SYNTHESIS AND APPLICATIONS OF ATROPISOMERIC QUINAZOLINONE PHOSPHINE LIGANDS

by

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Submitted to the Department of Chemistry
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Signature of Author .....
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Professor Timothy M. Swager _____

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ABSTRACT

Several novel atropisomeric phosphine ligands have been synthesized and evaluated. The syntheses of 2-methyl-3-[2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (**1a**) and its methyl-substituted analogs **1b** and **1c** were achieved in good yield by coupling *N*-acetylanthranilic acid with the corresponding phosphinoanilines **4a-c**. A practical resolution of ligands **1a-c** was accomplished using the benzenesulfonylhydrazone derivative (**10**) of (1*S*)-(+)-camphorsulfonic acid as a novel resolving agent. Several catalytic reactions including palladium-catalyzed asymmetric allylic alkylation, phosphine-catalyzed [3+2] cycloaddition of *N*-tosylimines with 2,3-butadienoate, and asymmetric intramolecular Heck reaction were performed. The 2-methyl group of this ligand series could be activated into the olefin form in the presence of $Rh(nbd)_2ClO_4$. The rhodium complex was found to be able to catalyze conjugate addition of the Grignard reagent (*n*-BuMgBr) to enones.

The synthesis of 3-[4',6'-dimethyl-2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (**1d**) was achieved by coupling 4*H*-3,1-benzoxazin-4-one (**71**) with 4,6-dimethyl-2-diphenylphosphinoaniline (**4c**). Ligand **1d** could be directly lithiated by lithium diisopropylamide (LDA). The hetero-substituted analogs **1e-g** were synthesized in good yield by quenching the lithium anion of ligand **1d** with electrophiles. Resolutions of ligands **1d** and **1e** were achieved using (-)-di-μ-chloro-bis[(*S*)-dimethyl-(1-naphthylethyl)aminato-C^2, *N*]dipalladium(II) (**78**) and (-)-di-μ-chloro-bis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2, *N*]dipalladium(II) (**7**), respectively.

Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

To my parents, my brother,

and my life partner -- Li.

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My friend Xiaohong Zhao and his wife have provided me with endless support and care since my first day at MIT. Visiting them is still the best part of my weekends. I feel very lucky to have friends like Chris Mellon, Jeff Song, Ke Tao, Ed Wang, and Chuan He etc. Their friendship and support have cheered up my life and study in Boston.

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Table of Contents

Chapter 1. Introduction

1.1 Background on Atropisomeric Phosphine Ligands

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, an important class of ligands devoid of chiral atoms are represented by the biaryl atropisomeric phosphine ligands (Figure 1). They derive their chirality from restricted rotation about single bonds caused by steric constraints.

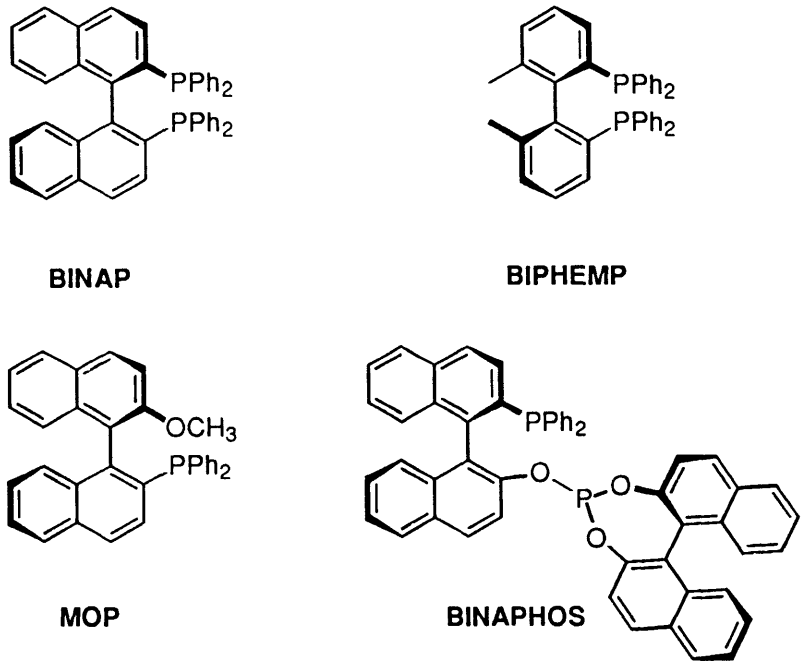

Figure 1. Biaryl atropisomeric phosphine ligands.

[1] (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

Since the introduction of BINAP ((*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, Figure 1) by Noyori and coworkers,[2] the synthesis of new atropisomeric phosphine ligands has become an active field in organic synthesis. A number of other atropisomeric phosphine ligands based on the biaryl structure have been developed, such as BIPHEMP,[3] MOP,[4] and BINAPHOS[5] (Figure 1). The chiral environment imposed by the orthogonal aryl rings has proven effective for inducing high stereoselectivity in a variety of asymmetric reactions.

Although most of the present atropisomeric ligands contain carbocyclic aromatic structures, the emergence of a few of heteroaryl phosphine ligands has attracted increasing attention (Figure 2). Aromatic heterocyclic chemistry is a subject of great industrial and academic significance. Many important pharmaceutical and agrochemical compounds are based on aromatic heterocycles. Consequently, the importance of aromatic heterocyclic chemistry has stimulated a vast amount of synthetic and theoretical work in this area.

Synthetic approaches to heterocyclic compounds are often more straightforward than those available for carbocyclic aromatic systems. For a carbocyclic system such as BINAP, it is difficult to regioselectively introduce substituents onto its skeleton. The structure of a heteroaromatic ligand is relatively easy to modify in order to modulate its catalytic activity for a given reaction. The nature of the heterocycle strongly influences the electronic properties of the electron lone pairs on the attached phosphorus atoms. Electronic tuning of phosphine ligands can therefore be brought about by changing the

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[2] BINAP: (a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187. (b) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

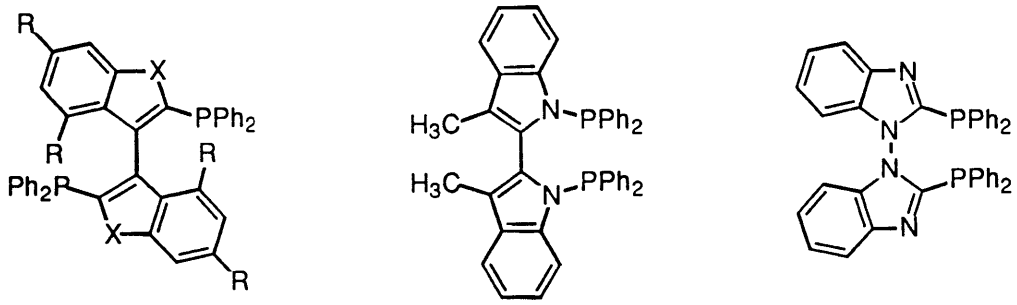
[3] BIPHEMP: Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.

[4] MOP: (a) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (b) Hayashi, T.; Iwamura, H.; Uozumi, Y.; Matsumoto, Y.; Ozawa, F. *Synthesis* **1994**, *15*, 526. (c) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

[5] BINAPHOS: (a) Sakai, N.; Mano, S.; Nozaky, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Sakai, N.; Nozaky, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395.

supporting heterocyclic system. Alternatively, electronic modification of the phosphine groups can be effected by changing their positions on a given heterocycle.

Recently, Sannicolò's group synthesized several new atropisomeric phosphine ligands based on three different five-membered heteroaromatic structures (Figure 2).[6] Two of the new diphosphine ligands (tetraMe-BITIANP and BITIANP) show quite similar stereoselectivity to that exhibited by BINAP in asymmetric hydrogenation. It is interesting to note that BIMIP was presented as the first atropisomeric ligand with chirality based on a nitrogen-nitrogen linkage.



X = S, R = CH_3 (**tetraMe-BITIANP**)
X = S; R = H (**BITIANP**)
X = O; R = H (**BIFURP**)

BISCAP

BIMIP

Figure 2. Atropisomeric phosphine ligands based on five-membered heteroaromatic structures.

Atropisomeric ligands with one carboaromatic and one heteroaromatic ring have also been designed. In the case of QUINAP (Figure 3), the quinoline nitrogen serves as an effective chelating site for transition metals such as palladium and rhodium.[7] Enantiomeric

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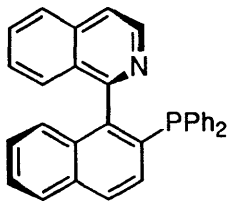
[6](a) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244. (b) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T.; Zotti, G. *J. Organomet. Chem.* **1997**, *529*, 445.

[7] QUINAP: (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743. (b) Brown, J. M.; Hulmes, D. I.; Layzell, T. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1673.

excess up to 98% has been achieved with the rhodium complex of QUINAP in the hydroboration-amination reaction of vinylarenes.[8]



QUINAP

Figure 3. QUINAP: An atropisomeric ligand with one carboaromatic and one heteroaromatic ring.

1.2 The Structures and Functions of Substituted Quinazolinones

Several compounds comprising a 4(3*H*)-quinazolinone moiety exhibit important biological activities (*e.g.* H1, H2-antihistaminic, antimalarial, sedative, anti-Parkinson, antimitotic, antihypertensive, antiinflammatory, anticonvulsant, antimicrobial , and CNS (central nervous system) activities).[9,10] The quinazolinones have thus been well-studied as pharmaceutical research and development candidates .

The following compounds are chosen to illustrate the range of the structural complexity of quinazolinones.

Three achiral alkaloids shown in Figure 4 have been isolated from natural sources.[11] Tryptanthrin has been found to have antimycotic activity against dermatophytes and has specific activity against those causing athlete's foot. Candidine is an inhibitor

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[8] Fernandez, E.; Hooper, M. W.; Knight, F. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1997**, 173.

[9] (a) Farghaly, A. M.; Chaaban, I.; Khalil, M.A.; Bekhit, A. A. *Arch. Pharm (Weinheim)* **1990**, *323*, 833. (b) Kurogi, Y.; Inoue, Y.; Tsutsumi, K.; Nakamura, S.; Nagao, K.; Yoshitsugu, H.; Tsuda, Y. *J. Med. Chem.* **1996**, *39*, 1433.

[10] For recent review on quinazoline alkaloids: Michael, J. P. *Nat. Prod. Rep.* **1997**, *6*, 605 and the references cited therein.

[11] For a review on tryptanthrin and candidine: Billimoria, A. D.; Cava, M. P. *Heterocycles*, **1996**, *42*, 453. For 1-methoxyrutaecarpine: Sheen, W.-S.; Tsai, I. -L.; Teng, C.-M.; Ko, F.-N.; Chen. I.-S. *Planta Med.* **1996**, *62*, 175.

against Lewis lung carcinoma in mice. 1-Methoxyrutaecarpine shows antiplatelet aggregation activity.

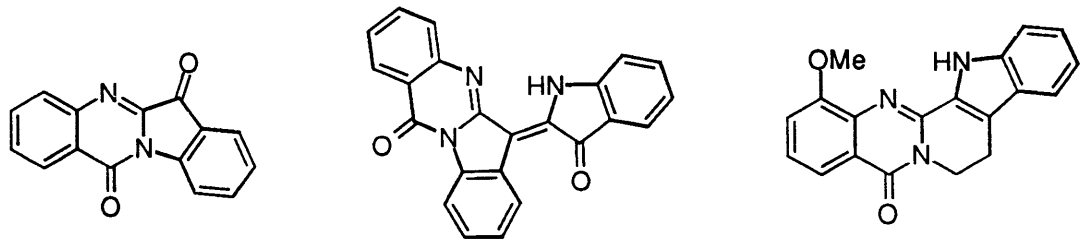

Figure 4. Achiral quinazolinone alkaloids.

Other structures which contain an atropisomeric N-C_{aryl} bond are synthesized and administered as racemates (Figure 5). Fluquinconazole (also known as SN-597265) is an effective fungicide against diseases in apple trees and was developed by scientists at Schering.[12] Methaqualone was introduced as a hypnotic-sedative in the early 1960s and soon became both widely prescribed and widely abused for its recreational property. By the early 1980s, it was withdrawn from most markets.[13]

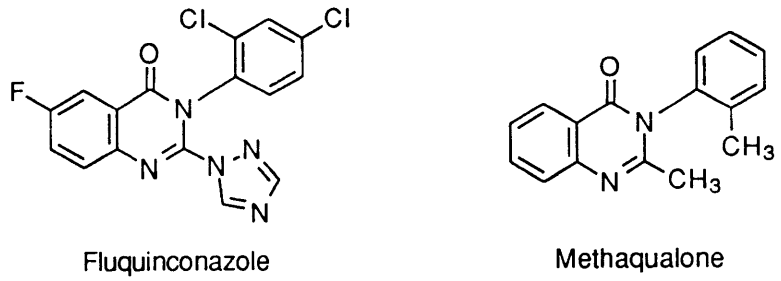

Figure 5. Quinazolinones containing an atropisomeric N-C_{aryl} bond.

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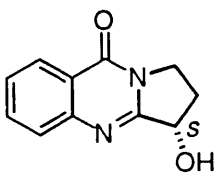
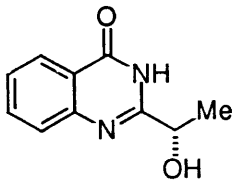
[12] Shannon, C. *Chem. Ind.* **1992**, 893.

[13] (a) *Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th Ed.; Merck & Co., Inc.: Rahway, NJ, 1989; pp 939-940. (b) Perrine, D. M. *The Chemistry of Mind-Altering Drugs -- History, Pharmacology, and Cultural Context* ; ACS: Washington, DC, 1996.

Some chiral quinazolinone compounds are listed in Figure 6. (-)-Vasicinone and (-)-chrysogine showed uterine stimulatory and bronchodilatory activity.[14] Recently, the absolute configuration of (-)-vasicinone has been revised to 3*S* based on X-ray crystallographic analysis[15] and synthetic correlation methods.[16]



(-)-Vasicinone



(-)-Chrysogine

Figure 6. Chiral quinazolinone compounds.

3-Acetoxyamino-2-substituted-quinazolinone systems (QNH_2OAc, Scheme 1) are closely related to the structures of (-)-vasicinone and (-)-chrysogine. They were found by Atkinson's group to be effective asymmetric aziridinating agents for a variety of alkenes.[17] Diastereoselectivity up to 50:1 has been achieved for styrene with QNH_2OAc in the presence of titanium *t*-butoxide. The mechanism for the aziridination appears to resemble that of the peroxyacid epoxidation of alkenes.

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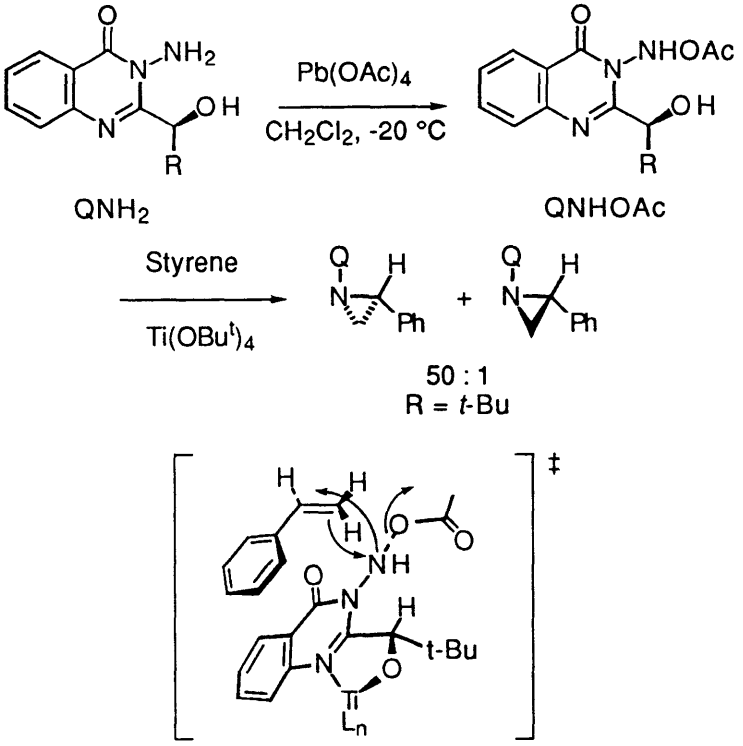
[14] Michael, J. P. *Nat. Prod. Rep.* **1995**, *4*, 472 and the references cited therein.
[15] Joshi, B. S.; Newton, M. G.; Lee, D. W.; Barber, A. D.; Pelletier, S. W. *Tetrahedron: Asymmetry* **1996**, *7*, 25.
[16] Bergman, J. *J. Chem. Res. (S)* **1997**, 224.
[17] Atkinson, R. S.; Gattrell, W. T.; Ayscough, A. P.; Raynjam, T. M. *J. Chem. Soc., Chem. Commun.* **1996**, 1935 and references cited therein.

Scheme 1



Benzomalvins A, C, and D are quinazolinones fused with benzodiazepine (Figure 7). These compounds were tested as inhibitors for substance P, an endogenous ligand for the neurokinin-1 receptor, which is implicated in inflammatory response and the perception of pain.[18] At room temperature, benzomalvin A and D are in conformational equilibrium in the ratio of 4:1.

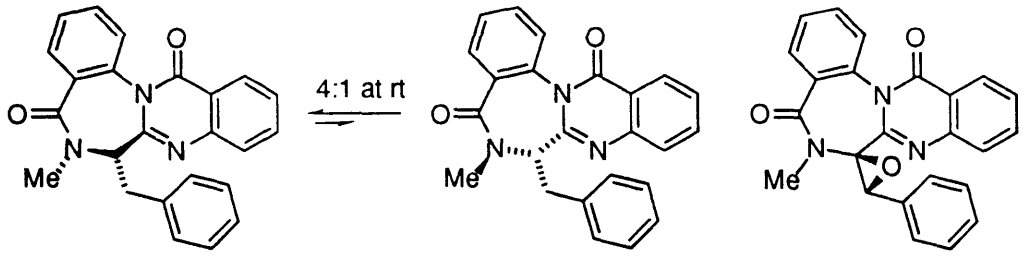


Figure 7. Quinazolinones fused with benzodiazepine structures.

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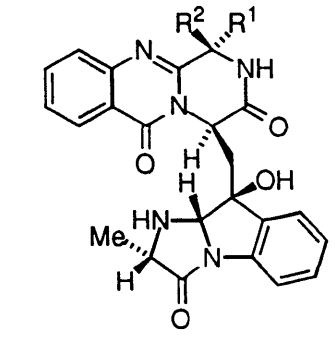
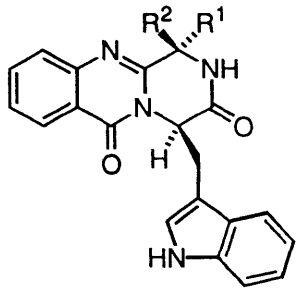
[18] Sun, H. H.; Barrow, C. J.; Sedlock, D. M.; Gillum, A. M.; Dooper, R. *J. Antibiot.* **1994**, *47*, 515.

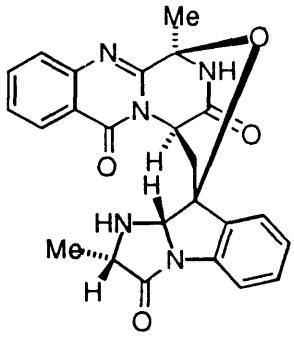
The intriguing structures of fumiquinazoline A-G (Figure 8) have led to several total synthesis studies of some of these compounds.[19] Their moderate cytotoxicity in the P388 lymphocytic leukemia test system has also attracted considerable attention among medicinal chemists.[20]



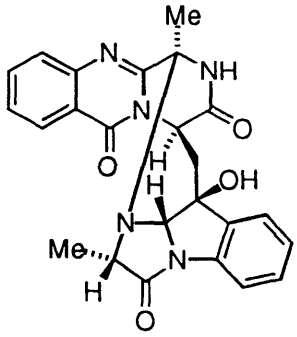
R^1 = Me, R^2 = H : Fumiquinazoline A
R^1 = H, R^2 = Me : Fumiquinazoline B
R^1 = Me, R^2 = OMe : Fumiquinazoline E



R^1 = Me, R^2 = H
Fumiquinazoline F
R^1 = H, R^2 = Me
Fumiquinazoline G



Fumiquinazoline C



Fumiquinazoline D

Figure 8. Quinazolinones with complicated structures.

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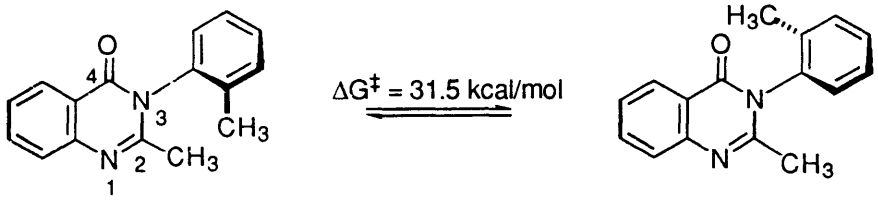
[19] (a) (-)-Fumiquinazoline G: Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432. (b) (+)-Fumiquinazoline G: He, F.; Snider, B. B. *Synlett* **1997**, 483.
[20] Malamas, M. S.; Millen, J. *J. Med. Chem.* **1991**, *34*, 1492.

1.3 Atropisomerism of Quinazolinones and Related Compounds

Of the types of quinazolinone compounds mentioned above, we are particularly interested in 3-aryl-4(3*H*)-quinazolinones (Scheme 2). These compounds are stereochemically analogous to biphenyls and undergo a similar interconversion process between enantiomeric rotational isomers. It has been noted that a 3-aryl-4(3*H*)-quinazolinone compound would be a resolvable atropisomer if the *ortho* substituents on its aryl ring were large enough to block the rotation of the N–C_{aryl} bond. In particular, the activation barrier ($\Delta G^{\ddagger}$) to racemization of 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone) was determined to be 31.5 kcal/mol at 135 °C in diphenyl ether by chiral liquid chromatography (Scheme 2).[21] It can be resolved by chiral liquid chromatography into two stable enantiomers that have different anticonvulsive activities.

Scheme 2



(*S*)-Methaqualone (*R*)-Methaqualone

In 1975, Colebrook *et al.* studied the rotational barriers of several 3-aryl-2-benzyl-4(3*H*)-quinazolinones (Figure 9).[22a] By ^{1}H-NMR analysis of the coalescence (at elevated temperatures) of the AB quartet from the diastereotopic 2-methylene protons, the rotational

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[21] (a) Activation barrier determination: Mannschreck, A.; Koller, H.; Stühler, G.; Davies, M. A.; Traber, J. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *19*, 381. NMR study: (b) Poropatich, A.; Rothchild, R. *Spectrosc. Lett.* **1990**, *23*, 29. (c) Blumenstein, M.; Ross. J.; Rothchild, R. *Spectrosc. Lett.* **1990**, *23*, 189. (d) Rothchild, R.; Wyss, H. *Spectrosc. Lett.* **1994**, *27*, 225.

[22] (a) Colebrook, L. D.; Giles, H. G. *Can. J. Chem.* **1975**, *53*, 3431. (b) Colebrook, L. D.; Giles, H. G.; Rosowsky, A.; Bentz, W. E.; Fehlner, J. R. *Can. J. Chem.* **1976**, *54*, 3757. (c) Colebrook, L. D. *Can. J. Chem.* **1991**, *69*, 1957.

barriers were measured to be at least 21.9 to over 23.7 kcal/mol depending on the size of the *ortho* substituents on the aryl ring.

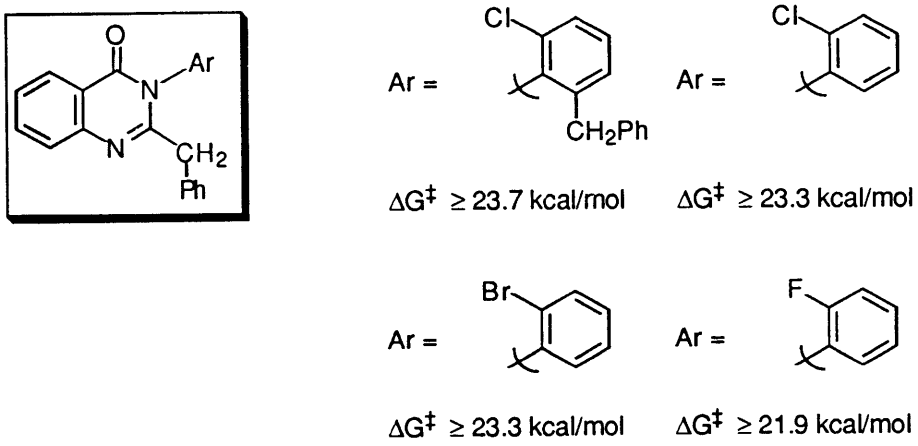

Figure 9. The rotational barriers of several 3-aryl-2-benzyl-4(3*H*)-quinazolinones.

The atropisomerism of restricted N-C_{aryl} rotation for several heterocyclic ring systems and acyclic systems has also been recognized and studied (Figure 10) including 4.6-diamino-1,2-dihydro-2,2-dimethyl-1-(*o*-tolyl)-*s*-triazine and 3-(*o*-tolyl)-5,5-dimethyl-hydantoins by Colebrook *et al.*,[22b,c] pyrimidone by Kashima *et al.*,[23] *N*-aryl-2(1*H*)-quinolones by Mintas *et al.*,[24] thiazolinone by Roussel *et al.*,[25] maleimide by Taguchi *et al.*,[26] and acyclic anilide by Taguchi, Shvo, Curran, and Shimpkins.[26,27]

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[23] Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin I*, **1980**, 1599.
[24] Mintas, M.; Mihaljevic, V. *J. Chem. Soc. Perkin Trans. 2* **1990**, 619.
[25] Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076.
[26] Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 2634.
[27] (a) Shvo, Y.; Taylor, E. C.; Mislow K.; Raban M. *J. Am. Chem. Soc.* **1967**, *89*, 4910. (b) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (c) Hughes, A. D.; Price, D. A.; Shishkin, O.; Shimpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607.

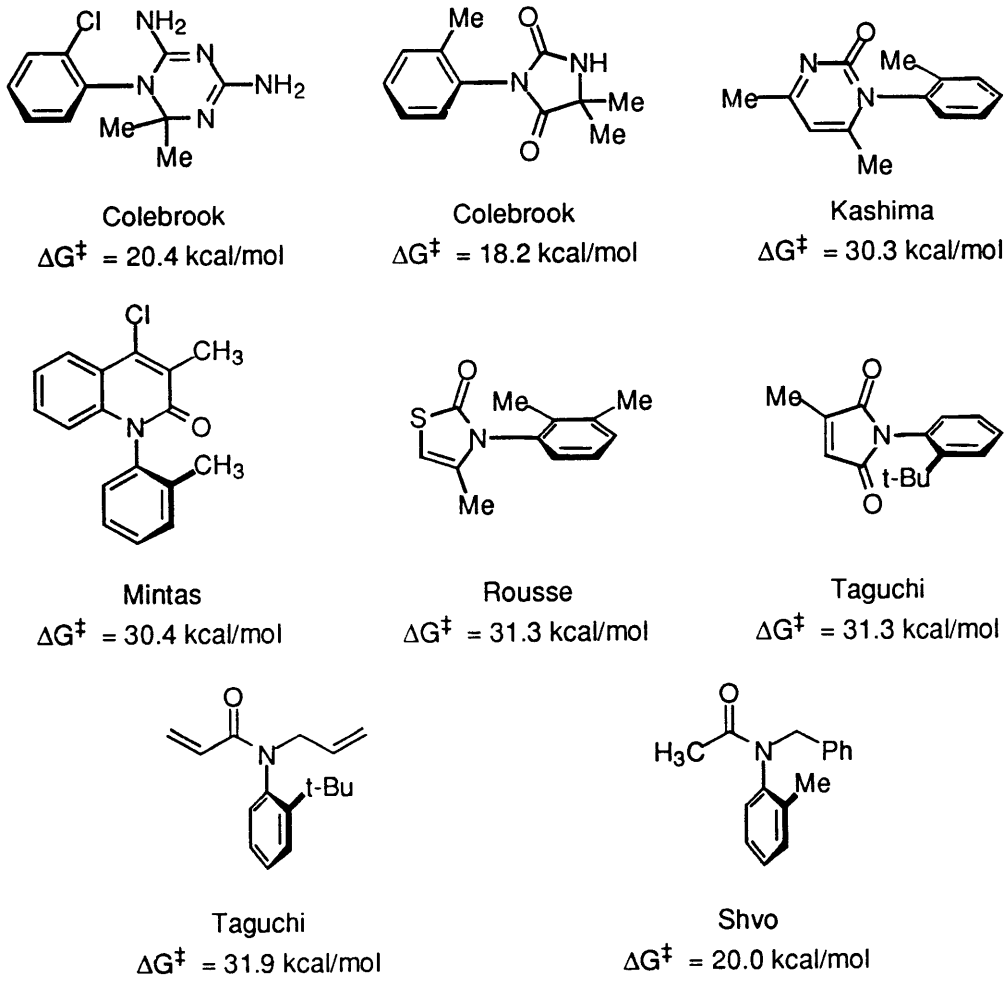
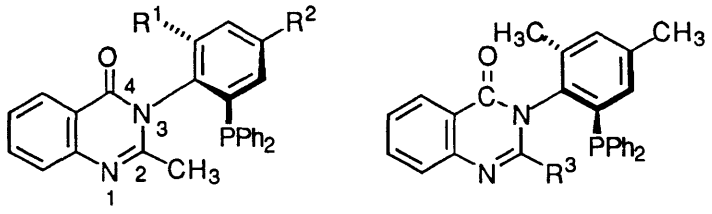


Figure 10. The atropisomerism of restricted N-C_{aryl} rotation for heterocyclic ring systems and acyclic systems.

1.4 Design of a New Class of Atropisomeric Phosphine Ligands Based on Quinazolinone Structures

We propose that by incorporating a phosphine group such as diphenylphosphino group (PPh_2) on the 3-phenyl ring of a 3-aryl-4(3*H*)-quinazolinone and adjusting the size of groups R_1, R_2, and R_3, system **1** should possess a high enough activation barrier to racemization ($\Delta G^{\ddagger}$) to allow the resolution of its enantiomers (Figure 11). This provides access to the pure enantiomers of 2-methyl-substituted monophosphine ligands **1a-c** and 2-heterosubstituted chelating ligands **1e-g**. The weak chelating property of the amide oxygen in ligands **1a-d** fine-tunes the ligands from monophosphines to chelating

phosphorus-oxygen ligands. The 2-heteroatoms of ligands **1e-g** provide these ligands with some unique coordination features.



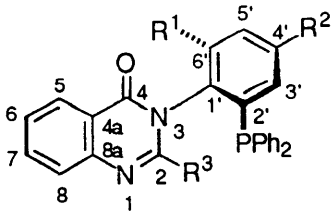
1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = CH_3$
1c $R^1 = R^2 = CH_3$

1d $R^3 = H$
1e $R^3 = PPh_2$
1f $R^3 = SH$
1g $R^3 = SMe$

Figure 11. A new class of atropisomeric phosphine ligands based on quinazolinone structures.

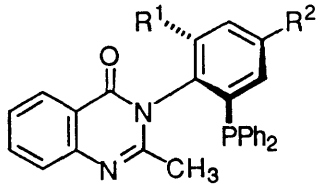
In the following chapters, the synthesis and resolution of ligands **1a-g** are discussed, the ease of structure modification is demonstrated, and the chelating properties and the applications of these chiral ligands in several asymmetric catalytic reactions are also described.

The conventional numbering scheme for 3-aryl-4(3*H*)-quinazolinone structure is used for the compounds described herein.



Chapter 2. Synthesis and Resolution of 2-Methyl-Substituted Quinazolinone Ligand System[28]

2.1 Introduction



1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = CH_3$
1c $R^1 = R^2 = CH_3$

We chose 2-methyl-3-aryl-4(3*H*)-quinazolinone system (**1a-c**) as the first target for the investigation of this novel class of atropisomeric phosphine ligands. There are several reasons for us to believe that ligands **1a-c** are candidates for a promising ligand system. First, in spite of considerable localization of π-electrons on the nitrogen atoms, the quinazolinone ring is sufficiently aromatic to possess substantial stability. This stability is essential for the ligand to survive the normal reaction conditions which would be used in metal-catalyzed asymmetric reactions. Second, there are several known methods for the efficient synthesis of quinazolinone systems as the stability of the quinazolinone ring presents a driving force toward formation of the heterocyclic ring.[29] Third, this system can be modified to create a series of ligand analogs simply by changing the substituents of the starting materials.

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[28] Part of the material in this chapter has appeared in print: Dai, X.; Wong, A.; Virgil, S. C. *J. Org. Chem.* **1998**, *63*, 2597-2600.

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

Although the weakly basic nitrogen at the 1-position of quinazolinone ($pK_a \approx 2.2$) can be protonated with strong acid to form a salt,[30] it is surprising that there has been no report on the successful resolution of quinazolinone atropisomers by acidic resolving agents.[31] On the other hand, most of the existing chiral phosphine ligands are obtained either by resolution with expensive chiral palladium complexes (see Section 2.3) or by resolution of the racemic phosphine oxide with a chiral acid (usually (1*S*)-(+)-camphorsulfonic acid or (2*R*,3*R*)-(-)-2,3-*O*-dibenzoyltartaric acid).[32] A subsequent reduction of each separated phosphine oxide enantiomer is required to afford the original phosphine ligand in optically active form. We therefore planned to investigate the resolution of ligands **1a-c** with readily available acidic resolving agents. If successful, this method would provide the most efficient access to the quinazolinone ligands in enantiopure form.

Considering the availability of the starting materials, the mildness of reaction conditions, and the reliability of the experimental procedures, the Grimmel-type synthesis[33] was chosen as the first strategy to prepare a series of ligands represented by structure **1** (Scheme 3).

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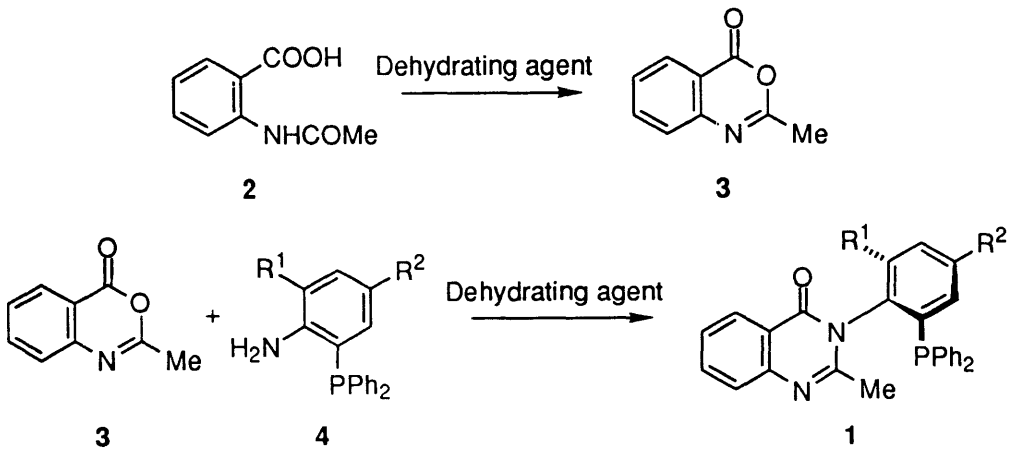
30 (a) Perrin, D., D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths: London, 1965, pp 277-283. (b) Perrin, D., D. *Dissociation Constants of Organic Bases in Aqueous Solution, Supplement 1972*, Butterworths: London, 1972, No. 6782-6888.

