# SYNTHESIS OF NOVEL PHOSPHINE LIGANDS

by

Xuedong Dai

B.S., University of Science and Technology of China
(1993)

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the
Degree of

Master of Science in Chemistry

at the

Massachusetts Institute of Technology

September 1995



Signature of Author .....
Department of Chemistry
July 24, 1995

Certified by .....
Professor Scott C. Virgil
Thesis Supervisor

Accepted by .....
Dietmar Seyferth
Chairman, Departmental Committee
on Graduate Students

# SYNTHESIS OF NOVEL PHOSPHINE LIGANDS

by

Xuedong Dai

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the
Degree of Master of Science in Chemistry

ABSTRACT

Several novel phosphorus-containing atropisomeric ligand systems were synthesized and evaluated.

The first part is the study on the synthesis of a 2'-*tert*-butyl-6'-(diphenylphosphino)-phenyl-4-methylbenzenesulfonamide system (**1**). The "directed ortho metalation" methodology was found effective to introduce the diphenylphosphino group to the benzene ring. The atropisomeric stability of **1** was studied by molecular mechanics calculations.

A 3-aryl-4(3*H*)-quinazolinone ligand system (**2**) is proposed in the second part. 2-Methyl-3-(6'-methyl-2'-diphenylphosphinophenyl)-4(3*H*)-quinazolinone was synthesized in a good yield (77%). Resolution of this ligand was achieved with (-)-di-$\mu$-chloro-bis[(*S*)-dimethyl(1-phenylethyl)aminato-$C^2$, *N*]dipalladium(II). The absolute configuration of (*R*)-(-)-**2a** was determined by a single crystal X-ray study of the palladium complex (*S*, *R*)-**28**.

Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

## Acknowledgments

I am indebted to my advisor Scott C. Virgil, for his support and guidance. His encouragement and insightful comments have been invaluable throughout my first two years at MIT. His original ideas, broad scope of chemistry knowledge and love of science are constant inspirations to me.

The members of my research group have created a pleasant and friendly working environment. Edcon Chang offered me a lot of help with both my research and English writing. I have also learned a great deal from Dan Allen, Jeff Eckert, Kristin Rosner, Paige Mahaney and Rebecca Carazza. I am grateful to all of them.

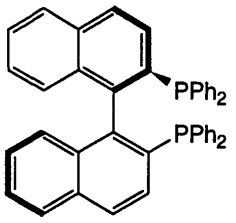
I thank Professor Glenn Berchtold, Frederick Greene, Gregory Fu, Stephen Buchwald, Rick Danheiser and Daniel Kemp for their advice and help.

At last, I feel very lucky to have friends like Zhao Xiaohong, Jeff Song, Ke Tao, Ed Wang, Pei Zhonghua and Bain Chin, etc. Their friendship and support have cheered up my life and study in Boston.

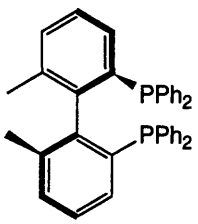
## Table of Contents

# Introduction

Asymmetric catalysis is one of many fascinating fields in modern organic chemistry. Well-designed chiral catalysts rival natural enzymes in creating chiral environments for stereoselective synthesis.[1] The chiral organic ligand is an essential part of these compact molecular catalysts in differentiating enantiotopic atoms, groups, and faces of a variety of achiral and some enantiomeric molecules. The chirality of most ligands derives from configurationally stable stereogenic centers (such as carbon, phosphorus, and sulfur, etc.). However, some ligands devoid of chiral centers derive their chirality from restricted bond rotation or molecular overcrowding. The most popular ligands of this type are the binaphthyl or biaryl atropisomers, such as BINAP and BIPHEMP.

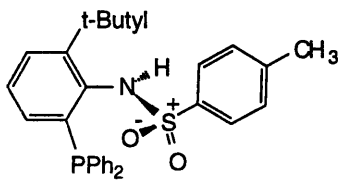



**BINAP**

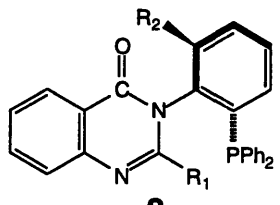



**BIPHEMP**

In the current study, our goal is to design new classes of phosphorus-containing atropisomerically chiral ligands (**1** and **2**) which could be easily synthesized and would exhibit desirable catalytic properties in catalytic asymmetric reactions, such as hydrosilylation of olefins.




**1**

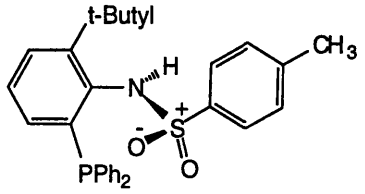



**2**

# Chapter 1. Synthetic Plan for Sulfonamide Ligand

## Introduction

In this project, we intended to synthesize system **1**, in which the diphenylphosphino ($PPh_2$) group and another large *ortho* substituent such as the *tert*-butyl group might block the rotation of the $C_{aryl}$–N bond and make compound **1** a resolvable atropisomeric phosphine ligand. The phosphorus atom would provide a binding site for the metal, and after deprotonation, the nitrogen or one of the sulfonamide oxygens might serve as another binding site.

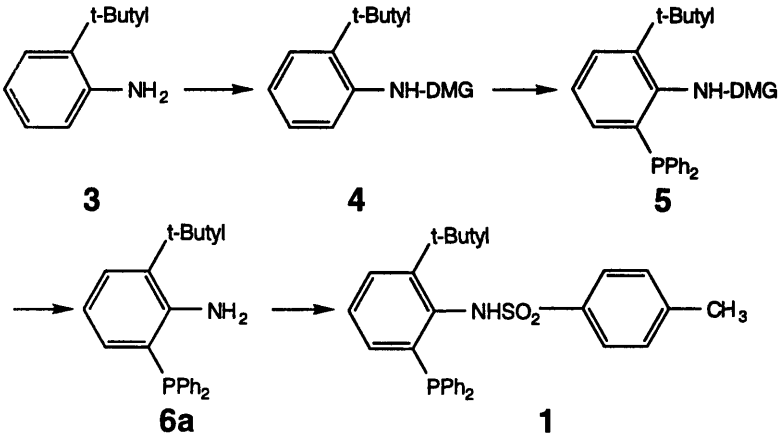



**1**

The proposed ligand **1** is a polysubstituted aromatic compound. With three bulky substituents adjacent to each other on one benzene ring, this severe crowding of this system creates a demanding challenge to traditional synthetic methods like electrophilic aromatic substitution,[2] which often suffers from harsh conditions and formation of regio-isomers. In our search for a better synthetic strategy, the "directed ortho metalation" methodology[3] is discovered to be very effective in introducing the diphenylphosphino group to the benzene ring.

The synthetic outline is shown in Scheme 1.

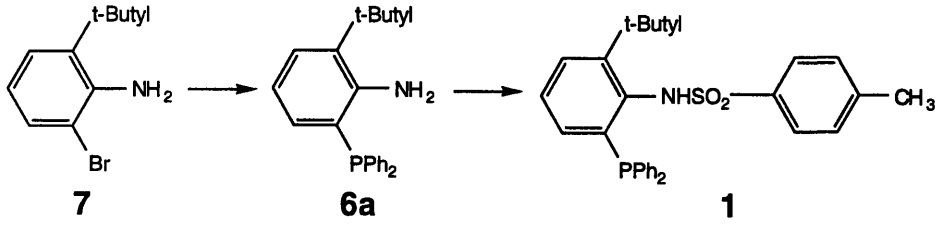
**Scheme 1**




First, a suitable directed metalating group (DMG) would be introduced to the starting material 2-*tert*-butylaniline (**3**). Lithiation of DMG-aniline **4** followed by addition of electrophile ($PPh_2Cl$) would give *ortho*-substituted diphenylphosphino compound **5**. Removal of DMG and introduction of a *p*-toluenesulfonyl group would yield the desired ligand 2'-*tert*-butyl-6'-(diphenylphosphino)-phenyl-4-methylbenzenesulfonamide (**1**).

An alternative route to compound **1** without using a DMG would be to convert compound **7** directly to **6** by Cooper's method[4] (Scheme 9, pp. 12), and then couple the *p*-toluenesulfonyl group with **6** to give the final product **1** (Scheme 2).

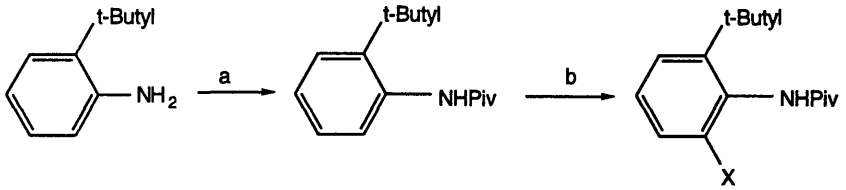
**Scheme 2**



## Results and Discussion

Trimethylacetyl (pivaloyl) and *tert*-butoxycarbonyl (*t*-BOC) groups are effective "directed metalating groups" (DMG) for ortho functionalization on the aromatic ring according to the literature.[3,5] The pivaloyl group was chosen as the first DMG in our initial synthetic route to **1** (Scheme 1 and Scheme 3).

**Scheme 3**




**3** **4a** **5a** (X = $PPh_2$) **5b** (X = I) **5c** (X = Br)

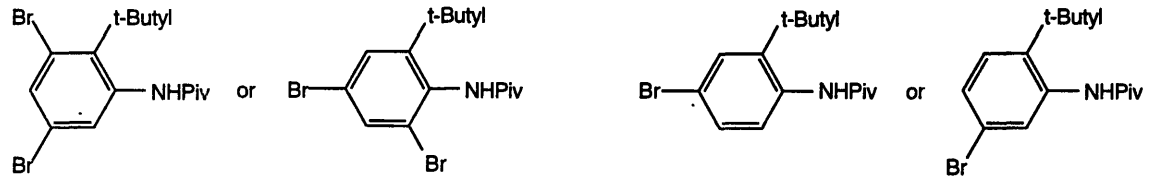
Conditions:
a: PivCl, ethyl acetate-$Na_2CO_3$/$H_2O$, rt, 20h (52%); b: i. 2.2 equiv. *n*-BuLi, ether, 0°C to rt; ii. 1.2 equiv. $PPh_2Cl$, 0°C to rt (**5a**, 47%, Table I, Run 7); or 1.2 equiv. $I_2$, 0°C to rt (**5b**, 80%, Table I, Run 5)

Amide **4a** was obtained in a 37g scale from the reaction of aniline **3** and pivaloyl chloride in a biphasic system of ethyl acetate and aqueous sodium carbonate. The proper reaction conditions for the ortho metalation of **4a** were discovered by many trial-and-errors (Table I).

**Table I**

| Run | Lithium reagent (2.2 equiv.) | solvent | temperature (°C) | electrophile (1.2 equiv.) | product | (yield)· |
|---|---|---|---|---|---|---|
| 1 | *n*-BuLi | THF | -78 to 0 | NBS | **5d** | (42%) |
| 2 | *n*-BuLi / TMEDA | THF | -78 to 0 | NBS | **5e** | (10%) |
| 3 | *s*-BuLi / TMEDA | THF | -78 to 0 | NBS | No product isolated | — |
| 4 | *t*-BuLi | ether | -78 | NBS | **5e** | (33%) |
| 5 | *n*-BuLi | ether | 0 to rt | $I_2$ | **5b** | (80%) |
| 6 | *t*-BuLi | ether | -10 | $I_2$ | **5b** | (50%) |
| 7 | *n*-BuLi | ether | 0 to rt | $PPh_2Cl$ | **5a** | (47%) |

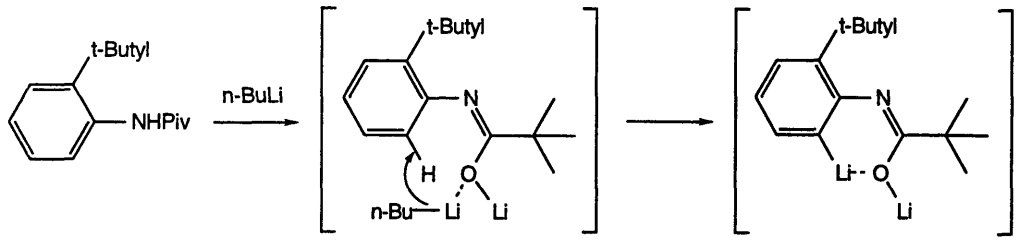
In runs 1–4, *N*-bromosuccinimide (NBS) was used as an electrophile in the model study on ortho metalation reactions. The reactions (except for run 3) yielded t not the desired product **5c**, but compound **5d** or **5e** which were products of the electrophilic substitution on the aromatic ring by NBS. The structural determination of compounds **5d** and **5e** was based on $^1$H NMR analysis. No effort was made to differentiate the two isomers of **5d** and **5e**.




**5d** **5e**

In the ortho lithiation of *N*-pivaloylaniline **4a**, the amide oxygen would serve as a binding site for a second equivalent of lithiating agent (*n*-BuLi).[5a, 6] Coplanarity of the deprotonated pivaloyl group with the aromatic ring is probably important in facilitating regiospecific protophilic attack of *n*-BuLi on the *ortho*-hydrogen to form the dilithio intermediate **8** (Scheme 4). High temperature might favor the coplanarity and the formation of ortho metalation products.

**Scheme 4** (Mechanism of ortho metalation reaction)

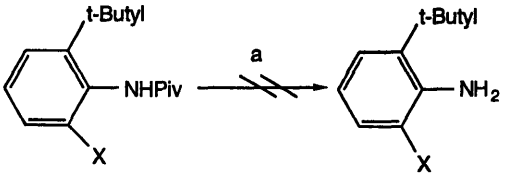



**4a** **8**

Thus, in run 5–7, the higher temperature (0°C to room temperature) and the less reactive electrophile ($I_2$ or $PPh_2Cl$) yielded only desired *ortho* substituted isomers (**5a** or **5b**) in good yield.

Despite literature precedents[5a, 5b], the removal of pivaloyl group in **5a** was very difficult (Scheme 5). Concentrated HCl, NaOH aqueous solution (from 3*N* to 12*N*) and even molten KOH had no effect on the amide. When $H_2SO_4$ was used, no reaction occurred if the concentration of $H_2SO_4$ was lower than 5*M* (Scheme 5); if the concentration was higher than 5*M*, ammonium salt **9** was obtained (Scheme 6).

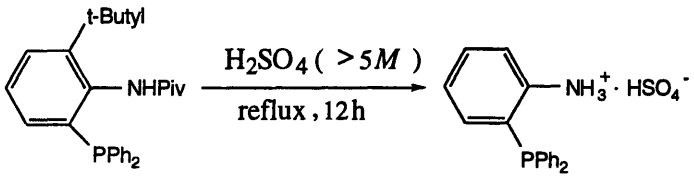
**Scheme 5**




**5a** (X = $PPh_2$) **6a** (X = $PPh_2$)
**5b** (X = I) **6b** (X = I)

Conditions:
a: 12*N* HCl, reflux, 24h; or NaOH/$H_2O$, relux, 24h; or melted KOH, 12h; or $H_2SO_4$ (<5*M*), reflux, 24h.

