Hz, 1H, H_3), 5.31 (s, 5H, C_5H_5), 4.59 (s, 3H, CH_3O), 2.61 (app. q, J = 1.6 Hz, 1H, H_5), 2.16 (s, 3H, CH_3), 1.93 (dt, J = 15.2, 4.4 Hz, 1H, H_6), 1.66 (d, J = 15 Hz, 1H, H_6), 1.05 (s, 3H, CH_3), 1.03 (s, 3H, CH_3). ^{13}C NMR (Ac-d_6, 100M Hz) δ 324.5 (C_7), 100.8 (C_2), 90.4 (C_5H_5), 85.3 (C_3), 75.9 (C_1), 68.5 (CH_3O), 41.5 (C_4), 30.3 (C_6), 28.7 (CH_3), 25.9 (CH_3), 24.5 (CH_3). HRMS (ESI): calculated for $C_{16}H_{22}OCo$ 289.0997; found 289.0994.

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