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

32 (a) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.

33 Grimmel, H. W.; Guenther, A.; Morgan, J. F. *J. Am. Chem. Soc.* **1946**, *68*, 542.

Scheme 3



In the presence of a dehydrating agent such as phosphorus trichloride (PCl_3), benzenesulfonyl chloride ($PhSO_2Cl$), or dicyclohexylcarbodiimide (DCC), *N*-acetylanthranilic acid **2** is first converted to the reactive intermediate 2-methylbenzoxazin-4-one (**3**), which then undergoes further condensation with aniline **4** to form 4(3*H*)-quinazolinone **1**.[34]

In this synthesis, unlike the "chiral bond" of the traditional atropisomeric ligands whose formation usually requires homocoupling of two aryl components, the "chiral N–C_{aryl} bond" of quinazolinone ligands **1a-c** is incorporated in the aniline starting material. The ligand can then be constructed by formation of the heteroaromatic ring component. This allows more flexible variations on ligand structure and presumably higher yields than homocoupling methods.

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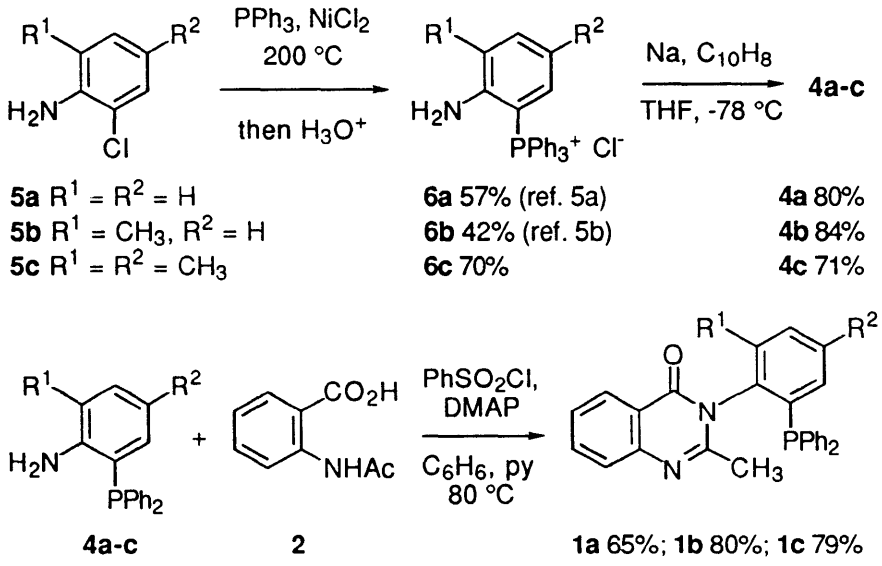
[34] (a) Jackman, G. B.; Petrow, V.; Stephenson, O. *J. Pharm. and Pharmacol.* **1960**, *12*, 529. (b) Mohan, A. G.; D'Antuono, J. III. *US Patent* 5342944, **1994**.

2.2 Two-stage Synthesis of 2-Methyl-Substituted Quinazolinone Ligands 1a-c

Our synthesis begins with the preparation of phosphinoanilines **4a-c** from the corresponding commercially available chloroanilines following Cooper's method (Scheme 4).[35] The anilines **5a-c** were treated with triphenylphosphine and anhydrous nickel(II) chloride at 200 °C to afford phosphonium salts **6a-c** after aqueous acidic work-up and recrystallization from tetrahydrofuran. Reduction of **6a-c** with sodium naphthalenide at -78 °C afforded phosphinoanilines **4a-c** in 71-84% yield after recrystallization. We found that the removal of naphthalene by sublimation using a Kugelrohr apparatus allowed a more straightforward isolation and higher yields than Cooper's reported two-step procedure involving nickel complexation and decomplexation.

Scheme 4. Preparation of the racemic ligands **1a-c**.



[35] (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.

The best yields for the formation of **1** were obtained when benzenesulfonyl chloride[36] ($PhSO_2Cl$) was used as the dehydrating reagent (Scheme 4). The pyridine solution of 2.7 equivalents of *N*-acetylanthranilic acid **2** and 2.2 equivalents of Ph_2SO_2Cl with a catalytic amount of DMAP was stirred at room temperature to form a slurry before the benzene solution of 1.0 equivalent aniline **4** was added. The mixture was heated at reflux for 18 h to afford quinazolinones **1a-c** in 65-80% yield. In particular, ligand **1c** can be obtained on a 25 gram scale from the inexpensive chloroaniline **6c**.

The mechanism proposed by Errede *et al.*[37] for the addition of a variety of amines to compound **3** can be used to understand the formation of ligand **1a-c**. The reaction starts with the generation of 2-methylbenzoxazin-4-one (**3**) from *N*-acetylanthranilic acid (**2**) and benzenesulfonyl chloride (Scheme 5). Two intermediates **3a** and **3b** produced by addition of anilines **4a-c** to the 2- and 4-positions, respectively, of compound **3**, are in equilibrium with each other. Although addition to the more electrophilic carbon at the 4-position may occur faster than to the less electrophilic carbon at the 2-position, nothing productive occurs until either cyclic transition state **3a** or **3b** rearranges to give the more stable product **3c** or **3d**, respectively. These are the rate-determining steps towards product formation.

Since oxygen is more electronegative than nitrogen, it should be easier to transfer negative charge from nitrogen to oxygen of **3a** via pathway A than from oxygen to nitrogen of **3b** via pathway B. Accordingly, pathway A occurs more readily than path B does. Therefore, quinazolinone **1** should form preferentially via amidine salt **3c** after elimination of water. Literature precedents support the fact that in the presence of sterically hindered amines, the reaction takes the electronically less favored pathway B to yield *o*-acetamidobenzamide **3e** via intermediate **3d**.[38] In our case, at elevated temperature (refluxing benzene) quinazolinone compounds **1a-c** were the only products formed from

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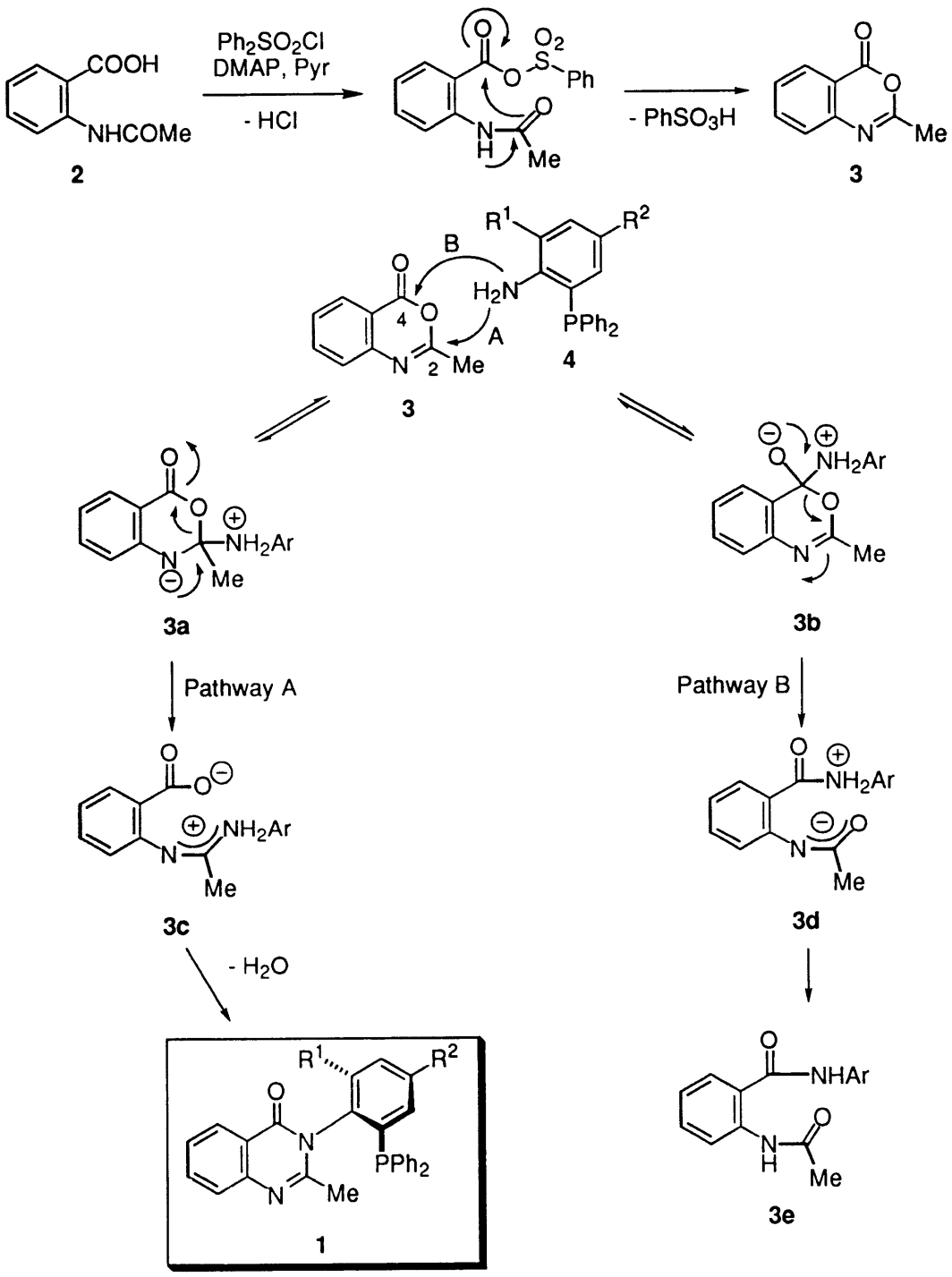
[36] Jackman, G. B.; Petrow, V.; Stephenson, O. *J. Pharm. and Pharmacol.* **1960**, *12*, 529.
[37] Errede, L. A.; McBrady, J. J.; Oien, H. T. *J. Org. Chem.* **1977**, *42*, 656.
[38] Errede, L. A. *J. Org. Chem.* **1976**, *41*, 1763.

the less hindered *ortho*-substituted aniline **4a** to the highly hindered 2,6-disubstituted aniline **4c** (Scheme 4).

Scheme 5. Mechanism of Quinazolinones **1a-c** Formation.



Because the water generated in the ring formation step could compete with aniline **4** to react with benzoxazin-4-one **3**, more than two equivalents of acid **2** and benzenesulfonyl chloride were used to generate an excess of compound **3** to ensure the complete consumption of aniline **4**.

2.3 Resolution of Ligand 1b Using the Chiral Palladium Complex and the Determination of the Absolute Configuration of Ligand (-)-1b

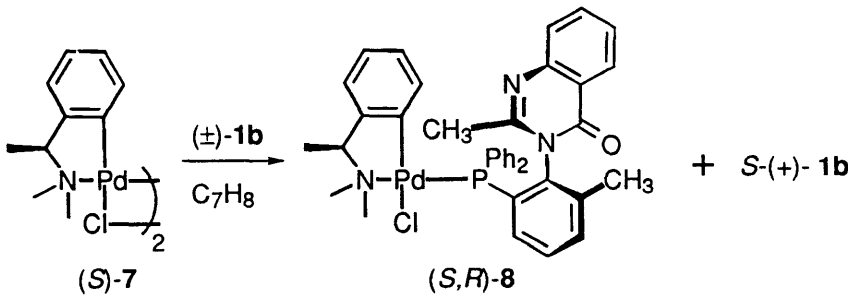
Racemic ligand **1b** was resolved on a 6 gram scale using (-)-di-μ-chloro-bis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2, *N*]dipalladium(II) (**7**), which has been used broadly as a conventional resolving agent for monophosphines (Scheme 6).[39] Treating dimer (*S*)-**7** with 4 equivalents of racemic **1b** in toluene yielded palladium complex **8** as a yellow crystalline precipitate which was collected by filtration. The antipode (+)-**1b** was recovered from the filtrate in good yield (82%) and high enantiomeric excess (96% ee as determined by chiral HPLC analysis). Treatment of complex **8** with ethylenediamine in methylene chloride released ligand (-)-**1b**, which was isolated in 91% yield and 99% ee (HPLC). The resulting palladium ethylenediamine complex was converted back to complex **7** in nearly quantitative yield using 2*N* aqueous hydrochloric acid.[40]

---

[39] (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.

[40] (a) Dunina, V. V.; Golovan', E. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2747. (b) Martin, J. W. L.; Palmer, J. A. L.; Wild, S. B. *Inorg. Chem.* **1984**, *23*, 2664.

Scheme 6



Complex **8** ($C_{38}H_{37}ClN_3OPPd$; M_w = 724.53) crystallized in the orthorhombic $P2_12_12_1$ space group with cell dimensions: a = 10.4822(7) Å, b = 17.3192(12) Å, c = 18.5003(12) Å and Z = 4. A total of 13752 reflections were collected at -85 °C using a Siemens SMART/CCD diffractometer. Least squares refinement of the data using 4839 reflections converged upon the structure shown in Figure 12 with R = 0.0308 and a goodness-of-fit = 1.114.

The X-ray structure of complex **8** displays significant π-stacking between one phenyl ring on phosphorus and the quinazolinone ring system with the palladium center oriented to the side of the quinazolinone methyl group (Figure 12). Based on the known *S*-stereochemistry of the phenylethylamine ligand, the absolute stereochemistry of the phosphine ligand chiral axis is assigned as *R* according to the Cahn-Ingold-Prelog rule.[41]

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[41] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, New York, 1994, pp 104.

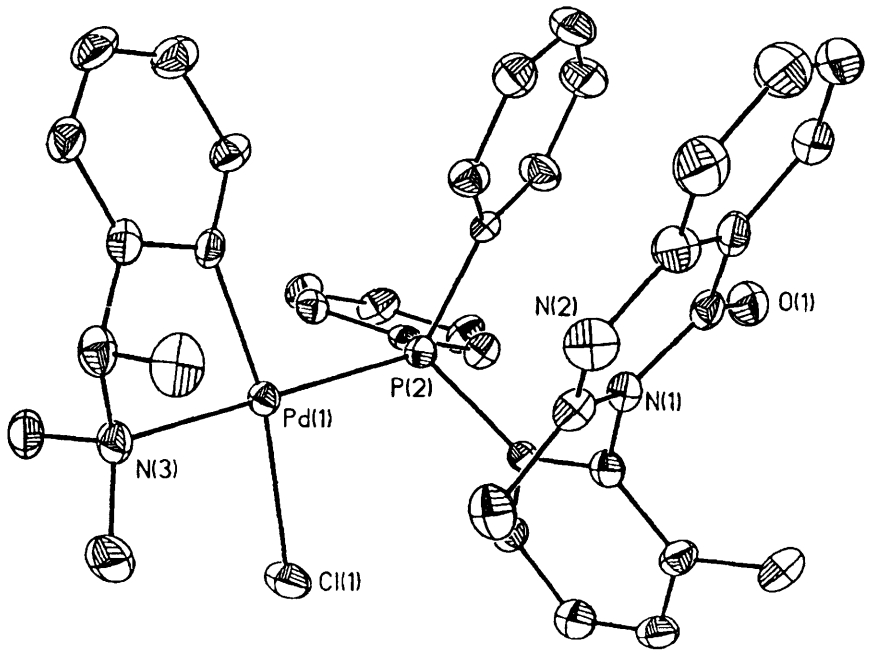

Figure 12. ORTEP plot of complex (*S,R*)-**8**.

2.4 Resolution of the Ligands 1a-c Using a New Resolving Agent

In order to achieve larger scale and economical resolution of the ligands **1a-c**, a suitable acid resolving agent was sought to ionize the nitrogen at the 1-position of the quinazolinone ring. Since quinazolinone derivatives are only weakly basic (pKa ≈ 2.2), the field of possible resolving acids appeared to be limited to camphorsulfonic acid.[42] When ligand **1a** and (1*S*)-(+)-10-camphorsulfonic acid (*S*-CSA) were combined in equimolar proportions in ethyl acetate, large hexagonal-shaped crystals (salt **9**) were obtained. A single salt crystal was composed of both (+)- and (-)-enantiomers of **1a** in a 1:1 ratio and 2 equivalents of *S*-CSA based on ^{1}H NMR and chiral HPLC analysis. Indeed, upon neutralization of the salt, only racemic **1a** was obtained. Similar results were obtained for ligand **1b** using *S*-CSA, and no crystalline salt was obtained using π-bromocamphorsulfonic acid.

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[42] Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin I*, **1980**, 1599.

Crystalline salt **9** ($C_{74}H_{74}N_4O_{10}P_2S_2$; M_w = 1305.58) crystallized in the monoclinic $P2_1$ space group with cell dimensions: a = 11.1602(5) Å, b = 10.8868(5) Å, c = 27.2325(12) Å, ß = 95.132 ° and Z = 2. A total of 8796 reflections were collected at 20 °C using a Siemens SMART/CCD diffractometer. Least squares refinement of the data using 4690 reflections converged upon the structure shown in Figure 13 with R = 0.1176 and a goodness-of-fit = 1.044.

X-ray diffraction analysis of the above hexagonal salt **9** confirmed the composition as (*S*-CSA)$_2$ • (*R*-**1a**) • (*S*-**1a**) and further revealed the structural features of this salt (Figure 13). The monoclinic $P2_1$ unit cell is divided into adjacent domains of homotopic salt cores extending along the crystallographic 2_1 screw axes. This led us to surmise that the stronger ionic interactions in the crystal had achieved the segregation of the two enantiomers of ligand **1a** while the weaker interactions between the aromatic rings and *S*-CSA had allowed the quasi-racemate unit cell to form.[43] Indeed, the hydrophobic and roughly spherical nature of the bicyclic portion of *S*-CSA seems to adopt analogous positions in the two salt bridge motifs.

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[43] Quasi-racemate: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, New York, 1994, Chapter 5. (b) Fredga, A. *Tetrahedron*, **1960**, *8*, 126. (c) Auburn, M.; Ciriano, M.; Howard, J. A. K.; Murry, M.; Pugh, N. J.; Spencer, J. L.; Stone, F. G. A.; Woodward, P. *J. Chem. Soc. Dalton Trans.* **1980**, 659. (d) Schurig, V.; Pille, W.; Winter, W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 327. (e) Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395. (f) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293.

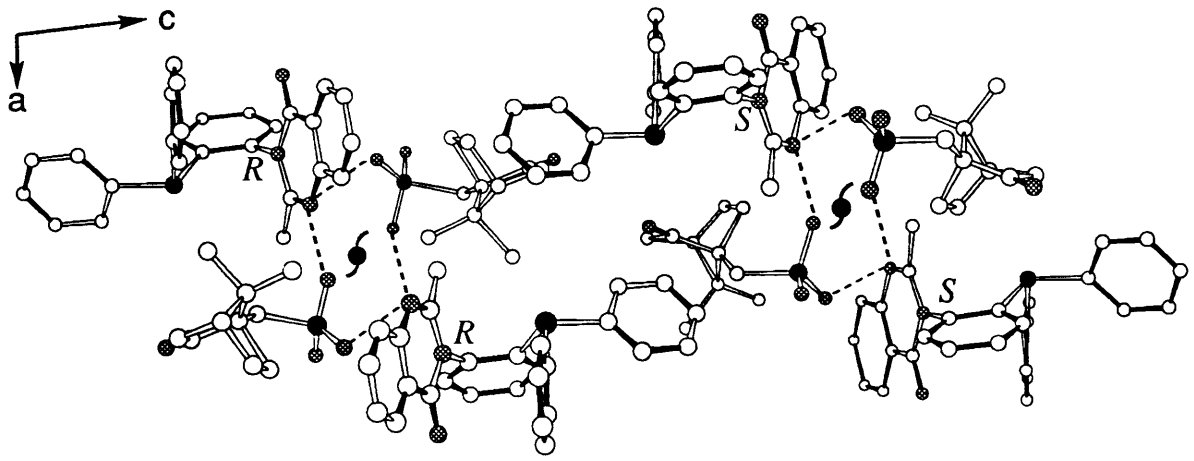

Figure 13. X-ray structure of the salt **9** ((*S*-CSA)$_2$ • (*R*-**1a**) • (*S*-**1a**)) showing adjacent crystallographic screw axes. Antipode *R*-**1a** and *S*-CSA comprise the extended salt core on the left, while *S*-**1a** and *S*-CSA are seen at right.

Our solution to the resolution of ligands **1a-c** was to investigate a simple derivative of camphorsulfonic acid which would more distinctly define the chirality about the bicyclic core without adversely affecting the salt bridge formation. The benzenesulfonylhydrazone derivative of *S*-CSA (*S*-CSZ, **10**) was readily prepared in 99% yield by the combination of solutions of benzenesulfonyl hydrazide and (*S*)-camphorsulfonic acid in ethyl acetate and filtration of the resulting precipitate (Scheme 7).[44] Addition of a solution of **1c** to 1 equivalent *S*-CSZ (**10**) in hot ethanol and slow cooling to 0 °C caused precipitation of one antipode as the sulfonate salt which was collected by filtration. Trituration of the crystalline salt with ethyl acetate freed the ligand into solution, leaving behind the recovered *S*-CSZ (**10**). After washing with aqueous sodium bicarbonate and recrystallization, the ethyl acetate solution afforded optically pure (+)-**1c** in 73% yield. The concentrated ethanol filtrate was treated in the same manner to afford the antipode (-)-**1c** in 72% yield. The above procedure which can be performed on a 25 gram scale for ligand **1c**, and also

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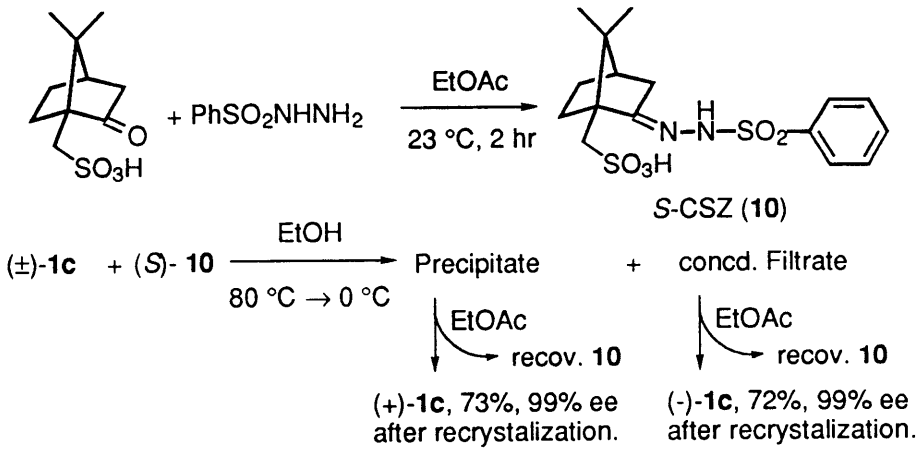
[44] For hydrazone derivatives: (a) Cremlyn, R.; Bartlett, M.; Lloyd, J. *Phosphorus and Sulfur* **1988**, *40*, 91. (b) Parekh, H.; Parikh, A. R.; Thaker, K. A. *J. Indian Chem. Soc.* **1974**, *51*, 1047. (c) Farber, L. *US patent* PI 3576916 710427 US AI 690520; *Chem. Abstr.* 75:36388. (d) Korosi, J. *Ger. Offen.* DE 1934809 700129 HU 680724; *Chem. Abstr.* 72:100334.

proceeds favorably for ligands **1a-b**, represents the first preparation of (1*S*)-(+)-10-camphorsulfonic acid derivatives such as **10** and their use as resolving agents (Scheme 7). The enantiomeric excess of both resolved samples in each case was greater than 99% based on HPLC analysis.

Scheme 7. Resolution of ligand **1c** using the *S*-CSZ (**10**) resolving agent.



2.5 Measurement of the Rotational Barriers of Ligands 1a-c

A study of the thermal racemization of (*R*)-(-)-**1a** and (*R*)-(-)-**1b** was conducted by heating their toluene solutions at reflux under argon. For ligand (*R*)-(-)-**1a**, three aliquots were removed and analyzed by chiral HPLC analysis to determine the ratio ([*S*]:[*R*]) of the enantiomers (*S*)-(+)-**1a** and (*R*)-(-)-**1a** (Table 1).

Table 1. [*S*]:[*R*] Ratios and k_r Values for the Thermal Racemization of (*R*)-(-)-1a.

Entry	Reaction time, t (h)	[*S*]:[*R*]	k_r (s^{-1})
1	24	1 : 3.47	3.43×10^{-6}
2	48	1 : 2.21	2.82×10^{-6}
3	96	1 : 1.54	2.24×10^{-6}

The racemization of ligand (*R*)-(-)-**1a** was treated as a first-order reaction with the rate expression shown below (Equation 1).[45]

$$2k_rt = \ln \frac{1+[S]/[R]}{1-[S]/[R]} \qquad \text{(Eq. 1)}$$

k_r: rate constant for the rotation about the atropisomeric bond.

t: reaction time

[S]: the concentration of (*S*)-(+)-**1a**

[R]: the concentration of (*R*)-(-)-**1a**

The average value of k_r was found to be 2.83×10^{-6} s^{-1}. Thus, the racemization half-life for (*R*)-(-)-**1a**, $\tau = \frac{\ln 2}{2k_r} = 34$ h at 111 °C.

The rotational barrier ($\Delta G^{\ddagger}$) to racemization for (*R*)-(-)-**1a** was obtained from the Eyring equation (Equation 2) as 32.3 kcal/mol, when $k_r = 2.83 \times 10^{-6}$ s^{-1}.

$$k_r = \frac{\kappa kT}{h} e^{-\Delta G^{\ddagger}/RT} \qquad \text{(Eq. 2)}$$

$R = 1.987 \times 10^{-3}$ kcal/mol·K; $\kappa = 0.9$

k = Boltzmann's constant = 1.3805×10^{-16} erg/K

h = Planck's constant = 6.6256×10^{-27} erg·sec

T = 384 K

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[45] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, New York, 1994, pp 424.

The rotational barrier for (*R*)-(-)-**1a** is the highest known value for any heteroaromatic atropisomer. In the case of (*R*)-(-)-**1b**, which has an extra *ortho* methyl group compared to (*R*)-(-)-**1a**, there was no detectable racemization after 96 hours in refluxing toluene. This suggested that the rotational barriers for (*R*)-(-)-**1b** and its analog (*R*)-(-)-**1c** were comparable to the rotational barriers for diphosphine ligand BINAP.

2.6 Summary

The quinazolinone ligand system (**1a-c**) represents the first example of an atropisomeric biaryl phosphine ligand about a central N–C_{aryl} bond. The quinazolinone ring structure facilitates a straightforward synthesis. The weakly basic nitrogen at the 1-position of this heterocycle is a unique feature allowing the resolution of ligands **1a-c** using the new class of camphorsulfonic acid benzenesulfonylhydrazone resolving agents (**10**). This convenient procedure is the first successful example of resolution of atropisomeric quinazolinone compounds. The rotational barrier for these ligands were measured to be high enough to prevent racemization under most catalytic reaction temperatures.

Chapter 3. Catalytic Reactions

After ligands **1a-c** were obtained in enantiopure form, several catalytic reactions were performed to test the effectiveness of this class of phosphines as chiral ligands. In the first section of this chapter, a palladium catalyzed asymmetric allylic alkylation is discussed. In the second and third sections, we report a novel phosphine complex of rhodium (I) formed by intramolecular activation of the 2-methyl group of quinazoline ligand **1b**, and the discovery of a rhodium-catalyzed conjugate addition of Grignard reagents to enones. In the fourth and fifth sections, we describe the preliminary results of the first phosphine-catalyzed asymmetric [3+2] cycloaddition of *N*-tosylimines with methyl 2,3-butadienoate, and an intramolecular asymmetric Heck reaction.

3.1 Palladium-Catalyzed Asymmetric Allylic Alkylation.

Palladium-catalyzed asymmetric allylic alkylation reactions (AAA reactions) have recently been the subject of a great deal of interest from the synthetic community due to their wide synthetic scope, practical simplicity and potential for asymmetric synthesis through the use of chiral ligands.[46] This reaction is also a convenient model reaction for the evaluation of new ligands. The successful chiral ligands developed to date can be either monodentate[47] or bidentate structures[48] such as diphosphines, diamines or ligands containing electronically different donor centers. With the phosphinoaryldihydrooxazole

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[46] Review: Trost, B. M., Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
[47] (a) Hamada, Y.; Seto, N.; Ohmori, H.; Hatano, K. *Tetrahedron Lett.* **1996**, *37*, 7565. and the references cited therein. (b) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521.
[48] Brenchlry, G.; Merifield, E.; Wills, M. *Tetrahedron Lett.* **1994**, *35*, 2791 and the references cited therein.

ligand **11**, Pfaltz, Helmchen, and Williams have been able to obtain substitution product **12** with enantiomeric purity of ≥98% (Figure 14).[49]

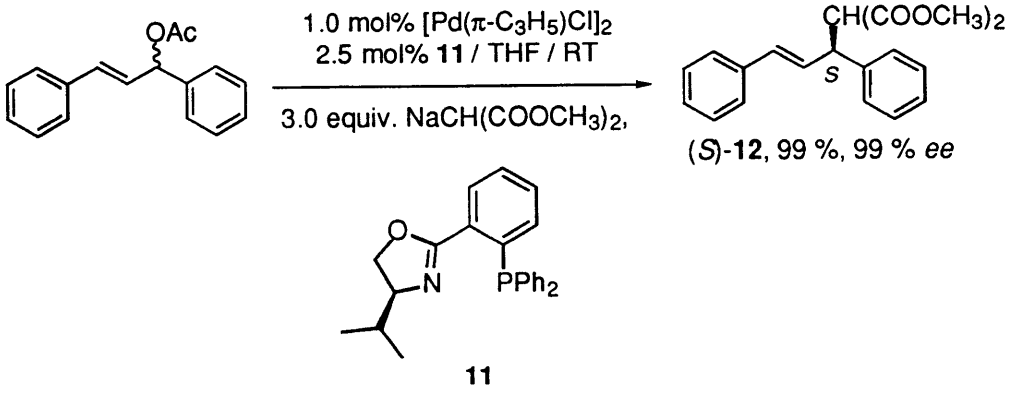

Figure 14. Palladium-catalyzed asymmetric allylic alkylation reactions with the phosphinoaryldihydrooxazole ligand **11**.

The asymmetric induction ability of monophosphine ligands **1a-c** towards this reaction was evaluated by using ligand (*R*)-**1b**. In order to optimize the conditions, a series of palladium-catalyzed AAA reactions were conducted as shown in Table 2. The catalyst was generated *in situ* by mixing ligand (*R*)-**1b** and the chloro-bridged palladium precursor ($[Pd(\pi\text{-}C_3H_5)Cl]_2$) at room temperature. A solution of racemic substrate (1,3-diphenyl-2-propenyl acetate) was then added followed by the addition of the base and the additive. The resulting mixture was stirred at room temperature for a given time before the product was isolated and analyzed

The reaction rate was slow for all entries, especially in toluene (Table 2, entry 4). The sodium dimethylmalonate anion generated by sodium hydride (NaH) gave better enantioselectivity than the potassium dimethylmalonate anion generated by *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate (Table 2, entry 1 and 2). The increased enantiomeric excess (ee) obtained by removal of chloride ion using silver (I)

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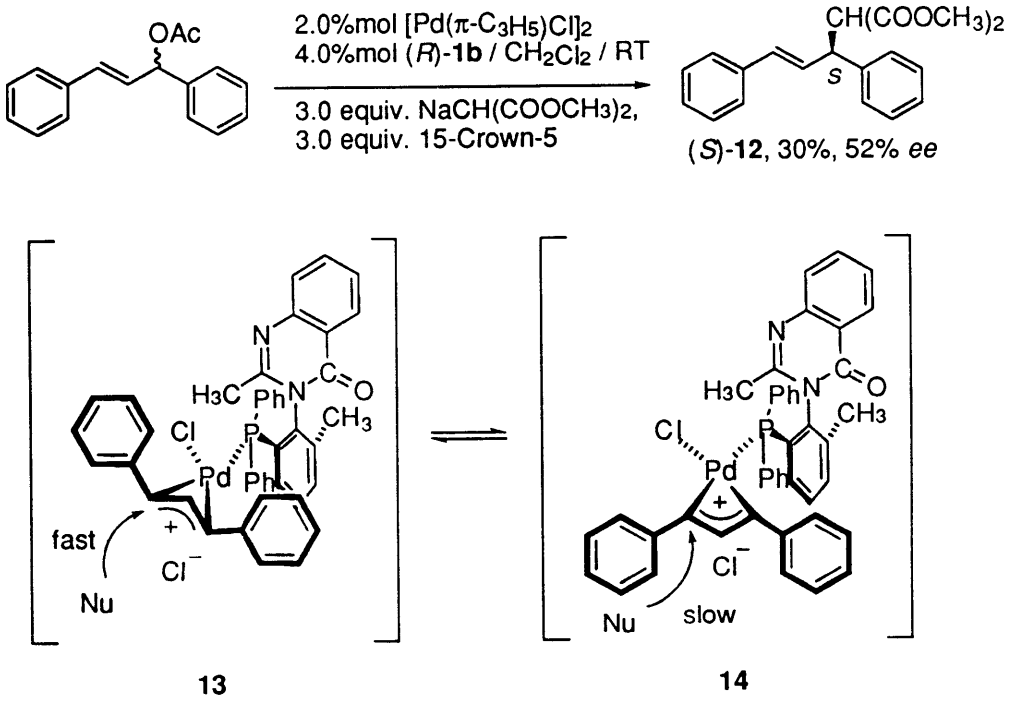
[49] (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

perchlorate ($AgClO_4$) suggested that chloride remained in the coordination sphere of the palladium (Table 2, entry 3). By adding a crown ether (15-crown-5) to improve the solubility of sodium dimethylmalonate, the enantiomeric excess increased to 52%.

We think the reaction should follow a mechanism similar to that proposed by Helmchen.[50] After elimination of the acetate group, the carbon skeleton of the substrate will form a π-allyl palladium complex in two possible conformations: **13** and **14** (Scheme 8). The nucleophile (sodium dimethylmalonate) attacks the π-allyl complexes opposite to the ligand at the carbon *trans* to the phosphorus atom (the better π-acceptor).[51]

Scheme 8



[50] Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 2108 and references cited therein.

[51] Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535.