**Scheme 6**



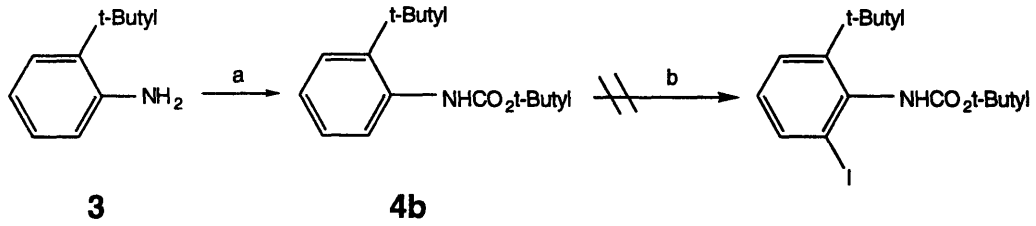

**5a** **9**

One possible explanation for these results could be that the carbonyl group of the amide of **5a** was surrounded by bulky *t*-butyl and $PPh_2$ groups which prevented nucleophile ($OH^-$ or $H_2O$) from attacking the carbonyl group. Sulfuric acid of higher concentration could cleave the aryl *tert*-butyl group by protonation at the aromatic carbon bearing the *tert*-butyl group (*ipso* substitution)[7]. Without the hindrance from *tert*-butyl group, the subsequent hydrolysis of the amide group proceeded in the acidic conditions to afford **9**.

Under the conditions in Scheme 5, the removal of the pivaloyl group of **5b** also failed because of the bulky *ortho* substituents (*tert*-butyl and iodo groups).

*tert*-BOC group and toluenesulfonamide group were also used as the DMG's (Scheme 7 and 8). *tert*-BOC group is more electrophilic than pivaloyl group and would be easier to remove after the ortho lithiation and substitution. Alternatively, the toluenesulfonamido group which is the required group in the target molecule (**1**) was investigated as the DMG.[6]

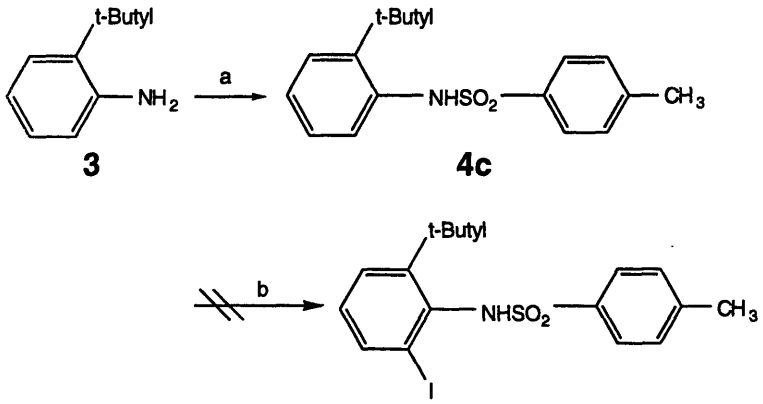
**Scheme 7**




**3** **4b**

Conditions:
a: 1.1 equiv. $(t\text{-BOC})_2O$, THF, reflux, 90h (76%); b: conditions of Run 1 to 7 in Table I ($I_2$ as the electrophile)

**Scheme 8**

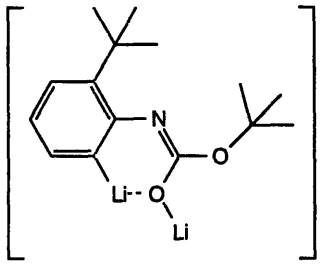



**3** **4c**

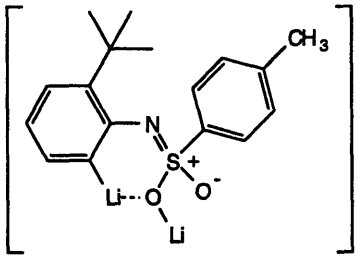
Conditions:
a: 1.2 equiv. *n*-BuLi, 1.2 equiv. *p*-toluenesulfonyl chloride, ether (55%); b: conditions of Run 1 to 7 in Table I ($I_2$ as the electrophile)

However, under the reaction conditions of Run 1–7 in Table I using iodine as the electrophile, no ortho metalation product was obtained from compound **4b** and **4c**. In previous "directed ortho metalation" work[5,6], where there was no bulky *ortho*-substituent next to *tert*-BOC or *p*-toluenesulfonamido group, no significant problem was encountered

by using the above conditions. The bulky *tert*-butyl group might exert some steric or electronic effect on the *tert*-BOC and the *p*-toluenesulfonamido group to prevent the formation of intermediates **10** and **11**.



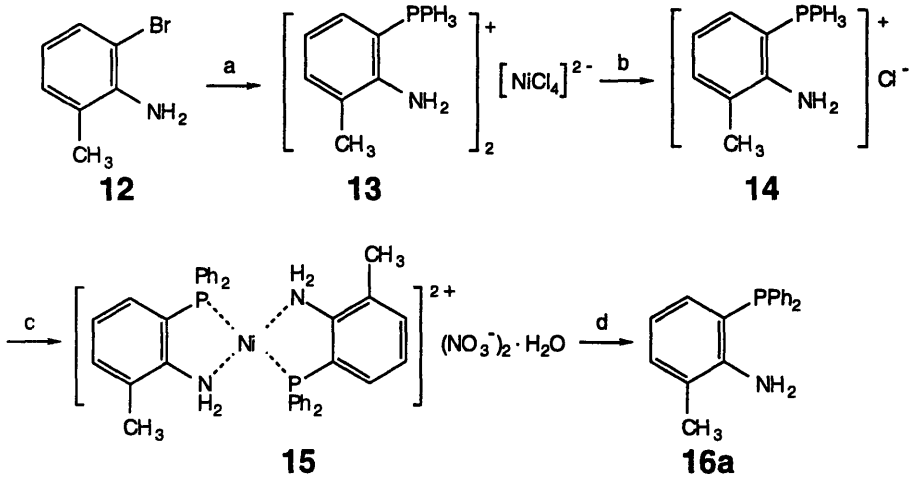
**10**



**11**

While the search for other effective DMG's continued, another strategy for making compound **6a** was investigated. Cooper's group used the following method (Scheme 9) for the synthesis of (2-amino-3-methylphenyl)-diphenylphosphine (**16a**).[4b]

**Scheme 9**



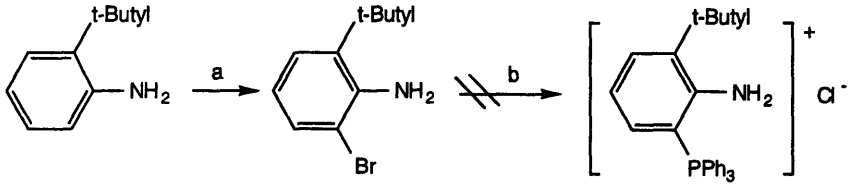
Conditions:
a: $PPh_3$, $NiCl_2$, 200°C; b: $H_2O$; c: i. Na, naphthalene; ii. AcOH then $Ni(NO_3)_2{\cdot}6H_2O$;
d: $H^+/C_6H_6$-$H_2O$.

Reaction of 2-bromo-6-methylaniline (**12**) with triphenylphosphine and nickel(II) chloride at 200°C afforded nickel complex **13**. Careful acid hydrolysis gave phosphonium salt **14**. Reduction of **14** with sodium naphthalenide, acidification, and treatment with nickel nitrate(II) hexahydrate gave nickel complex **15**. Heating the benzene solution of **15** to reflux with aqueous HCl and benzene afforded the free ligand **16a** (compound **16a** was

used as a starting material in the second project (Scheme 2, Chapter 2)). After optimization, the yield was improved to 84% from **14** (reported yield:[4b] 39%).

When the method was applied to 2-bromo-6-*tert*-butylaniline (**7**), which was obtained from the ortho bromination of 2-*tert*-butylaniline (**3**) in 46% yield (reported yield:[8] 41%, Scheme 10), the *tert*-butyl group did not survive the high temperature (150 - 250°C) necessary for the formation of tetra-arylphosphonium salt (**17**)[9]. Some compounds lacking the *tert*-butyl group were isolated instead.

**Scheme 10**




**3** **7** **17**

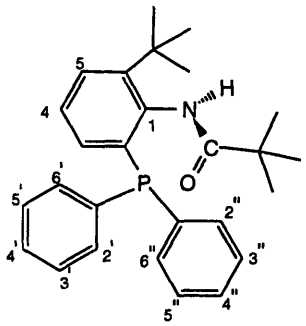
Conditions:
a: 1.0 equiv. NBS, benzene, rt (46%); b: $PPh_3$, $NiCl_2$, 200°C.

After the problems with the synthesis of compound **1**, it was necessary to reevaluate this system. The difficulty to removing the pivaloyl group from compounds **5a** and **5b** came from the highly congested nature of these systems. It could be conceived that even if the pivaloyl group were removed, it would not be easy to introduce a group larger than pivaloyl group into the amino position.

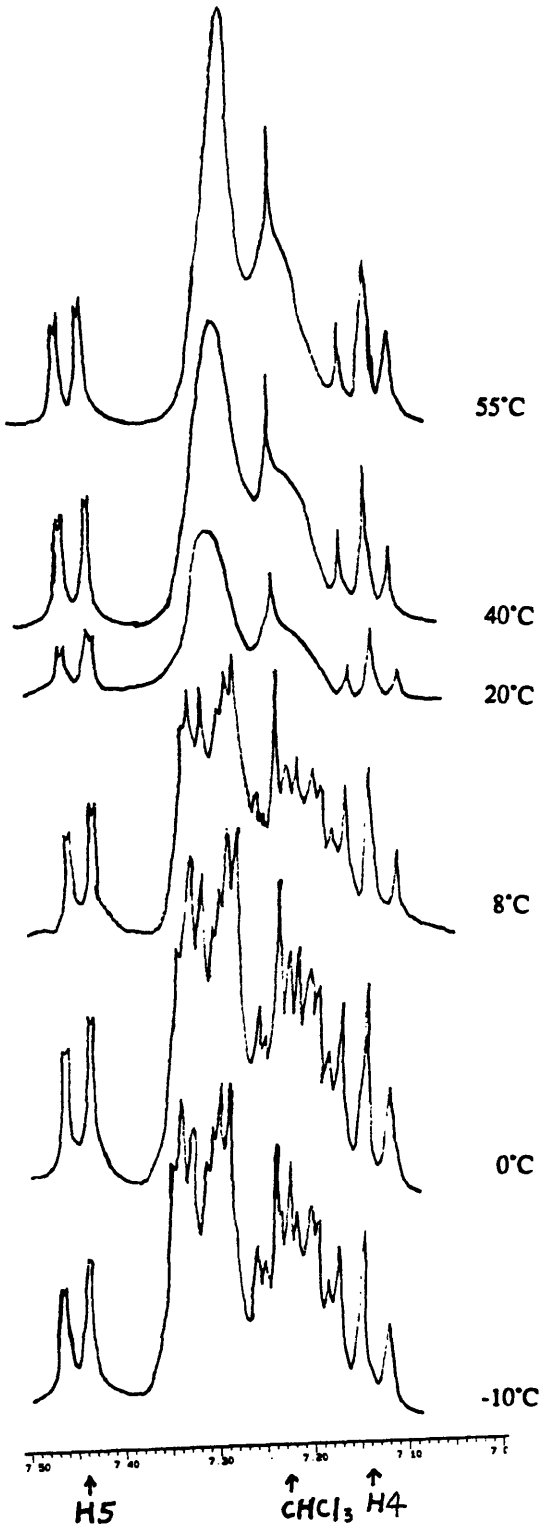
On the other hand, a congested system like **1**, might have high transition state energy ($E_t$) for the $C_{aryl}$–N bond rotation, but the congestion also raises the ground state energy ($E_g$). If the increase of $E_g$ is more than the increase of $E_t$, the actual rotational barrier $\Delta G^{\ddagger}$ (free energy of activation) of the $C_{aryl}$–N bond will decrease[10a]. In other words, a congested atropisomeric system does not necessarily have high barrier to be resolvable.

Variable temperature $^1H$ NMR studies were carried out on **5a** to estimate the rotational barrier of the $C_{aryl}$–N bond. Figure 1 showed the aromatic region of the $^1H$ NMR spectra at different temperatures.

**Figure 1.** Variable temperature $^1H$ NMR studies on compound **5a**.




**5 a**



If the rotation of the pivaloylamido group was restricted by the $PPh_2$ and *tert*-butyl groups, all of the aromatic protons on the $PPh_2$ group should give different signals with distinct splitting patterns, since these protons would be in .different chemical environments.

If the rotation of the pivaloylamido group was not restricted, protons 2', 6', 2", 6" would show the same signal. Also, protons 3', 5' would be equivalent to 3", 5" and 4' to 4", respectively. This would result in a much simpler splitting pattern for the $PPh_2$ group.

In Figure 1, when the temperature was 20°C, the signals of the aromatic protons on the $PPh_2$ group were two broad singlets with an integration ratio of 6H:4H. When the temperature was increased, the two singlets became sharper and higher. When the temperature was 8°C, each of the broad singlets began to split. When the temperature reached -10°C, large and more distinct splitting could be observed. This suggested that a) the coalescence temperature ($T_C$) was between 8°C and 20°C and the estimated $\Delta G^{\ddagger}$ was between 14.6 and 16.1 kcal/mol; b) the pivaloyl group was not large enough to be a chirality generating group at room temperature. Due to the complexity of peaks in the aromatic region, it was not possible to rigorously analyze the coalescence behavior. However, it could be conceived that the *p*-toluenesulfonamide group would not raise the $T_C$ and $\Delta G^{\ddagger}$ significently.

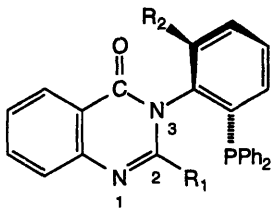
The molecular mechanics calculations (see "Appendix" part) were carried out on compound **1**. The $\Delta G^{\ddagger}$ is 12.7 kcal/mol when the two aryl groups of the sulfonamide are in *E* conformation (more stable). This value is much smaller than the lower $\Delta G^{\ddagger}$ limit for a resolvable system which is 23.5 kcal/mol at room temperature[10b]. The low $\Delta G^{\ddagger}$ would be due to the elevated ground state energy ($E_g$) of this highly congested system.

In light of the aforementioned results , the structure of system **1** needs further improvement in order to make it into a stable atropisomeric ligand.

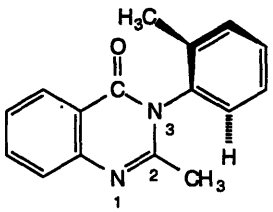
# Chapter 2. Design of Quinazolinone Ligand

## Introduction

The current project involves the design of a 3-aryl-4(3*H*)-quinazolinone phosphine ligand system (**2**).




**2**




**18**

Several compounds comprising a 3-aryl-4(3*H*)-quinazolinone moiety exhibit important biological activities (e.g., H1, H2-antihistaminic, hypnotic, antiinflammatory, anticonvulsant, antimicrobial, and CNS-activities).[11] They have thus been well-known pharmaceutical research subjects .

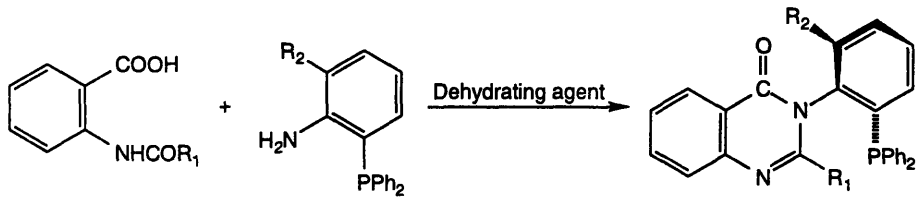
In addition, it has been noticed that a 3-aryl-4(3*H*)-quinazolinone compound would be a resolvable heterocyclo-biaryl atropisomer if its *ortho* substituents are large enough to block the rotation of the N–$C_{aryl}$ bond. This is demonstrated by 2-methyl-3-(2'-methyl-phenyl)-4(3*H*)-quinazolinone (methaqualone, **18**). The rotational barrier of its N–$C_{aryl}$ bond is $\Delta G^{\ddagger}$ = 31.5 kcal/mol at 135°C in diphenyl ether.[12] It can be resolved into two stable enantiomers that have different anticonvulsive activities.

We propose that by incorporating a phosphine group like the diphenylphosphino group ($PPh_2$) on the 3-phenyl ring of 3-aryl-4(3*H*)-quinazolinone and adjusting the size of group $R_1$ and $R_2$, system **2** would have a higher barrier to the rotation of N–$C_{aryl}$ bond than that of methaqualone (**18**). This will ensure the formation of pure enantiomers of **2** that will not racemize under normal reaction conditions.

There are some other reasons for us to believe that the 3-aryl-quinazolinone system (**2**) is an attractive target as a promising candidate for an atropisomeric ligand system. First, in spite of considerable localization of π-electons on the nitrogen atoms, the pyrimidine ring system in compound **2** is sufficiently aromatic to possess substantial stability. This stability is essential for the ligand to survive reaction conditions. Second, there are several known methods for the efficient synthesis of this system. The aforementioned stability of the ring system has a great advantage in the formation of compound **2**.[13] Third, the basic quinazolinone[14] atropisomers can be resolved by many readily available acidic resolving agents.[15] Fourth, by simply changing the substituents of the starting materials, this system can be easily modified to create a series of ligand analogs.

Considering the availability of the starting materials, the mildness of reaction conditions, and the reliability of the experimental procedures, Grimmel type synthesis[16] (Scheme 1) was chosen as the first strategy to prepare compound **2**.

**Scheme 1**



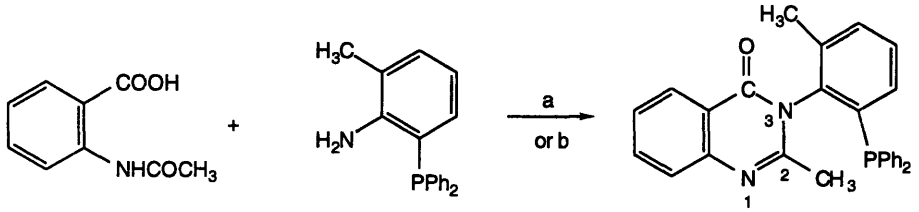

**19** **16** **2**

In the presence of a dehydrating agent, such as phosphorus trichloride ($PCl_3$), benzenesulphonyl chloride ($PhSO_2Cl$), or dicyclohexylcarbodiimide (DCC), *o*-acyl-amidobenzoic acid **19** could be condensed with aniline **16** to form 4(3*H*)-quinazolinone **2**.[17]

## Results and Discussion

Although Grimmel type synthesis[16, 17] of quinazolinone **2** is a one-step condensation of acylanthranilic acid **19** with aniline **16** (Scheme 1), a considerable period of time was spent on searching for a suitable reaction condition for compound **2a** (Scheme 2). Heating *N*-acetylanthranilic acid (**19a**) and aniline **16a** (obtained using Cooper's method, see Scheme 9, pp. 12) to reflux with phosphorus trichloride ($PCl_3$) in benzene gave complicated tarred products without any formation of the desired product **2a**. Refluxing a toluene solution of **19a** and **16a** with a mixture of oxalyl chloride and 4-dimethyl-aminopyridine (DMAP) also gave tarred products. We believed that hydrochloric acid (HCl) produced under above reaction conditions could convert the hindered aniline **16a** into less reactive ammonium salt.

**Scheme 2**




**19a** **16a** **2a**

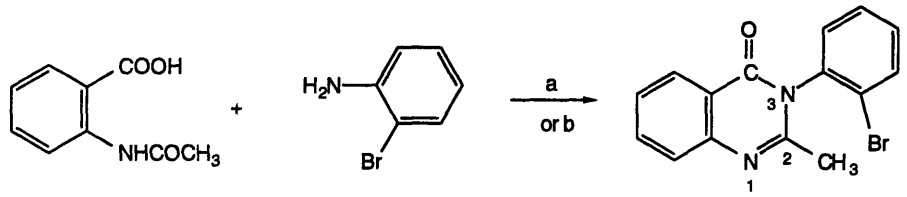
Conditions:
a: $PCl_3$, benzene, reflux (no product isolated); or oxalyl chloride, cat. DMF, cat. DMAP, toluene, reflux (no product isolated).
b: $PhSO_2Cl$, pyridine, cat. DMAP, toluene, reflux (77%).

In light of the above results, a tetrahydrofuran solution of **19a** and **20** was stirred with DCC at room temperature in a model study. The desired product **21** was obtain in a low yield (10%) (Scheme 3). Extended reaction time (24 hours) did not show further conversion of starting materials into the product **21**.

The best yields for **2a** and **21** were obtained when the benzosulfonyl chloride ($Ph_2SO_2Cl$) was used as the dehydrating reagent in the following procedure (Scheme 2 and

Scheme 3): The pyridine solution of 2.7 equiv. acylanthranilic acid **19a** and 2.2 equiv. $Ph_2SO_2Cl$ with a catalytic amount of DMAP was stirred for 30 minutes before the toluene solution of 1.0 equiv. aniline **16a** or **20** was added. Refluxing of the mixture overnight afforded the quinazolinones **2a** or **21** in good yields. By this procedure, **2a** was prepared on a scale of 11.5 g.

**Scheme 3**



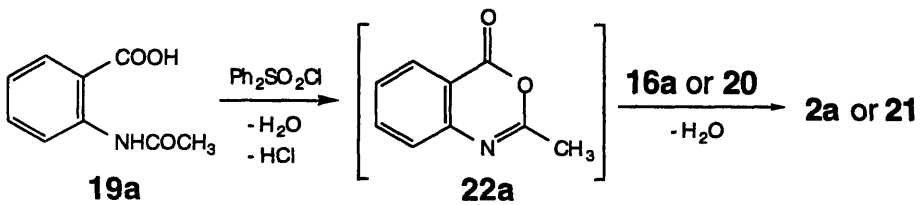

**19a** **20** **21**

Conditions:
a: DCC, THF, RT (10%);
b: $PhSO_2Cl$, pyridine, cat. DMAP, toluene, reflux (46%)

In the DCC reaction, no acid was generated during the reaction. In the $Ph_2SO_2Cl$ reaction, the HCl generated in the dehydrating step (Scheme 4) was absorbed by pyridine so that aniline **16a** or **20** would not be deactivated by free acid. Thus reactions in Scheme 2 and Scheme 3 took place in the desired direction.

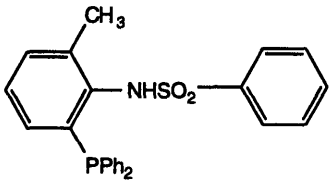
A possible mechanism[18] was that the *o*-acylamidobenzoic acid **19a** reacted with $C_6H_5SO_2Cl$ to give the active benzoxazolinone intermediate **22a**, which further reacted with aniline **16a** or **20**, with one equivalent of $H_2O$ eliminated, to yield **2a** or **21** (Scheme 4). Because the $H_2O$ generated in the second step could compete with aniline **16a** or **20** to react with **22a**, more than two equivalents of **19a** were used to generate excess **22a** to ensure the complete consumption of the aniline.

**Scheme 4**



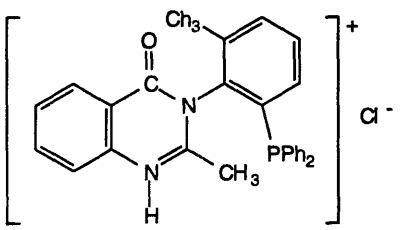

**19a** **22a**

Alternatively, when it was attempted to employ simply an excess of dehydrating agent $Ph_2SO_2Cl$ (2.2 equiv.) in the reaction of **19a** (1.2 equiv.) and **16a** (1.0 equiv.), only sulfonamide **23** was isolated. This indicated that $Ph_2SO_2Cl$ was more reactive toward **16a** than **22a** was.

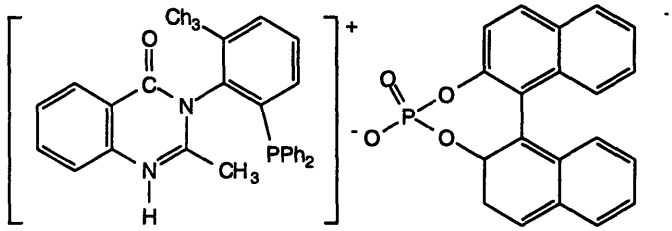



**23**

The basicity of compound **2a** was demonstrated by the facile formation of its hydro-chloride salt **24** when **2a** was heated in ethyl acetate with concentrated hydrochloric acid. Compound **2a** could also form the crystalline salt **25** with racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.




**24**

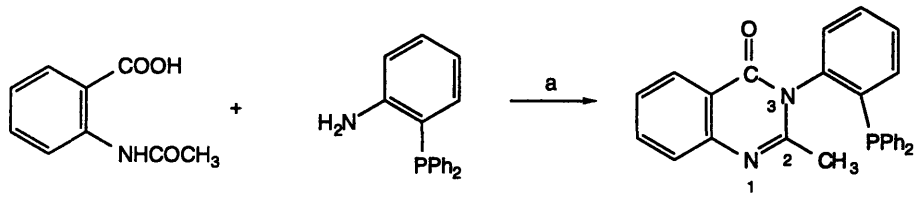



**25**

The HPLC trace of **2a** (Chiralcel OJ, 98:2 hexane/2-propanol, flow rate 1.5 mL/min, l = 295 nm) showed one sharp peak (retention time $t_R$ = 8.9 min) and one broad peak ($t_R$ = 13.5 min) with an 1:1 ratio of peak area. This indicated the possible presence of two resolvable enantiomers of **2a** at room temperature. A substantial number of conventional acidic resolving reagents were attempted for the resolution of **2a**, including L-tartaric acid, dibenzoyl-L-tartaric acid, (1*S*)-(+)-10-camphorsulphonic acid, ammonium salt of *d*-a-bromocamphor-p-sulfonic acid and (*R*)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate. Either salt formation was not apparent or an inseparable oil was produced.

Compound **2b** was synthesized under the similar reaction conditions as for **2a** (Scheme 5).*

**Scheme 5**




**19a** **26** **2b**

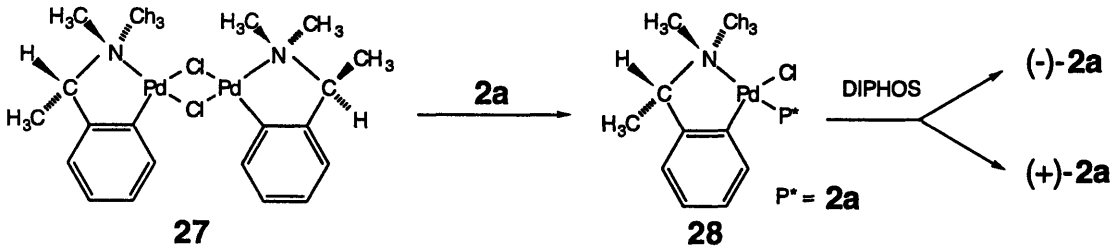
Conditions:
a: $PhSO_2Cl$, pyridine, cat. DMAP, toluene, reflux (40%)

The HPLC trace of **2b** also showed two peaks with a 1:1 ratio of peak area (Chiralcel OJ, 99:1 hexane/2-propanol, flow rate 1.1 mL/min, l = 295 nm; $t_R$ = 30.7 min (broad), $t_R$ = 38.3 min (broad)). **2b** could form camphorsulfonic salt **2b·(+)-CSA** as hexagonal crystals when a hot solution of **2b** and (1*S*)-(+)-10- camphorsulfonic acid in a 1:1 ethyl acetate/hexanes solvent mixture was cooled down slowly. A single salt crystal was composed of equal molar of both (+) and (-) enantiomers of **2b** and 2 equiv. of (1*S*)-(+)-10-camphorsulfonic acid based on $^1$H NMR and chiral HPLC.

When a solution of **2a** and (1*S*)-(+)-10-camphorsulfonic acid in ethyl acetate was seeded with salt crystals of **2b·(+)-CSA** and kept in 0°C overnight, salt **2a·(+)-CSA** was obtained in crystalline form. However, the salt crystal was also composed of equal molar of both **2a** enantiomers and 2 equiv. of (1*S*)-(+)-10-camphorsulfonic acid based on $^1$H NMR and chiral HPLC.

* The work on preparation of **2b** was performed by Scott Cohen as a 1995 summer UROP student: mp 181-182°C; mp of **2b·(+)-CSA**: 217-218°C.

Resolution of **2a** was finally achieved with the chloro-bridged chiral Pd complex, di-$\mu$-chlorobis[(*S*)-dimethyl(1-phenylethyl)aminato-$C^2$, *N*]dipalladium(II) (**27**).[19]




**27** **28**

Stirring a toluene solution of 1.0 equiv. of **27** and 2.0 equiv. of **2a** at ambient temperature yielded a yellow solution. Upon addition of a small amount of hexanes, a slow precipitation of the less soluble diastereomeric complex **28** ensued. The proton NMR spectrum indicated that after one Pd–Cl bridge bond was broken, **2a** served as a monodentate ligand with phosphorus coordinating to Pd(II) to form complex **28**.

Treatment with bis(diphenylphosphino)ethane (DIPHOS), followed by chromatography and crystallization from ethyl acetate/hexanes, yielded (-)-**2a** . The mother liquor was also treated with DIPHOS followed by chromatography and crystallization from ethyl acetate/hexanes to give (+)-**2a** . In this manner, 75 mg of enantiomerically pure (-)-**2a** (100% ee based on chiral HPLC, $[\alpha]_D^{23} = -250°$) and 48 mg of enantiomerically enriched (+)-**2a** (96% ee based on chiral HPLC, $[\alpha]_D^{23} = +194°$) were prepared.

Crystallization of the less soluable complex **28** from methylene chloride/toluene/hexane at room temperature provided yellow crystals suitable for single crystal X-ray analysis. The crystal structure was shown in figure 2. The absolute configuration of (-)-**2a** was confirmed to be *R*. It is interesting to note that the absolute configuration of (-)-mathequalone (**18**) is *S*[12] and the *R*-enantiomers of atropisomeric monophosphinobinaphthyls and diphosphinobinaphthyls always have positive rotation at the Na D-line.[20]

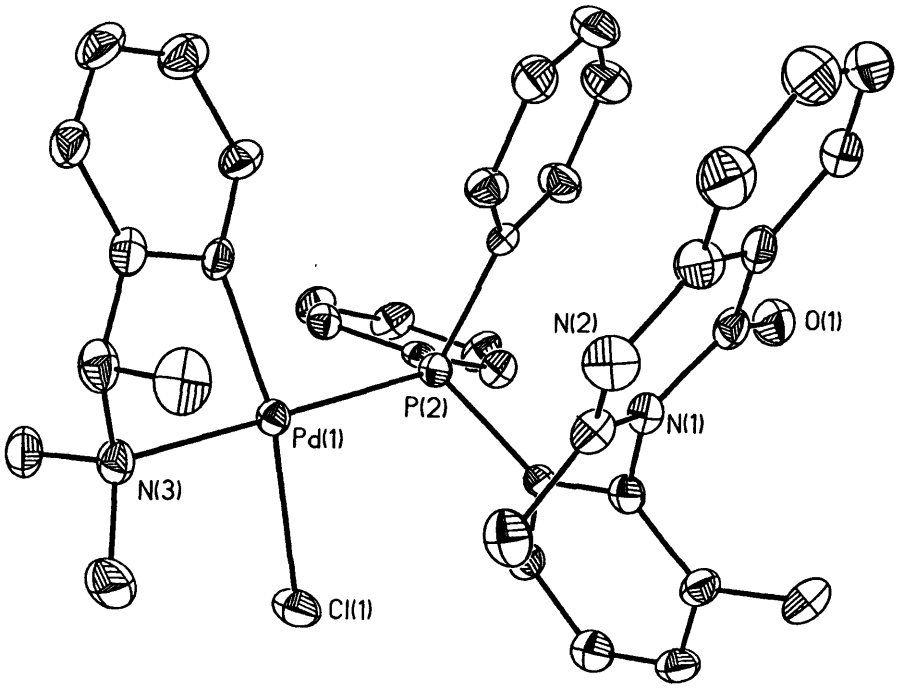
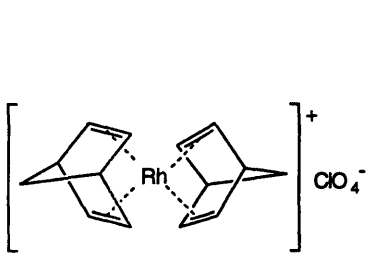
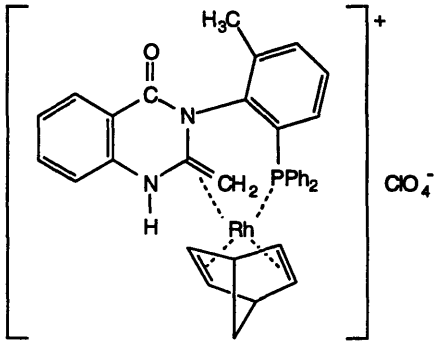



**Figure 2.** ORTEP drawing of (*S*, *R*)-**28**. The unlabeled atoms are carbons. A detailed data report is in preparation.