Table 2: Palladium-Catalyzed AAA reaction with Monophosphine Ligand (*R*)-1b.[a]

Entry	[Pd] (mol%)	Ligand (mol%)	Solvent	Time (h)	Base[b]	Additive	Yield[c] (%)	% ee[d]
1	2.5	10.0	CH_2Cl_2	96	1.5 equiv. BSA	3 mol% KOAc	40	28 (*S*)-(-)
2	2.5	10.0	THF	48	1.05 equiv. NaH	_	37	37 (*R*)-(+)
3	2.5	5.0	THF	48	3.0 equiv. NaH	5.0% mol% $AgClO_4$	27	44 (*R*)-(+)
4	2.0	4.8	Toluene	48	3.0 equiv. NaH	_	8	44 (*R*)-(+)
5	2.0	4.0	CH_2Cl_2	96	3.0 equiv. NaH	3.0 equiv. 15-crown-5	30	**52** (*S*)-(-)

a) The reaction was carried out at room temperature under argon using 1,3-diphenyl-2-propenyl acetate as the substrate, dimethylmalonate (1 equivalent in respect to the base) with the base as the nucleophile, additive, solvent, [Pd] (allylpalladium chloride dimer: $[Pd(\pi\text{-ally})Cl]_2$), and ligand (*R*)-(-)-**1b**. b) BSA: *N*,*O*-bis(trimethylsilyl)acetamide. c) Isolated yield by flash chromatography. d) % ee was determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent in $CDCl_3$. The absolute configuration was determined by comparing the optical rotation with literature values.[52]

[52] von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A. Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573.

Recently, a detailed NMR study by Helmchen *et al.* indicated that the π-allyl palladium complexes equilibrate rapidly between *endo* and *exo* conformers.[53] In our case, in order to achieve a high enantiomeric excess in the product **12**, one of the conformers **13** and **14** must react much faster with the nucleophile than the other.

The *S* configuration of product **12** in the best run (Table 2, entry 5) suggested that the dimethyl malonate reacted faster with complex **13** than with **14**. However, the moderate enantiomeric excess showed that the monophosphine ligand (*R*)-**1b** was not very efficient in rendering a high reactivity difference between conformers **13** and **14**.

Based on the encouraging preliminary study of asymmetric allylic alkylation with monophosphine (*R*)-**1b**, we decided to modify the structure of **1b** into a phosphorus-nitrogen chelating ligand related to ligand **11** in the hopes of achieving higher enantioselectivity in this reaction.

Lithiation of the 2-methyl group of the 3-aryl-4(3*H*)-quinazolinones (**15**) with sodium hydride, lithium diisopropylamide, and *n*-butyllithium has been used frequently in the preparation of quinazolinone derivatives.[54] The facile deprotonation of this methyl group is presumably due to the resonance-stabilization of the resulting anion (**16**) by the neighboring nitrogen at the 1-position (Scheme 9). Anion **16** can be quenched with a variety of electrophiles to afford substitution products.[55]

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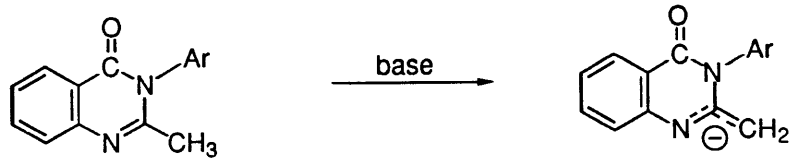
[53] Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523 and references cited therein.

[54] Rathman, T. L.; Sleevi, M. C.; Krafft, M. E.; Wolfe, J. F. *J. Org. Chem.* **1980**, *45*, 2169.

[55] Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 656 and references cited therein.

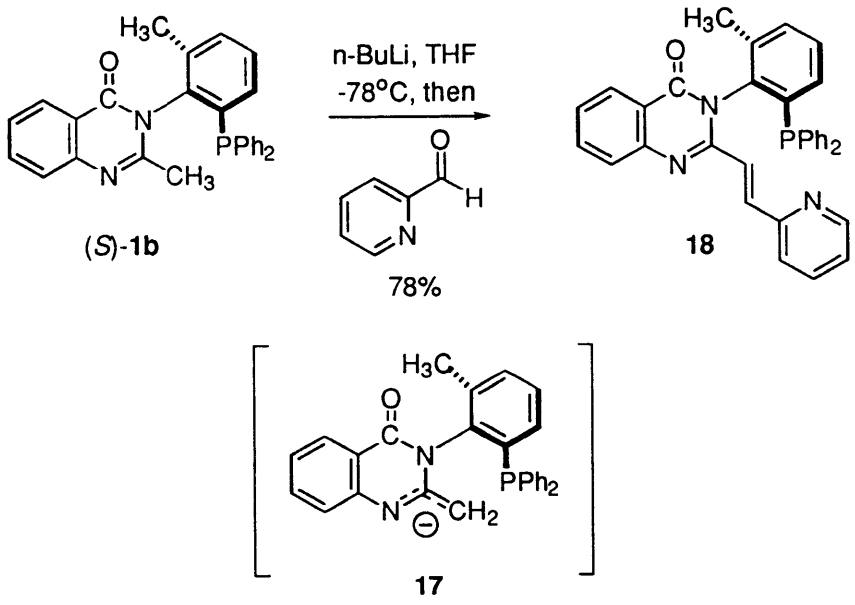
Scheme 9



15 **16**

The 2-methyl group of (*S*)-**1b** reacted smoothly with 1.2 equivalent *n*-BuLi in THF at -78 °C to yield dark red anion **17** (Scheme 10). Claisen-Schmidt reaction of **17** with pyridinecarboxaldehyde afforded bidentate ligand **18** in 78% yield after aqueous workup. Only the thermodynamically favored *trans* double bond was formed based on ^{1}H NMR analysis.

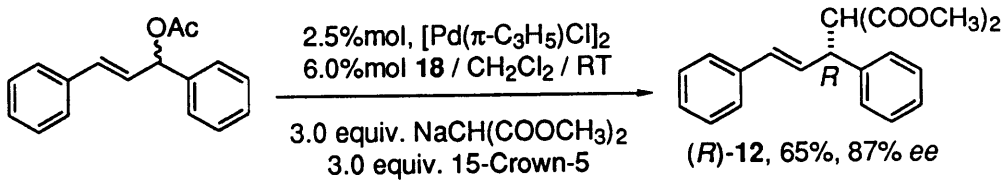
Scheme 10



When bidentate ligand **18** was used for the palladium catalyst under the asymmetric allylic alkylation conditions described above, the reaction rate was faster than for the reactions catalyzed by the palladium catalyst with monophosphine ligand (*R*)-**1b** (Table 3). Unlike the monophosphine ligand which gave variable ee's and configurations of the

product **14**, chelating ligand **18** consistently afforded product **14** in higher ee's and in the *R* configuration. In THF and toluene, the reaction was slower than in methylene chloride (Table 3, entry 1, 2, 4, and 5). In methylene chloride, deprotonation of dimethylmalonate with BSA-KOAc combination gave satisfying enantiomeric excess (80%, based on HPLC analysis) (Table 3, entry 3). However, sodium hydride in the presence of crown ether (15-crown-5) gave the highest enantiomeric excess (87%) (Table 3, entry 6).

Table 3: Palladium-Catalyzed AAA Reaction with Chelating Ligand 18.[a]

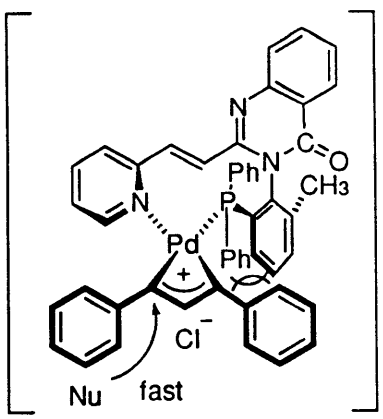


entry	[Pd] (mol%)	Ligand (mol%)	Solvent	Time (h)	Base[b]	Additive	Yield[c] (%)	ee[d,e] (%)
1	2.5	6.0	THF	48	BSA	3 mol% KOAc	64	68[e] (*R*)-(+)
2	2.5	6.0	Toluene	48	BSA	3 mol% KOAc	53	73[e] (*R*)-(+)
3	2.5	5.5	CH_2Cl_2	48	BSA	3 mol% KOAc	90	**86**[d], **80**[e] (*R*)-(+)
4	2.5	5.5	THF	24	3.0 equiv. NaH	3.0 equiv. 15-crown-5	75	56[d] (*R*)-(+)
5	2.5	5.5	Toluene	48	3.0 equiv. NaH	3.0 equiv. 15-crown-5	44	67[e] (*R*)-(+)
6	2.5	6.0	CH_2Cl_2	36	3.0 equiv. NaH	3.0 equiv. 15-crown-5	65	**87**[e] (*R*)-(+)
7	2.5	6.0[f]	CH_2Cl_2	36	3.0 equiv. NaH	3.0 equiv. 15-crown-5	68	78[e] (*R*)-(+)

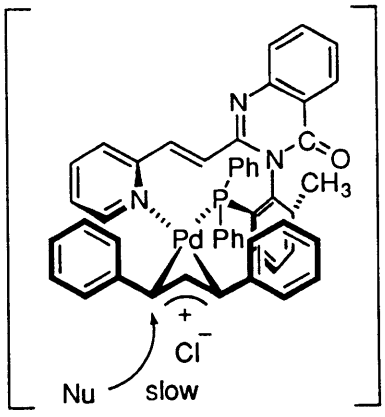
a) The reaction was carried out at room temperature under argon using 1,3-diphenyl-2-propenyl acetate as the substrate, dimethylmalonate (1 equiv. in respect to the base) with the base as the nucleophile, additive, solvent, [Pd] (allylpalladium chloride dimer: [Pd(p-ally)Cl]$_2$), and ligand **18**. b) BSA: *N*,*O*-bis(trimethylsilyl)acetamide. c) Isolated yield by flash chromatography. d) % ee was determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent in $CDCl_3$. The absolute configuration was determined by comparing the optical rotation with literature values (see Table 2). e) % ee was determined by HPLC using a Chiralcel OD-H column (98:2 Hexane:*i*-PrOH, 0.3 mL/min). f) Ligand **21** was used.

The consistent configuration of the product as well as the increase in the reaction rates, enantiomeric excesses, and yields are consistent with a reaction catalyzed by a more ordered palladium complex. In accordance with Helmchen's model for the transition state (Scheme 11),[49] we believe that ligand **18** coordinates with palladium through the nitrogen and phosphorus centers in a chelating fashion. Although the resulting palladocycle is a ten-membered ring, it is rather rigid because its entropy is reduced due to the presence of the *trans* double bond. The oxidative addition of palladium-phosphine species with substrate **11** would form two possible conformers **19** and **20**. The rigidity of the palladocycle can effectively differentiate the reactivity of the two conformers **19** and **20**. Attack of the sodium dimethylmalonate nucleophile on the carbon of the allyl group which is *trans* to the phosphorus atom in conformer **19** would lead to the observed *R* configuration of product **12**. Based on the modeling study, complex **19** experiences more steric crowding due to the close proximity of the phenyl rings of the substrate to the diphenylphosphino group. This is consistent with the conclusion drawn by Brown and Bosnich that more sterically demanding π-allyl complexes react faster with nucleophiles.[56]

Scheme 11



19



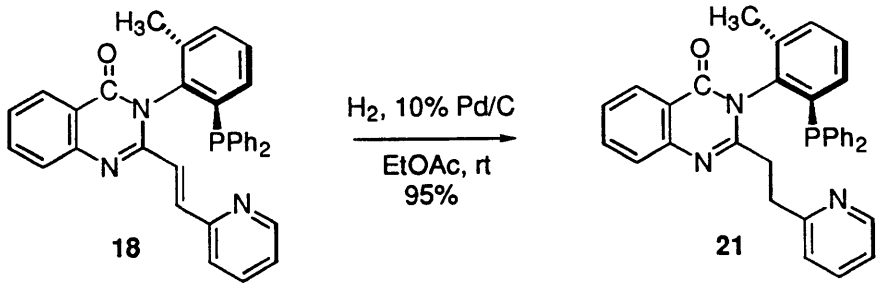
20

[56] (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (b) Mackanzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

The large distance between nitrogen and phosphorus in ligand **18** provides a big bite angle for metal coordination to form a deep chiral "pocket". Trost proposed that an increase in the bite angle of chelating ligands would enhance the chiral recognition of the "pocket" for the substrate in AAA reactions.[57] The higher enantiomeric excess induced by the palladium catalyst with ligand **18** is in good agreement with this idea.

In order to prove the *trans* double bond in ligand **18** was necessary for high chiral induction, ligand **18** was hydrogenated easily in 95% yield to produce the new ligand **21** with an ethylene group linkage (Scheme 12).

Scheme 12



When ligand **21** was subjected to the optimized conditions of asymmetric allylic alkylation (Scheme 13), product (*R*)-**12** was obtained in good yield and 78% ee (Table 3, entry 7).

Comparing with the products from the reactions catalyzed by palladium complex with ligand **18**, the unchanged *R* configuration of product **12** suggested that the structures of the π-allyl intermediates **22** and **23** formed from the palladium metal, ligand **21**, and the substrate should be similar to that of **19** and **20** (Scheme 13). The nucleophile would then attack π-allyl complex **22** preferentially. However, due to the presence of the ethylene linkage of ligand **21**, the palladocycle in complex **22** became more flexible than the

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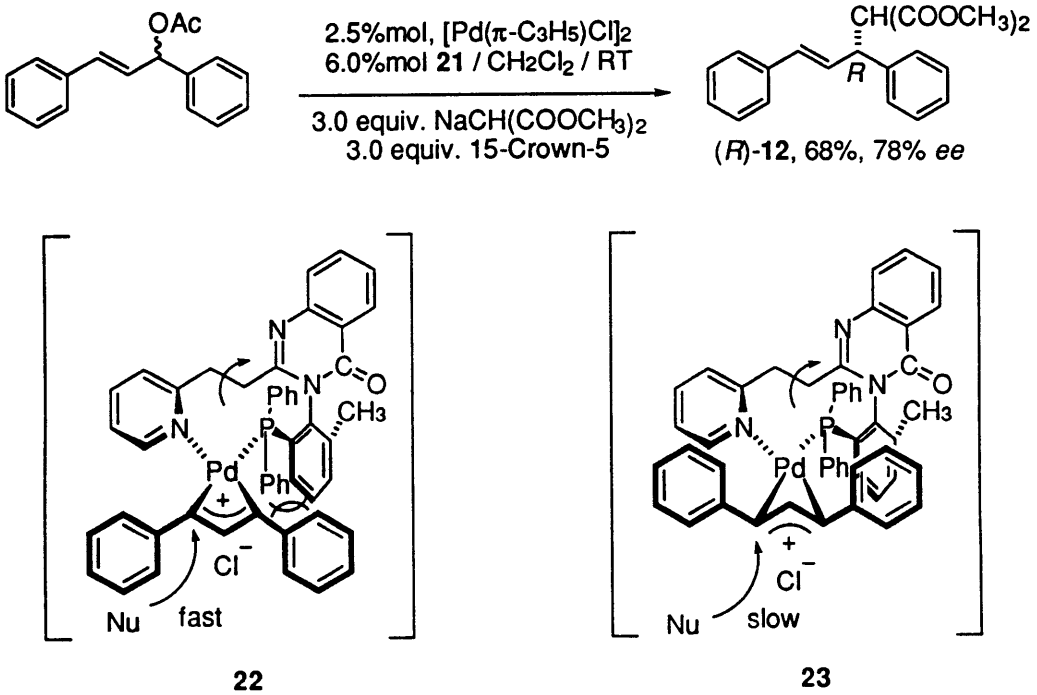
[57] (a) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662. (b) Zhu, G.; Terry, M.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 4475 and references cited therein.

palladocycle in complex **19**. This would decrease the reactivity difference between complexes **22** and **23**, which would lead to a decrease of enantiomeric excess of product **12** (Table 3, entries 6 and 7).

Scheme 13



3.2 NMR Study of the Chelating Properties of Ligand 1b with Rh(I)

The moderate enantioselectivity obtained in the Pd-catalyzed AAA reaction with ligand **1b** demonstrated that the amide oxygen of this monophosphine was not an effective coordination site for Pd(II). However, the coordination of the amide carbonyl group with Rh(I) has been well-known.[58] Therefore, we decided to investigate the phosphorus-oxygen (P-O) chelating properties of ligands **1a-c** with rhodium (I).

In an NMR tube, racemic **1b** and bis(bicyclo[2,2,1]hepta-2,5-diene)rhodium(I) perchlorate ($[Rh(nbd)_2]ClO_4$, **24**) were mixed in equal molar in $CDCl_3$. The resulting

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[58] (a) Sjövall, S.; Kloo, L.; Nikitidis, A.; Andersson, C. *Organometallics*, **1998**, *17*, 579. (b) Vigalok, A.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 7873 and references cited therein.

orange-colored solution was observed by NMR analysis to consist of a single product (Figure 15). Key features of the ^{1}H NMR spectrum included a down-field singlet at 11.0 ppm with an integration of 1H relative to four individual olefinic signals of the new product at 6.32 ppm (m, 1H), 5.41 ppm (dd, J = 3.9, 7.6 Hz, 1H), 4.08 ppm (br, 1H), and 3.92 ppm (q, J = 3.9 Hz, 1H). A set of free norbornadiene signals was also observed at 6.78 ppm (s, 4H), 3.56 ppm (s, 2H), and 1.98 ppm (s, 2H) (denoted by *).

The $^{31}P\{^{1}H\}$ NMR of the reaction mixture displayed a doublet with coupling constant of 172.6 Hz which is within the ^{103}Rh-^{31}P coupling constant range.[59] When either complex **24** or **1b** was in excess, the same set of NMR signals was observed. The rest of the starting material remained in the solution unchanged. This suggested that the new complex with 1:1 ratio of ligand **1b** and rhodium metal was a relatively stable structure.

In order to further elucidate the structure of the new complex, more material was produced by stirring a CH_2Cl_2 solution of Rh complex **24** (155 mg, 0.4 mmol) and ligand **1b** (174 mg, 0.4 mmol) in a Schlenk tube for one hour at ambient temperature. A yellow powder was obtained in 56% yield after filtration, drying with $MgSO_4$, and solvent removal.

Efforts in getting a suitable single crystal for X-ray analysis of this complex have been unsuccessful. Crystallization of the yellow powder from several solvents and solvents combinations lead to either a fine powder or an oil. Anion exchange with BF_4^-, PF_6^-, and $SO_3CF_3^-$ did not induce crystallization.

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[59] Naaktgeboren, A. J.; Nolte, R. J. M.; Drenth, W. *J. Am. Chem. Soc.* **1980**, *102*, 3350.

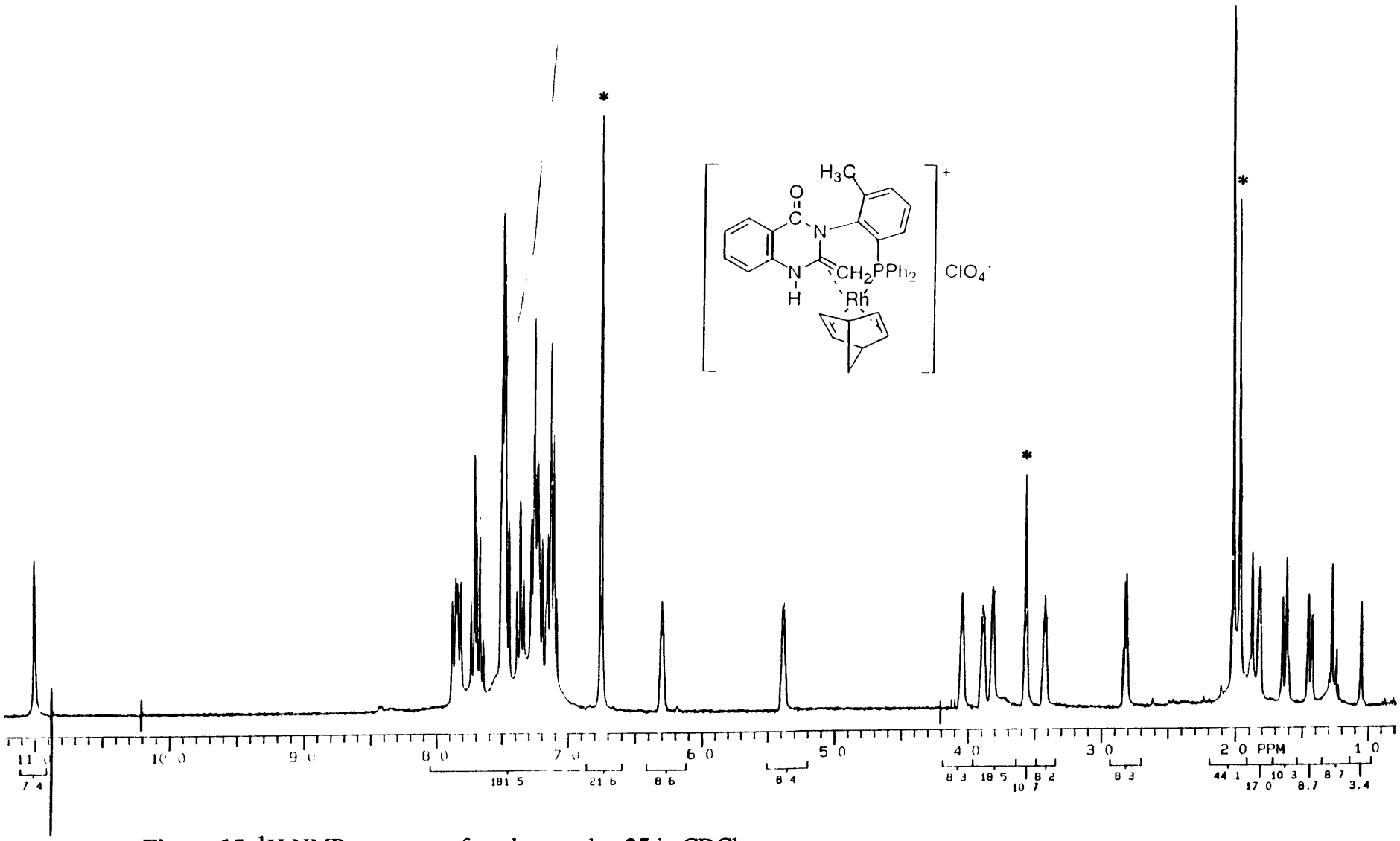


Figure 15. ^{1}H NMR spectrum of crude complex **25** in $CDCl_3$.

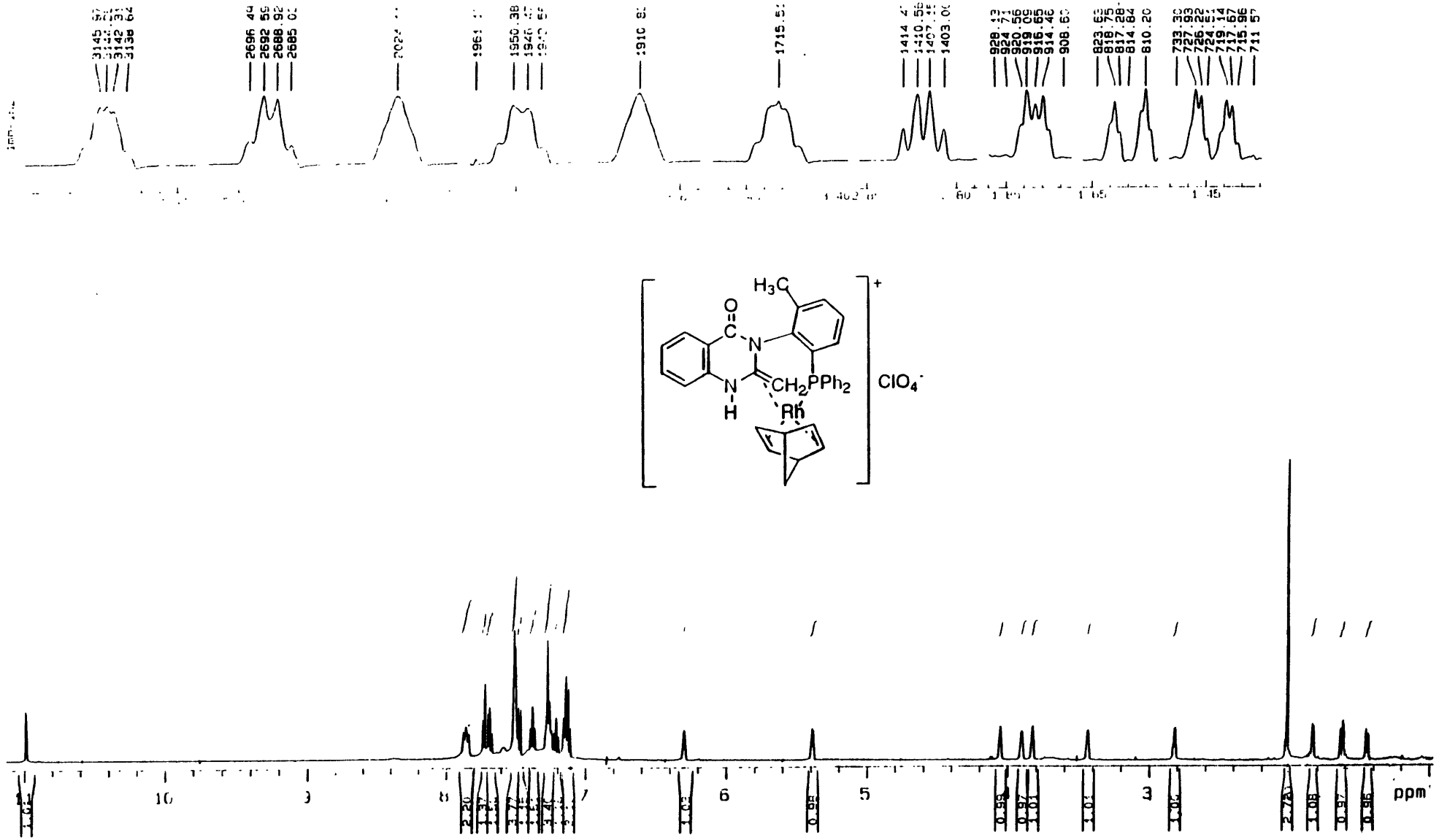


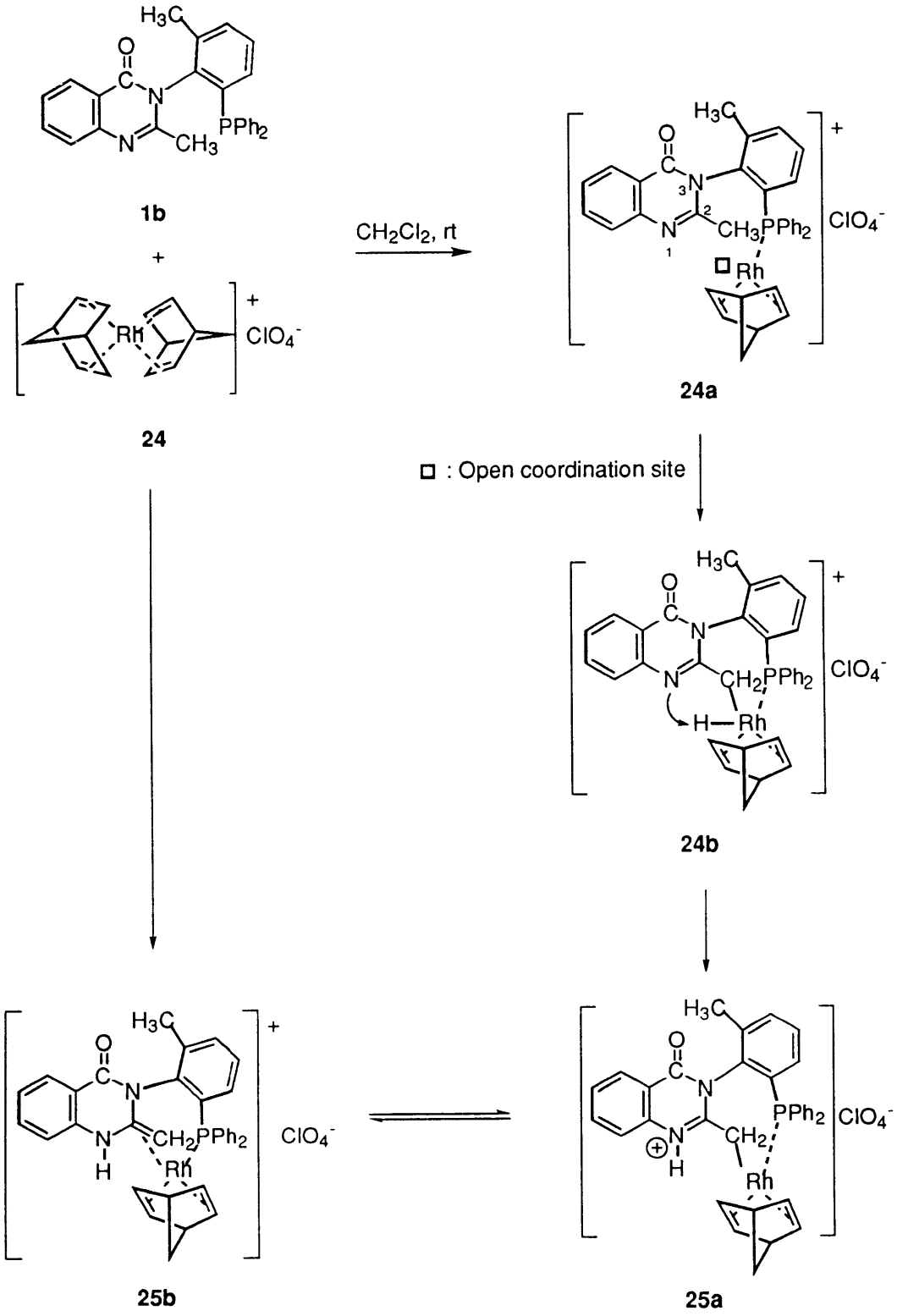
Figure 16. ^{1}H NMR spectrum of purified complex **25** (removal of solvent and nbd followed by filtration).

This material was analyzed as a pure compound by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum shown in Figure 16 exhibited another intriguing feature. It showed that the 2-methyl group of ligand **1b** had disappeared from the ^{1}H NMR spectrum, and two upfield multiplets appeared at 2.84 ppm (q, J = 3.8 Hz, 1H) and 1.86 ppm (ddd, J = 2.3, 2.3, 4.6 Hz, 1H).

Based on the spectroscopic evidence, it was clear that the rhodium had associated with the phosphine ligand and in some way activated the 2-methyl group of ligand **1b** to produce a methylene group. We propose the following mechanism for this reaction (Scheme 14). After the release of one norbornadiene molecule, the complexation of Rh(I) in complex **24** with the phosphorus atom in **1b** produces intermediate **24a** with one vacant coordination site on Rh(I). The C-H bond insertion leads to intermediate **24b**. The transfer of the hydride from Rh to the nitrogen at the 1-position gives intermediate **25a** in which the Rh(I) attaches to the carbon at the 2-position. This complex may be in equilibrium with complex **25b** in which the Rh(I) coordinates to the enamine carbon-carbon double (Scheme 14).

The absence of hydride signal in the ^{1}H NMR spectrum ruled out complex **24b** as a detectable intermediate. The lack of the large $^{1}J_{Rh\text{-}C}$ coupling constant (usually over 30 Hz) from the direct Rh-C bonding in the ^{13}C NMR spectrum suggested that structure **25b** should be the major form for the new complex. Due to the asymmetric environment imposed by ligand **2a**, the signals of norbornadiene coordinated with Rh(I) were split from three singlets (4H:2H:2H) in **24** into 8 broad singlets (each has 1H integration) in the ^{1}H NMR spectrum of complex **25** (Figure 16). The down-field singlet at 11.0 ppm (1H) in the ^{1}H NMR spectrum together with a broad peak at 3378 cm^{-1} in FTIR spectrum further indicated the presence of an amino proton flanked by conjugate systems.

Scheme 14



In the FTIR spectrum, the small change of carbonyl frequency from 1683 cm^{-1} in **1b** to 1677 cm^{-1} in **25b** was negligible compared to the large decrease (at least 30-50 cm^{-1}) in wave number of metal-coordinating carbonyl groups.[60] This suggested that the carbonyl group of ligand **1b** did not serve as a binding site for Rh(I).

The transformation of the imine part (N1=C2–CH_3) of ligand **1b** to the enamine structure (NH–C2=CH_2) of complex **25b** can be regarded as the tautomerism of the 2-methyl group in the presence of Rh(I). Tautomerism of the 2-methyl group of 4(3*H*)-quinazolinone in the presence of acids or bases has been documented.[61] There were also reports on the activation of C-H bond by rhodium complexes.[62] However, to our best knowledge, our observation is the first case of tautomerism of the 2-methyl group in the presence of organometallic compound.

When 1.0 equivalent of complex (bicyclo-[2,2,1]hepta-2,5-diene)rhodium(I) chloride dimer ($[Rh(nbd)Cl]_2$, **26**) was mixed with 2.0 equivalent of racemic ligand **1b** in $CDCl_3$ (Scheme 15), complex **27** was formed in quantitative yield based on ^1H NMR analysis. The olefinic proton signals of the Rh(I)-coordinated norbornadiene were split into four broad signets as in complex **25b**, but the signals of the bridgehead protons and the methylene protons of the nbd were not distinctively split. The absence of any down field signal and the intact singlets from the two methyl group in ligand **1b** indicated there was no activation of the 2-methyl group of ligand **1b** (Figure 17). The doublet in the $^{31}P\{^1H\}$ NMR of complex **27** suggested ligand **1b** serve as a normal monodentate ligand with its phosphorus atom coordinating to Rh(I) center.

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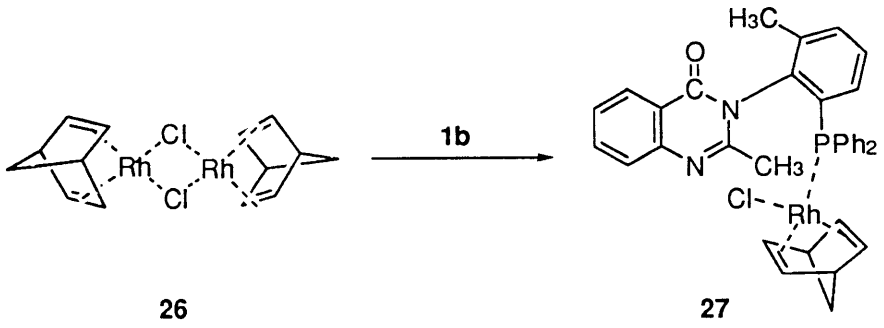
[60] (a) Gioria, J. M.; Susz, B. P. *Helv. Chim. Acta* **1971**, *54*, 2251. (b) Paul, R. C.; Moudgil, A. K.; Chadha, S. L.; Vasisht, S. K. *Indian J. Chem.* **1970**, *8*, 1017.

[61] Elguero, J.; Marzin C.; Katritzky A. R.; Linda P. *The Tautomerism of Heterocycles*; Academic Press: New York, 1976, pp 179-183.

[62] (a) Sjövall, S.; Kloo, L.; Nikitidis, A.; Andersson, C. *Organometallics* **1998**, *17*, 579. (b) Vigalok, A.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 7873 and references cited therein.