In the $^1$H NMR study on Rh(I) complex of ligand **2a**, complex **30** was obtained by the mixing $CDCl_3$ solutions of 1.0 equiv. of complex bis(bicyclo[2,2,1]hepta-2,5-diene)rhodium(I) perchlorate ($Rh(nbd)_2ClO_4$, **29**) and 1.0 equiv. of racemic **2a** in an NMR tube.



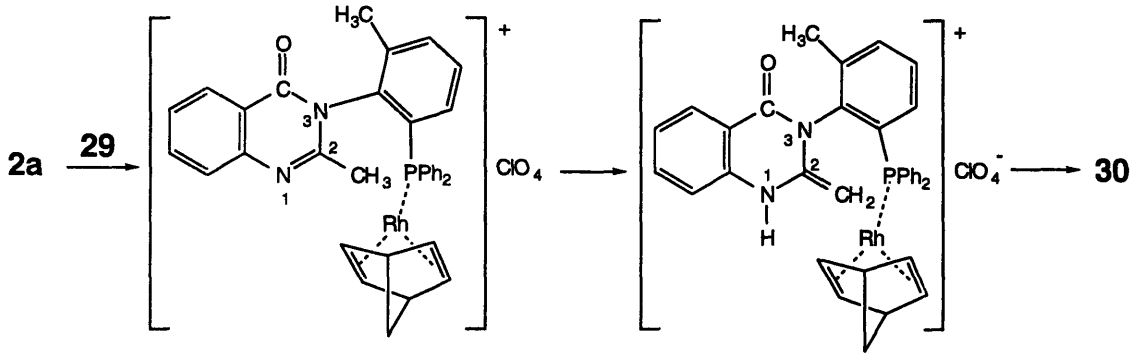

**29**




**30**

One set of free bicyclo[2,2,1]hepta-2,5-diene (2,5-norbornadiene, nbd) signals was observed in the $^1H$ NMR spectrum. The signals of the Rh(I) coordinated nbd were split from three singlets (4H:2H:2H) in **29** into 8 broad siglets (each has 1H integration) in **30** due to the asymmetric environment in the presence of ligand **2a**. Two additional protons in the olefinic region and only one methyl group signal at 2.05 ppm were observed. A down-field (11.0 ppm) peak with an integration of 1H in $^1H$ NMR spectrum and a broad peak at 3378 $cm^{-1}$ in IR spectrum indicated the presence of an amino proton flanked by conjugated systems. The $^{31}P$ NMR of complex **30** displayed a clear doublet whose coupling constant (150 Hz) was within the $^{103}Rh$-$^{31}P$ coupling range. When **29** or **2a** was in excess, only the above complex was formed. The rest of the starting material remained in the solution unchanged.

The spectrographic information suggested that Rh(I) in complex **29** first released one nbd to coordinate with the phosphorus in **2a**, then tautomerized the N1=C2–$CH_3$ part in the ligand into NH–C2=$CH_2$. The carbon-carbon double bond coordinated to Rh(I) to retain the square planar configuration and yield complex **30**.

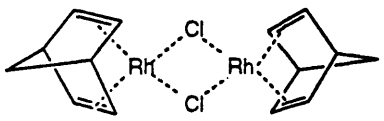



The carbonyl group did not serve as a binding site as was expected. From the IR spectrum, the small change of carbonyl frequency from 1684 $cm^{-1}$ in **2a** to 1677 $cm^{-1}$ in **30** was negligible compared to the large decrease (30-50 $cm^{-1}$) in wave number of metal-coordinating carbonyl groups[21].

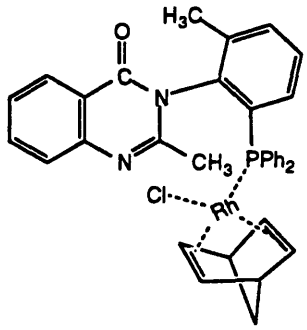
When $CDCl_3$ solution of **32** (20 mg) was loaded on a small silica gel column and eluted with $CH_2Cl_2$, the complex was decomposed, and the regenerated ligand **2a** was isolated.

The activity and tautomerism of 2-methyl group in 4(3*H*)-quinazolinone in the presence of acids or bases were well-documented.[22] However, the tautomerism of the 2-methyl group at the presence of organometallic compound was seldom reported.

Complex **32** was formed when 1.0 equiv. of complex (bicyclo-[2,2,1]hepta-2,5-diene)rhodium(I) chloride dimer ($[Rh(nbd)Cl]_2$, **31**) was mixed with 2.0 equiv. of racemic ligand **2a** in $CDCl_3$. The olefinic proton signals of the Rh(I)-coordinated nbd were split into four broad siglets as in complex **30**, but the signals of the bridgehead protons and the methylene protons were not distinctively split. The $^{31}P$ NMR of complex **32** was also a doublet. Unlike in complex **30**, no tautomerism of the N1=C2–$CH_3$ bonds in **2a** was observed.




**31**

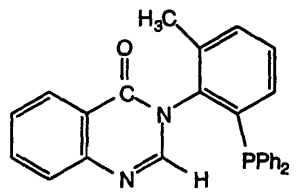



**32**

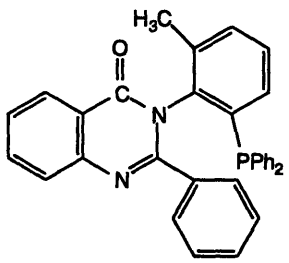
The mechanism about the formation of **32** was supposed to be similar to that of Pd(II) complex **28**. After one Rh-Cl bridge bond was broken in **31**, **2a** served as a monodentate ligand with phosphorus coordinating to Rh(I) to form complex **32**.

The syntheses of some analogs of **2a** (**2c**, **2d**, and **2e**) were also investigated. Based on the molecular mechanics calculations (see "Appendix" part), the rotational barrier ($\Delta G^{\ddagger}$) of the $C_{aryl}$–N bond in **2c** is 54.8 kcal/mol. Although the C2 substituent (H) makes

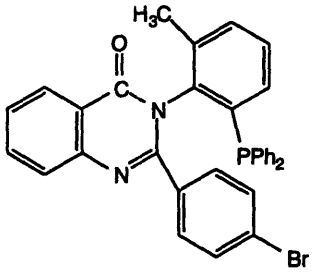
the $\Delta G^{\ddagger}$ lower than that of **2a** which is 68.0 kcal/mol, the $\Delta G^{\ddagger}$ would still be large enough to ensure **2c** to be an isolable atropisomeric compound under normal conditions.



**2c**



**2d**

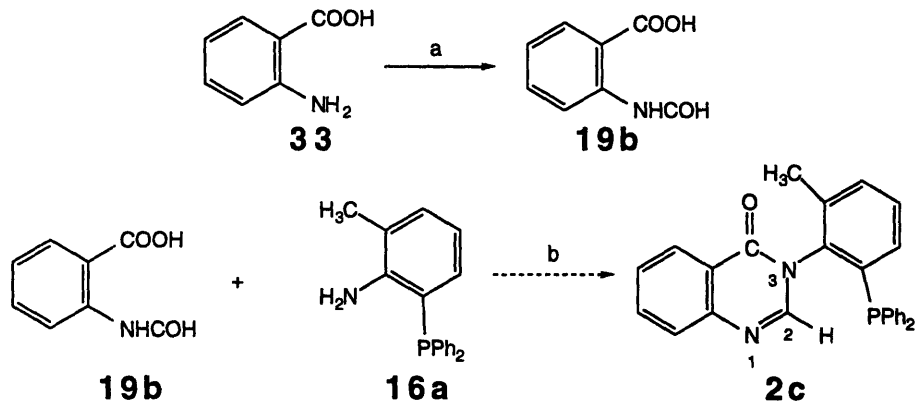


**2e**

In **2c**, the N1 position is less hindered than N1 in **2a**. We believe that this might increase the chance for **2c** to form crystalline salts with acidic resolving agents. In **2d** and **2e**, the C2 substituents are highly symmetric phenyl rings, which might facilitate **2d** and **2e** to form crystalline salts with resolving agents.

The synthesis of **2c**, which is now under investigation, might follow a similar procedure as the synthesis of **2a** (Scheme 6):

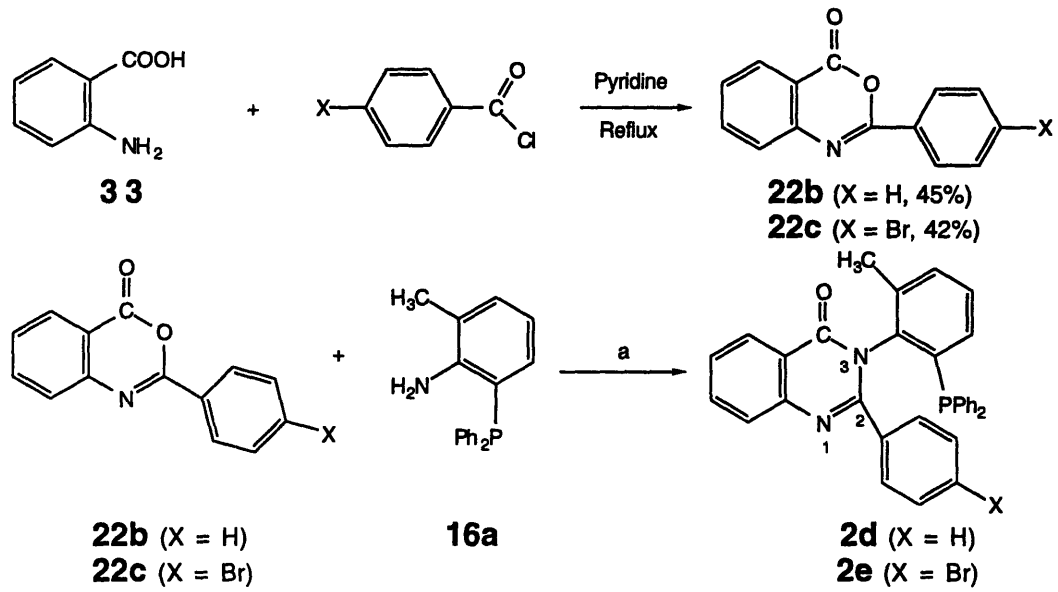
**Scheme 6**



Conditions:
a: HCOOH, $Ac_2O$, RT (80%);[23] b: $PhSO_2Cl$, pyridine

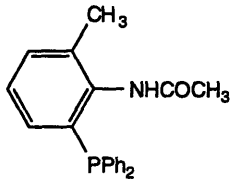
According to literature[24], the synthesis of 2-aryl-3-aryl-4(3*H*)-quinazolinone would require higher temperature and more reactive starting materials (2-aryl-benzoxazolinone) than the synthesis of 2-alkyl-3-aryl-4(3*H*)-quinazolinone. The syntheses of compounds **2d** and **2e** were shown in Scheme 7.

**Scheme 7**




Conditions:
a: (for **2d**) 300°C, 1h, 20%

Reaction of anthranilic acid (**33**) with benzoyl chloride or *p*-bromobenzoyl chloride afforded benzoxazinone **22b** or **22c**. No reaction occurred when **22b** or **22c** was heated with **16a** in ethanol or DMF to reflux.[24a] Heating a solution of **22b** and **16a** in glacial acetic acid with freshly fused NaOAc as catalyst[24a] only afforded **34**. **2d** was finally obtained in a low yield (20%) by heating a mixture of **22b** and **16a** under an atmosphere of argon at 300°C for 1 hour (Scheme 7).[24b] A similar procedure might also yield compound **2e**.




**34**

In summary, we have synthesized the monophosphine ligand **2a** and have found some strategies to the preparation of its analogs **2c**, **2d**, and **2e**. The syntheses of **2c**, **2d**, and **2e** are in progerss.

Recently, monophosphine ligands, such as 2-methoxy-2'-diphenylphosphino-1,1'-binaphthyl (MOP), have achieved much attention for their higher catalytic activity and

selectivity than chelating biphosphine ligands in certain types of catalytic asymmetric reactions[25], such as 1) asymmetric hydrosilylation of terminal and internal olefins; 2) asymmetric reduction of allylic esters with formic acid; 3) asymmetric 1,4-hydroboration of 1,3-enynes. Our search for the proper metal complexes of ligand **2a-2e** to test their catalytic activity in the above reactions is in progress.

# Chapter 3. Experimental Section

## General Procedures

Commercially available reagents were used without further purification unless noted. Solvents were dried and distilled immediately prior to use under nitrogen. Dichloromethane, hexanes, and triethylamine were distilled from $CaH_2$. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium benzophenone ketyl.

$^1H$ NMR and $^{13}C$ NMR spectra were obtained with a Varian XL-300, Varian Unity-300, or a Varian VXR-500 spectrometer using the deuterated solvent as internal standard. $^{31}P$ NMR spectra were measured on a Varian XL-300 (121MHz) spectrometer and chemical shifts were reported in ppm relative to 85% phosphoric acid as the external standard. Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublets of doublet), and br (broad). NMR assignments are presented in accord with the numbering of the corresponding structure shown above each experimental procedure.

Gas chromatography-mass spectra were recorded on a Hewlett Packard 5890 series II gas chromatography instrument (HP-1 column) with a Hewlett Packard 5971 series mass selective detector. High resolution mass spectra (HRMS) were recorded on a Finnigan-Mat system 8200 mass spectrometer. Electron impact (EI) was used for generation of the $M^+$ ions. Spectra are reported in units of mass to charge (*m/e*).

Melting points were determined on a Fischer-Johns hot stage apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR infrared spectrophotometer. Optical rotation measurements were measured on a Perkin-Elmer 241 polarimeter.

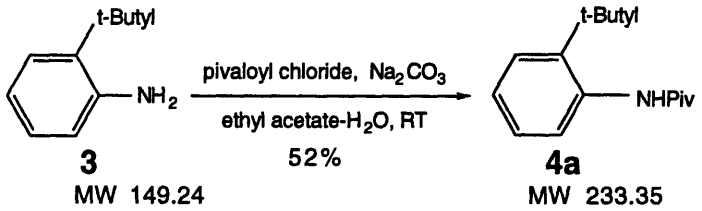
Flash column chromatography was performed using Silica Gel 60 (230-400 mesh) obtained from EM Science according to the method of Still[26]. Analytical thin-layer chromatography (TLC) was performed using EM Science precoated silica gel plates (0.25 mm

thickness) impregnated with a 254 nm fluorescence indicator. After elution using the solvent mixture indicated, the chromatogram was visualized by (a) illumination with 254 nm ultraviolet light, or (b) dipping in an ethanolic solution of 2.5% *p*-anisaldehyde or an ethanolic solution of 10% phosphomolybdic acid reagent (PMA), followed by heating on a hot plate.