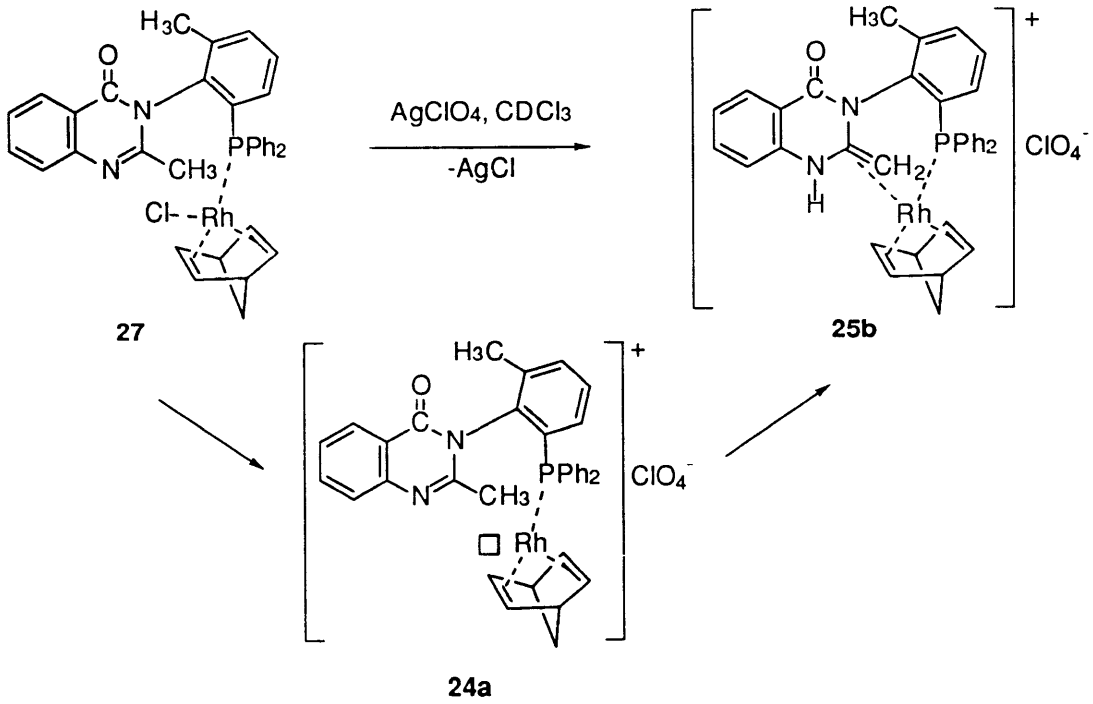
Scheme 15



26 **27**

When $AgClO_4$ was added to the NMR tube containing complex **27**, the ^1H NMR spectrum gradually changed to the pattern very similar to the one of complex **25b**. This further confirmed that the presence of an open coordination site of Rh(I) (generated by removing the chloride with the silver salt) induced the activation of the 2-methyl group of ligand **1b** (Scheme 16). In the case of ligands **1a** and **1c**, similar activation phenomena were observed.

Scheme 16



27 **25b**

24a

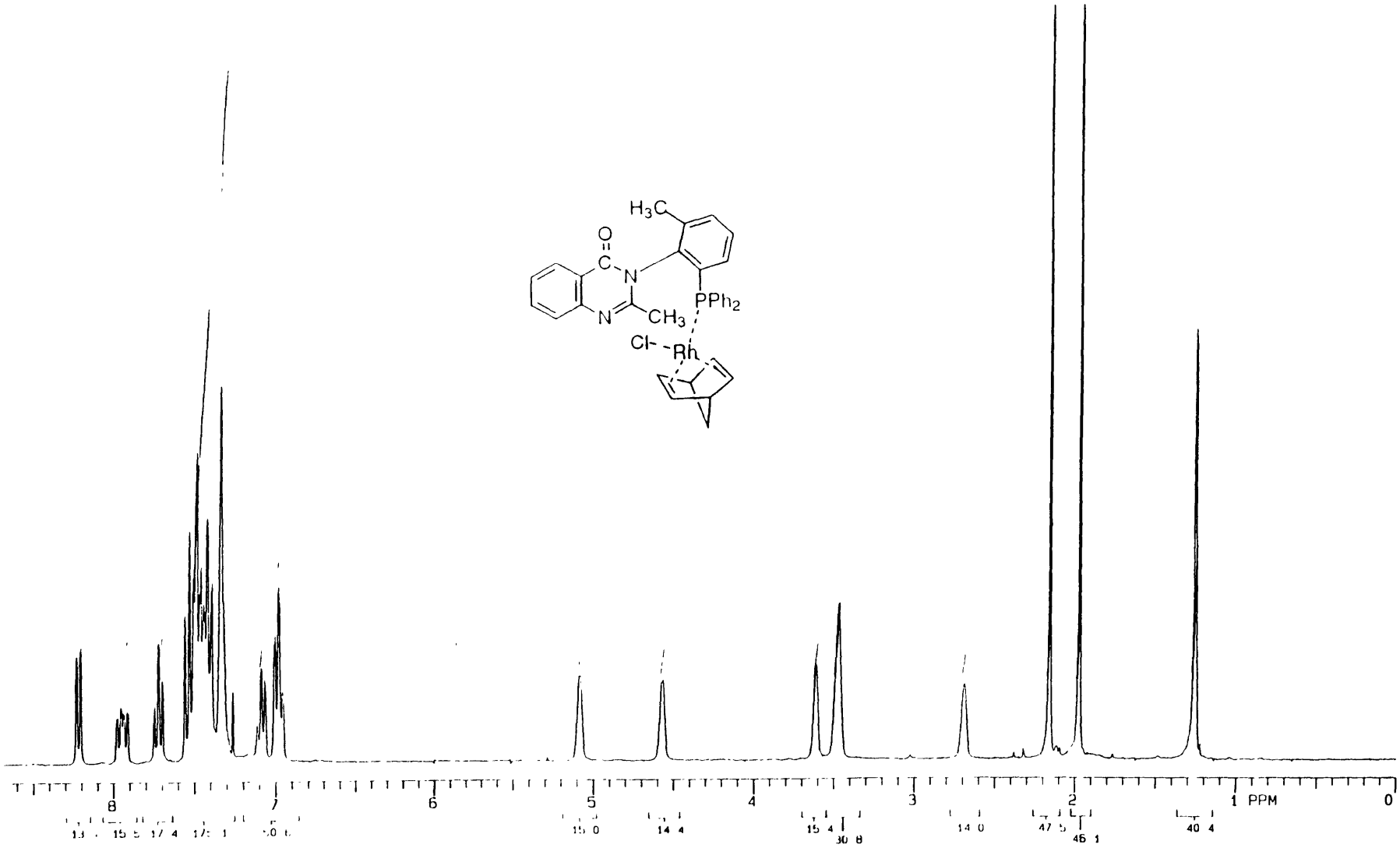
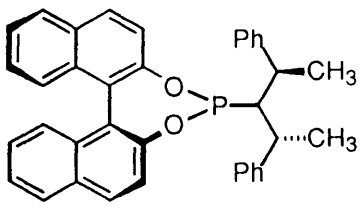


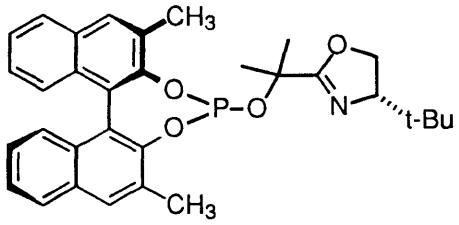
Figure 17. ^{1}H NMR spectrum of complex **27**.

3.3 Rh Complex Catalyzed Conjugate Addition

Asymmetric conjugate addition is a topic of very active research nowadays. Most of the efforts are presently directed towards the use of a catalytic amount of chirally modified copper salts with Grignard reagents and diorganozinc reagents as organometallic sources.[63] Recently, Feringa *et al.* achieved high enantioselectivities (≥94% ee) in copper-catalyzed conjugate additions of diorganozinc reagents to numerous six-membered cyclic enones with the phosphorus amidite ligand **I**.[63a] Pfaltz *et al.* obtained good enantioselectivities in copper-catalyzed conjugate additions of diorganozinc reagents to cyclopentenone (72% ee) and cycloheptenone (77-80% ee) with the phosphite ligand **II**.[63b] Alexakis *et al.* reported the preliminary results (0-44% ee) of conjugate additions of diethylzinc to cyclohexen-2-one, chalcone and benzalacetone catalyzed by the copper complexes of a variety of chiral bidentate aryl- and alkyl phosphine ligands.[63c]



I



II

Conjugate additions catalyzed by other transition metals are methodologies in their early stages compared with the copper catalyzed conjugate addition. Only a few examples were reported about other transition metal (like Ni, Pd, Rh, Ru) catalyzed conjugate addition of enones with organo-boron, -zinc, -zirconium, -aluminum, and -mercury reagents.[64]

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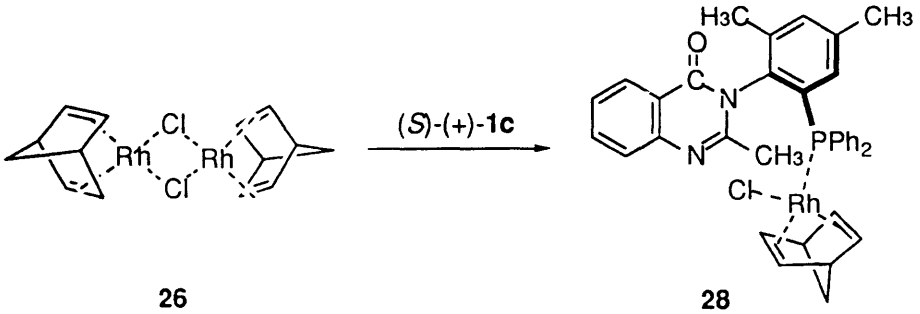
[63] (a) de Vries A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 2374. (b) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett*, **1997**, 1429. (c) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3987.

[64] Conjugate addition with metals other than Cu: (a) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83. (b) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics*, **1997**,

In the study of the Rh complex with ligand **1**, we found that complex **28**, which is an analog of complex **27** (Scheme 17), could catalyze the conjugate addition of the Grignard reagent *n*-butylmagnesium bromide (*n*-BuMgBr) to enones.

Scheme 17

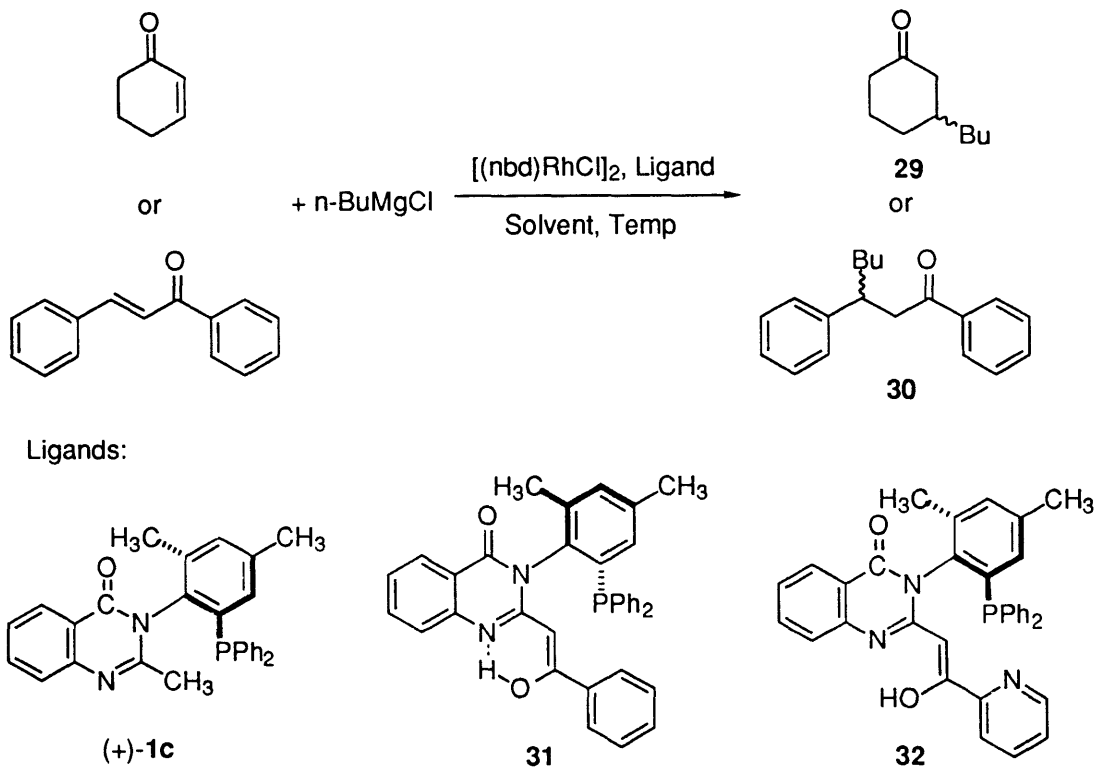


26 **28**

Treatment of 2-cyclohexen-1-one with the Grignard reagent (*n*-BuMgCl) in the presence of catalytic amount of complex **28** (generated *in situ* from $[(nbd)RhCl]_2$ and ligand (*S*)-(+)-**1c**) afforded the 1,4-adduct **29** in good yield (75%) (Scheme 18). We were encouraged by the facility of this reaction at -20 °C as well as the high propensity of 1,4-addition versus 1,2-addition (Without the Rh catalyst, the reaction between 2-cyclohexen-1-one and *n*-BuMgCl was slow. Only a small amount of 1,2-adduct product was isolated). When the product of this reaction was analyzed, no chiral induction for the 1,4-adduct **29** was detected (Table 4, entry 1 and 2). Other substrates were selected in an attempt to realize asymmetric induction. When chalcone was used as the substrate, product **30** was be obtained in good yield (63%) but also low enantiomeric excess (9%) (Table 4, entry 3). Copper(I) salts (CuBr, CuI, and $[Cu(MeCN)_4]PF_6$) with ligand (*S*)-(+)-**1c** gave 1,4-adducts **29** and **30** in good yield (over 70% isolated yield) with no chiral induction.

16, 4229 and references cited therein. (c) Kauffmann, T.; Hulsdunker, A.; Manges, D.; Nienaber, H.; Rethmeier, L.; Robbe, S.; Scherler, D.; Schrickel, J.; Wingbermuhle, D. *Tetrahedron Lett.* **1990**, *31*, 1553.

Scheme 18



Based on the experience of Pd-catalyzed AAA reaction, we decided to develop some chelating ligands for the conjugate addition. Ligand **18** bearing a pendant pyridine ring was proven to be a superior ligand in the palladium-catalyzed AAA reaction (see Section 3.1). However, the *trans* double bond of ligand **18** may not be stable under the conjugate addition conditions. In order to modify our ligands to build extra coordination sites, we investigated the synthesis and reactions of ligands **31** and **32** (Scheme 18). We expect these new ligands to have two binding domains: one for a hard metal (like the Mg in the Grignard reagents) and one for a softer metal (like Rh). If the two domains could interact with each other, an increase in the enantioselectivity of the conjugate addition reaction might be realized. This idea of structural design was proven to be effective in several conjugate addition studies.[65] Under strongly basic conditions, both ligands **31** and

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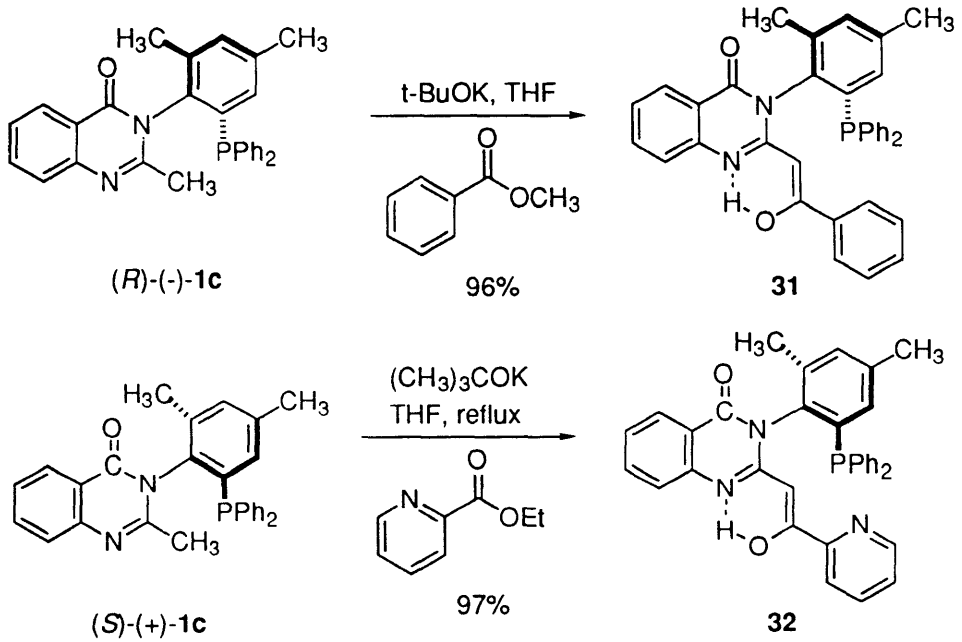
[65] Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339.

32 are expected to form rigid anionic ligands which would fit in the above structural requirements (Scheme 18).

Ligand **31** was synthesized by heating at reflux the solution of ligand (*R*)-(-)-**1c** and methyl benzoate in THF in the presence of potassium *t*-butoxide. Ligand **31** was synthesized analogously from (*S*)-(+)-**1c** and ethyl picolinate. Both of ligand **31** and **32** were obtained in good yield (96-97%). When sodium hydride was employed according to the literature[66], ligand **31** and **32** were obtained in much lower yield (less than 10%) (Scheme 19). The ^{1}H NMR spectra of ligands **31** and **32** indicated that only enol tautomers were present in $CDCl_3$. Unlike the *trans* double bond in ligand **18**, ionization of ligands **31** and **32** should render the ligands stable under the conjugate addition conditions.

Scheme 19



The catalyst **33** or **34** was formed *in situ* by mixing ligand **31** or **32** with $[(nbd)RhCl]_2$ and *n*-BuMgBr, respectively (Scheme 20).

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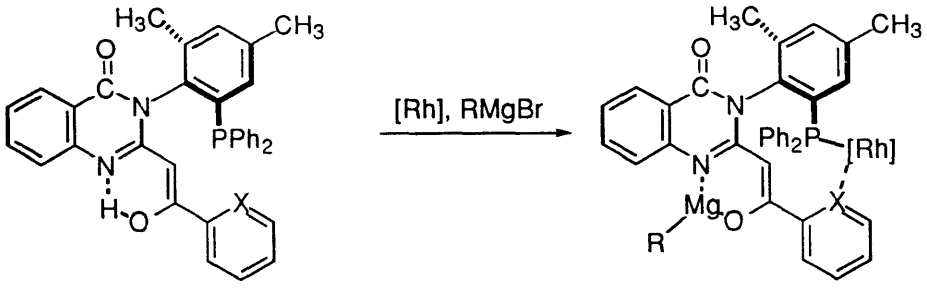
[66] Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161.

Scheme 20



31: X = CH
32: X = N

33: X = CH
34: X = N

Indeed, when catalyst **33** was used, 1,4-adducts from both 2-cyclohexen-1-one and chalcone were obtained in good yield and a detectable enantiomeric excess (9%) (Table 4, entry 4 and 5). Further investigation is needed to find out whether the increased enantiomeric excess was due to the communication of the two domains in the catalyst or due to the increased steric effect of the ligand. When catalyst **34** was used, it was surprising that no conjugate addition occurred (Table 4, entry 6). Only a small amount of 1,2-adduct product was isolated. We think the reason might be that after the Rh center coordinated with the N-P domain of ligand **32**, it became too hindered for the substrate to bind with Rh to get activated for conjugate addition.

It is satisfying to discover that the Rh complex with ligand **1c** and **31** could catalyze conjugate addition as indicated by a rate increase. However, more studies need to be carried out to investigate the mechanism of this reaction and to improve the enantioselectivity of the Rh catalyst with quinazolinone phosphine ligands.

Table 4. Rh-Catalyzed Conjugate-Addition with Grignard Reagent.

Entry	[Rh][a] (mol%)	Ligand (mol%)	Substrate	Solvent	Time (h)	Temp (°C)	1,4-Product Yield[b] / (ee[c]) (%)
1	2.5	(*S*)-(+)-**1c** (5.0)	2-cyclohexen-1-one	CH_2Cl_2	2	-20	76 (0)
2	2.5	(*S*)-(+)-**1c** (5.0)	2-cyclohexen-1-one	THF	2	-20	75 (0)
3	2.5	(*S*)-(+)-**1c** (5.0)	chalcone	THF	2	0	**63 (9)**
4	2.5	(*R*)-(+)-**31** (5.0)	2-cyclohexen-1-one	CH_2Cl_2	2	0	**77 (9)**
5	5	(*R*)-(+)-**31** (10)	chalcone	CH_2Cl_2	1	0	**70 (9)**
6	2.5	(*S*)-(-)-**32** (5.0)	2-cyclohexen-1-one	CH_2Cl_2	2	-20	0 (-)

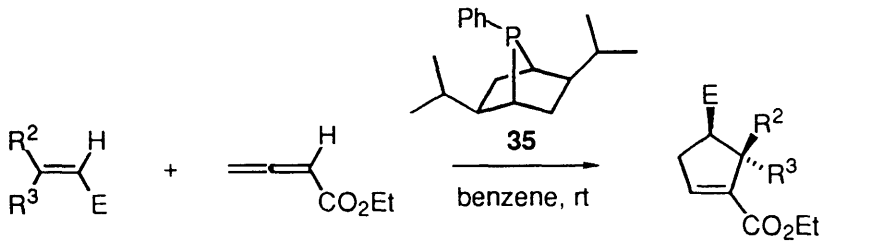
a)The reaction was carried out at room temperature under argon using 1,3-diphenyl-2-propenyl acetate as the substrate, dimethylmalonate (1 equiv. in respect to the base) with the base as the nucleophile, additive, solvent, [Pd] (allylpalladium chloride dimer: $[Pd(p\text{-}ally)Cl]_2$), and ligand **18**. b) [Rh]: $[(nbd)RhCl]_2$. c) Isolated yield by flash chromatography. For product **29**, % ee was determined by ^{13}C NMR analysis of the cyclic aminal formed by mixing product with (*R*,*R*)-1,2-diphenylethylenediamine in the NMR tube;[67] for product **30**, % ee was determined by HPLC using a Chiralcel OJ column (95:5 Hexane:*i*-PrOH, 1.0 mL/min, λ = 285 nm).

[67] Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.

3.4 Phosphine-Catalyzed [3+2] Cycloaddition

Cycloaddition reactions have a predominant place among methods in synthetic organic chemistry. Among the reported methods, [3+2] cycloaddition is an efficient strategy for the construction of the five-membered ring system directly from simple building blocks. Transition metal-catalyzed, anionic, cationic, and free radical mediated [3+2] cycloaddition have been investigated.[68] Recently, Lu's group showed that triphenylphosphine could catalyze a [3+2] cycloaddition reaction of electro-deficient olefins or *N*-tosylimines with 2,3-butadienoate.[69] Zhang's group developed a novel phosphine ligand (2,5-diisopropyl-7-phenyl-7-phosphabicyclo[2,2,1]heptane, **35**) as an efficient catalyst for the cycloaddition of acrylate **36** and ethyl 2,3-butadienoate (**37**) (Scheme 21).[70] Enantiomeric excess as high as 93% of the product **38** was achieved .

Scheme 21



36 **37** **38**

E = $CO_2{}^tBu$, $R_2 = R_3 = H$

88%, 93%ee

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[68] Reviews: (a) Little, R. D.; Chan, D. M. T. [3+2] Cycloadditions: Thermal Cycloadditions. Transition Metal Mediated Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 239-314. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49 and references cited therein. (d) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (e) Pyne, S. G.; Schafer, K.; Skelton, B. W.; White, A. H. *J. Chem. Soc. Chem. Commun.* **1997**, 2267.

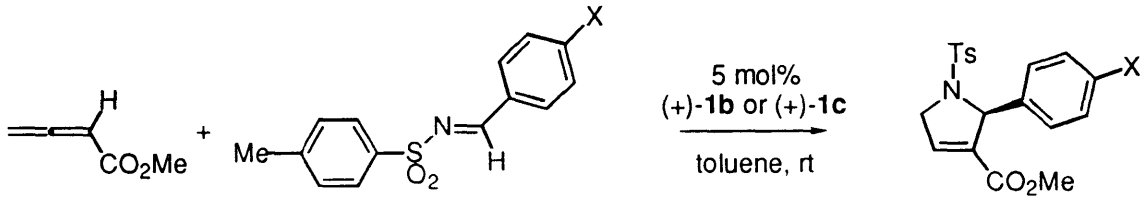
[69] (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461.

[70] Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.

With chiral quinazolinone phosphines in hand, it was of interest to try the asymmetric version of [3+2] cycloaddition of *N*-tosylimines with 2,3-butadienoate using ligand **1b** and **1c**.

Treatment of methyl 2,3-butadienoate (**39**) with *N*-toluenesulfonylbenzaldimine (**40**) in the presence of 5 mol% ligand (*S*)-(+)-**1b** in toluene at room temperature afforded cycloaddition product **42** in 70% yield (Scheme 22). The reaction rate was slower than the control reaction catalyzed by triphenylphosphine, which suggests that ligand **1b** is more hindered than triphenylphosphine. This is consistent with the mechanism proposed by Lu (see below, Scheme 24). After 48 hours, the reaction was stopped and analyzed. The enantiomeric excess of the product was determined to be 11% by both 1H NMR analysis with the chiral shift reagent $Eu(hfc)_3$ and by chiral HPLC (Chiralcel OJ) analysis (Table 5, entry 1). When ligand (+)-**1c** was used, the product **42** was obtained in a similar yield (69%) and enantiomeric excess (12%) (Table 5, entry 2).

Scheme 22



39

40: X = H
41: X = OCH_3

42: X = H
43: X = OCH_3

Treatment of methyl 2,3-butadienoate (**39**) with *N*-toluenesulfonyl *p*-methoxybenzaldimine (**41**) in the presence of 5 mol% ligand (+)-**1b** in toluene at room temperature afforded cycloaddition product **43** (Scheme 22). in 65% yield and 12% ee after 48 hours of reaction. When ligand (+)-**1c** was used, the product **43** was obtained in 63% yield and 12% ee (Table 5, entry 3 and 4).

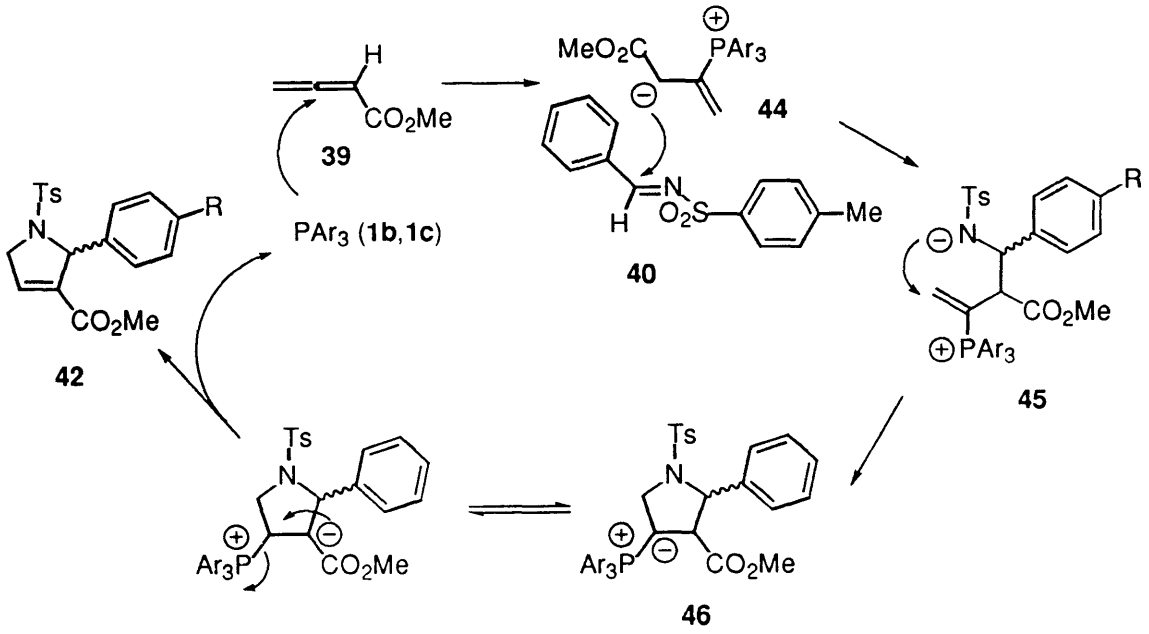
Table 5. Quinazolinone Phosphine-Catalyzed [3+2] Cycloaddition Reaction.[a]

entry	Ligand (5 mol%)	*N*-tosylimine	Time (h)	[3+2] product	Yield[b] (%)	% ee[c] (config.)
1	(*S*)-(+)-**1b**	**40**	48	**42**	70	11 (-)
2	(*S*)-(+)-**1c**	**40**	48	**42**	69	11[d] (-)
3	(*S*)-(+)-**1b**	**41**	48	**43**	65	12 (-)
4	(*S*)-(+)-**1c**	**41**	60	**43**	63	12[e] (-)

a) The reaction was carried out by mixing substrate **39** with **40** or **42**, and phosphine in dry toluene at room temperature under argon. b) Isolated yield by flash chromatography. c) % ee was determined by ^{1}H NMR using Eu(hfc)$_3$ in $CDCl_3$ as chiral shift reagent for **42** and **43**, or by HPLC using a Chiralcel OJ column (75:25 Hexane:*i*-PrOH, 1.0 mL/min) for **42**. d) $[\alpha]_D^{23}$ = -21.3° (*c* = 5.88, $CHCl_3$). d) $[\alpha]_D^{23}$ = -22.1° (*c* = 1.01, $CHCl_3$).

Scheme 23 shows Lu's proposed mechanism.[69b] A catalytic amount of phosphine acts as a nucleophilic trigger. It attacks the β-carbon atom of the allene to generate the reactive dipolar intermediate **44**, which is trapped by the dipolarophilic imine **40** to form an open chain intermediate **45**. Subsequent intramolecular nucleophilic addition affords intermediate **46**. Subsequent hydrogen transfer of **46** affords the cycloadduct **42** along with the regeneration of phosphine catalyst.

Scheme 23.



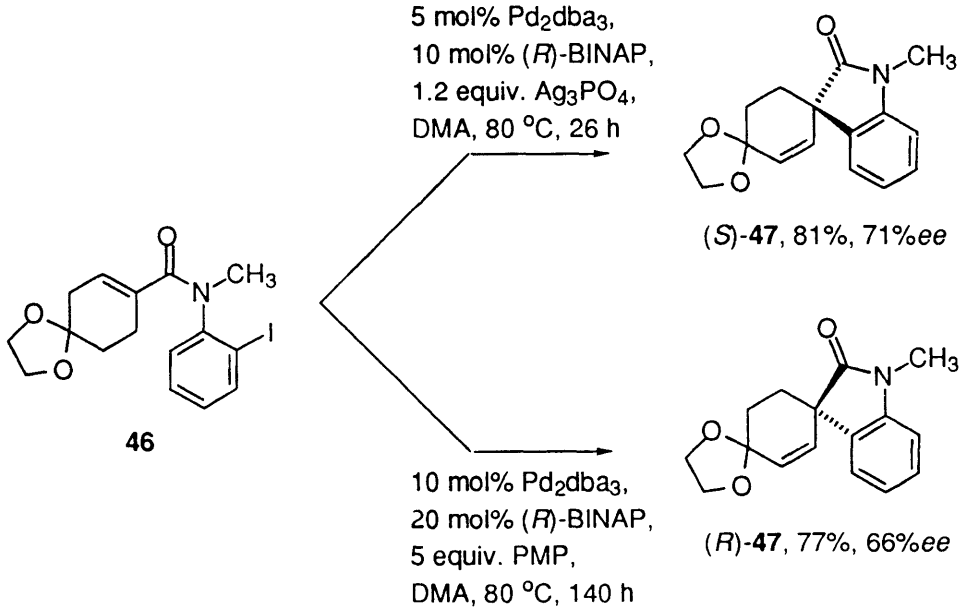
Since ligand **1b** and **1c** are more steric hindered than triphenylphosphine, formation of dipolar intermediate **44** will be more difficult than with triphenylphosphine. This may explain the slow reaction rate catalyzed by ligand **1b** and **1c**. The stereo-determining step is influenced by the chiral dipolar intermediate **44**. The low enantiomeric excess of product **42** and **43** indicates that the chiral environment created by ligands **1b** or **1c** is not very effective in differentiating the two *pro*chiral faces of C-N double bond of *N*-tosylimines.

The chiral quinazolinone phosphine-catalyzed [3+2] cycloaddition reaction represents the first asymmetric version of this reaction. The structures of quinazolinone phosphines need to be further optimized to improve their reactivity and ability to induce enantioselectivity.

3.5 Intramolecular Heck Reaction

The Pd-catalyzed arylation or vinylation of alkenes, generally referred as the Heck reaction, has been known since late 1960s.[71] However, successful examples of the asymmetric Heck reaction (AHR) were not reported until 20 years later.[72] Overman *et al.* pioneered the work of enantioselective formation of quaternary carbon centers using AHR with chelating (BINAP) ligand system (Scheme 24).[73]

Scheme 24



The mechanism of the Heck reaction with bidentate ligands is generally proposed to follow a cationic or a neutral pathway after the oxidative addition step as shown in Scheme 25. The cationic pathway begins with the dissociation of X from complex **49** to generate the tricoordinated 14 electron complex **50** with accompanying X^- counterion. Complexation of alkene into the vacant site then gives the 16 electron species **51**, and

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[71] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
[72] Review: Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.
[73] (a) Carpenter, N. E.; Kucera, D. J.; Overman. L. E. *J. Org. Chem.* **1989**, *54*, 5846. (b) Ashimori, A.; Overman. L. E. *J. Org. Chem.* **1992**, *57*, 4571.

insertion of alkene into the Pd-Ar bond followed by reformation of the Pd-X bond gives **52**. The bidentate ligand remained fully chelated throughout the process.

The neutral pathway has two branches. The widely-accepted pathway (I) starts with dissociation of one arm of the bidentate ligand giving the neutral species **53a**. Complexation of the alkene into the vacant site gives the neutral complex **54**. Alkene insertion into the Pd-Ar bond and re-complexation of the previously displaced phosphine moiety gives **52**. Recently, Overman *et al.* proposed an alternative neutral pathway (II).[74] Without the dissociation of the phosphine ligand, either the formation of pentacoordinate intermediate **53b** from complex **49** or the evolution of complex **53b** to complex **51** by halide rearrangement and dissociation would be the enantioselective step. This enantioselective step would be influenced quite differently by a chiral chelating phosphine ligand than an enantioselective step involving the four-coordinate intermediate **51** formed through the cationic pathway by dissociative in-plane coordination of alkene. Therefore, different asymmetric inductions were observed in the reaction illustrated in Scheme 24.

The β- or β'-hydride elimination from **52** can give either **55** or **56** with the formation of complex **57**. Reductive elimination regenerates **48** from **57**. The obvious attraction of intramolecular AHR is to generate important quaternary carbon centers by ruling out the competing β-hydride elimination step.

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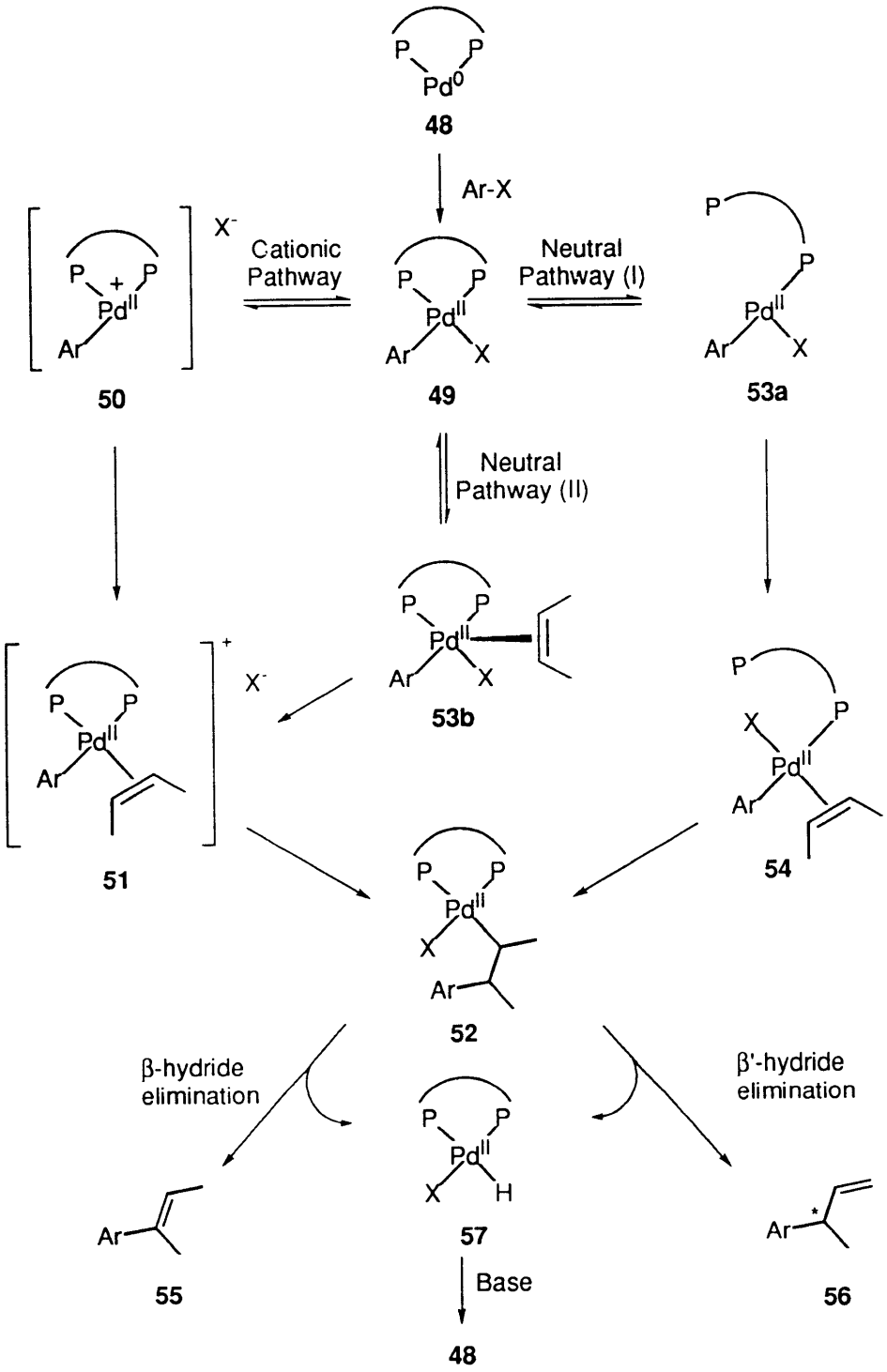
[74] Overman, L. E.; Poon, D. J. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 518.

Scheme 25. Mechanism of the Heck Reaction



In practice it has been proven possible to influence the pathways in a given Heck process. The cationic pathway is likely to take place by using aryl/vinyl triflate substrates

(the Pd-OTf bond being weak)[75] or by adding silver salts to the reaction of an aryl/vinyl halide to sequester the halide from intermediate **49** and replacing it with the anion of the silver salts[76]. The neutral pathway is likely to take place by using aryl/vinyl halide substrates (the Pd-X bond being strong) or by adding excess of halide anions to the reaction of either an aryl/vinyl halide or triflate.[77]

By choosing substrate **58** (X = I)[78], we assumed the reaction would follow the neutral pathway. The enantiomeric excess of the product could reflect the chiral induction of monophosphine ligand **1b** in the formation of quaternary carbon centers. The catalyst was generated *in situ* from (*R*)-(-)-**1b** and $Pd(OAc)_2$ or $Pd_2(dba)_3$. When compound **58** was subjected to the AHR conditions, two products **59** and **60** were isolated (Scheme 26). The results are summarized in Table 6. The highest enantiomeric excess (26%) was obtained when 1,2,2,6,6-pentamethylpiperidine was used as a base (Table 6, entry 5). This base has been previously shown to be beneficial in the intramolecular AHR.[77a] Addition of halide in this reaction did not improve the enantiomeric excess as in the case reported by Overman *et al.* (Table 6, entry 1 and 2).[74] The palladium precursor $Pd(OAc)_2$ gave slightly better enantioselectivity than $Pd_2(dba)_3$ (Table 6, entry 3, 4, 5 and 6).

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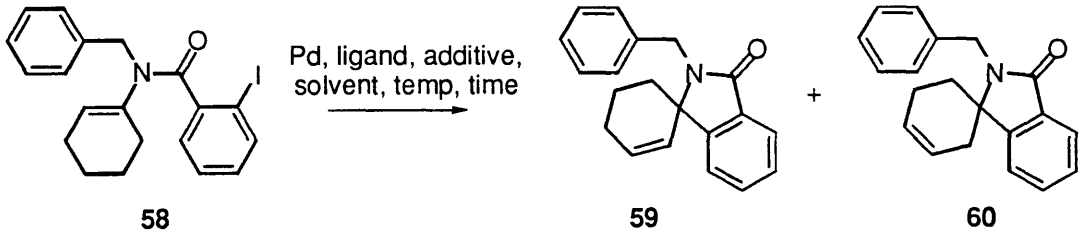
[75] Dekker, G. P. C. M.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1992**, *11*, 1598.

[76] Shibasaki, M.; Sodeoka, M. *J. Syn. Org. Chem. Jpn.* **1994**, *52*, 956.

[77] (a) Ashimori, A.; Matsuura, T.; Overman. L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.

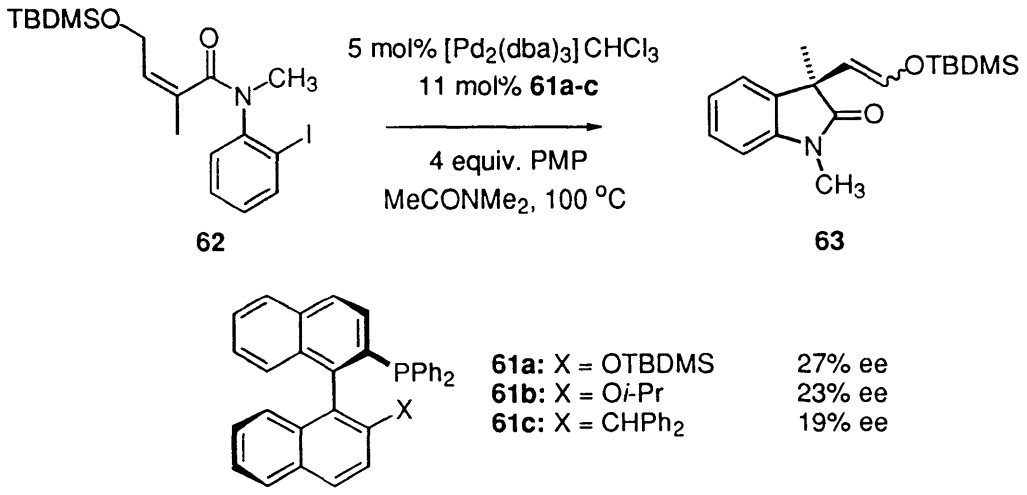
[78] (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557.

Scheme 26



The low enantiomeric excesses can be explained in two ways. The monophosphine ligand **1b** has a lower chiral induction ability than chelating ligands like BINAP. It behaves similarly to monophosphine ligands **61a-c** in asymmetric Heck cyclization of (Z)-butenanilide iodide (**62**) (Scheme 27);[74] Alternatively, double bond isomerization, which is common in palladium chemistry caused by the readdition-elimination process of Pd-H species,[79] might be responsible for scrambling the enantiomers of product **59** and product **60** to reduce the enantioselectivity.

Scheme 27



[79] Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345.

Table 6. Palladium-Catalyzed Intramolecular AHR with Ligand (*R*)-(-)-1b:[a]

Entry	[Pd] (mol%)	Ligand (mol%)	Solvent[b]	Time (h)	Temp (°C)	Base[c] / additive	Product **59** Yield[d]/(ee[e]) (%)	Product **60** Yield[d]/(ee[e]) (%)
1	$Pd(OAc)_2$ (10)	20	DMF	12	100	3.0 equiv. Et_3N / –	26/19	25/14
2	$Pd(OAc)_2$ (10)	20	DMF	24	65	3.0 equiv. K_2CO_3 / 1.0 equiv. Et_4NCl	25/11	25/17
3	$Pd_2(dba)_3$ (5)	20	DMF	12	80	3.0 equiv. K_2CO_3 / –	29/11	26/10
4	$Pd(OAc)_2$ (10)	20	DMF	42	25	3.0 equiv. K_2CO_3 / –	45/20	43/12
5	$Pd(OAc)_2$ (10)	40	DMA	18	60	5.0 equiv. PMP / -	**62/26**	**31/19**
6	$Pd_2(dba)_3$ (5)	40	DMA	56	80	2.5 equiv. PMP / –	29/22	14/3.5

a) The reaction was carried out at 60 °C under argon using compound **58** as the substrate with the base, solvent, [Pd] and ligand (*R*)-(-)-**1b**. b) DMA: *N*,*N*-dimethylacetamide. c) PMP: 1,2,2,6,6-pentamethylpiperidine. d) Isolated yield by flash chromatography. e) % ee was determined by HPLC using a Chiralcel OJ column (95:5 Hexane:*i*-PrOH, 1.0 mL/min, λ = 285 nm).

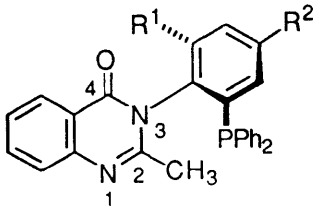
The results prompted us to develop chelating phosphine ligands (see part II) and to use a substrate like compound **46** that can prevent double-bond isomerization for the further study of AHR.

3.6 Summary

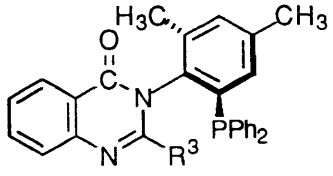
In conclusion, the studies of catalytic reactions demonstrated that monophosphine ligand (*R*)-(-)-**1b** and its chelating analog **18** are effective in palladium catalyzed asymmetric allylic alkylation reaction. Enantiomeric excess up to 87% was obtained using ligand **18**. The structure of ligand **1b** can be easily modified at the 2-methyl group by electrophilic substitution of its lithium anion. The tautomerism of 2-methyl group of quinazolinone ligand **1b** in the presence of $[Rh(nbd)_2]ClO_4$ was observed for the first time. Along with this study, a high yielding conjugate addition of enone with Grignard reagent catalyzed by the Rh complex of ligand **1c** and **31** was discovered. The first asymmetric version of phosphine-catalyzed [3+2] cycloaddition of *N*-tosylimines with 2,3-butadienoate indicates the quinazolinone phosphines are hindered nucleophilic catalysts. Asymmetric intramolecular Heck reaction with monophosphine ligand (*R*)-(-)-**1b** gave comparable enantiomeric excess to the literature results.[76b] The results prompt us to design the chelating version of quinazolinone phosphine ligands.

Chapter 4. Synthesis and Resolution of 2-Unsubstituted and 2-Heterosubstituted Quinazolinone Ligand System

4.1 Introduction



1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = CH_3$
1c $R^1 = R^2 = CH_3$



1d $R^3 = H$.
1e $R^3 = PPh_2$.
1f $R^3 = SH$.
1g $R^3 = SMe$.

The successful syntheses and resolutions of ligands **1a-c** encouraged us to develop 2-heterosubstituted quinazolinone phosphine ligands, such as **1e-g**. The heteroatoms at the 2-position of the quinazolinone ring together with the PPh_2 group on the 3-aryl ring are designed to chelate with metals in a similar way as BINAP does. Many variations of bidentate ligands have been shown to associate strongly with the metal centers to bring the metals closer to the chiral environment provided by ligands. This feature has led to their enhanced stereoselectivity in asymmetric catalysis.

In a traditional procedure, 2-mercapto-3-aryl-4(3*H*)-quinazolinone (**64**) can be obtained from the condensation reaction of anthranilic acid with either an aryl thiourea or an aryl isothiocyanate (Scheme 28).[80] Compound **64** can be transformed into 2-ethylthioquinazolinone (**65**) using sodium and ethyl iodide, and further to 2-aminosubstituted-quinazolinone (**66**) by reacting with amines, anilines, or hydrazines (Scheme 28).[81]

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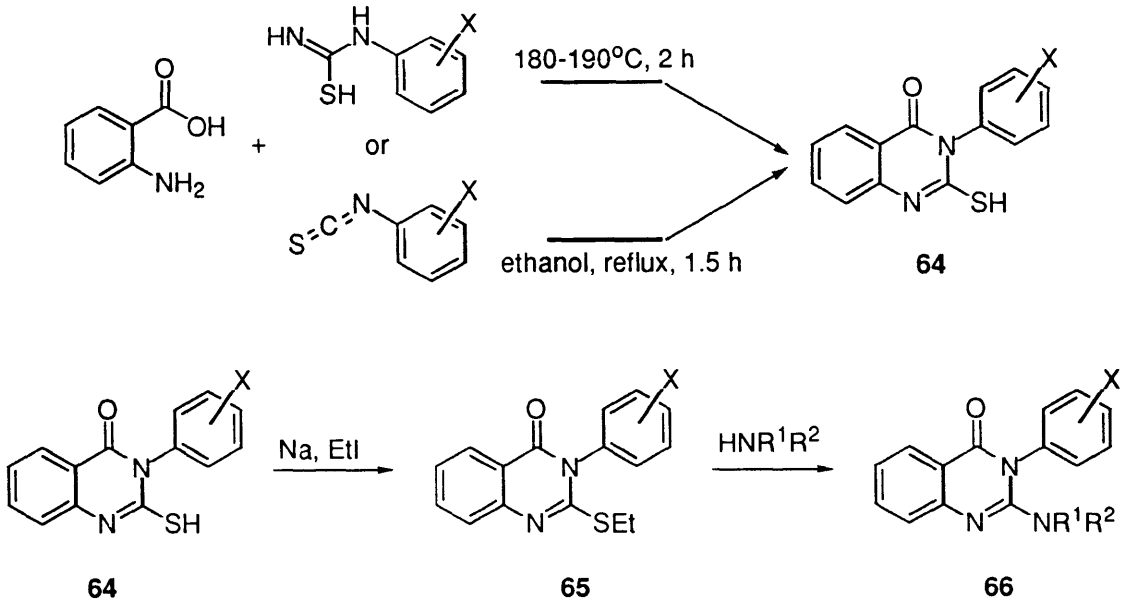
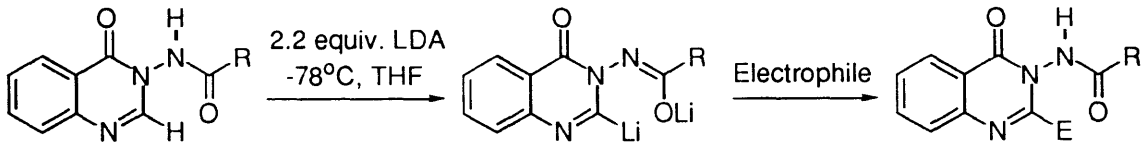
[80] Dave, G. R.; Mewada, G. S.; Amin, G. C. *J. Indian Chem. Soc.* **1960**, *37*, 595.
[81] (a) Hori, M.; Iemura, R.; Hara, H.; Sukamoto, T.; Ito, K.; Ohtaka, H. *Chem. Pharm. Bull.* **1991**, *39*, 367. (b) Farghaly, A. M.; Chaaban, I.; Khalil, M.A.; Bekhit, A. A. *Arch. Pharm (Weinheim)* **1990**, *323*, 833. (c) Gupta, C. M.; Bhadui, A. P.; Khanna, N. M. *J.*

Scheme 28



Recently, Smith *et al.* reported another method for the synthesis of 2-substituted quinazolinone by lithiation of 2-unsubstituted quinazolinones (**67** and **68**) with LDA followed by reaction of the resulting lithium reagent **69** with a variety electrophiles (Scheme 29).[82] They claimed that the *ortho*-directing groups (3-pivaloylamino and 3-acetylamino group) were necessary for the lithiation of quinazolinones **67** and **68** to take place.

Scheme 29



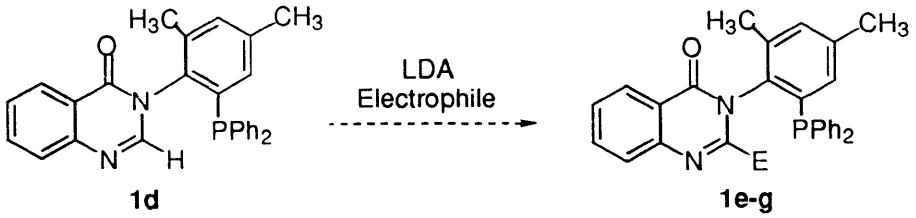
Med. Chem. **1968**, *11*, 392. (d) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. *J. Med. Chem.* **1998**, *41*, 1042.

[82] Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 647 and references cited therein.

However, they also pointed out that the lithiation of 2-position occurred in the presence of acidic α-protons of 3-acetylamino group in the case of compound **68**. Deprotonation at the α-protons of simple acetanilides takes place easily and accounts for the preferred use of the pivaloylamino group in directed lithiation reactions.[83] Clearly, the regioselective lithiation of compound **68** suggests that the proton at 2-position is more acidic than the methyl protons of the 3-acetylamino group.

We anticipated that the proton at 2-position of quinazolinone ligand **1d** would be acidic enough to be directly lithiated without an apparent directing group. If the regioselective lithiation could be realized, subsequent quenching of the carbanion with electrophiles (such as PPh_2Cl, S_8, and MeSSMe) would afford chelating ligand **1e-g** in a straight-forward fashion (Scheme 30).

Scheme 30



1d **1e-g**

4.2 Synthesis of 2-Unsubstituted Ligands 1d

In order to obtain the 2-unsubstituted ligand **1d**, we first tried the procedure which was successful for the synthesis of ligands **1a-c** (Scheme 31). *N*-formylanthranilic acid (**70**) was obtained in good yield from anthranilic acid according to the literature procedure.[84] However, under the conditions similar to the synthesis of ligands **1a-c** (benzenesulfonyl chloride, pyridine), no condensation product **1d** was formed with acid **70** and aminophosphine **4c** in refluxing benzene.

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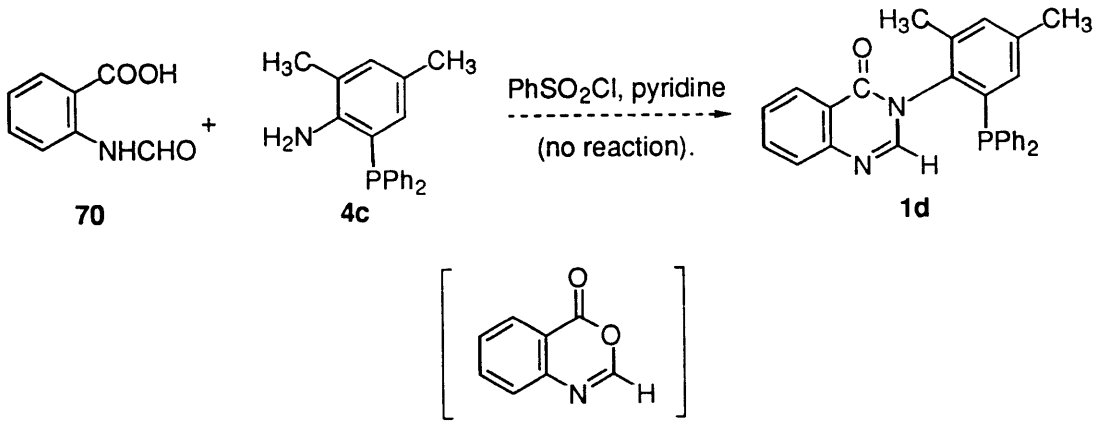
[83] (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Wakefield, B. J. *Organolithium Methods*; Academic Press, 1988.

Scheme 31



70 **4c** **1d**

71

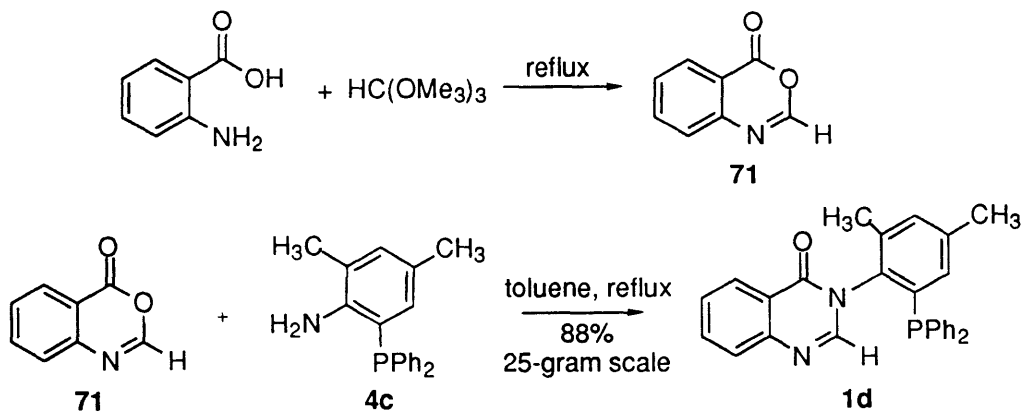
The formation of ligand **1d** should have followed a similar mechanism to that for ligands **1a-c** (see part I). The absence of **1d** suggested that the intermediate 4*H*-3,1-benzoxazin-4-one (**71**) might not form under the above condensation conditions.

Recently, Khajavi *et al.* reported a highly efficient method for the synthesis of benzoxazin-4-one by the condensation of anthranilic acid with orthoesters.[85] Following their conditions, the mixture of 2.2 equivalents anthranilic acid and 5.0 equivalents trimethyl orthoformate was heated to reflux for 3 h. The excess of orthoformate and the resulting methanol were removed by distillation followed by azeotropic distillation together with toluene to afford a light yellow slurry. To this crude hygroscopic 4*H*-3,1-benzoxazin-4-one (**71**) was added a solution of 1.0 equivalents aminophosphine **4c** in toluene. The mixture was heated to reflux for 6 h to afford quinazolinone **1d** in 88% yield on a 25 gram scale (Scheme 32). As in the synthesis of ligands **1a-c**, an excess of anthranilic acid and orthoformate were used to generate 2.2 equivalents of compound **71** to ensure the complete conversion of the aminophosphine **4c**.

---

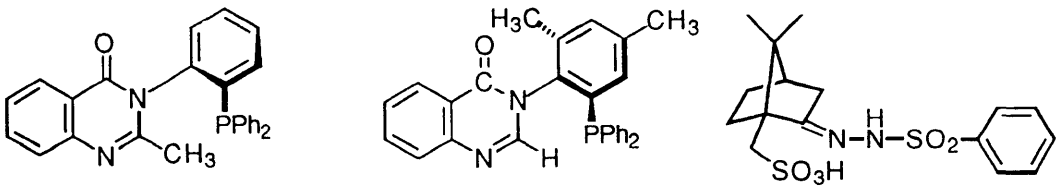
[84] Sheehan, J., C.; Yang, D., H. *J. Am. Chem. Soc.* **1958**, *80*, 1154.
[85] Preparation of Benzoxazinone: Khajavi, M. S.; Montazari, N.; Hosseini, S. S. S. *J. Chem. Research (S)*, **1997**, 286. Use of orthoformate for quinazolinone synthesis: Kornet, M. J.; Varia, T.; Beaven, W. *J. Heterocyclic Chem.* **1983**, *20*, 1553.

Scheme 32



4.3 Resolution of Ligand 1d

Based on their structural similarity, we assumed that ligand **1d** would have a similar rotational barrier as that of ligand **1a**. Hence, the two enantiomers of **1d** should be resolvable. This is confirmed by the trace of chiral HPLC (Chiralcel-OD column) which shows two peaks of equal area with baseline separation. Since ligand **1a** can be easily resolved by using the hydrazone derivative of (*S*)-(+)-camphorsulfonic acid (*S*-CSZ, **10**), we attempted to use it for the resolution of ligand **1d**.

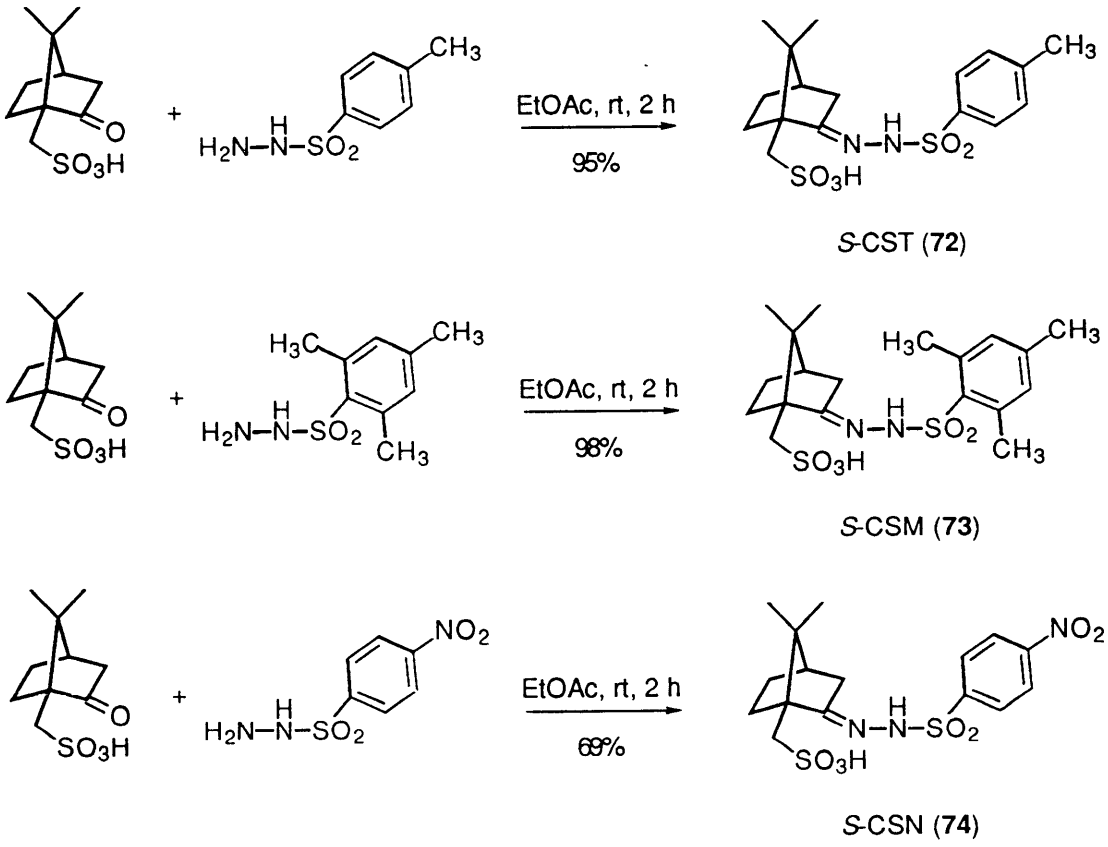


1a **1d** *S*-CSZ (**10**)

Upon mixing ligand **1d** with either (1*S*)-(+)-camphorsulfonic acid or acid **10** in a variety of conventional solvents (ethyl acetate, methanol, ethanol, acetone, acetonitrile, and THF), no apparent salt formation was observed. Several other hydrazone derivatives of camphorsulfonic acid (**72-74**, Scheme 33) with varied steric and electronic properties were

synthesized in good yield from (1*S*)-(+)-camphorsulfonic acid and the corresponding arylsulfonyl hydrazides following the same procedure as for acid **10**. These new chiral acids were also not effective in salt formation with ligand **1d**. One possible explanation is that 2-unsubstituted ligand **1d** is less basic than 2-methylsubstituted ligands **1a-c**. In the latter, the hyperconjugation effect of the 2-methyl group renders the nitrogen at the 1-position more basic.

Scheme 33

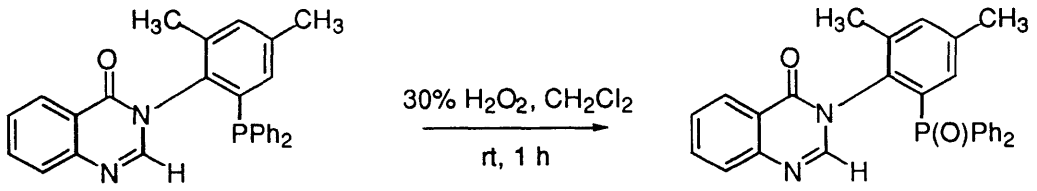


Formation of inclusion compounds[86] from phosphine oxides and chiral acids followed by reduction of phosphine oxides is a conventional way of phosphine resolution.[2b] Phosphine oxide **75** was obtained in good yield by reacting ligand **1d** with

[86]Arad-Yelilin, R.; Green, B. S.; Knossow, M.; Tsoucaris, G. *Inclusion Compounds*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 3, pp 263-292.

hydrogen peroxide in CH_2Cl_2 (Scheme 34). No inclusion precipitation could be obtained when compound **75** was mixed with (1*S*)-(+)-camphorsulfonic acid or (2*R*,3*R*)-(-)-2,3-*O*-dibenzoyltartaric acid in ethyl acetate, ethanol, methanol, or acetone.

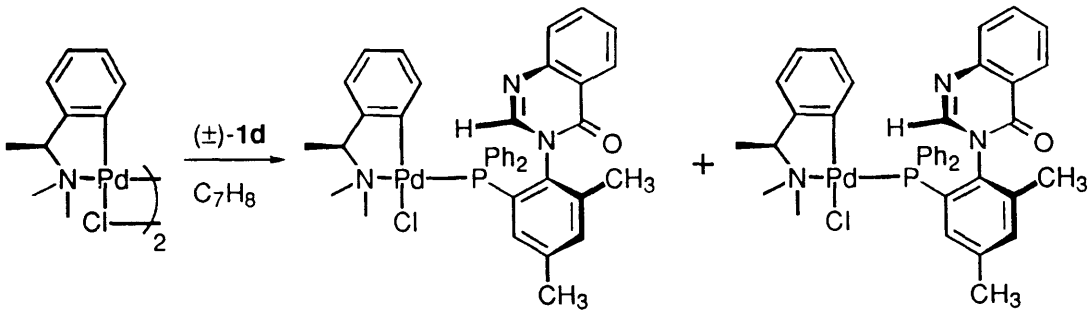
Scheme 34



1d **75**

We then sought to use (-)-di-μ-chlorobis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2, *N*]dipalladium(II) (**7**),[39] which we found to be a successful resolving agent for ligand **1b**. Light yellow crystals were formed when ligand **1d** was mixed with complex **8** in toluene (Scheme 35). However, the crystal was a quasi-racemate composed of roughly equal amount of complex (*S*, *R*)-**76** and complex (*S*, *S*)-**77** based on the ^1H NMR analysis of the crystals and chiral HPLC analysis of the free ligand released by the treatment of the crystals with ethylene diamine. Recrystallization of the yellow crystals from several solvent systems (benzene/hexane, benzene/pentane, benzene/acetone, CH_2Cl_2/hexane, CH_2Cl_2/ether, toluene/pentane) did not achieve any separation of complexes **76** and **77**.

Scheme 35



(*S*)-**7** (*S,R*)-**76** (*S,S*)-**77**

(-)-Di-μ-chloro-bis[(*S*)-dimethyl-(1-naphthylethyl)aminato-C^2, *N*]dipalladium(II) (**78**)[87] has been known to differentiate phosphine enantiomers more effectively. Therefore, this reagent is a good alternative for the resolution of phosphine ligands when complex **7** fails to work.[88] The proposed explanation is that the benzylic methyl group of complex **78** adopts an axial disposition to avoid an unfavorable steric interaction with 8-H of its naphthalene ring, which results in a increased conformation rigidity in the five-membered palladocycle unit of the ligated complexes. In complex **7**, the corresponding palladocycle is much more flexible, and the benzylic methyl group can adopt both axial and equatorial conformations.[89]

The ^{1}H NMR spectra of the unseparable mixture of complexes **76** and **77** exhibited benzylic chemical shift associated with two distinct compounds in 1:1 ratio: C*H*Me δ 3.52 (doublets of quartet, J = 6.2 Hz), 4.64 (quartet, J = 6.8 Hz). The latter (quartet) chemical shift was assigned to the equatorial benzylic methyl group because of the absence of benzylic C*H*-coupling to phosphorus. This observation confirmed the existence of the flexible palladocycles.

Complex **78** turned out to be effective in the resolution of monophosphine ligand **1d**. When 2.0 equivalents ligand **1d** was mixed with 1.0 equivalents complex **78** in a 1:2 toluene/hexanes mixture, complex (*S*, *R*)-**79** precipitated first. Complex (*S*, *S*)-**80** was recovered from the mother liquor (Scheme 36).

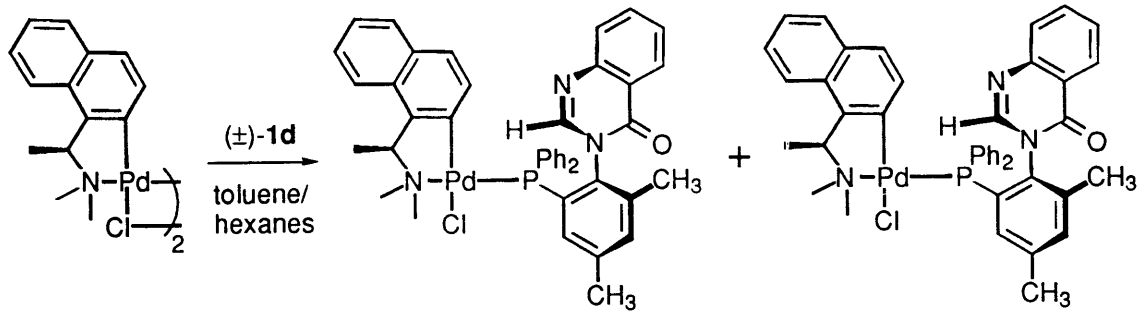
---

[87] Preparation: (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.

[88] (a) Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285. (b) Chelucci, G.; Cabras, M. A.; Saba, A.; Sechi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1027. (c) Valk, J.-M.; Claridge, T. D. W.; Brown, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2597.

[89] (a) Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395 and references cited therein. (b) Pabel, M.; Willis, A. C.; Wild, S. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2369.