High-performance liquid chromatography (HPLC) analyses were carried out on a Perkin-Elmer Series 400 Liquid Chromatography instrument equipped with a Perkin-Elmer LC 90 UV spectrometric detector and a Hewlett Packard 3393A integrator. A 4.6 mm × 25 cm Daicel CHIRALCEL OJ column was used.

All reactions involving organometallic reagents were carried out under an atmosphere of dry argon. (-)-Di-$\mu$-chlorobis[(*S*)-dimethyl(1-phenylethyl)aminato-$C^2$, *N*]di-palladium (II) was prepared according to the literature procedure.[27]

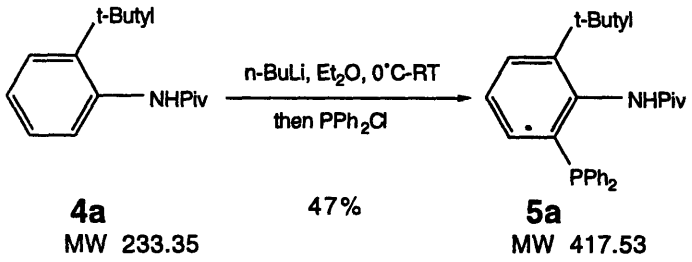
## Synthesis of the Sulfonamide Ligand System




**3**
MW 149.24

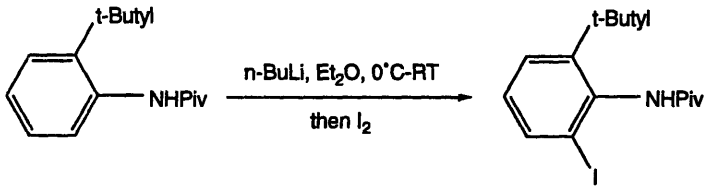
**4a**
MW 233.35

**2'-*tert*-Butyl-2,2-dimethylpropionanilide (4a):** Pivalyol chloride (38.3 mL, 0.311 mol) was added dropwise with stirring to a biphasic system of 200 mL ethyl acetate solution of 2-*tert*-butylaniline (**3**) (46.6g, 0.312 mol) and 200 mL of sodium carbonate aqueous solution. After the mixture was vigorously stirred for 12h at room temperature, it was acidified to pH 2 by the addition of concentrated HCl solution. The two resulting phases were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Crystallization from hexane provided product **4a** (37.6 g, 52%) as white needles: mp 123.9-124.2°C; $Rf$ = 0.24 (silica, 1:8 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3282, 2966, 1651(C=O), 1504, 1364, 1287, 1234, 1175, 755.8; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.63 (dd, 1H, J = 1.2, 7.2 Hz), 7.41 (br, 1H, N*H*Piv), 7.38 (dd, 1H, J = 1.3, 7.3 Hz), 7.22 (ddd, 1H, J = 1.2, 7.0, 7.0 Hz), 7.14 (ddd, 1H, J = 1.2, 7.0, 7.0 Hz), 1.37 (s, 9H, *t*-Bu), 1.31 (s, 9H, *t*-Bu).



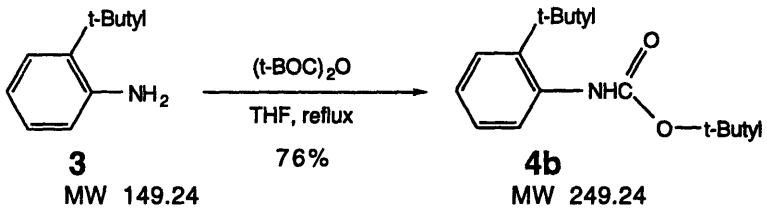

**4a** MW 233.35 — 47% — **5a** MW 417.53

**2'-*tert*-Butyl-6'-diphenylphosphino-2,2-dimethylpropionanilide (5a):** A hexane solution of 2.4 M butyllithium (0.5 mL, 1.2 mmol) was added dropwise to a solution of **4a** (0.1165 g, 0.5 mmol) in dry ether (15 mL) at 0°C under argon. The mixture was slowly warmed up to room temperature and stirred for 48 hours before it was cooled down again to 0°C in an ice bath. Chlorodiphenylphosphine ($PPh_2Cl$, 0.11 mL, 0.6 mmol) was added slowly. The mixture was then stirred for another period of 2 hours at room temperature, diluted with ether and quenched with cold water. The layers were separated and the aqueous phase was washed with ether (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried by filtration through anhydrous $MgSO_4$. After the solvent was evaporate *in vacuo*, the crude product was crystallized from ethyl acetate/hexanes solvent mixture to give 0.0985 g of **5a** (47%) as white needles: mp 146-148°C; $Rf$ = 0.20 (silica, 1:6 ethyl acetate/hexanes); FTIR (thin film, $cm^{-1}$): 3355, 3052, 2960, 1682 (C=O), 1479, 1362, 1255, 1223, 1158, 792, 744, 698; $^1H$ NMR (300MHz, $CDCl_3$) δ : 7.47 (dd, 1H, J = 1.5, 7.2 Hz), 7.33 (br s, 6H), 7.25 (br s, 4H), 7.16 (t, 1H, J = 7.8 Hz), 6.83 (br s, 1H, N*H*Piv), 6.71 (ddd, 1H, J = 1.5, 3.6, 7.0 Hz), 1.36 (s, 9H, *t*-Bu), 1.18 (s, 9H, *t*-Bu); GC-MS (EI) *m/e* (relative intensity) 417 ($M^+$, 2), 402 ($M^+ - CH_3$, 5), 360 ($M^+$ – *t*-Bu, 100), 340 (6), 333 (6), 281 (5), 207 (19), 183 (8), 107 (4), 77 (4), 57 (*t*-Bu, 31).




**4a** MW 233.35 — 80% — **5b** MW 359.25

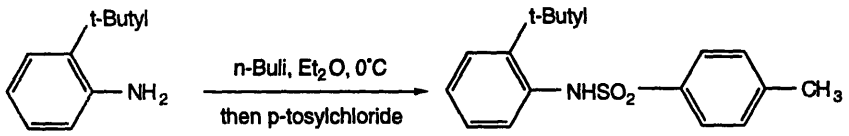
**2'-*tert*-Butyl-6'-iodo-2,2-dimethylpropionanilide (5b):** A solution of **4a** (0.1165 g, 0.5 mmol) in dry ether (15 mL) was lithiated as described for **5a.** After a solution of iodine ( 0.1532 g, 0.6 mmol) in ether (15 mL) was added, the mixture was stirred for 2 hours. The reaction was diluted with ether and quenched with cold water. The layers were separated and the organic phase was washed with brine (10 mL), dried by filtration through anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from ethyl acetate-hexanes solvent mixture to give 0.1437 g of **5b** (80%) as white needles: mp 245-247°C; $R_f$ = 0.49 (silica, 1:6 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$): 3306, 2952, 1658 (C=O), 1488, 1362, 1172, 778, 724, 648; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 1.5, 7.6 Hz), 7.42 (dd, 1H, J = 1.5, 8.1 Hz), 7.06 (br s, 1H, N*H*Piv), 6.94 (t, 1H, J = 8.0 Hz), 1.40 (s, 9H, *t*-Bu), 1.35 (s, 9H, *t*-Bu); GC-MS (EI) *m/e* (relative intensity) 344 ($M^+$ – CH3, 0.5), 302 ($M^+$ – *t*-Bu, 6), 260 (9), 232 ($M^+$ – I, 100), 217 (10), 202 (3), 176 (4), 147 (3), 132 (13), 117 (10), 91 (8), 77 (7), 57 (*t*-Bu, 63).




**3**
MW 149.24

**4b**
MW 249.24

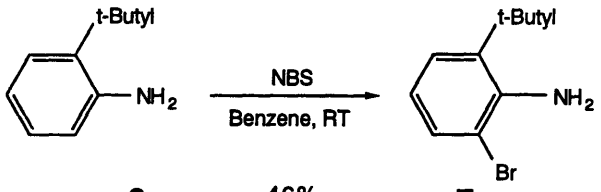
**2-*tert*-Butyl-*N*-(*t*-butoxycarbonyl)aniline (4b)**: A solution of 2-*tert*-butylaniline (**3**) (0.671 g, 4.5 mmol) in tetrahydrofuran (10 mL) containing di-*tert*-butyl dicarbonate (1.96 g, 9.0 mmol) was heated at reflux temperature for 24 hours. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (15 mL), and this solution was washed successively with saturated aqueous sodium carbonate solution (2 × 10 mL) and brine (10 mL). The two layers were separated and the organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was crystallized from hexane to give 1.12 g of **4b** (76%) as white needles: mp 74.5-75.0°C; $R_f$ = 0.44 (silica, 1:6 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3282, 2966, 1651(C=O), 1504, 1364, 1287, 1234, 1175, 755.8; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.55 (br d, 1H, J = 7.8 Hz), 7.36 (dd, 1H, J = 1.5, 7.8 Hz), 7.21 (ddd, 1H, J = 1.5, 7.8, 7.8 Hz), 7.10 (ddd, 1H, J = 1.5, 7.8, 7.8 Hz), 6.34 (br s, 1H, N*H*t-BOC), 1.51 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu).




**3**
MW 149.24

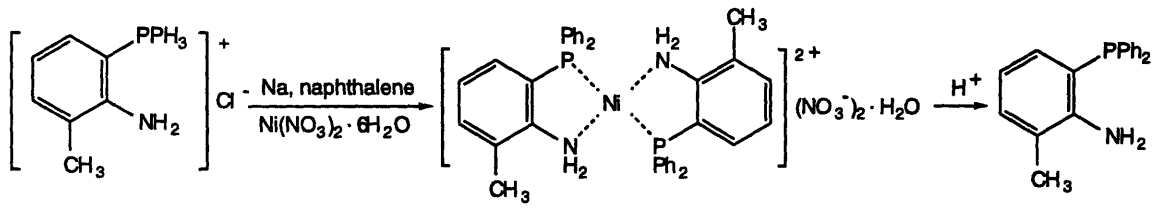
**4c**
MW 303.42

**2'-*tert*-Butyl-phenyl-4-methylbenzene-sulfonamide (4c):** To a dry ether solution (10 mL) of 2-*tert*-butylaniline (**3**) (0.30 g, 3 mmol) was added dropwise a hexane solution of 2.5 M butyllithium (1 mL, 2.5 mmol) at 0 °C. After 30 min stirring, a dry ether solution (8 mL) of *p*-toluenesulfonyl chloride (0.45 g, 2.4 mmol) was added dropwise to the above mixture. The resulting mixture was stirred for another period of 2 hours at 0°C. The reaction was then quenched with cold water and washed with saturated aqueous sodium bicarbonate solution and brine. The two layers were separated and the organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate and hexanes to give 0.3307 g of **4c** (55%) as white plates: mp 102.5-104.0°C; $R_f$= 0.18 (silica, 1:6 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3425, 2964, 1490, 1438, 1388, 1328, 1158, 1087, 916, 814, 757, 661; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 7.8 Hz), 7.43 (dd, 1H, J = 1.1, 7.8 Hz), 7.32 (dd, 1H, J = 2.4, 7.8 Hz), 7.25 (d, 2H, J = 7.8 Hz), 7.13 (ddd, 1H, J = 1.4, 7.8, 7.8 Hz), 7.06 (ddd, 1H, J = 1.5, 7.8, 7.8 Hz), 6.69 (br s, 1H, N*H*$SO_2$), 2.38 (s, 3H, C*H*$_3$), 1.34 (s, 9H, *t*-Bu).




**3** MW 149.24 — 46% — **7** MW 228.13

**2-Bromo-6-*t*-butylaniline (7)[8]:** To a solution of 2-*tert*-butylaniline (26.7 g, 0.179 mol) in benzene (300 mL) was added 31.9 g (0.179 mol) of *N*-bromosuccinimide all at once. The mixture was stirred overnight. After the solvent was removed, the residue was suspended in pentane and filtered. Ice was added to the pentane solution, followed by the addition of 8.5 mL of acetic anhydride with stirring. The solid was filtered off and the filtrate was evaporated *in vacuo*. The resulting oil was distilled under reduced pressure to give 20.5 g of **4b** (46%) as light yellow oil; bp 126-129°C/4mmHg; *Rf*= 0.73 (silica, 1:10 ethyl acetate/hexane); FTIR (neat, $cm^{-1}$): 3510, 3396, 2967, 1618, 1560, 1466, 1437, 1397, 1368, 1258, 1195, 1051, 854, 771, 731; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.346 (dd, 1H, J = 1.6, 7.5 Hz), 7.188 (dd, 1H, J = 1.4, 7.8 Hz), 6.583 (t, 1H, J = 7.8 Hz), 4.400 (br s, 2H, $NH_2$), 1.425 (s, 9H, *t*-Bu).




**14**
MW 403.89

84%

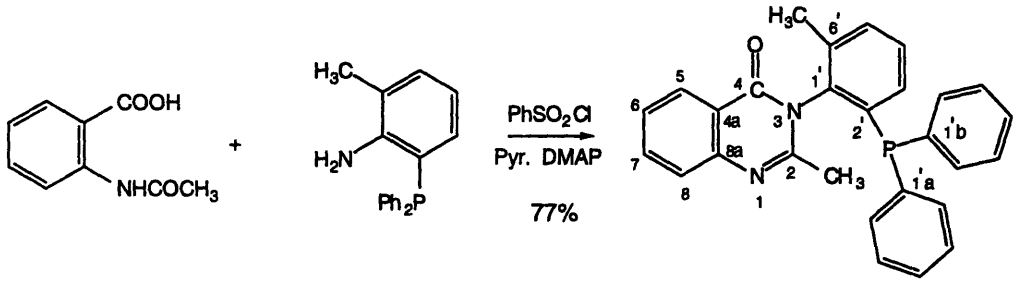
**16a**
MW 291.33

**(2-Amino-3-methylphenyl)-diphenylphosphine (16a):** An oven dried, three-necked, round-bottomed 500 mL flask equipped with a mechanical stirrer was charged with 250 mL of anhydrous tetrahydrofuran, 25.5 g (0.199 mol, 2.4 equiv.) of naphthalene and . Sodium pieces (4.15 g, 0.180 mol, 2.2 equiv.) were quickly added to the above solution. The mixture was stirred under argon until the sodium was completely dissolved. The resulting dark green solution was cooled in a dry ice-acetone bath until it turned into a thick slurry. Phosphonium salt **14**‡ (33.1 g, 0.082 mol, 1.0 equiv.) was added and the mixture was warmed slowly, with slow stirring, to room temperature, then stirred for 1 hour. Acetic acid (2 mL) was added dropwise to discharge the last of the green color. The orange mixture is treated slowly with sufficient water to dissolve all of the solid. The two resulting phases were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated. The residue was taken up in 250 mL of boiling 90% ethanol and treated with a solution of nickel(II) nitrate hexahydrate (13.0 g, 0.045 mol, 0.55 equiv.) in 100 mL boiling 90% ethanol. The metal complex precipitated out as golden crystals. The resulting dark brown solution was treated with 2 mL of trifluoroacetic acid.

‡ Phosphonium salt **14** was made from 2-chloro-6-methylaniline by Scott Cohen as a 1995 summer UROP student (36%, reported yield:[4b] 57%).