Scheme 36



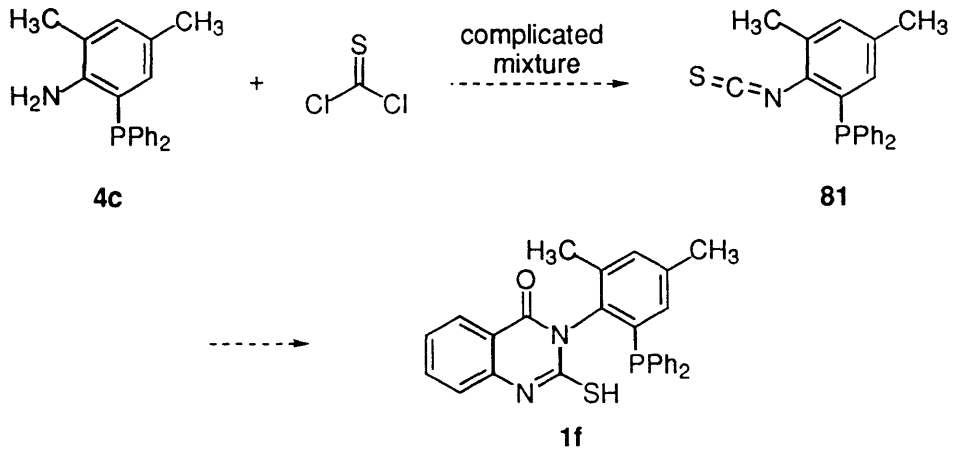
The ^{1}H NMR spectra of the naphthylethylamino complexes (*S*, *R*)-**79** and (*S*, *S*)-**80** exhibit C*H*Me resonances at δ 4.24 (doublets of quartet, J = 6.2 Hz) and 4.36 (doublets of quartet, J = 5.7 Hz), respectively. These doublets of quartets showed that both of the benzylic protons in complex **79** and **80** coupled to the chelating phosphorus atoms. This confirmed the axial conformation for both benzylic methyl groups in complexes **79** and **80** due to the presence of the rigid palladocycles.

The free chiral phosphine was released from complex **79** by treatment with ethylenediamine in CH_2Cl_2. Crystallization from CH_2Cl_2/hexanes afforded (-)-**1d** in 28% yield (99% ee by HPLC analysis). As with the palladium resolution of ligand **1b**, the resolving agent **78** was recovered using 2*N* aqueous HCl. Based on the sign of optical rotation value, the absolute configuration of ligand **1d** was correlated with ligands **1a-c** to be *R*. The antipode (*S*)-(+)-**1d** was recovered analogously from complex **80** in 24% (>99.5% ee by HPLC analysis). The resolution was carried out on a 2 gram scale.

4.4 Synthesis of 2-Heterosubstituted Ligands 1e-g

Our initial plan for making ligand **1f** from isothiocyanate **81** and anthranilic acid following the traditional synthesis was not successful. Conditions used to form the isothiocyanate **81** from aminophosphine **4c** and thiophosgene afforded a complicated black mixture (Scheme 37).[90] Product **81** could not be isolated. The complication of this reaction may be caused by the reaction of thiophosgene with the phosphorus atom of **4c**.

Scheme 37



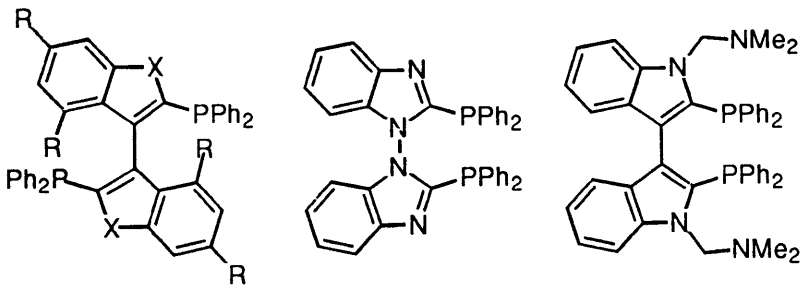
We subsequently started to explore the possible lithiation of 2-unsubstituted quinazolinone **1d**. Direct metalation of five-membered heteroaromatic rings (especially indoles and imidazoles) has been very well documented.[91] Some recent syntheses of chiral phosphine ligands demonstrated the promising applications of this methodology.[6,92]

---

[90] Isothiocyanate preparation: Stanley, R. S.; Karo, W. *Organic Functional Group Preparations*; 2nd Ed. Vol. 1, 1983, pp 373.

[91] (a) Davies, D. T. *Aromatic Heterocyclic Chemistry*; Oxford University Press: New York, 1992 and references cited therein. (b) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: San Diego, 1997.

[92] For the synthesis of ligand **82**: Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285.



X = S, R = CH_3 (**tetraMe-BITIANP**)
X = S; R = H (**BITIANP**)
X = O; R = H (**BIFURP**)

BIMIP

82

However, direct lithiation of six-membered aromatic heterocycles, especially for diaza compounds, is a less studied field, possibly because of their high reactivity toward nucleophilic addition. Although there are some recent reports about lithiation of pyrimidine using lithium alkylamides such as LDA (lithium diisopropylamide) or LTMP (lithium 2,2,6,6-tetramethylpiperidylamide) which are less prone to nucleophilic addition than alkyl- or aryllithium, to our best knowledge, there is no report on direct lithiation of quinazolinone ring system,[93] except for the report by Smith *et al.* on the *ortho*-directed lithiation of quinazolinones (see Section 4.1).

To our delight, the lithiation of ligand **1d** using LDA proceeded smoothly at -78 °C in THF to give yellow solution of anion **83** even without apparent an *ortho*-directing group (due to the atropisomeric feature of Ligand **1d**, the 3-phenyl ring is almost perpendicular to the quinazolinone ring, so we expect little *ortho*-directing effect from the "PPh_2" group if this group can be regarded as a directing group) (Scheme 38). This anion was found to be unstable at temperatures higher than -20 °C. Hence, the subsequent addition of electrophiles was carried out at a temperature lower than -70 °C.

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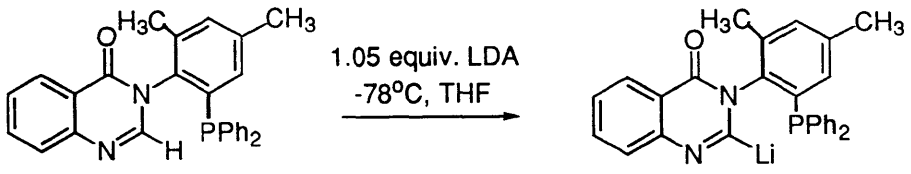
[93] Review: Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1994**, *37*, 2149.

Scheme 38. Direct lithiation of Ligand 1d



1d **83**

The lithium anion **83** was quenched with different electrophiles. When neat chlorodiphenylphosphine (PPh_2Cl) was added to the cold solution of anion **83** in THF, the yellow color disappeared immediately. The reaction mixture was stirred at -75 °C for one hour before warming up slowly to room temperature. After normal workup procedure, diphosphine ligand **1e** was isolated in 88% yield (Scheme 39).

When solid sulfur (S_8) was added to the cold solution of anion **83**, the solid was dissolved slowly over one hour to result a clear yellow solution. After an additional two-hour stirring at room temperature, ligand **1f** was isolated in 84% yield as an off-white solid (Scheme 40).

Ligand **1g** was obtained analogously in 88% when dimethyl disulfide (MeSSMe) was used as the electrophile. All the reactions were carried out on a three-gram scale and ligands **1e-g** were fully characterized. In particular, ligand **1f** is only in the thioamide form based on ^1H NMR and ^{13}C NMR analysis (Scheme 40).[94]

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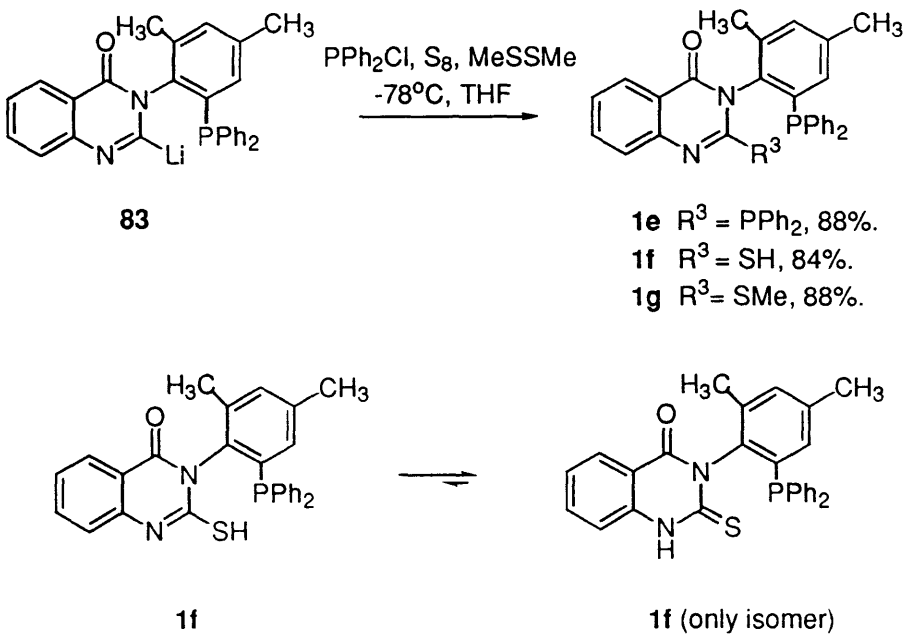
[94] Thioamide form of quinazolinone: Brown, D. J. *Quinazolines. Supplement 1*; Wiley: New York, 1996.

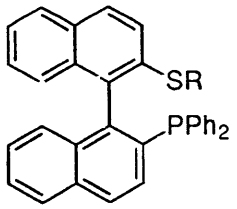
Scheme 39. Synthesis of Ligand 1e-g



The syntheses of ligands **1f** and **1g** are worth commenting. Recently, interest in heterobidentate ligands has increased and many new ligands have been developed, among which N-S ligands as well as P-N ligands have achieved remarkable success.[95] However, P-S ligands have been relatively less studied. Only one class of P-S atropisomeric ligand (**84**) has been developed by Gladiali *et al.*[96] followed by Kang *et al.*[97] (Figure 18). This ligand series was synthesized from binaphthol by a multiple-step transformation. Promising results for these ligands have been obtained from the studies of copper-catalyzed conjugate addition, palladium-catalyzed asymmetric allylic alkylation, and rhodium-catalyzed asymmetric hydroformylation with ligand **84**. In contrast, the concise one-pot synthesis of ligands **1e-g** offers an efficient access to a new class of P-S and P-P chelate ligands.

---

[95] (a) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (b) Reick, J.; Helmchen, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687.
[96] Gladiali, S.; Dore, A.; Fabbri, D. *Tetrahedron: Asymmetry* **1994**, *5*, 1143.
[97] Kang, J.; Yu, S. H.; Kim J. I.; Cho, H. G. *Bull. Korean Chem. Soc.* **1995**, *16*, 439.



84

R = H, Me, *i*-Pr, CH_2Ph

Figure 18.

4.5 Resolution of Ligand 1e Using the Chiral Palladium Complex

Although enantiomers of ligands **1e-g** can be theoretically obtained from chiral enantiomers of ligand **1d**, we were still interested in the resolution of ligands **1e-g** with readily available chiral acid. We expected the 2-position heteroatoms in ligands **1e-g** would increase the basicity of the nitrogen at the 1-position to form salts with sulfonic acid derivatives.

Despite of repeated efforts, no apparent salt formation was observed when ligand **1e-g** were mixed with (1*S*)-(+)-camphorsulfonic acid or its hydrazone derivatives **10, 72, 73,** and **74** in a variety of solvents (ethyl acetate, methanol, ethanol, acetone, acetonitrile, and THF).

However, diphosphine **1e** could be successfully resolved using (-)-di-μ-chlorobis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2, *N*]dipalladium(II) (**7**) (Scheme 40).[98] A suspension of 1 equivalents complex **7** and 2 equivalents of ligand **1e** in methanol was stirred at ambient temperature to give a clear, almost colorless, solution. The gradual addition of a solution of 2 equivalents of $NaBF_4$ in water to the above solution selectively precipitated the white complex (*S*,*S*)-**85** in 91% yield. Crystallization from benzene afforded colorless crystals in 85%. X-ray analysis of the crystals confirmed the absolute configuration of (*S*,*S*)-**85** according to Cahn-Ingold-Prelog rule.[41]

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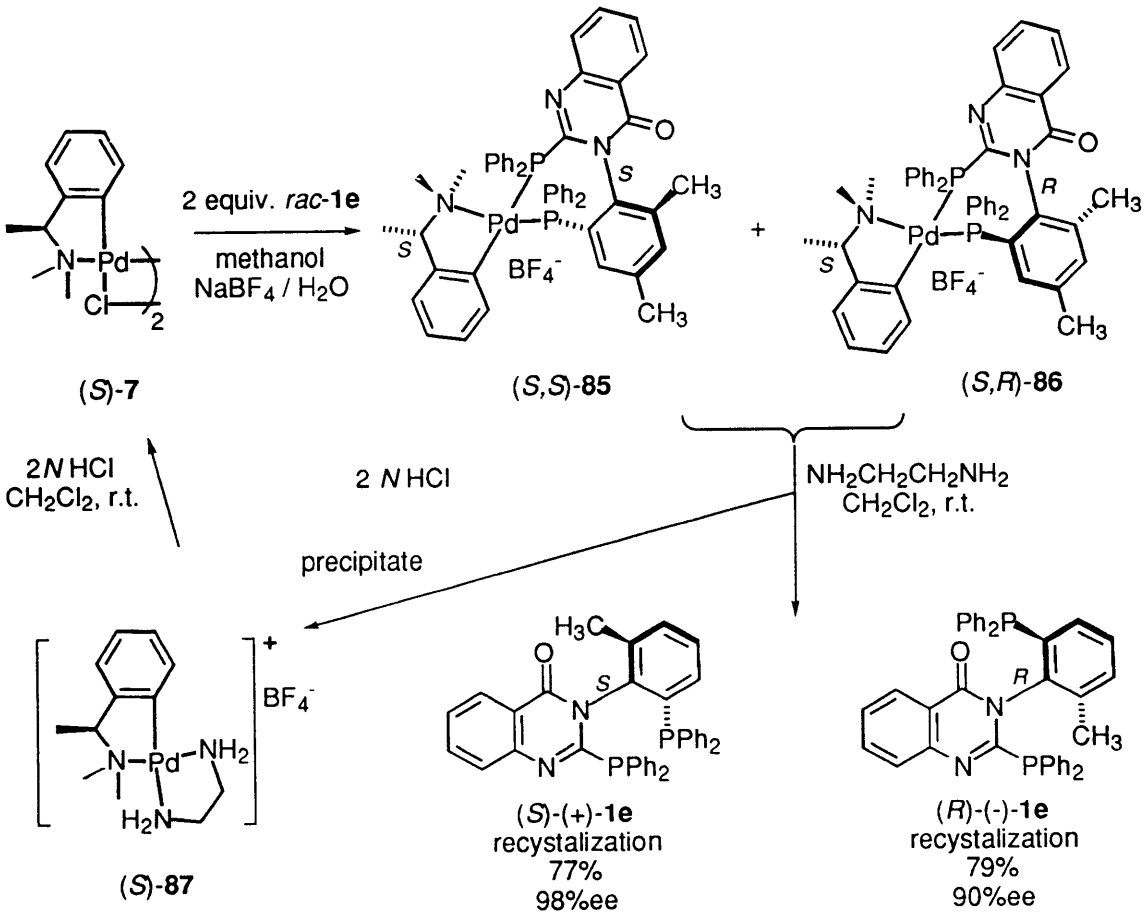
[98] Roberts N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254.

Scheme 40



Traditionally, strong coordinating agent DIPHOS (1,2-bis(diphenylphosphino)-ethane) has been employed for liberating diphosphine ligands from their palladium complexes. Using this method, resolving agent **7** could not be recovered directly.[40b] We found ethylenediamine was as effective for the liberation of ligand **1e** from the palladium complex as for ligand **1b** (see Section 2.3). Therefore, treatment of complex (*S*,*S*)-**85** with ethylenediamine in CH_2Cl_2 released (*S*)-(-)-**1e** with the formation of complex **87**. Crystallization from ethyl acetate/hexanes afforded the free phosphine ligand in 77% yield and 98% ee. The resolving agent **7** was then directly recovered from complex **87** by treatment with 2 *N* hydrochloric acid. Ligand (*R*)-(+)-**1e** was recovered 79% (90% ee)

following the same procedure from the aqueous methanol mother liquor containing (*S*,*R*)-**86**.

Complex **85** ($C_{50}H_{46}BF_4N_3OP_2Pd$; M_w = 960.10) crystallized (benzene) in the orthorhombic $P2_12_12_1$ space group with cell dimensions: a = 15.6576(3) Å, b = 16.1037(4) Å, c = 19.6933(3) Å and Z = 4. A total of 14973 reflections were collected at -90 °C using a Siemens SMART/CCD diffractometer. Least squares refinement of the data using 4640 reflections converged upon the structure shown in Figure 19 with R = 0.0932 and a goodness-of-fit = 1.061.

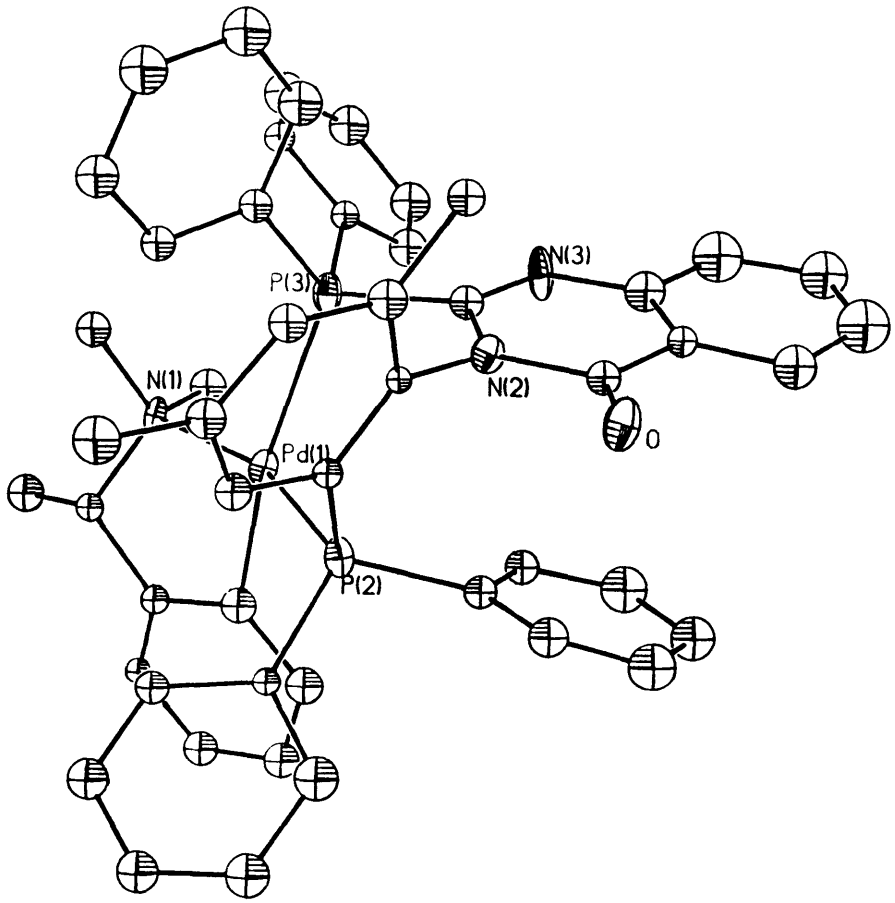


Figure 19. ORTEP plot of complex (*S*,*R*)-**85**. The counter anion (BF_4^-) has been omitted for clarity.

The X-ray analysis of complex (*S*,*S*)-**85** further revealed that the PPh_2 group on the 3-aryl ring of ligand (*S*)-(-)-**1e** was *trans* to the dimethylamino group; the PPh_2 group at the 2-position was *cis* to the dimethylamino group. This was the only atom connection pattern in the whole crystal. ^1H NMR study was also consistent with a single diastereomeric complex (*S*,*S*)-**85**. These data suggest that the two phosphine groups are electronically different. This feature may have special utility for the catalyst design.

4.6 Summary

We have achieved the syntheses of that 2-unsubstituted and heterosubstituted atropisomeric quinazolinone phosphine ligands **1d-g** in good yield by a straightforward electrophilic substitution strategy. This discovery had added a new tool for the structural modification of quinazolinone ring system. These new ligands, along with the 2-methylsubstituted quinazolinone ligands **1a-c**, provide useful tools for asymmetric catalysis study.

Experimental Section

General Procedures

Reaction mixtures were stirred magnetically with a Teflon®-coated stirring bar unless otherwise noted. All reactions involving moisture and/or air sensitive reagents were carried out in oven-dried glasswares under a positive pressure of dry argon. Solvents and liquid reagents were transferred via syringe or cannula unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC). Organic solvents were removed through concentration on a Büchi rotary evaporator connected to a water aspirator.

Instrumentation

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.

^{1}H NMR and ^{13}C NMR spectra were obtained on 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 (121.4 MHz) 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), quin (quintet), 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.

Optical rotation measurements were measured on a Perkin-Elmer 241 polarimeter using a sodium lamp (D line) at 25 °C. Concentration (*c*) is indicated as units of 10 mg/mL.

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) or FAB was used for generation of the M^+ ions. Spectra are reported in units of mass to charge (*m/e*).

Elemental analyses (Anal.) were performed by Galbraith Laboratories at Knoxville, Tennessee.

High-performance liquid chromatography (HPLC) analyses were carried out using a 4.6 mm × 25 cm Daicel CHIRALCEL OJ column a Daicel CHIRALCEL OD-H column, or a Daicel CHIRALCEL OD column 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.

Chromatography

Flash column chromatography was performed using Silica Gel 60 (230-400 mesh) obtained from EM Science according to the method of Still.[99] Commercial HPLC grade solvents were used.

Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel 60-F_{254} plates (0.25 mm thickness, E. Merck) impregnated with a 254 nm fluorescence indicator. After elution using the solvent mixture indicated, the chromatogram was visualized with 254 nm ultraviolet light and the phosphomolybdic acid stain (PMA, an ethanolic solution of 10% phosphomolybdic acid) or the *p*-anisaldehyde stain (an ethanolic solution of 2% *p*-anisaldehyde with 5% concentrated sulfuric acid and 1.5% acetic acid in ethanol) followed by heating on a hot plate.

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

Materials

Commercially available solvents and reagents were used without further purification with the following exceptions:

Solvents:

The following solvents were dried and distilled immediately prior to use under nitrogen: Dichloromethane, and hexanes were distilled from CaH_2.

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl.

Toluene was distilled from sodium.

Dimethyl sulfoxide was distilled at 20 mmHg from calcium hydride.

Reagents:

n-Butyllithium was titrated prior to use with sec-butyl alcohol in tetrahydrofuran at 0°C using 1,10-phenanthroline as an indicator.[100]

Pyridine was distilled from calcium hydride under argon.

Triethylamine was distilled from calcium hydride under nitrogen.

N,N-dimethylformamide was stored over activated 4Å molecular sieves.

(-)-Di-μ-chlorobis[(*S*)-dimethyl(1-phenylethyl)aminato-C^2,*N*]di-palladium(II) (**7**) was prepared according to the literature procedure.[101]

(-)-Di-μ-chloro-bis[(*S*)-dimethyl-(1-naphthylethyl)aminato-C^2, *N*]dipalladium(II) (**78**) was prepared according to the literature procedure.[102]

Lithium diisopropylamide (1.0 M) was prepared by the addition of 1.50 *M* *n*-BuLi (6.67 mL) to a mixture of *N,N*-diisopropylamine (1.44 mL) and tetrahydrofuran (1.89 mL) at -78 °C and warming to 0 °C.

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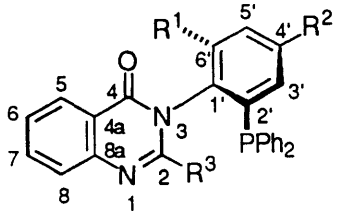
[100] Waston, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
[101] Roberts N. K.; Wild, S. B. *J. Chem. Soc. Dalton Trans.* **1979**, 2015.
[102] (a) Roberts, N. K.; Wild, S. B. *J. Chem. Soc., Dalton Trans.* **1979**, 2015. (b) Allen, D. G.; McLaughlin, G. M.; Robertson, G. B.; Steffem, W. L.; Salem, G.; Wild, S. B. *Inorg. Chem.* **1982**, *21*, 1007.

Nomenclature

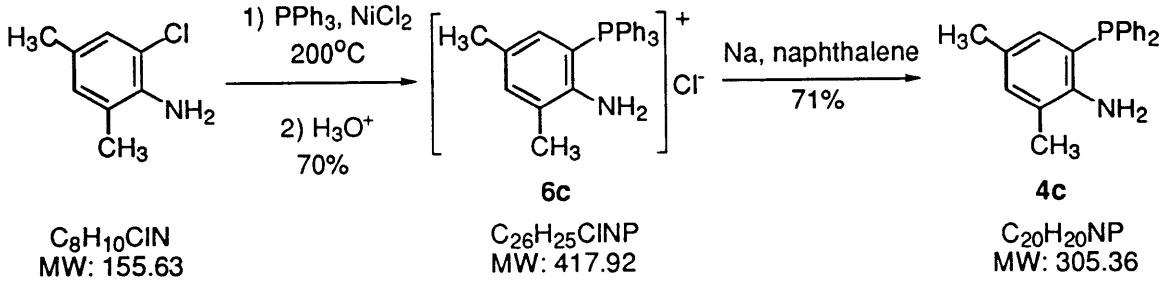
The conventional numbering scheme for 3-aryl-4(3*H*)-quinazolinone structure is used for the compounds described herein.



Experimental Procedures

2-Diphenylphosphinoaniline (**4a**, 80%) and **6-Methyl-2-(diphenylphosphino)-aniline** (**4b**, 84%) were prepared according to Cooper's procedure[35] with modifications as described below for **4c**.

4,6-Dimethyl-2-(diphenylphosphino)aniline (**4c**).



6c

4c

$C_8H_{10}ClN$
MW: 155.63

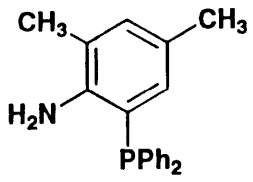
$C_{26}H_{25}ClNP$
MW: 417.92

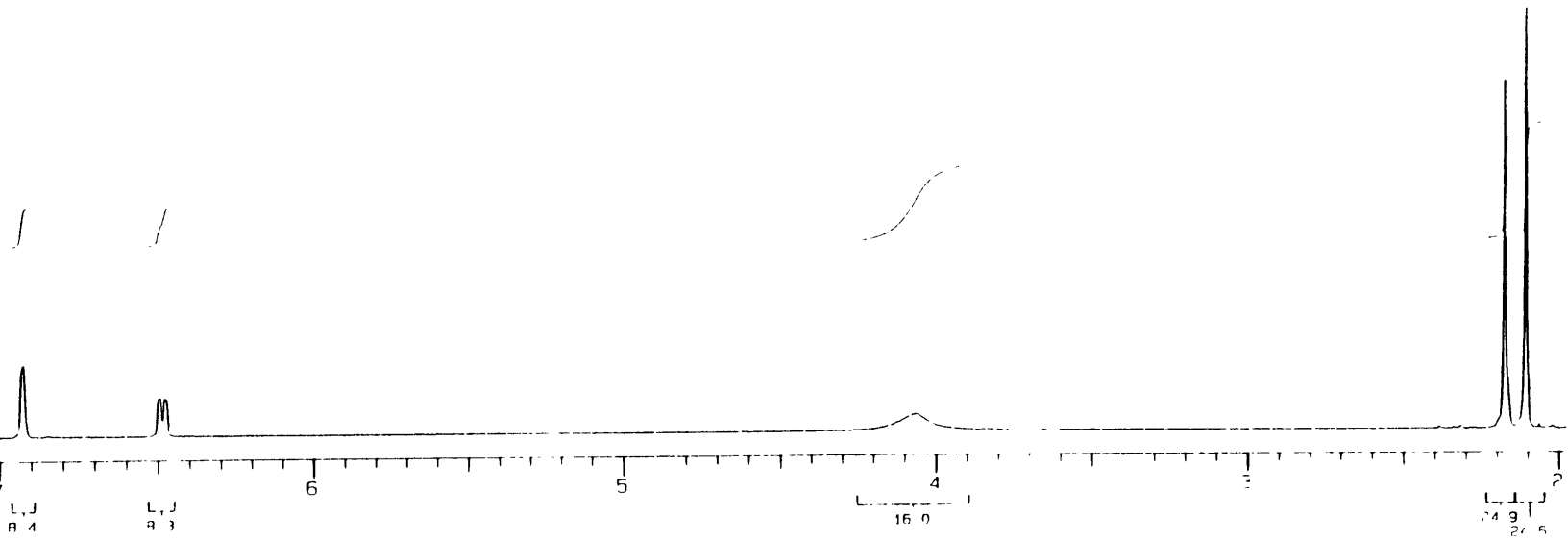
$C_{20}H_{20}NP$
MW: 305.36

2-Chloro-4,6-dimethyl aniline (25.0 g, 0.16 mol), triphenylphosphine (42.6 g, 0.16 mol) and anhydrous nickel chloride (10.5 g, 0.08 mol) were combined and heated to 200 °C with stirring and removal of residual water for 4 hours. The blue melt was poured into water (300 mL) and concd HCl (2 mL) and stirred to dissolve. The aqueous phase was extracted with diethyl ether (4 x 40 mL), then dichloromethane (4 x 50 mL). The combined CH_2Cl_2 extracts were dried through $MgSO_4$ and evaporated to an oil. After addition of tetrahydrofuran (300 mL) and cooling at 4 °C overnight, the resulting white crystals were collected by filtration, washed with ether and vacuum dried to afford 47.0 g (70%) of phosphonium salt **3c** (mp 131.3-132.5 °C).

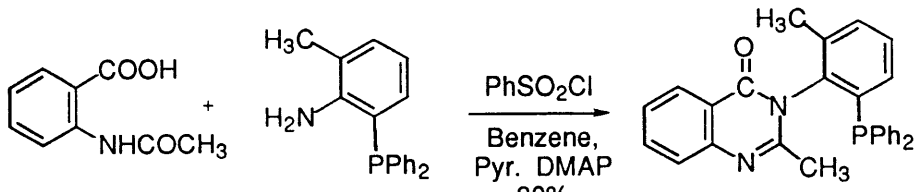
An oven dried, 3-neck 1L round bottom flask equipped with a mechanical stirrer was charged with naphthalene (34.7 g, 0.27 mol), in THF (300 mL) under argon and sodium metal pieces (5.7 g, 0.25 mol) were added. After stirring the solution for 3 h at room temperature, the solution was cooled to -78 °C. The powdered phosphonium salt **3c** (47.0 g, 0.11 mol) was added with stirring, and the mixture was left overnight to warm to room temperature. Acetic acid (2.8 mL) was added dropwise followed by 20% aqueous

ammonium chloride solution (69 mL). The resulting phases are separated, and the aqueous layer is extracted with diethyl ether (2 x 100 mL). The combined organic phases were dried through $MgSO_4$ and evaporated to a brown oil. The naphthalene was removed by sublimation at 60 °C and 0.1 mm Hg using a Kugelrohr apparatus. Recrystallization from ethyl acetate and hexane (2:3) afforded 24.44 g (71%) of the phosphinoaniline **4c**: mp 58.5-59.5 °C; R_f = 0.47 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3455, 3354, 3050, 2913, 1616, 1585, 1473, 1434, 1236, 743, 696, 490; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.46 (m, 10H), 6.92 (br s, 1H), 6.48 (dd, 1H, J = 1.5, 5.5 Hz), 4.07 (br s, 2H), 2.16 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.80, 145.56, 135.98, 135.89, 133.88, 133.61, 132.71, 132.41, 132.39, 128.77, 128.68, 128.59, 127.42, 122.52, 122.43, 119.01, 118.90, 103.61, 20.82, 18.11; $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -19.83 (s); HRMS calcd for $C_{20}H_{20}NP$ (M^+): 305.1334. Found: 305.1332.


CH3
CH3
H2N
PPh2


6
5
4
3
16.0

2-Methyl-3-[6'-methyl-2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1b).



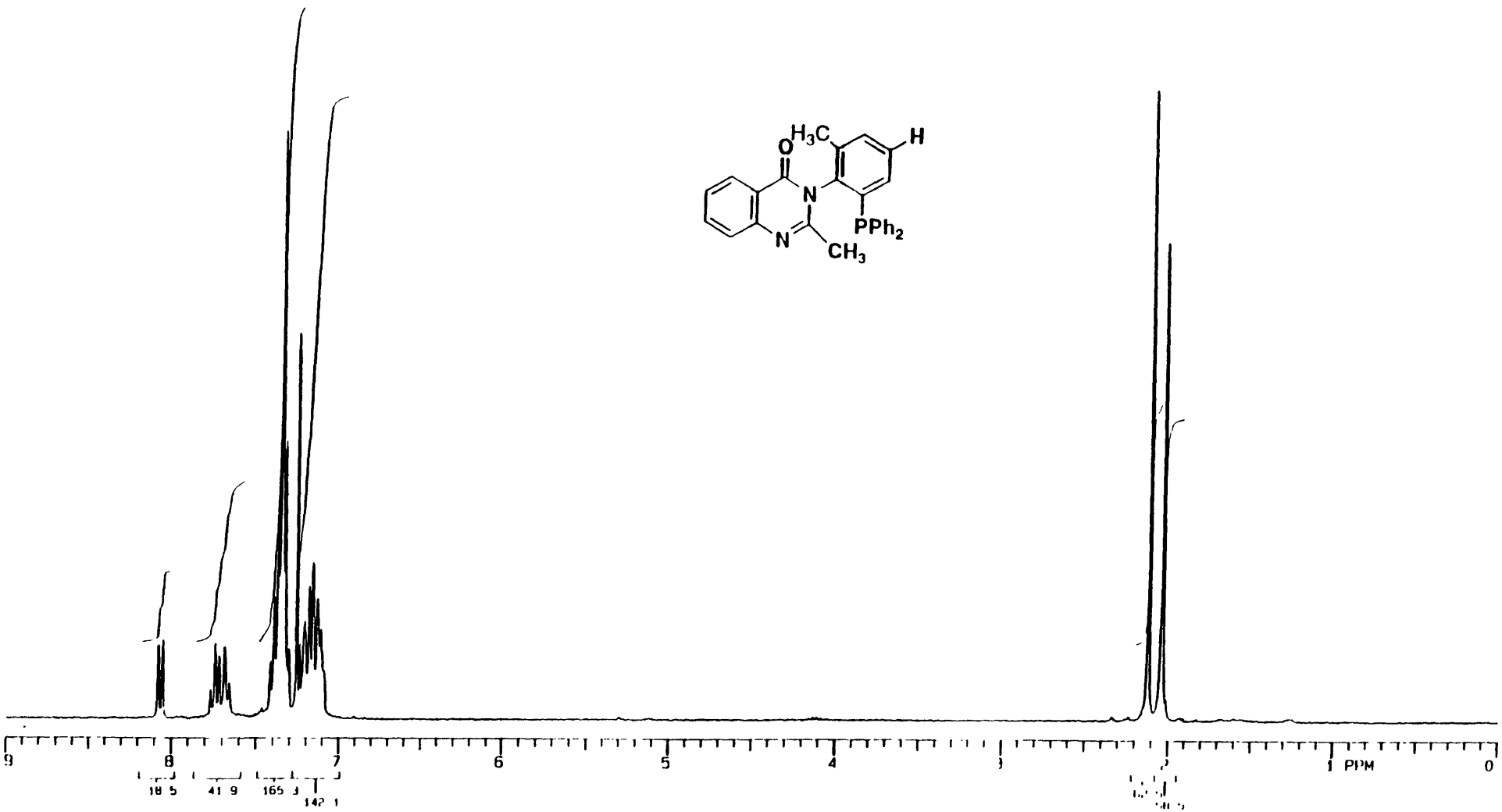
$C_9H_9NO_3$
MW: 179.17

4b
$C_{19}H_{18}NP$
MW: 291.33

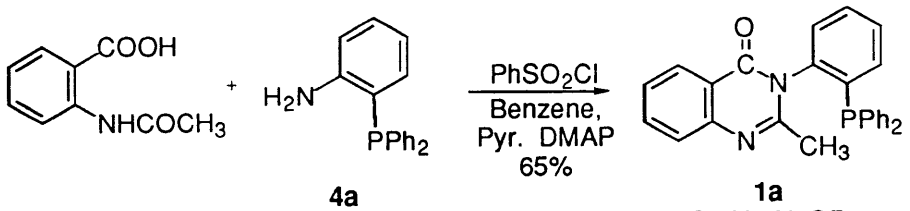
1b
$C_{28}H_{23}N_2OP$
MW: 434.48

To a solution of *N*-acetylanthranilic acid (16.58 g, 92.5 mmol) and 4-dimethylaminopyridine (50 mg) in pyridine (27 mL) was added dropwise benzenesulfonyl chloride ($PhSO_2Cl$, 9.64 mL, 75.5 mmol). After stirring at room temperature for 0.5h, the resulting slurry was treated with a solution of aminophosphine **4b** (10.0 g, 34.4 mmol) in benzene (100 mL). The mixture was heated for 18 h at reflux temperature and monitored by TLC until the complete consumption of **4b** was indicated. After cooling, the solvent was evaporated and the residue was partitioned with ethyl acetate (250 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and the combined ethyl acetate fractions were dried over anhydrous $MgSO_4$. After removal of the solvent, crystallization from ethyl acetate (80 mL) and hexane (80 mL) afforded ligand **1b** (11.96 g, 80%) as white needles: mp 170.5-171.5 °C; R_f = 0.28 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3054, 1683, 1603, 1569, 1472, 1434, 1377, 1326, 1267, 1116, 774, 743, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1H, *J* = 1.2, 7.8 Hz), 7.74 (ddd, 1H, *J* = 1.5, 6.9, 8.4 Hz), 7.67 (d, 1H, *J* = 7.8 Hz), 7.33-7.42 (m, 8H), 7.10-7.25 (m, 6H), 2.13 (s, C6'CH_3), 2.04 (s, C2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 161.08, 154.20, 147.56 , 141.09 (d, *J* = 25.1 Hz'), 137.15 (d, *J* = 14.6 Hz), 136.04 (d, *J* = 3.25 Hz), 135.35 (d, *J* = 9.1 Hz), 135.03 (d, *J* = 10.5 Hz), 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, $^5J_{CP}$ = 5.0 Hz,

C2*Me*), 17.79 (d, $^4J_{CP}$ = 2.4 Hz, C6'*Me*); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -18.2 (s); HRMS 434.1548 (calcd for $C_{28}H_{23}N_2OP$ 434.1548); Anal. C 77.33, H 5.49, N 6.30 (calcd for $C_{28}H_{23}N_2OP$: C 77.41, H 5.34, N 6.45).


O
H3C
H
N
PPh2
N
CH3
9
8
7
6
5
4
3
2
1 PPM
0
18 5
41 9
165 3
142 1

2-Methyl-3-[2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1a).



$C_9H_9NO_3$
MW: 179.17

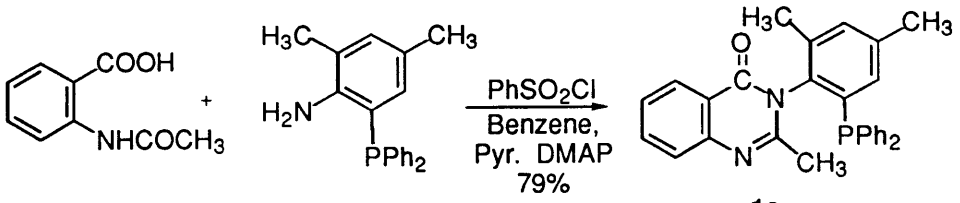
4a
$C_{18}H_{16}NP$
MW: 277.30

1a
$C_{27}H_{21}N_2OP$
MW: 420.45

Compound **1a** was obtained as white needles (65%) under conditions analogous to the reaction producing **1b**: mp 181-182 °C; R_f = 0.21 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3053, 1684 (C=O), 1604 (C=N), 1566, 1471, 1435, 1377, 1340, 1275, 771, 744, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, 1H, J = 1.3, 8.1 Hz), 7.73 (ddd, 1H, J = 1.3, 6.9, 8.2 Hz), 7.66 (d, 1H, J = 8.1 Hz), 7.53 (ddd, 1H, J = 1.5 , 7.6, 7.6 Hz), 7.30-7.47 (m, 8H), 7.15-7.29 (m, 6H), 2.05 (s, C2C*H*3); ^{13}C NMR (125 MHz, $CDCl_3$): 161.87, 154.27, 147.47 , 142.23 (d, $^2J_{CP}$ = 25.6 Hz, C1'), 137.57 (d, $^1J_{CP}$ = 14.4 Hz, C6'), 135.50, 135.35, 134.93, 134.80, 134.56, 134.38, 134.29, 133.66, 133.40, 130.85, 129.65, 129.47, 128.91, 128.82, 128.74, 128.37, 128.28, 127.24, 126.69, 126.33, 120.91, 24.46 (d, $^5J_{CP}$ = 4.8 Hz, C2*Me*); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -16.87 (s); HRMS: 420.1392 (calcd for $C_{27}H_{21}N_2OP$: 420.1392).

O
H
H
N
PPh2
N
CH3
9
8
7
6
5
4
3
PPM
0

2-Methyl-3-[4',6'-dimethyl-2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1c).

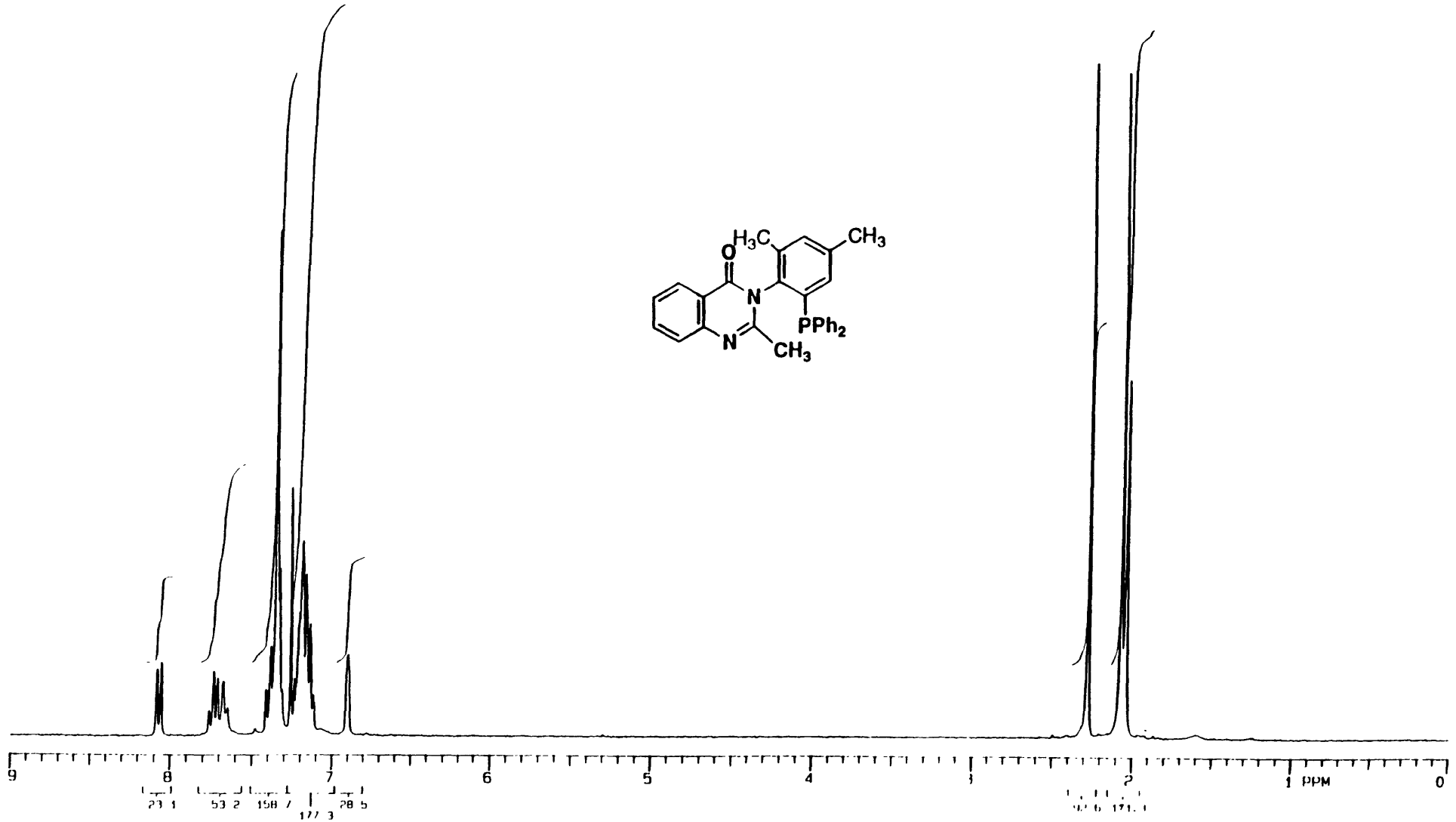


$C_9H_9NO_3$
MW: 179.17

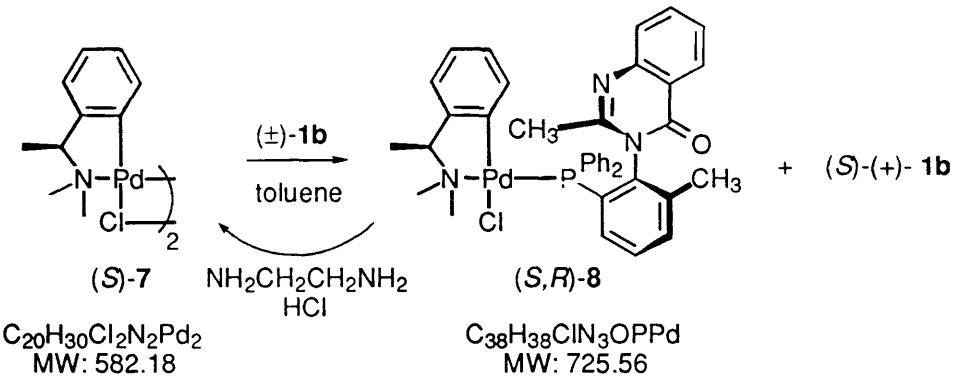
4c
$C_{20}H_{20}NP$
MW: 305.36

1c
$C_{29}H_{25}N_2OP$
MW: 448.50

Compound **1c** was obtained as white needles (79%) under conditions analogous to the reaction producing **1b**: mp 179-180 °C; R_f = 0.34 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3052, 1682 (C=O), 1602 (C=N), 1570, 1471, 1434, 1377, 1340, 1325, 773, 741, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.072 (dd, 1H, J = 1.2, 7.9 Hz), 7.732 (ddd, 1H, J = 1.4, 6.9, 6.9 Hz), 7.658 (d, 1H, J = 7.3 Hz), 7.110-7.420 (m, 13H), 6.905 (br s, 1H), 2.282 (s, 3H), 2.081 (s, 3H), 2.047 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 161.22, 154.46, 147.61, 139.18, 138.81, 138.48, 136.68, 136.49, 135.61, 135.57, 135.46, 135.34, 135.20, 134.37, 134.14, 134.09, 133.72, 133.47, 133.18, 129.12, 128.69, 128.59, 128.54, 128.15, 128.06, 127.14, 126.58, 126.00, 120.80, 23.54 (d, $^5J_{CP}$ = 4.9 Hz, C2*Me*), 21.20, 17.64 (d, $^4J_{CP}$ = 2.3 Hz, C6'*Me*); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -16.27 ppm (s); HRMS: 448.1704 (calcd for $C_{29}H_{25}N_2OP$ 448.1705).


O
H3C
CH3
N
PPh2
N
CH3
9
8
7
6
5
4
3
2
1 PPM
0

Resolution of Ligand 1b Using (-)-Di-μ-chloro-bis[(*S*)-dimethyl-(1-phenylethyl)-aminato-C^2, *N*]dipalladium(II) (7).

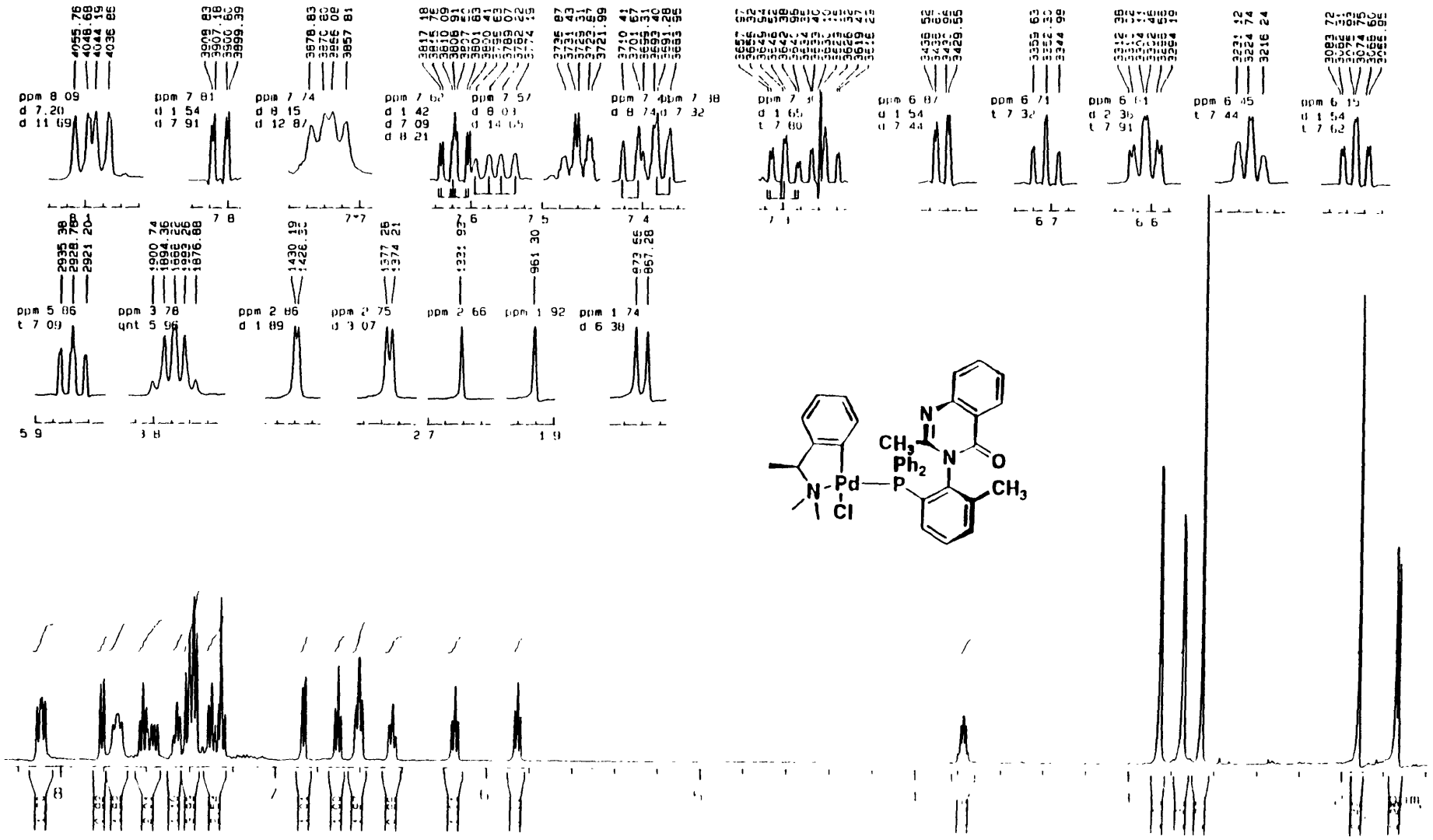


To a solution of complex **7** (2.00 g, 3.44 mmol) in toluene (80 mL) was added **1b** (6.00 g, 13.8 mmol) and the solution was stirred for 4 hours at ambient temperature. The mixture was treated with hexane (50 mL) and stored at 0 °C overnight. Yellow crystals of (*S, R*)-**8** were collected by filtration (4.79 g, 96% yield): mp 185 °C (dec.); R_f = 0.67 (silica, ethyl acetate); FTIR (thin film, cm^{-1}) 3448, 1676, 1601, 1474, 1437, 1340, 1267, 1092, 774, 731, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, 2H, *J* = 7.2, 11.6 Hz), 7.81 (dd, 1H, *J* = 1.4, 8.0 Hz), 7.74 (dd, 2H, *J* = 7.7, 12.1 Hz), 7.54 - 7.67 (m, 2H), 7.22 - 7.52 (m, 7H), 6.87 (dd, 1H, *J* = 2.0, 7.2 Hz), 6.71 (t, 1H, *J* = 7.3 Hz), 6.61 (ddd, 2H, *J* = 2.0, 7.3, 7.3 Hz), 6.45 (ddd, 1H, *J* = 1.3, 7.2, 7.2 Hz), 6.16 (ddd, 1H, *J* = 1.2, 7.5, 7.5 Hz), 5.86 (t, 1H, *J* = 6.9 Hz), 3.78 (quin, 1H, *J* = 5.5 Hz), 2.86 (d, 3H, *J* = 1.7 Hz), 2.75 (d, 3H, *J* = 3.0 Hz), 2.67 (s, 3H), 1.93 (s, 3H), 1.74 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.97, 154.69, 153.50, 153.48, 150.08, 147.36, 138.17, 137.51, 137.34, 137.31, 137.17, 135.28, 135.22, 134.96, 134.78, 133.69, 132.95, 132.92, 132.02, 131.42, 130.72, 130.69, 130.60, 129.93, 129.19, 129.15, 127.97, 127.88, 127.73, 127.35, 127.08, 126.91, 126.65, 126.61, 126.50, 125.89, 125.19, 124.24, 124.17, 123.32, 121.62, 119.80, 74.96, 74.92, 50.10, 46.55, 24.56, 21.36,

17.44; $^{31}P\{^{1}H\}$ NMR (121.4 MHz, $CDCl_3$): 45.53 (s); $[\alpha]_D^{23}$ = -10.5° (*c* = 1.04, $CHCl_3$); HRMS (FAB, 3-nitrobenzyl alcohol) 723.1397 (calcd for $C_{38}H_{37}N_3OPPd$ 723.1398);

The mother liquor was concentrated to afford (*S*)-(+)-**1b** (2.45 g, 82%) by recrystallization from ethyl acetate/hexanes (1:3) solvent mixture (96% ee based on chiral HPLC analysis, Chiralcel OJ column, 98:2 hexane/2-propanol, flow rate 1.5 mL/min, λ = 295 nm, t_R = 18.3 min).

Treatment of the complex (*S*,*R*)-**8** with ethylenediamine (0.115 mL, 1.72 mmol) in CH_2Cl_2 (30 mL), followed by filtration and crystallization from ethyl acetate-hexanes (1:3) solvent mixture, gave 2.73 g (91%) of free ligand (*R*)-(-)-**1b** as white needles (99% ee based on chiral HPLC analysis, Chiralcel OJ column, 98:2 hexane/2-propanol, flow rate 1.5 mL/min, λ = 295 nm, t_R = 8.9 min).


CH3
Ph2
N
N
O
N
Pd
P
Cl
CH3

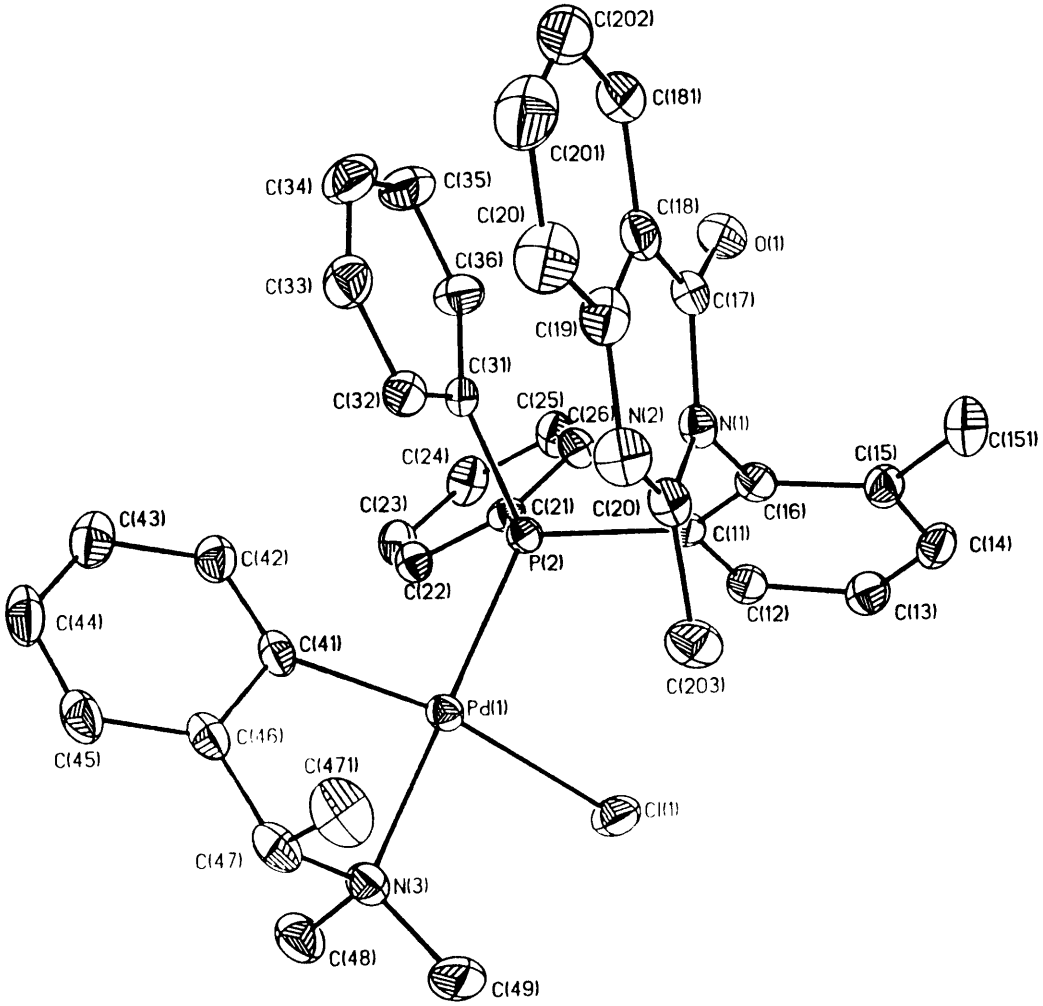


Figure A. ORTEP plot of complex (*S*,*R*)-**8**.

Table A1. Crystal Data and Structure Refinement for complex (*S,R*)-**8**.

A. Crystal data

Empirical formula	$C_{38}H_{37}ClN_3OPPd$	
Formula weight	724.56	
Temperature	188 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.4822 (7) Å	$\alpha = 90°$
	b = 17.3192 (12) Å	$\beta = 90°$
	c = 19.085(7) Å	$\gamma = 90°$
Volume, Z	3358.6 (4) $Å^3$, 4	
Density (calcd)	1.433 Mg/m^3	
Absorption coefficient	0.715 mm^{-1}	
F(000)	1488	
Crystal morphology	yellow, prismatic	
Crystal size	0.22 x 0.18 x 0.12 mm	

B. Data Collection and Reduction

Diffractometer	Siemens SMART/CCD
Crystal-Detector distance	6.0 cm
Scan type	ω Scans
Scan angle	0.30°
θ range for data collection	1.61 to 23.28°
Limiting indices	$-10 \leq h \leq 11$, $-13 \leq k \leq 19$, $-18 \leq l \leq 20$
Reflections collected	13752
Independent reflections	4839 (R_{int} = 0.0384)
Absorption correction	None

C. Structure Solution and Refinement

Refinement method	Full-matrix least-squares on F^2
No. of data/restraints/parameters	4834 / 0 / 407
Goodness of fit on F^2	1.114
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0282, wR_2 = 0.0708
R indices (all data)	R_1 = 0.0308, wR_2 = 0.0864
Maximum shift/esd	-0.012
Absolute structure parameter	-0.04 (2)
Extinction coefficient	0.0022 (3)
Largest diff. peak and hole	0.460 and -0.341 eÅ^{-3}

Notes:

$R_1 = \Sigma \, | \, |F_0| - |F_c| \, | \, / \, \Sigma \, |F_0|$

$wR_2 = \{ \, \Sigma [\, w \, (F_0^2 - F_c^2)^2 \, / \, [\, \Sigma \, (F_0^2)^2 \,] \} ^{1/2}$

Weighting scheme

calcd $w = 1 \, / \, [\, \sigma^2(F_0^2) + (0.0316P)^2 + 2.9688P]$ where $P = (F_0^2 + 2F_c^2) \, / \, 3$

Refinement on F^2 for ALL reflections. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors are based on F, with F set to zero for negative F_0^2. The observed criterion for $F^2 > 2\sigma(F^2)$ is used only for calculating R_1 and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 8. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Pd(1)	2844(1)	4103(1)	1760(1)	26(1)
Cl(1)	2168(1)	2818(1)	1491(1)	45(1)
P(2)	800(1)	4527(1)	1839(1)	25(1)
O(1)	-1934(3)	5592(2)	528(2)	44(1)
N(1)	-101(3)	4977(2)	206(2)	28(1)
N(2)	1491(4)	5561(2)	-512(2)	43(1)
N(3)	4796(3)	3770(2)	1593(2)	35(1)
C(11)	-269(3)	4016(2)	1205(2)	26(1)
C(12)	-697(4)	3290(2)	1422(2)	33(1)
C(13)	-1425(4)	2831(2)	960(2)	38(1)
C(14)	-1760(4)	3097(3)	293(2)	38(1)
C(15)	-1363(4)	3822(2)	47(2)	34(1)
C(16)	-592(3)	4260(2)	507(2)	29(1)
C(17)	-911(4)	5622(2)	221(2)	32(1)
C(18)	-400(4)	6294(3)	-163(2)	38(1)
C(19)	776(5)	6246(3)	-504(2)	42(1)
C(20)	1040(4)	4970(2)	-181(2)	34(1)
C(20)	1277(6)	6897(3)	-851(3)	57(1)
C(21)	81(4)	4307(2)	2716(2)	27(1)
C(22)	874(4)	4275(2)	3321(2)	32(1)
C(23)	359(4)	4158(3)	4000(2)	39(1)
C(24)	-936(4)	4064(3)	4086(2)	43(1)
C(25)	-1735(4)	4094(3)	3496(2)	40(1)
C(26)	-1234(4)	4220(2)	2813(2)	33(1)
C(31)	511(3)	5563(2)	1751(2)	29(1)
C(32)	1370(4)	6020(2)	1356(2)	34(1)
C(33)	1185(4)	6812(3)	1316(3)	45(1)
C(34)	178(5)	7154(3)	1671(3)	54(1)
C(35)	-667(5)	6712(3)	2060(3)	53(1)
C(36)	-488(4)	5923(3)	2106(2)	42(1)
C(41)	3699(4)	5071(2)	2114(2)	33(1)
C(42)	3271(4)	5631(2)	2594(2)	37(1)
C(43)	4075(5)	6227(3)	2829(3)	49(1)
C(44)	5314(5)	6269(3)	2591(3)	51(1)
C(45)	5777(4)	5713(2)	2123(3)	44(1)
C(46)	4989(4)	5118(2)	1884(2)	35(1)
C(47)	5454(4)	4508(3)	1380(3)	41(1)
C(48)	5319(5)	3492(3)	2292(3)	50(1)
C(49)	4996(5)	3159(3)	1050(3)	57(1)
C(151)	-1753(4)	4109(3)	-686(2)	47(1)
C(181)	-1076(5)	6994(3)	-169(3)	52(1)
C(201)	604(7)	7580(3)	-851(3)	66(2)
C(202)	-567(6)	7630(3)	-508(3)	63(2)
C(203)	1756(4)	4225(3)	-216(3)	45(1)
C(471)	5188(5)	4744(3)	607(3)	57(1)

Table A3. Bond lengths [Å] and angles [°] for (*S*,*R*)-8.

Pd(1)-C(41)	2.011(4)	Pd(1)-N(3)	2.149(3)
Pd(1)-P(2)	2.2692(10)	Pd(1)-Cl(1)	2.3870(10)
P(2)-C(31)	1.827(4)	P(2)-C(21)	1.828(4)
P(2)-C(11)	1.848(4)	O(1)-C(17)	1.215(5)
N(1)-C(20)	1.394(5)	N(1)-C(17)	1.404(5)
N(1)-C(16)	1.455(5)	N(2)-C(20)	1.283(6)
N(2)-C(19)	1.404(6)	N(3)-C(49)	1.473(6)
N(3)-C(48)	1.483(6)	N(3)-C(47)	1.505(6)
C(11)-C(12)	1.395(6)	C(11)-C(16)	1.399(6)
C(12)-C(13)	1.394(6)	C(13)-C(14)	1.363(6)
C(14)-C(15)	1.399(6)	C(15)-C(16)	1.397(6)
C(15)-C(151)	1.502(6)	C(17)-C(18)	1.464(6)
C(18)-C(19)	1.387(7)	C(18)-C(181)	1.405(7)
C(19)-C(20)	1.401(7)	C(20)-C(203)	1.493(6)
C(20)-C(201)	1.377(8)	C(21)-C(22)	1.395(5)
C(21)-C(26)	1.399(5)	C(22)-C(23)	1.383(6)
C(23)-C(24)	1.376(6)	C(24)-C(25)	1.377(6)
C(25)-C(26)	1.385(6)	C(31)-C(36)	1.385(6)
C(31)-C(32)	1.404(6)	C(32)-C(33)	1.389(6)
C(33)-C(34)	1.376(7)	C(34)-C(35)	1.375(7)
C(35)-C(36)	1.381(7)	C(41)-C(42)	1.388(6)
C(41)-C(46)	1.420(6)	C(42)-C(43)	1.402(6)
C(43)-C(44)	1.373(7)	C(44)-C(45)	1.382(7)
C(45)-C(46)	1.393(6)	C(46)-C(47)	1.491(6)
C(47)-C(471)	1.513(7)	C(181)-C(202)	1.375(7)
C(201)-C(202)	1.384(9)		

C(41)-Pd(1)-N(3)	81.2(2)	C(41)-Pd(1)-P(2)	97.44(12)
N(3)-Pd(1)-P(2)	174.43(10)	C(41)-Pd(1)-Cl(1)	167.80(11)
N(3)-Pd(1)-Cl(1)	90.15(10)	P(2)-Pd(1)-Cl(1)	92.00(4)
C(31)-P(2)-C(21)	102.5(2)	C(31)-P(2)-C(11)	108.2(2)
C(21)-P(2)-C(11)	102.3(2)	C(31)-P(2)-Pd(1)	117.94(12)
C(21)-P(2)-Pd(1)	112.25(13)	C(11)-P(2)-Pd(1)	112.10(12)
C(20)-N(1)-C(17)	122.4(3)	C(20)-N(1)-C(16)	119.5(3)
C(17)-N(1)-C(16)	117.3(3)	C(20)-N(2)-C(19)	118.2(4)
C(49)-N(3)-C(48)	108.0(4)	C(49)-N(3)-C(47)	111.4(4)
C(48)-N(3)-C(47)	109.6(3)	C(49)-N(3)-Pd(1)	115.2(3)
C(48)-N(3)-Pd(1)	108.3(3)	C(47)-N(3)-Pd(1)	104.2(2)
C(12)-C(11)-C(16)	117.4(4)	C(12)-C(11)-P(2)	116.3(3)
C(16)-C(11)-P(2)	126.1(3)	C(13)-C(12)-C(11)	120.9(4)
C(14)-C(13)-C(12)	120.2(4)	C(13)-C(14)-C(15)	121.4(4)
C(16)-C(15)-C(14)	117.5(4)	C(16)-C(15)-C(151)	121.8(4)
C(14)-C(15)-C(151)	120.7(4)	C(15)-C(16)-C(11)	122.5(4)
C(15)-C(16)-N(1)	115.8(3)	C(11)-C(16)-N(1)	121.6(3)
O(1)-C(17)-N(1)	120.6(4)	O(1)-C(17)-C(18)	125.7(4)
N(1)-C(17)-C(18)	113.7(3)	C(19)-C(18)-C(181)	119.8(4)
C(19)-C(18)-C(17)	119.9(4)	C(181)-C(18)-C(17)	120.4(4)
C(18)-C(19)-C(20)	119.6(5)	C(18)-C(19)-N(2)	122.0(4)
C(20)-C(19)-N(2)	118.4(5)	N(2)-C(20)-N(1)	123.6(4)
N(2)-C(20)-C(203)	118.9(4)	N(1)-C(20)-C(203)	117.5(4)
C(201)-C(20)-C(19)	120.0(6)	C(22)-C(21)-C(26)	118.7(4)
C(22)-C(21)-P(2)	118.3(3)	C(26)-C(21)-P(2)	122.9(3)
C(23)-C(22)-C(21)	120.1(4)	C(24)-C(23)-C(22)	120.6(4)
C(23)-C(24)-C(25)	120.2(4)	C(24)-C(25)-C(26)	119.9(4)
C(25)-C(26)-C(21)	120.5(4)	C(36)-C(31)-C(32)	118.6(4)

C(36)-C(31)-P(2)	121.7(3)	C(32)-C(31)-P(2)	119.6(3)
C(33)-C(32)-C(31)	119.6(4)	C(34)-C(33)-C(32)	120.5(4)
C(35)-C(34)-C(33)	120.3(4)	C(34)-C(35)-C(36)	119.7(4)
C(31)-C(36)-C(35)	121.3(4)	C(42)-C(41)-C(46)	117.3(4)
C(42)-C(41)-Pd(1)	130.2(3)	C(46)-C(41)-Pd(1)	112.0(3)
C(41)-C(42)-C(43)	121.2(4)	C(44)-C(43)-C(42)	120.6(5)
C(43)-C(44)-C(45)	119.7(4)	C(44)-C(45)-C(46)	120.4(4)
C(45)-C(46)-C(41)	120.8(4)	C(45)-C(46)-C(47)	122.0(4)
C(41)-C(46)-C(47)	117.3(4)	C(46)-C(47)-N(3)	106.7(3)
C(46)-C(47)-C(471)	109.9(4)	N(3)-C(47)-C(471)	113.2(4)
C(202)-C(181)-C(18)	119.9(5)	C(20)-C(201)-C(202)	120.5(5)
C(181)-C(202)-C(201)	120.2(5)		

Table A4. Anisotropic displacement parameters [$Å^2$ x 10^3] for (*S*, *R*)-8.