The metal complex was filtered off and washed first with 90% ethanol and then with diethyl ether to remove the naphthalene. The nickel complex obtained was suspended in a mixture of benzene (350 mL) and water (350. mL) to which a few drops of concentrated HCl were added. The mixture was heated to reflux overnight and the crystals dissolved completely. The two phases were separated and the green aqueous layer was extracted with benzene (50 mL). The combined organic fractions were washed with brine ($2 \times 25$ mL), dried by filtration through anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Crystallization from ethyl acetate (50 mL) and hexane (50 mL) provided the product (19.99 g, 83.7%) as white needles: mp 72-73°C (reported mp 97-98°C[4b]); $R_f$ = 0.73 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3463, 3356, 3055, 1610, 1455, 1431, 1239, 742, 694; $^1H$ NMR (300MHz, $CDCl_3$) δ 7.27-7.39 (m, 10H), 7.05-7.12 (m, 1H), 6.59-6.71 (d of m, 2H, J = 6.7 Hz), 4.20 (br s, $NH_2$), 2.19 (s, $CH_3$); $^{13}C$ NMR (75MHz, $CDCl_3$) $\delta_C$ 148.196 (d, $^2J_{CP}$ = 19.8 Hz, C1), 135.835 (d, $^1J_{CP}$ = 7.5 Hz, C1a), 133.952, 133.696, 132.417, 131.738, 128.897, 123.761, 128.668, 122.252 (d, $^3J_{CP}$ = 2.8 Hz, C6), 118.903 (d, $^1J_{CP}$ = 7.1 Hz, C2), 118.424 (d, $^3J_{CP}$ = 2.8 Hz, C4), 17.949 (d, $^4J_{CP}$ = 3.1 Hz, Ar*Me*); $^{31}P$ NMR (121.4 MHz): -22.3 (s).

## Synthesis of Quinazolinone Ligand System




**19a**
MW 179.18

**16a**
MW 291.12

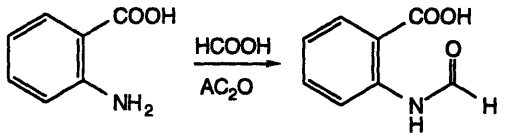
**2a**
MW 434.48

**2-Methyl-3-(6'-methyl-2'-diphenylphosphinophenyl)-4(3*H*)-quinazolinone (2a)**[17] : To a solution of *N*-acetylanthranilic acid (**19a**) (16.58 g, 92.5 mmol, 2.7 equiv.) and 4-dimethylaminopyridine (DMAP, 50 mg) in pyridine (27 mL) was added dropwise benzenesulfonyl chloride ($PhSO_2Cl$, 9.64 mL, 75.5 mmol, 2.2 equiv.). The clear solution was stirred vigorously at ambient temperature for 30 minutes until it turned into a yellow slurry. A solution of (2-amino-3-methylphenyl)-diphenylphosphine (**16a**, 10.00 g, 34.4 mmol, 1.0 equiv.) in benzene (100 mL) was added all at once to the above slurry. The mixture was heated for 36 hours at reflux temperature and monitored by TLC until the complete consumption of **16a** was indicated. After cooling, the solvent was evaporated. Ethyl acetate (250 mL) and water (50 mL) were added to dissolve the resultant solid. The aqueous layer was extracted with ethyl acetate (50 mL). The combined ethyl acetate fractions were washed with water (3 × 25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Crystallization from ethyl acetate (80 mL) and hexane (80 mL) provided the product (11.48 g, 77%) as white needles: mp 169.2-170.2°C; $R_f$ = 0.28 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3054, 1683 (C=O), 1603 (C=N), 1569, 1472, 1434, 1377, 1326, 1267, 1116, 774, 743, 696; $^1H$ NMR (300MHz, $CDCl_3$) δ 8.070 (dd, 1H, J = 1.2, 7.8 Hz), 7.742 (ddd, 1H, J = 1.5, 6.9, 8.4 Hz), 7.667 (d, 1H, J = 7.8 Hz), 7.333-7.418 (m, 8H), 7.104-7.252 (m, 6H), 2.128 (s, C6'$CH_3$), 2.043 (s, C2$CH_3$); $^{13}C$ NMR (125MHz, $CDCl_3$) $\delta_C$ 161.08 (C4),

154.20 (C2), 147.56 (C8a), 141.09 (d, $^2J_{CP}$ = 25.1 Hz, C1'), 137.15 (d, $^1J_{CP}$ = 14.6Hz, C6'), 136.04 (d, $^3J_{CP}$ = 3.25, C2'), 135.35 (d, $^1J_{CP}$ = 9.1, C1'a or C1'b), 135.03 (d, $^1J_{CP}$ = 10.5, C1'a or C1'b), 134.36, 134.26, 134.19, 133.70, 133.54, 133.06, 132.25, 129.38, 129.23, 128.73, 128.67, 128.64, 128.17, 128.12, 127.14 (C8), 126.60 (C6), 126.12 (C5), 120.76 (C4a), 23.56 (d, $^5J_{CP}$ = 5.0Hz, C2*Me*), 17.79 (d, $^4J_{CP}$ = 2.4Hz, C6'*Me*); $^{31}$P NMR (121.4 MHz): -18.2 (s); MS (EI) *m/e* (relative intensity) 434 ($M^+$, 100); HRMS (EI) calcd for $C_{28}H_{23}N_2OP$ 434.15480, found 434.15476; Anal. Calcd for $C_{28}H_{23}N_2OP$: C, 77.41; H, 5.34; N, 6.45. Found: C, 77.33; H, 5.49; N, 6.30; HPLC: $t_R$ = 8.9 (sharp peak), 13.5 (broad peak) min (Chiralcel OJ, 98:2 hexane/2-propanol, flow rate 1.5 mL/min, $\lambda$ = 295 nm).

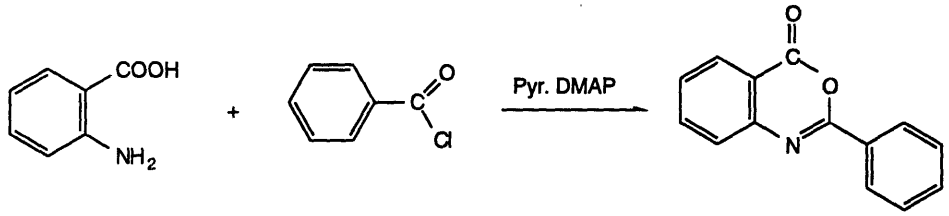
**Hydrochloride Salt 24:** To a boiling solution of compound **2a** (0.434 g, 1 mmo;) in ethanol (12 mL) was added 2 mL of concentrated hydrochloride acid. The resulting solution was heated to reflux for 10 min and cooled down to room temperature. After 12 hours, the salt was collected by filtration. Recrystallization from 95% ethanol afforded the hydrochloride salt (0.386 g, 82%) as white granular crystals : mp 169 - 178°C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.53 (d, 1H, J = 8.1 Hz), 7.90 - 8.02 (m, 2H), 7.61 (ddd, 1H, J = 0.6, 7.5, 7.5 Hz), 7.36 - 7.48 (m, 5H), 7.24 - 7.32 (m, 3H), 7.14 - 7.22 (m, 2H), 7.06 - 7.14 (m, 3H), 2.66 (s, 3H), 2.13 (s, 3H).

**Phosphate salt 25:** A mixture of racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (87.1 mg, 0.25 mmol) and compound **2a** (108.5 mg, 0.25 mmol) was heated with 4 mL of acetone to reflux until a clear solution was obtained. The solution was cooled down to room temperature and then put in 0°C fridge for overnight. Filtration afforded the salt as light yellow crystals (0.1448 g, 74%): mp 251-256°C; $^1$H NMR (300 MHz, $CD_3COCD_3$) $\delta$ 8.18 (d, 2H,J = 8.5 Hz), 8.10 (d, 2H, J = 8.1 Hz), 8.03 (dd, 1H, J = 1.5, 8.0 Hz), 7.82 (ddd, 1H, J = 1.5, 7.5, 7.5 Hz), 7.69 (d, 1H, J = 8.1 Hz), 7.08 - 7.64 (m, 22H), 2.18 (s, 3H), 2.08 (s, 3H).



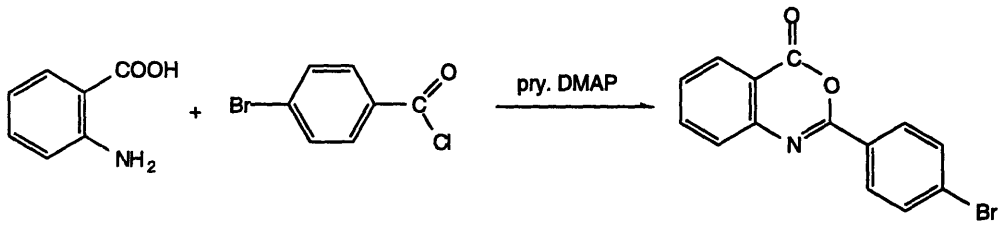

**33** 80% **19b .**

***N*-Formylanthranilinc acid (19b):** Acetic anhydrid (7 mL, 7.5 equiv.) was slowly added to a solution of anthranilic acid (1.4 g, 1.0 equiv.) in 96% formic acid (18.8 mL). The mixture was stirred vigorously for 4 hours, diluted with ethyl acetate, and evaporated under reduced pressure. The residue was crystallized from ethanol to give the product as light yellow crystals (80%): *Rf* = 0.08 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3184, 2924, 2806, 2605, 1690 (C=O), 1647, 1591, 1528, 1456, 1407, 1270, 750; $^1H$ NMR (300MHz, $CDCl_3$) δ 10.87 (br, 1H), 8.38 (d, 1H, J = 8.4 Hz), 8.20 (s, 1H), 7.79 (dd, J = 1.7, 8.0 Hz), 7.22 (ddd, 1H, J = 1.6, 8.5, 8.5 Hz), 6.82 (ddd, 1H, J = 1.2, 8.4, 8.4 Hz).



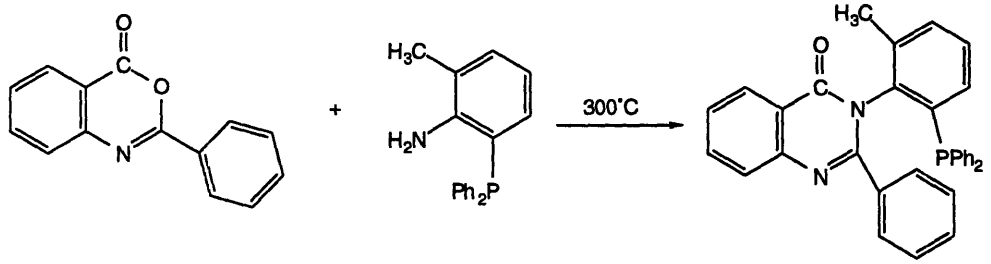

**33** MW 137.14 MW 140.57 45% **22b** MW 223.23

**2-Phenyl-4*H*-3,1-benzoxazin-4-one (22b):** A solution of anthranilic acid (2.7428g, 20 mmol), benzoyl chloride (4.6089 g, 1.05 equiv.), and 4-dimethylaminopyridine (DMAP, 20 mg) in pyridine (15 mL) was heated to reflux for 4 hours. The reaction mixture was evaporated under reduced pressure. The residue was taken up with ethyl acetate (20 mL). The organic layer was washed with aqueous sodium bicarbonate and brine (10 mL), dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Crystallization from ethyl acetate and hexanes mixture gave the product as white needles: mp 120 - 122°C; *Rf* = 0.59 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 1763 (C=O);$^1H$ NMR (300MHz, $CDCl_3$) δ 8.326 (dd, 2H, J = 2.4, 8.1 Hz), 8.258 (dd, 1H, J = 1.5, 7.8 Hz), 7.838 (dt, 1H, J = 1.5, 6.3 Hz), 7.710 (dd, J = 1.5, 8.7 Hz), 7.44-7.61 (m, 4H).



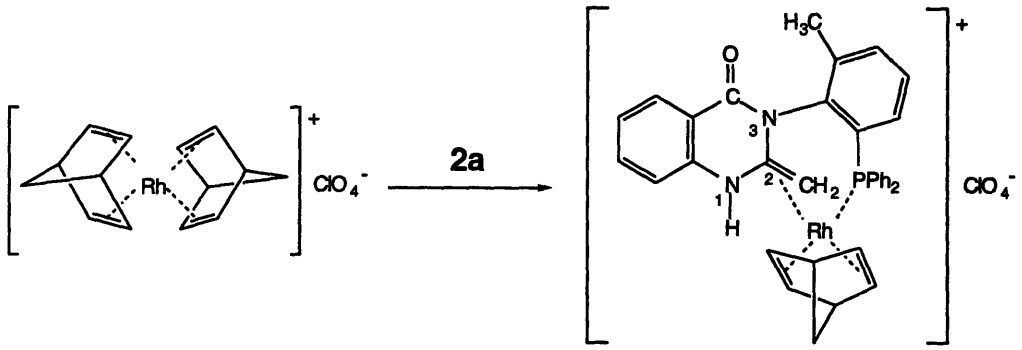

**33** MW 137.14 MW 219.47 42% **22c** MW 290.12

**p-bromophenyl-4*H*-3,1-benzoxazin-4-one (22c)** was obtained using the same procedure for **22b** as white needles: mp 185 - 186°C; *Rf* = 0.36 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 1764 (C=O); $^1H$ NMR (300MHz, $CDCl_3$) δ 8.253 (dd, 1H, J = 1.5, 7.8 Hz), 8.185 (br d, 2H, J = 8.4 Hz), 7.846 (ddd, 1H, J = 1.5, 8.4, 10.2 Hz), 7.615-7.660 (m, 3H), 7.545 (ddd, 1H, J = 1.0, 7.8, 7.8 Hz);




**22b** MW 223.23 **16a** MW291.12 20% **2d** MW 320.1

**2-Phenyl-3-(6'-methyl-2'-diphenylphosphinophenyl)-4(3*H*)-quinazolinone (2d):** A mixture of **22b** (0.8929 g, 4 mmol) and **16a** (0.5822 g, 2 mmol) was melted at 300°C under argon with stirring. After one hour, the mixture was cooled down to room temperature. Purification by chromatography (1:3 ethyl acetate/hexanes) gave the product as white needles: mp 238 - 240°C; *Rf* = 0.5 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, $cm^{-1}$) 3060, 1684 (C=O), 1590 (C=N), 1560, 1472, 1437, 1329, 1267, 769; $^1H$ NMR (300MHz, $CD_2Cl_2$) δ 8.32 (dd, 1H, J = 1.5, 7.8 Hz), 7.76 - 7.84 (m, 2H), 7.10 - 7.51 (m, 10H), 7.08 (ddd, 2H, J = 1.5, 6.7, 6.7 Hz), 6.76 - 6.89 (m, 3H), 2.31 (s, 3H).

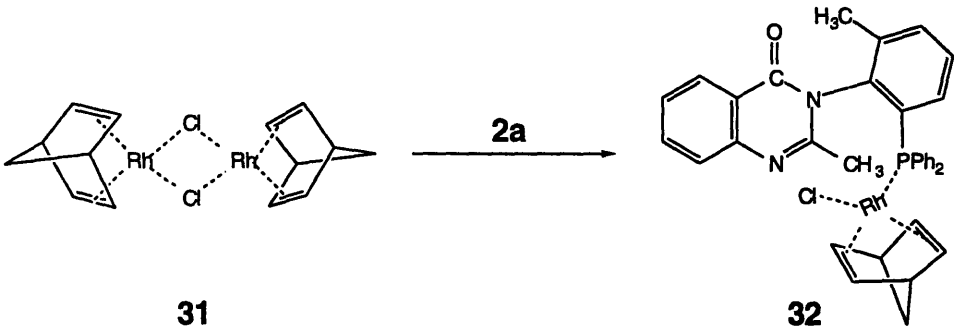



**29**
MW 386.64

56%

**30**
MW 458.75

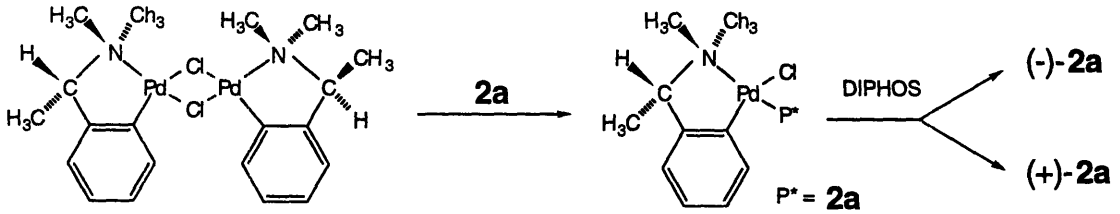
**Complex 30**: A $CH_2Cl_2$ solution of Rh complex **29** (15.5 mg, 0.04 mmol)) and compound **2a** (17.4 mg, 0.04 mmol) in a Schlenk tube was stirred for one hour at ambient temperature until a clear orange solution was obtained. 35 mL of hexanes was added slowly on the top of the above $CH_2Cl_2$ solution without disturbing the interface. The Schlenk tube was then put in 0°C fridge for two days. The product was collected by filtration under a stream of nitrogen as yellow powder (10.2 mg, 56%): FTIR ($CDCl_3$, $cm^{-1}$) 3378, 3063, 2983, 2930, 1677, 1604, 1566; $^1H$ NMR (300MHz, $CDCl_3$) δ 11.01 (s, $N_1H$), 7.88 (dd, 7.7, 11.5 Hz, 2H), 7.75 (dd, J = 2.0, 8.0 Hz, 1H), 7.70 (ddd, J = 1.5, 6.8, 6.8 Hz, 1H), 7.55-7.47 (m, 5H), 7.40 (ddd, 1.6, 7.7, 7.7 Hz, 1H), 7.33-7.22 (m, 4H), 7.22-7.11 (m, 3H), 6.32 (m, 1H ), 5.41 (dd, J = 3.9, 7.6 Hz, 1H), 4.08 (br, 1H), 3.92 (q, J = 3.9Hz, 1H), 3.85 (br, 1H), 3.46 (m, 1H), 2.84 (q, J = 3.8 Hz, 1H), 2.04 (s, $CH_3$), 1.86 (ddd, J = 2.3, 2.3, 4.6 Hz, 1H), 1.65 (ddd, J = 1.5, 1.5, 8.6 Hz, bridgehead *H*), 1.47 (dddd, J = 1.7, 1.7, 1.7, 8.6 Hz, bridgehead *H*); $^{13}C$ NMR (75MHz, $CDCl_3$) $\delta_C$ 165.14, 157.57, 138.88 (dd, J = 5.1 Hz), 138.71, 136.47, 136.20, 136.00, 134.29, 133.59, 133.44, 132.41, 131.15, 129.86, 1129.76, 129.43, 129.33, 129.16, 129.01, 128.96, 128.89, 127.79, 127.44, 127.20, 126.83, 126.68, 124.23, 117.41, 115.25, 91.41 (dd, J = 5.9, 9.0 Hz), 86.75 (dd, J = 5.4, 10.6 Hz), 68.83 (d, J = 9.6 Hz), 67.24 (d, J = 4.3 Hz), 63.82 (d, J = 8.8 Hz), 52.80 (bridgehead *C*), 52.34 (bridgehead *C*), 39.75, 34.16 (dd, J = 3.4, 14.2), 33.29, 31.59, 17.30, 16.44, 15.28.




**31**
MW 461.00

**32**
MW 664.98

**Complex 32** was obtained by mixing **2a** (38.5 mg, 0.089 mmol.) and complex **31** (20.4, 0.044 mmol) in $CDCl_3$ in an NMR tube. FTIR ($CDCl_3$, $cm^{-1}$) 2986, 2902, 1677, 1604; $^1H$ NMR (300MHz, $CDCl_3$) δ 8.22 (br d, 1 h, J = 8.1 Hz), 7.96 (ddd, 1H, J = 1.8, 7.5, 12.3 Hz), 7.72 (ddd, 1H, J = 1.8, 7.2, 8.7 Hz), 7.28-7.58 (m, 11H), 7.09 (dt, 1H, J = 1.5, 7.5 Hz), 6.98 (dt, 2H, J =1.5, 6.6 Hz), 5.09 (br s, 1H), 4.58 (br s, 1H), 3.62 (br s, 1H), 3.48 (br s, 2H), 2.70 (br s , 1H), 2.17 (s, 3H, $CH_3$), 1.98 (s, 3H, $CH_3$), 1.27 (s, 2H).




**27**
MW 580.17

**28**
MW 724.56

**Resolution of Compound 2a:** A toluene solution of (-)-di-μ-chloro-bis[(*S*)-dimethyl(1-phenylethyl)aminato-$C^2$, *N*]dipalladium(II) (**27**) (100 mg, 0.172 mol) and **2a** (150 mg, 0.345 mmol) was stirred for 4 hours at ambient temperature. The mixture was treated with 2 mL of hexanes and stored at 0°C overnight. Yellow crystals of (*S*, *R*)-**28** precipitated in 99.8% yield (124.8 mg): mp 185°C (dec.); $Rf$ = 0.67 (silica, ethyl acetate); FTIR (thin film, $cm^{-1}$) 3448, 1676, 1601, 1474, 1437 (P-Ph), 1340, 1267, 1092, 774, 731, 697; $^1H$ NMR (300MHz, $CDCl_3$) δ 8.09 (dd, 2H, J = 7.5, 10.5 Hz), 7.82 (dd, 1H, J = 1.4, 8.3 Hz), 7.74 (dd, 2H, J = 7.7, 12.1 Hz), 7.54 - 7.67 (m, 2H), 7.22 - 7.52 (m,

8H), 6.87 (d, 1H, J = 7.2 Hz), 6.71 (t, 1H, J = 7.4 Hz), 6.62 (br t, 1H, J = 6 Hz), 6.46 (t, 1H, J = 7.2 Hz), 6.16 (ddd, 1H, J = 1.2, 7.6, 7.6 Hz), 5.86 (br t, 1H, J = 7.1 Hz), 3.78 (m, 1H), 2.86 (d, 3H, J = 2.0 Hz), 2.75 (d, 3H, J = 3.0 Hz), 2.67 (s, 2H), 1.93 (s, 3H), 1.74 (d, 3H, J = 6.5Hz), 1.55 (s, 3H).

Treatment of the less soluable complex (*S*, *R*)-**28** with bis(diphenylphosphino)-ethane (DIPHOS, 70 mg, 0.176 mmol) in $CH_2Cl_2$ (3 mL), followed by chromatogrphy and crystallization from ethyl acetate-hexanes mixture, gave 74.6 mg (99.7%) of free ligand (*R*)-(-)-**2a** as white needles: mp 138 - 140 °C; $[\alpha]_D^{23}$ = – 250° (*c* = 0.28, $CH_2Cl_2$; 100% ee based on chiral HPLC). The mother liquor was treated with DIPHOS followed by chromatography and crystallization from ethyl acetate/hexanes to give (*S*)-(+)-**2a** (48.4 mg, 65%): mp 148-153°C; $[\alpha]_D^{23}$ = + 194° (*c* = 0.42, $CH_2Cl_2$; 96% ee based on chiral HPLC ).

## References


1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**, Chap.1.
2. Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533.
3. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
4. (a) Cooper, M. K.; Downes, J. M.; Duckworth, P. A. *Inorg. Synth.* **1989**, *25*, 129. (b) Cooper, M. K.; Downes, J. M.; Duckworth, P. A.; Tiekink, R. T. *Aust. J. Chem.* **1992**, *45*, 595-609.
5. (a) Fuhrer, W.; Gschwend, H. *J. Org. Chem.* **1979**, *44*, 1133. (b) Turner J. A. *J. Org. Chem.* **1983**, *48*, 3401. (c) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (d) Macdonald, J. E.; Poindexter, G. S. *Tetrahedron Lett.* **1987**, *28*, 1851. (e) Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725. (f) Wakefield, B. J. *Organolithium Methods*, Academic Press, 1988.
6. Gschwend, H. W.; Rodriguez, H. R. *Organic Reactions* **1976**, *26*, 1.
7. Carey, F. A.; Sunberg, R. J. *Advanced Organic Chemistry* 3rd Ed., **1990**, Part A, pp. 578.
8. Chupp, J. P. *US Patent* 4,188,342, **1980**.
9. Horner, L.; Luckenbach, R.; Balzer, W.D. *Tetrahedron Lett.* **1968**, *9*, 3157.
10. (a) Oki, M *The chemistry of Rotational Isomers*, Springer-Verlag, **1993**, pp. 7-10. (b) Oki, M *Recent Advances in Atropisomerism* in *Topics in Stereochemistry, 14*, Allinger, N.; Eliel, E., L. and Wilen, S., H., Ed. John Wiley & Sons: New York, **1983**, chapt. 1.
11. Farghaly, A. M.; Chaaban, I.; Khalil, M.A.; Bekhit, A. A. *Arch. Pharm (Weinheim)* **1990**, *323*, 833.

12. Mannschreck, A.; Koller, H.; Sthühler, G.; Davies, M. A.; Traber, J. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *19*, 381.

13. Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry,* ed. Boulton A. J.; Mckillop A., Pergamon Press, **1984**, Vol. 3, pp.106-155.

14. a) Perrin, D., D. *Dissociation Constants of Organic Bases in Aqueous Solution,* Butterworths: London, **1965**, pp. 277 - 283.

b) Perrin, D., D. *Dissociation Constants of Organic Bases in Aqueous Solution, Supplement 1972*, Butterworths: London, **1972**, Nos. 6782 - 6888.

15. Newman, P. *Optical Resolution Procedures for Chemical Compounds, Vol. I: Amines and Related Compounds*, Riverdale, New York: optical Information Center, Manhattan College, **1981**.

16. Grimmel; Guenther; Morgan *J. Am. Chem. Soc.* **1946**, *68,* 542.

17. Jackman, G. B.; Petrow, V.; Stephenson, O. *J. Pharm. and Pharmacol.* **1960**, *12,* 529.

18. Mohan, A. G.; D'Antuono, J., III *US Patent* 5,342,944, 1994.

19. (a) Otsuka, S.; Nakamura, A.; Kano, T.; Tani, K. *J. Am. Chem. Soc.* **1971**, *93,* 4301.

(b) Tani, K.; Brown, L. D.; Ahmed, J.; Ibers, J. A.; Yokota, M.; Nakamura, A.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99,* 7876.

20. Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

21. (a) Gioria, J. M.; Susz, B. P. *Helv. Chim. Acta* **1971**, *54*, 2251.

(b) Paul, R. C.; Moudgil, A. K.; Chadha, S. L.; Vasisht, S. K. *Indian J. Chem.* **1970**, *8*, 1017.

22. (a) Elguero, J.; Marzin C.; Katritzky A. R.; Linda P. *The tautomerism of Heterocycles* Academic Press: New York, pp. 129-183 **1976**.

(b) Rathman, T. L.; Sleevi, M. C.; Krafft, M. E.; Wolfe J. F. *J. Org. Chem.* **1980**, *45*, 2169 and references cited therein.

23. Sheehan, J., C.; Yang, D., H. *J. Am. Chem. Soc.* **1958**, *80*, 1154.

24. (a) Levy, P., R.; Stephen, H. *J. Chem. Soc.* **1956**, 985.

(b) Soliman, F. M.; Islam, I. E.; Kassab, R. R.; Souka, L. M.; El Kady, M. Y. *Rev. Roum. Chim.* **1994**, *39*, 405.

25. (a) Hayashi, T *Yuki Gosei Kagaku Kyokaishi* **1994**, 52, 900.

(b) Uozumi, Y; Kitayama, K; Hayashi, T *Tetrahedron: Asymmetry* **1993**, *4*, 2419.

26. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

27. (a) Roberts, N. K.; Wild, S. B. *J. Chem. Soc., Dalton Trans.* **1979**, 2015.

(b) Allen, D. G.; McLaughlin, G. M.; Robertson, G. B.; Steffem, W. L.; Salem, G.; Wild, S. B. *Inorg. Chem.* **1982**, *21*, 1007.

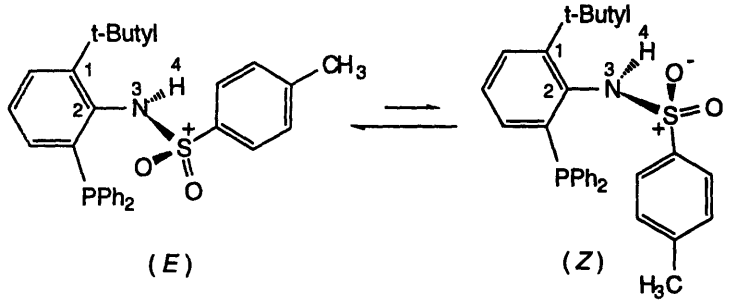
## Appendix: Results of Molecular Mechanics Calculations

All molecular mechanics calculations of compound **1**, **18**, **2a**, and **2c** were carried out with "Insight II (Version 2.3.5): Discover" program from Biosym on a "Silicon Graphic - Indigo" workstation. The barrier to rotation about the $C_{aryl}$–N bond was evaluated by rigid rotation of the phenyl ring in 30° intervals (in the calculations of **18**, **2a**, and **2c**, some smaller intervals were used to smooth the energy curves). Minimization was performed until the energy gradient was ≤ 0.01 kcal/(mol·Å) by holding the dihedral angel that defined the phenyl-ring orientation.

Since $\Delta S^{\ddagger}$ is very small in these bond-rotating processes, the rotational barrier $\Delta G^{\ddagger}$ (free energy of activation) equals $\Delta H^{\ddagger}$ in good approximation. $\Delta H^{\ddagger}$ is defined as the difference between the minimized energy at a certain dihedral angle and the lowest minimized energy of each compound. The $\Delta G^{\ddagger}$ is the smaller one of the two $\Delta H^{\ddagger}$'s at dihedral angle 0° and dihedral angle 180°.

1). Sulfonamide **1**:

Molecular mechanics calculations of sulfonamide **1** were carried out on both of its *E* and *Z* conformations (Figure 1 and Figure 2). The dihedral angle is the angle of C1-C2-N3-H4. The $\Delta G^{\ddagger}$ of the *E* conformation is 12.7 kcal/mol. The $\Delta G^{\ddagger}$ of the *Z* conformation is 20.9 kcal/mol. The *E* conformation is the lowest energy conformation.




(*E*) (*Z*)

**1**

The author would like to thank Mr. Tao Ke of Prof. Klibanov group for providing help and instruments on the molecular mechanics calculations.

Figure 1

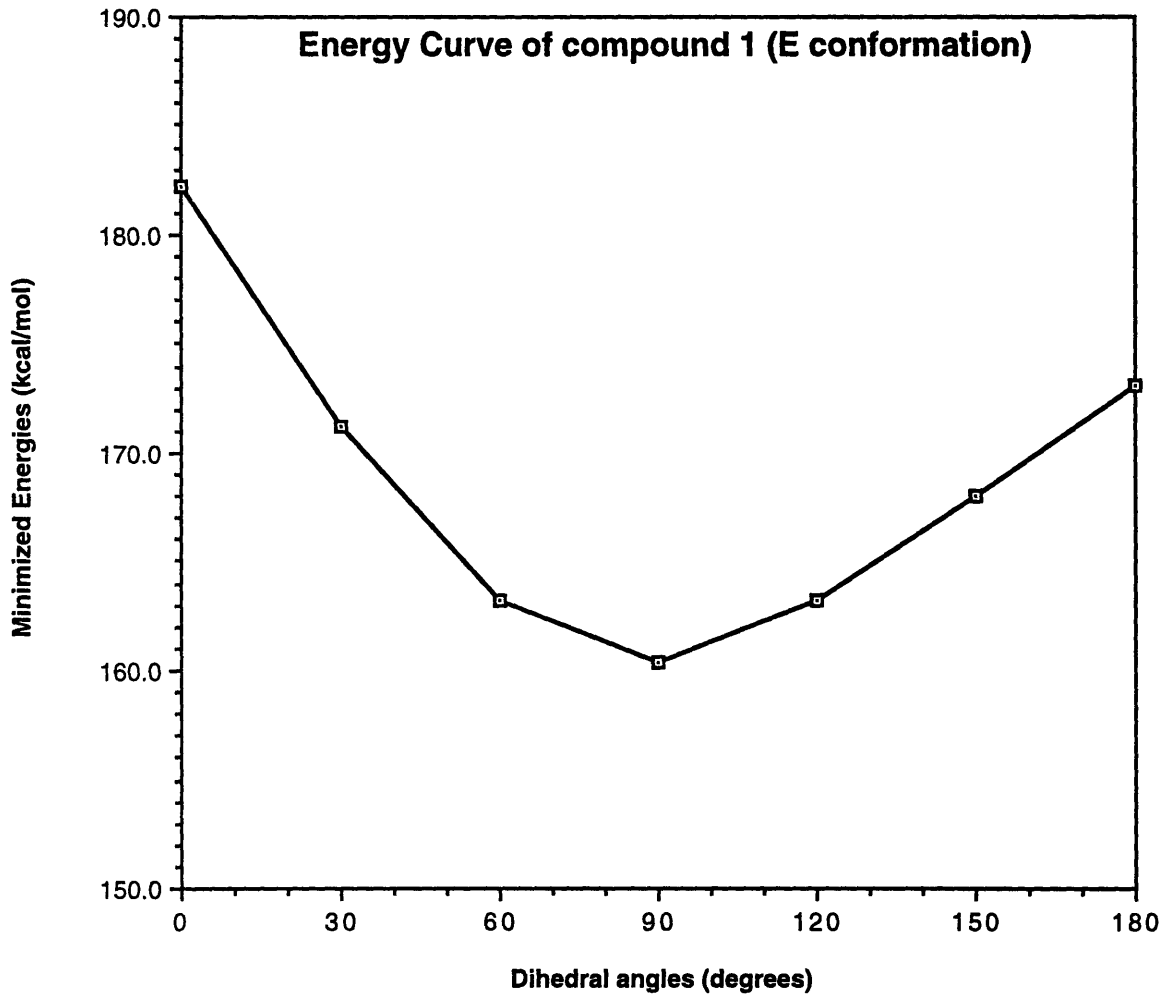
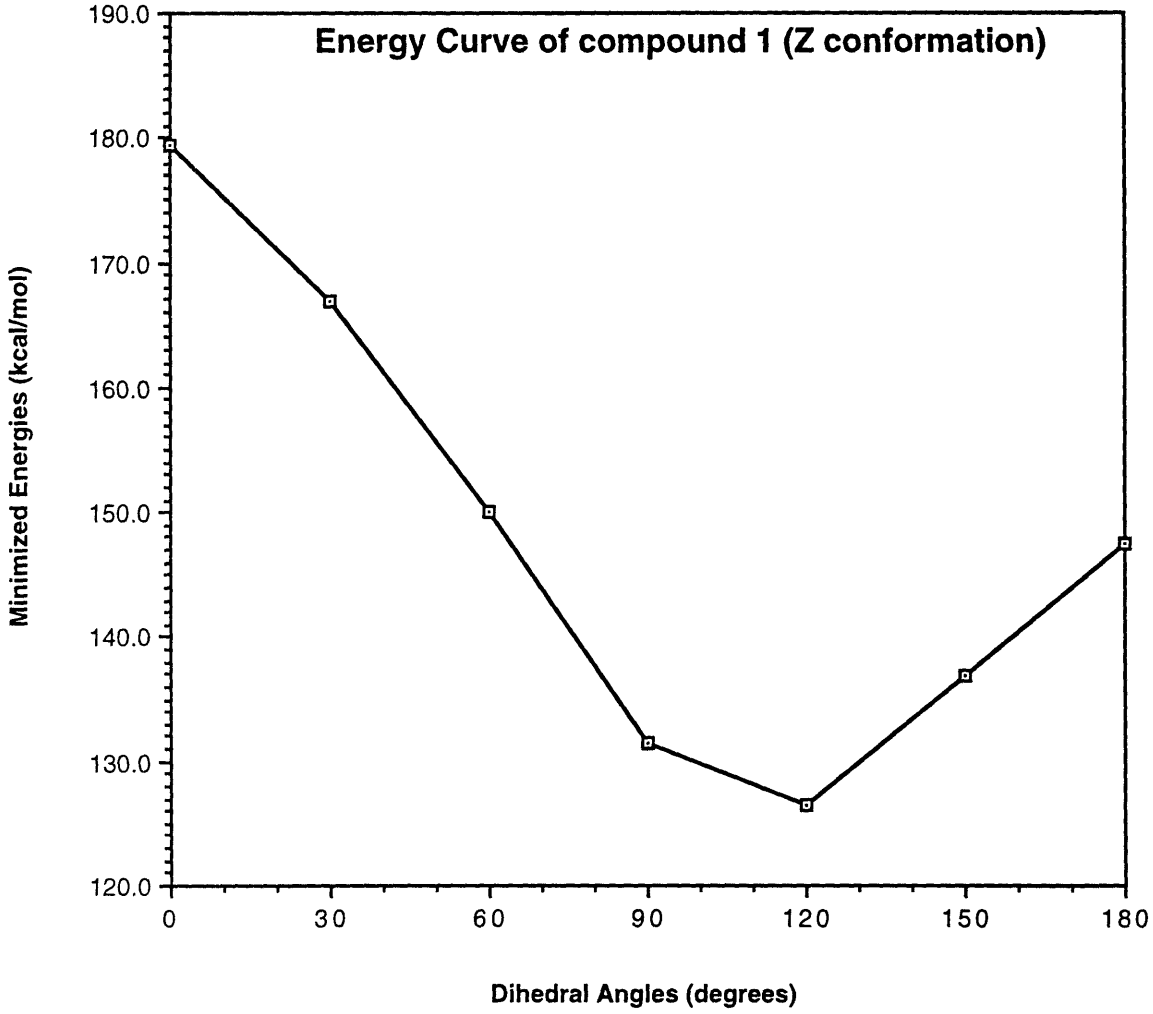
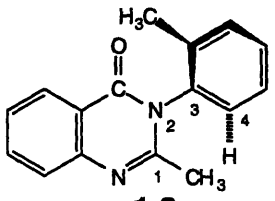

Energy Curve of compound 1 (E conformation)
Minimized Energies (kcal/mol)
190.0
180.0
170.0
160.0
150.0
0
30
60
90
120
150
180
Dihedral angles (degrees)

Figure 2


Energy Curve of compound 1 (Z conformation)
Minimized Energies (kcal/mol)
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
0
30
60
90
120
150
180
Dihedral Angles (degrees)

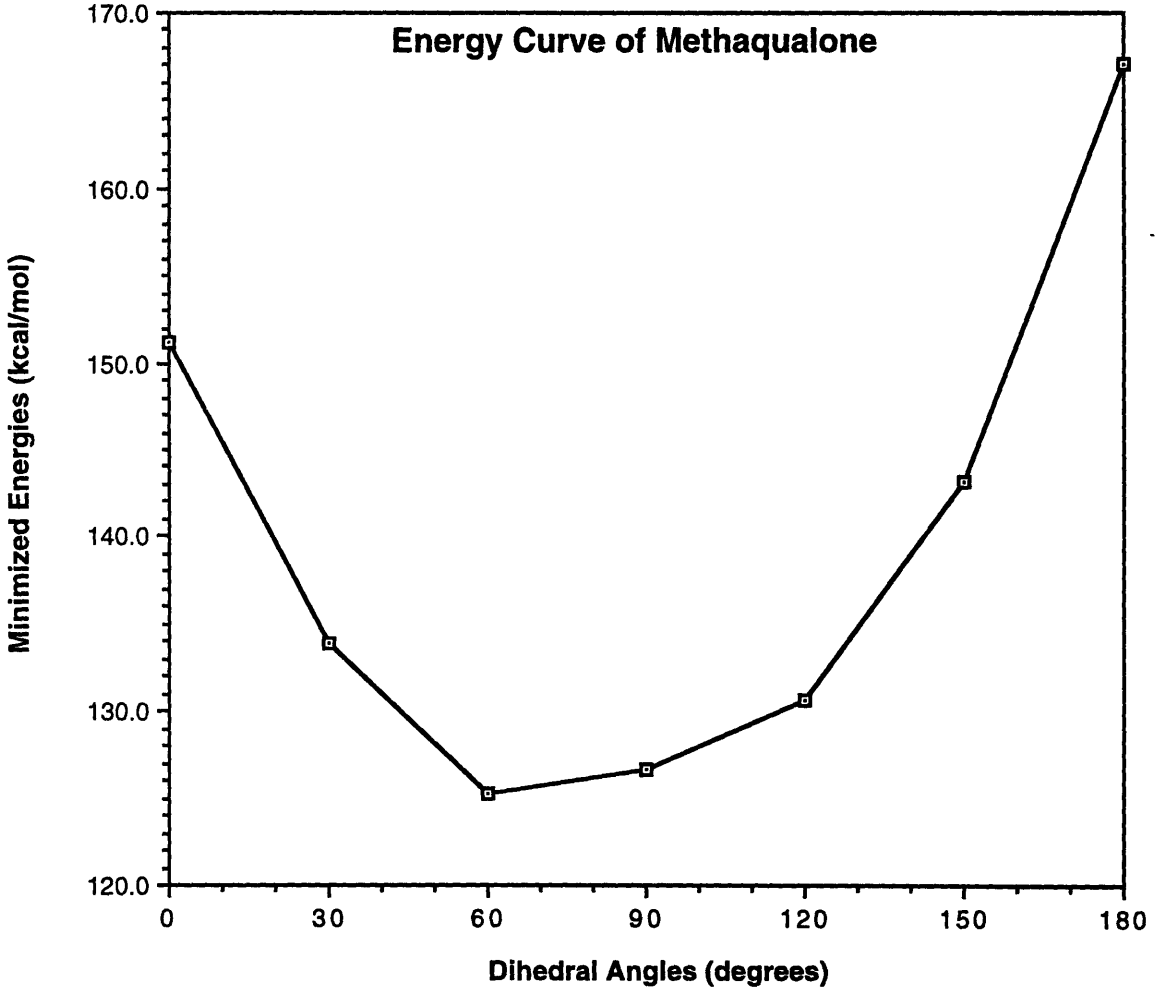
2). Methaqualone **18**:

The dihedral angle is the angle of C1-N2-C3-C4. The $\Delta G^{\ddagger}$ is 25.9 kcal/mol (Figure 3). This value is close to the experimental $\Delta G^{\ddagger}$ which is 31.5 kcal/mol.[12] This indicates the method used for the molecular mechanics calculations is reliable to some extent.



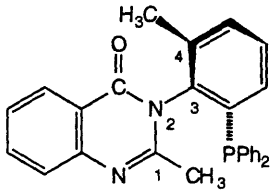

**18**

**Figure 3**



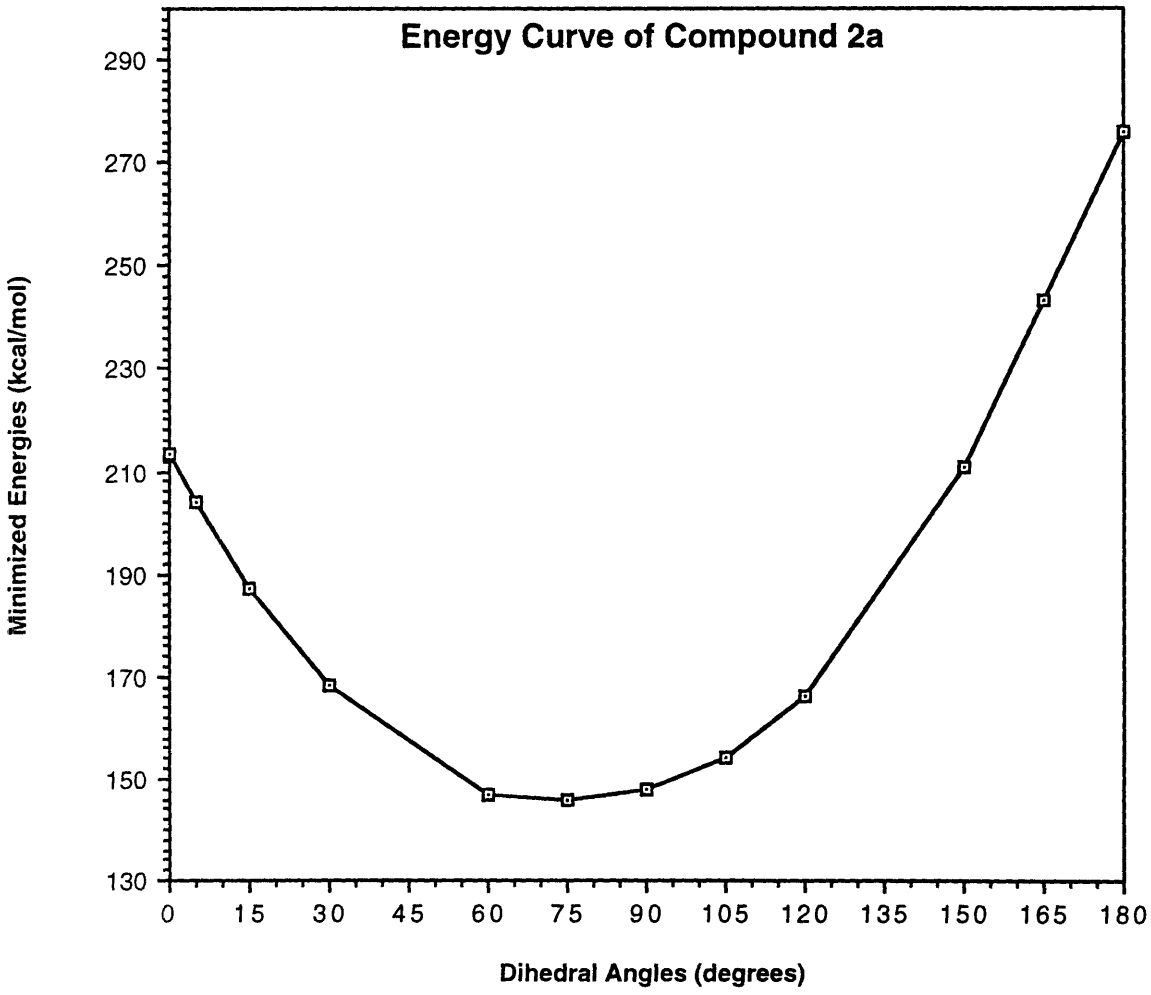
3). Compound **2a**:

The dihedral angle is the angle of C1-N2-C3-C4. The $\Delta G^{\ddagger}$ is 68.0 kcal/mol (Figure 4).



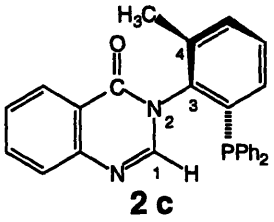

**2 a**

**Figure 4**



4). Compound **2c**:

The dihedral angle is the angle of C1-N2-C3-C4. The average $\Delta G^{\ddagger}$ is 54.8 kcal/mol (Figure 5).




**2 c**

**Figure 5**