The anisotropic displacement factor exponent takes the form:

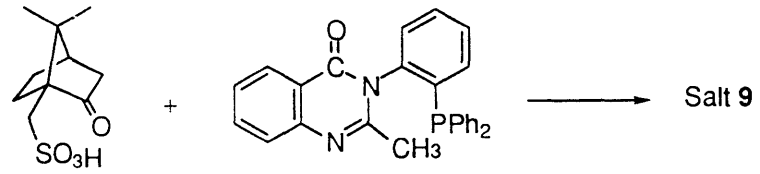
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Pd(1)	21(1)	28(1)	30(1)	1(1)	2(1)	0(1)
Cl(1)	36(1)	29(1)	70(1)	-7(1)	10(1)	-1(1)
P(2)	21(1)	26(1)	28(1)	0(1)	2(1)	-2(1)
O(1)	32(2)	48(2)	53(2)	-4(1)	0(2)	5(1)
N(1)	24(2)	35(2)	25(2)	-1(1)	1(1)	-3(1)
N(2)	42(2)	50(2)	36(2)	4(2)	10(2)	-5(2)
N(3)	25(2)	38(2)	42(2)	0(2)	-1(2)	1(2)
C(11)	21(2)	27(2)	29(2)	-5(2)	3(2)	2(2)
C(12)	27(2)	36(2)	35(2)	-4(2)	4(2)	0(2)
C(13)	33(2)	34(2)	48(3)	-2(2)	5(2)	-5(2)
C(14)	33(2)	36(2)	46(3)	-14(2)	2(2)	-6(2)
C(15)	29(2)	39(2)	33(2)	-11(2)	1(2)	1(2)
C(16)	20(2)	33(2)	34(2)	-2(2)	6(2)	0(2)
C(17)	28(2)	36(2)	34(2)	-2(2)	-7(2)	-1(2)
C(18)	39(2)	39(2)	37(2)	1(2)	-16(2)	-3(2)
C(19)	52(3)	40(2)	33(2)	6(2)	-6(2)	-7(2)
C(20)	29(2)	42(2)	30(2)	-1(2)	-1(2)	-2(2)
C(20)	74(4)	53(3)	43(3)	13(2)	-1(3)	-10(3)
C(21)	28(2)	20(2)	32(2)	1(2)	5(2)	-1(2)
C(22)	31(2)	32(2)	32(2)	4(2)	0(2)	-5(2)
C(23)	44(3)	45(2)	27(2)	-1(2)	-3(2)	-4(2)
C(24)	50(3)	49(3)	31(2)	-6(2)	11(2)	-11(2)
C(25)	29(2)	49(2)	43(2)	-7(2)	9(2)	-10(2)
C(26)	26(2)	39(2)	33(2)	1(2)	0(2)	-2(2)
C(31)	29(2)	27(2)	30(2)	-5(2)	-7(2)	-1(2)
C(32)	37(2)	34(2)	32(2)	1(2)	-2(2)	-1(2)
C(33)	48(3)	37(2)	51(3)	5(2)	-3(2)	-8(2)
C(34)	73(3)	30(2)	57(3)	0(2)	-9(3)	4(2)
C(35)	55(3)	42(3)	63(3)	-10(2)	6(3)	14(2)
C(36)	39(2)	34(2)	53(3)	1(2)	7(2)	4(2)
C(41)	29(2)	35(2)	36(2)	6(2)	-10(2)	-6(2)
C(42)	35(2)	36(2)	40(2)	1(2)	-3(2)	-6(2)
C(43)	59(3)	44(3)	43(3)	0(2)	-9(2)	-9(2)
C(44)	49(3)	42(3)	60(3)	9(2)	-21(2)	-20(2)
C(45)	32(2)	39(3)	62(3)	14(2)	-11(2)	-11(2)
C(46)	25(2)	40(2)	41(3)	10(2)	-6(2)	-5(2)
C(47)	23(2)	52(3)	47(3)	9(2)	1(2)	-2(2)
C(48)	41(3)	46(3)	64(3)	12(3)	-15(2)	2(2)
C(49)	34(3)	58(3)	78(4)	-19(3)	15(3)	7(2)
C(151)	49(3)	54(3)	39(2)	-7(3)	-8(2)	-9(2)
C(181)	54(3)	43(3)	60(3)	-1(2)	-23(2)	4(2)
C(201)	95(5)	48(3)	55(3)	16(3)	-16(3)	-16(3)
C(202)	82(4)	41(3)	65(4)	5(3)	-33(3)	0(3)
C(203)	33(2)	56(3)	45(3)	-1(2)	11(2)	7(2)
C(471)	49(3)	76(4)	48(3)	16(3)	7(2)	-10(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 8.

	x	y	z	U(eq)
H(12A)	-490(4)	3105(2)	1891(2)	39
H(13A)	-1688(4)	2332(2)	1111(2)	46
H(14A)	-2275(4)	2783(3)	-11(2)	46
H(20A)	2081(6)	6868(3)	-1087(3)	68
H(22A)	1770(4)	4334(2)	3266(2)	38
H(23A)	903(4)	4141(3)	4410(2)	46
H(24A)	-1280(4)	3979(3)	4555(2)	52
H(25A)	-2628(4)	4029(3)	3557(2)	48
H(26A)	-1788(4)	4247(2)	2407(2)	39
H(32A)	2074(4)	5787(2)	1116(2)	41
H(33A)	1757(4)	7121(3)	1042(3)	54
H(34A)	67(5)	7698(3)	1648(3)	64
H(35A)	-1371(5)	6947(3)	2297(3)	64
H(36A)	-1061(4)	5622(3)	2387(2)	50
H(42A)	2418(4)	5609(2)	2766(2)	45
H(43A)	3761(5)	6605(3)	3156(3)	59
H(44A)	5851(5)	6678(3)	2748(3)	61
H(45A)	6638(4)	5738(2)	1964(3)	53
H(47A)	6395(4)	4444(3)	1445(3)	49
H(48A)	5197(5)	3889(3)	2662(3)	76
H(48B)	6231(5)	3383(3)	2237(3)	76
H(48C)	4873(5)	3019(3)	2437(3)	76
H(49A)	4655(5)	3329(3)	584(3)	85
H(49B)	4554(5)	2688(3)	1204(3)	85
H(49C)	5911(5)	3054(3)	1003(3)	85
H(15A)	-2287(4)	3720(3)	-924(2)	71
H(15B)	-990(4)	4204(3)	-979(2)	71
H(15C)	-2236(4)	4590(3)	-634(2)	71
H(18A)	-1885(5)	7029(3)	61(3)	62
H(20B)	947(7)	8021(3)	-1087(3)	79
H(20C)	-1020(6)	8105(3)	-507(3)	75
H(20D)	1299(4)	3831(3)	62(3)	67
H(20E)	2611(4)	4297(3)	-11(3)	67
H(20F)	1829(4)	4060(3)	-721(3)	67
H(47B)	5493(5)	4340(3)	279(3)	86
H(47C)	5631(5)	5229(3)	501(3)	86
H(47D)	4268(5)	4815(3)	541(3)	86

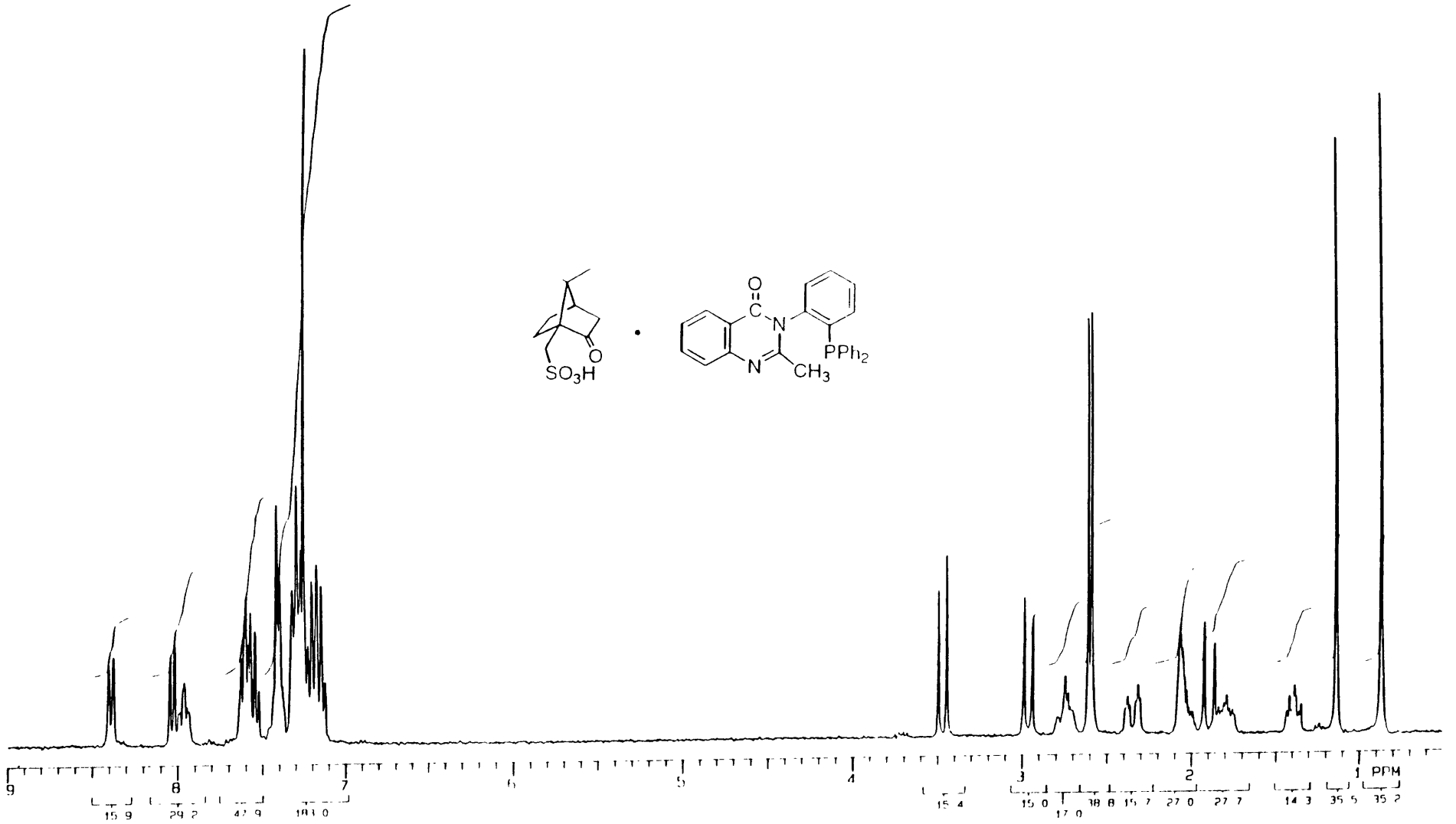
Salt 9 ((*S*-CSA)$_2$ • (*R*-**1a**) • (*S*-**1a**)).



(+)-**CSA**
$C_{10}H_{16}O_4S$
MW: 232.29

1a
$C_{27}H_{21}N_2OP$
MW: 420.45

Racemic ligand **1a** (0.50g, 1.19 mmol) and camphorsulfonic acid (0.28 g, 1.20 mmol) were dissolved in ethyl acetate (8 mL). The solution was heated to reflux for one hour before cooled down to room temperature. The solution was concentrated to 5 mL by evaporating excess of ethyl acetate. The salt precipitated as hexagonal crystals (0.74 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, 1H, J = 1.2, 8.2 Hz), 8.03 (dd, 1H, J = 1.2, 8.1 Hz), 7.95 (ddd, 1H, J = 1.5, 7.8, 8.2 Hz), 7.09-7.65 (m, 15H), 3.47 (d, 1H, J = 14.8 Hz), 2.96 (d, 1H, J = 14.6 Hz), 2.71-2.84 (m, 1H), 2.63 (s, 3H), 2.59 (s, 3H), 2.28-2.51 (m, 1H), 2.28-2.40 (m, 1H), 1.96-2.10 (m, 1H), 1.88 (d, 1H, J = 18.4 Hz), 1.72-1.84 (m, 1H), 1.32-1.44 (m, 1H), 1.14 (s, 3H), 0.87 (s, 3H).


O
SO3H
O
N
N
CH3
PPh2
9
8
7
6
5
4
3
2
1 PPM

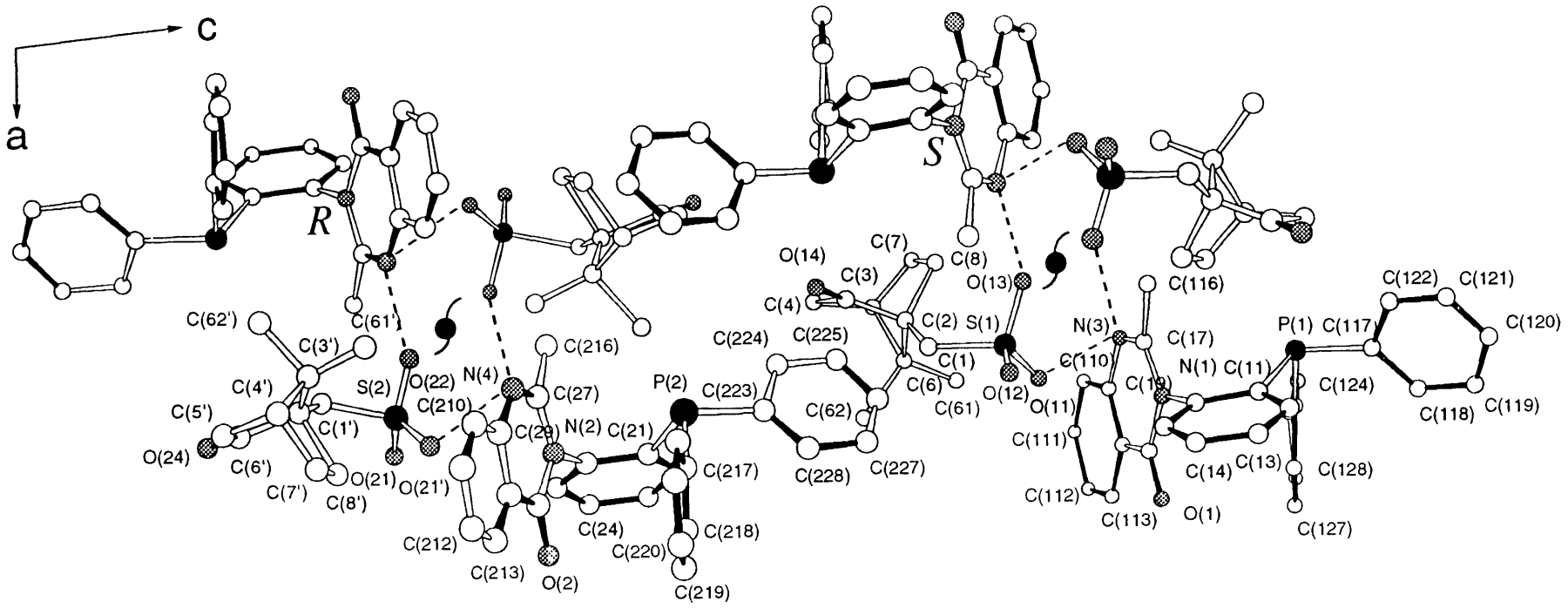


Figure B. X-ray structure of the salt **9** [(*S*-CSA)$_2$ • (*R*- **1a**) • (*S*- **1a**)].

Table B1. Crystal Data and Structure Refinement for salt **9** ((*S*-CSA)$_2$ • (*R*- **1a**) • (*S*-**1a**))

A. Crystal data

Empirical formula	$C_{74}H_{74}N_4O_{10}P_2S_2$	
Formula weight	1305.50	
Temperature	293 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.1602 (5) Å	α = 90°
	b = 10.8868 (5) Å	β = 95.1320 (10)°
	c = 19.085(7) Å	γ = 90°
Volume, Z	3295.5 (3) Å^3, 4	
Density (calcd)	1.316 Mg/m^3	
Absorption coefficient	0.191 mm^{-1}	
F(000)	1336	
Crystal morphology	colorless, prismatic	
Crystal size	0.2 x 0.4 x 0.4 mm	

B. Data Collection and Reduction

Diffractometer	Siemens SMART/CCD
Crystal-Detector distance	6.0 cm
Scan type	ω Scans
Scan angle	0.30°
θ range for data collection	1.50 to 19.00°
Limiting indices	$-11 \leq h \leq 12, -12 \leq k \leq 8, -30 \leq l \leq 30$
Reflections collected	8796
Independent reflections	4690 (R_{int} = 0.0387)
Absorption correction	None

C. Structure Solution and Refinement

Refinement method	Full-matrix least-squares on F^2
No. of data/restraints/parameters	4662 / 1 / 435
Goodness of fit on F^2	1.044
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.1133, wR_2 = 0.3021
R indices (all data)	R_1 = 0.1176, wR_2 = 0.3109
Absolute structure parameter	-0.04 (2)
Extinction coefficient	-0.1 (3)
Largest diff. peak and hole	1.163 and -0.728 eÅ^{-3}

Notes:

$R_1 = \Sigma \| |F_0| - |F_c| \| / \Sigma |F_0|$

$wR_2 = \{ \Sigma [w (F_0^2 - F_c^2)^2 / [\Sigma (F_0^2)^2] \}^{1/2}$

Weighting scheme

calcd $w = 1 / [\sigma^2(F_0^2) + (0.0316P)^2 + 2.9688P]$ where $P = (F_0^2 + 2F_c^2) / 3$

Refinement on F^2 for ALL reflections. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors are based on F, with F set to zero for negative F_0^2. The observed criterion for $F^2 > 2\sigma(F^2)$ is used only for calculating R_1 and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 9. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	8439(3)	1636(3)	445(1)	28(1)
S(2)	8292(3)	9380(5)	5459(1)	47(1)
P(1)	2271(3)	8842(4)	1921(1)	31(1)
P(2)	7787(3)	7160(4)	3076(1)	36(1)
O(1)	4938(7)	8908(9)	816(3)	32(2)
O(2)	5232(8)	7022(10)	4212(3)	35(3)
O(11)	7715(7)	2588(9)	173(3)	30(2)
O(12)	7888(8)	454(10)	414(3)	40(3)
O(13)	9654(7)	1607(10)	291(3)	33(2)
O(14)	9964(19)	2184(24)	1986(8)	161(8)
O(21')	7661(17)	8214(22)	5179(7)	49(6)
O(21)	7537(24)	10296(28)	5476(9)	68(7)
O(22)	9012(16)	10760(20)	5415(7)	49(5)
O(22')	9431(23)	9329(27)	5341(9)	75(7)
O(23)	7027(20)	9738(23)	5405(7)	49(6)
O(23')	8766(15)	8646(19)	5098(6)	37(5)
O(24)	8096(16)	8505(19)	7023(6)	133(6)
N(1)	2890(8)	8783(11)	835(4)	21(3)
N(2)	7259(9)	7279(12)	4157(4)	30(3)
C(1)	8564(11)	2031(15)	1076(5)	30(4)
C(1')	8729(21)	9043(29)	6075(9)	29(7)
C(2)	9125(10)	3216(12)	1264(4)	22(3)
C(2')	8598(15)	7801(19)	6263(6)	61(5)
C(3)	9668(30)	3152(39)	1742(13)	165(13)
C(3')	9291(17)	6686(20)	6185(7)	74(5)
C(4)	9678(17)	4538(19)	2007(7)	76(6)
C(4')	8620(24)	5681(32)	6439(10)	130(9)
C(5)	9456(14)	5190(18)	1528(6)	58(5)
C(5')	8307(29)	6474(34)	6895(12)	58(9)
C(6)	8341(16)	4441(20)	1275(7)	69(5)
C(6')	8245(21)	7625(26)	6763(9)	23(6)
C(7)	10297(22)	5213(25)	1200(9)	110(8)
C(7')	7441(28)	5903(35)	6122(11)	56(9)
C(8)	10210(21)	3831(25)	1009(9)	112(8)
C(8')	7290(34)	7158(41)	5952(14)	198(16)
C(11)	3003(13)	7599(16)	1617(5)	37(4)
C(12)	3395(12)	6522(16)	1865(6)	37(4)
C(13)	3839(12)	5538(16)	1609(5)	38(4)
C(14)	3876(11)	5573(15)	1097(5)	29(4)
C(15)	3500(10)	6590(14)	844(5)	23(3)
C(16)	3093(11)	7590(14)	1103(5)	27(4)
C(17)	1795(11)	9220(13)	692(4)	21(3)
N(3)	1668(8)	10352(10)	498(3)	20(3)
C(19)	2636(10)	11079(12)	401(4)	12(3)
C(21)	7029(10)	8422(13)	3377(5)	19(3)
C(22)	6647(12)	9482(16)	3130(6)	37(4)
C(23)	6184(14)	10484(18)	3383(6)	51(5)
C(24)	6155(14)	10424(19)	3871(6)	56(5)

C(25)	6564(13)	9354(17)	4138(6)	48(4)
C(26)	6990(12)	8396(15)	3889(5)	35(4)
C(27)	8405(13)	6899(15)	4284(5)	35(4)
N(4)	8614(10)	5876(12)	4485(4)	36(3)
C(29)	7784(13)	5075(16)	4601(5)	42(4)
C(61)	7838(17)	5024(20)	852(7)	82(6)
C(61')	9751(18)	6394(22)	5708(7)	92(6)
C(62)	7292(19)	4172(24)	1611(8)	104(7)
C(62')	10450(24)	6904(30)	6580(9)	137(10)
C(110)	2443(11)	12262(13)	197(4)	22(3)
C(111)	3422(10)	12936(13)	115(4)	21(3)
C(112)	4584(11)	12501(13)	221(4)	23(3)
C(113)	4777(10)	11390(13)	412(4)	18(3)
C(114)	3781(10)	10645(12)	506(4)	15(3)
C(115)	2953(11)	9385(13)	721(4)	22(3)
C(116)	658(12)	8473(15)	730(5)	41(4)
C(117)	2387(11)	8305(14)	2550(5)	33(4)
C(118)	3288(10)	8696(16)	2920(5)	33(4)
C(119)	3330(10)	8216(16)	3390(5)	45(4)
C(120)	2425(10)	7406(17)	3511(6)	51(5)
C(121)	1350(11)	7078(17)	3165(5)	44(4)
C(122)	1313(12)	7516(15)	2699(5)	38(4)
C(123)	264(12)	10028(16)	1909(6)	40(4)
C(124)	2383(13)	11202(19)	1933(14)	155(12)
C(125)	3496(13)	12237(50)	1860(15)	200(18)
C(126)	4797(20)	12108(34)	1907(10)	129(10)
C(127)	5343(12)	10923(18)	1898(6)	52(5)
C(128)	4597(12)	9948(16)	1894(5)	37(4)
C(210)	8008(12)	3948(20)	4804(6)	68(5)
C(211)	7166(17)	3141(21)	4916(7)	78(6)
C(212)	8339(13)	3460(21)	4840(7)	83(6)
C(213)	9644(13)	4666(17)	4649(6)	50(4)
C(214)	9530(12)	5435(15)	4523(5)	37(4)
C(215)	8256(12)	6570(15)	4288(5)	33(4)
C(216)	7389(11)	7728(17)	4204(6)	53(5)
C(217)	9690(11)	5907(15)	3078(5)	31(4)
C(218)	9163(11)	6068(15)	3073(5)	30(4)
C(219)	9731(11)	5103(17)	3097(6)	48(4)
C(220)	7171(11)	3951(36)	3123(10)	138(10)
C(221)	6454(11)	3795(43)	3161(13)	186(15)
C(222)	7226(10)	4775(22)	3134(8)	82(6)
C(223)	7660(11)	7662(14)	2423(4)	22(3)
C(224)	8530(13)	8532(16)	2313(6)	47(4)
C(225)	8501(14)	8991(18)	1828(6)	54(5)
C(226)	7644(12)	8565(16)	1500(6)	42(4)
C(227)	6822(12)	7773(14)	1592(5)	31(4)
C(228)	6815(11)	7321(14)	2069(4)	27(4)

Table 3. Bond lengths [Å] and angles [°] for $(S\text{-CSA})_2 \cdot R\text{-1a} \cdot S\text{-1a}$

S(1)-O(12)	1.426(11)	S(1)-O(13)	1.454(9)
S(1)-O(11)	1.472(10)	S(1)-C(1)	1.765(14)
S(2)-O(21)	1.31(3)	S(2)-O(22')	1.34(2)
S(2)-O(23')	1.41(2)	S(2)-O(23)	1.46(2)
S(2)-O(21')	1.61(2)	S(2)-O(22)	1.71(2)
S(2)-C(1')	1.74(3)	P(1)-C(123)	1.78(2)
P(1)-C(117)	1.804(14)	P(1)-C(11)	1.82(2)
P(2)-C(217)	1.83(2)	P(2)-C(21)	1.843(14)
P(2)-C(223)	1.854(13)	O(1)-C(115)	1.223(14)
O(2)-C(215)	1.24(2)	O(14)-C(3)	1.27(4)
O(21')-O(23')	1.36(3)	O(21)-O(23)	0.84(3)
O(21)-O(22)	1.74(3)	O(22)-O(22')	1.64(4)
O(22')-O(23')	1.21(3)	O(24)-C(6')	1.21(3)
N(1)-C(17)	1.34(2)	N(1)-C(115)	1.41(2)
N(1)-C(16)	1.50(2)	N(2)-C(27)	1.36(2)
N(2)-C(215)	1.43(2)	N(2)-C(26)	1.44(2)
C(1)-C(2)	1.50(2)	C(1')-C(2')	1.46(4)
C(2)-C(3)	1.39(4)	C(2)-C(6)	1.60(2)
C(2)-C(8)	1.60(3)	C(2')-C(6')	1.46(3)
C(2')-C(3')	1.46(3)	C(2')-C(8')	1.77(4)
C(3)-C(4)	1.67(4)	C(3')-C(61')	1.48(3)
C(3')-C(4')	1.53(3)	C(3')-C(62')	1.62(3)
C(4)-C(5)	1.49(2)	C(4')-C(7')	1.53(4)
C(4')-C(5')	1.58(4)	C(5)-C(7)	1.35(3)
C(5)-C(6)	1.59(3)	C(5')-C(6')	1.30(4)
C(6)-C(61)	1.39(2)	C(6)-C(62)	1.58(3)
C(7)-C(8)	1.59(3)	C(7')-C(8')	1.45(5)
C(11)-C(16)	1.41(2)	C(11)-C(12)	1.40(2)
C(12)-C(13)	1.39(2)	C(13)-C(14)	1.40(2)
C(14)-C(15)	1.35(2)	C(15)-C(16)	1.39(2)
C(17)-N(3)	1.34(2)	C(17)-C(116)	1.52(2)
N(3)-C(19)	1.38(2)	C(19)-C(114)	1.37(2)
C(19)-C(110)	1.41(2)	C(21)-C(22)	1.38(2)
C(21)-C(26)	1.40(2)	C(22)-C(23)	1.41(2)
C(23)-C(24)	1.33(2)	C(24)-C(25)	1.43(2)
C(25)-C(26)	1.35(2)	C(27)-N(4)	1.25(2)
C(27)-C(216)	1.45(2)	N(4)-C(29)	1.33(2)
C(29)-C(210)	1.36(2)	C(29)-C(214)	1.45(2)
C(110)-C(111)	1.35(2)	C(111)-C(112)	1.39(2)
C(112)-C(113)	1.33(2)	C(113)-C(114)	1.42(2)
C(114)-C(115)	1.50(2)	C(117)-C(122)	1.39(2)
C(117)-C(118)	1.42(2)	C(118)-C(119)	1.38(2)
C(119)-C(120)	1.40(2)	C(120)-C(121)	1.34(2)
C(121)-C(122)	1.35(2)	C(123)-C(124)	1.39
C(123)-C(128)	1.38(2)	C(124)-C(125)	1.34(5)
C(125)-C(126)	1.45(4)	C(126)-C(127)	1.43(4)
C(127)-C(128)	1.35(2)	C(210)-C(211)	1.34(3)
C(211)-C(212)	1.41(3)	C(212)-C(213)	1.44(3)
C(213)-C(214)	1.36(2)	C(214)-C(215)	1.41(2)
C(217)-C(218)	1.39	C(217)-C(222)	1.37(2)
C(218)-C(219)	1.35(2)	C(219)-C(220)	1.36(4)
C(220)-C(221)	1.44(4)	C(221)-C(222)	1.38(4)
C(223)-C(228)	1.34(2)	C(223)-C(224)	1.41(2)
C(224)-C(225)	1.41(2)	C(225)-C(226)	1.33(2)
C(226)-C(227)	1.30(2)	C(227)-C(228)	1.39(2)

O(12)-S(1)-O(13)	111.8(6)	O(12)-S(1)-O(11)	113.0(5)
O(13)-S(1)-O(11)	110.8(5)	O(12)-S(1)-C(1)	105.8(7)
O(13)-S(1)-C(1)	106.9(6)	O(11)-S(1)-C(1)	108.0(6)
O(21)-S(2)-O(22')	132(2)	O(21)-S(2)-O(23')	137.9(13)
O(22')-S(2)-O(23')	52.0(12)	O(21)-S(2)-O(23)	34.9(13)
O(22')-S(2)-O(23)	156.5(14)	O(23')-S(2)-O(23)	120.2(12)
O(21)-S(2)-O(21')	111(2)	O(22')-S(2)-O(21')	103.8(14)
O(23')-S(2)-O(21')	52.9(10)	O(23)-S(2)-O(21')	77.6(12)
O(21)-S(2)-O(22)	69(2)	O(22')-S(2)-O(22)	63.8(14)
O(23')-S(2)-O(22)	103.9(10)	O(23)-S(2)-O(22)	102.4(13)
O(21')-S(2)-O(22)	147.7(10)	O(21)-S(2)-C(1')	104.5(14)
O(22')-S(2)-C(1')	91.9(13)	O(23')-S(2)-C(1')	117.5(12)
O(23)-S(2)-C(1')	109.8(11)	O(21')-S(2)-C(1')	111.3(13)
O(22)-S(2)-C(1')	99.2(12)	C(123)-P(1)-C(117)	105.1(7)
C(123)-P(1)-C(11)	101.3(7)	C(117)-P(1)-C(11)	101.2(7)
C(217)-P(2)-C(21)	102.8(6)	C(217)-P(2)-C(223)	103.2(6)
C(21)-P(2)-C(223)	102.0(6)	O(23')-O(21')-S(2)	55.8(12)
O(23)-O(21)-S(2)	82(3)	O(23)-O(21)-O(22)	144(3)
S(2)-O(21)-O(22)	66.5(13)	O(22')-O(22)-S(2)	47.0(11)
O(22')-O(22)-O(21)	91(2)	S(2)-O(22)-O(21)	44.5(11)
O(23')-O(22')-S(2)	67(2)	O(23')-O(22')-O(22)	119(2)
S(2)-O(22')-O(22)	69.2(14)	O(21)-O(23)-S(2)	63(2)
O(22')-O(23')-O(21')	131(2)	O(22')-O(23')-S(2)	61(2)
O(21')-O(23')-S(2)	71.3(12)	C(17)-N(1)-C(115)	122.3(12)
C(17)-N(1)-C(16)	123.1(11)	C(115)-N(1)-C(16)	114.6(9)
C(27)-N(2)-C(215)	120.9(13)	C(27)-N(2)-C(26)	122.4(12)
C(215)-N(2)-C(26)	116.8(11)	C(2)-C(1)-S(1)	122.3(10)
C(2')-C(1')-S(2)	120(2)	C(3)-C(2)-C(1)	114(2)
C(3)-C(2)-C(6)	103(2)	C(1)-C(2)-C(6)	120.7(11)
C(3)-C(2)-C(8)	98(2)	C(1)-C(2)-C(8)	121.3(13)
C(6)-C(2)-C(8)	95.5(14)	C(1')-C(2')-C(6')	120(2)
C(1')-C(2')-C(3')	130(2)	C(6')-C(2')-C(3')	103(2)
C(1')-C(2')-C(8')	108(2)	C(6')-C(2')-C(8')	97(2)
C(3')-C(2')-C(8')	92(2)	O(14)-C(3)-C(2)	127(3)
O(14)-C(3)-C(4)	122(3)	C(2)-C(3)-C(4)	110(3)
C(61')-C(3')-C(2')	122(2)	C(61')-C(3')-C(4')	118(2)
C(2')-C(3')-C(4')	104(2)	C(61')-C(3')-C(62')	107(2)
C(2')-C(3')-C(62')	101(2)	C(4')-C(3')-C(62')	102(2)
C(5)-C(4)-C(3)	93(2)	C(3')-C(4')-C(7')	94(2)
C(3')-C(4')-C(5')	97(2)	C(7')-C(4')-C(5')	97(2)
C(7)-C(5)-C(4)	121(2)	C(7)-C(5)-C(6)	107(2)
C(4)-C(5)-C(6)	101(2)	C(6')-C(5')-C(4')	109(3)
C(61)-C(6)-C(62)	108(2)	C(61)-C(6)-C(2)	123(2)
C(62)-C(6)-C(2)	107(2)	C(61)-C(6)-C(5)	112(2)
C(62)-C(6)-C(5)	116(2)	C(2)-C(6)-C(5)	91.6(12)
O(24)-C(6')-C(5')	127(3)	O(24)-C(6')-C(2')	120(2)
C(5')-C(6')-C(2')	112(2)	C(5)-C(7)-C(8)	100(2)
C(8')-C(7')-C(4')	114(3)	C(7)-C(8)-C(2)	106(2)
C(7')-C(8')-C(2')	99(3)	C(16)-C(11)-C(12)	115.1(14)
C(16)-C(11)-P(1)	122.0(12)	C(12)-C(11)-P(1)	122.5(11)
C(13)-C(12)-C(11)	120.7(13)	C(12)-C(13)-C(14)	122(2)
C(15)-C(14)-C(13)	119.6(14)	C(14)-C(15)-C(16)	118.9(12)
C(15)-C(16)-C(11)	124.1(14)	C(15)-C(16)-N(1)	118.2(10)
C(11)-C(16)-N(1)	117.2(12)	N(1)-C(17)-N(3)	120.1(11)
N(1)-C(17)-C(116)	122.5(13)	N(3)-C(17)-C(116)	117.4(11)
C(17)-N(3)-C(19)	122.9(10)	C(114)-C(19)-N(3)	119.6(12)
C(114)-C(19)-C(110)	120.2(11)	N(3)-C(19)-C(110)	120.2(10)

C(26)-C(21)-P(2)	119.0(11)	C(21)-C(22)-C(23)	121.1(13)
C(24)-C(23)-C(22)	119(2)	C(23)-C(24)-C(25)	121(2)
C(26)-C(25)-C(24)	119(2)	C(25)-C(26)-C(21)	122(2)
C(25)-C(26)-N(2)	117.6(12)	C(21)-C(26)-N(2)	120.0(13)
N(4)-C(27)-N(2)	121.0(13)	N(4)-C(27)-C(216)	120.2(14)
N(2)-C(27)-C(216)	119(2)	C(27)-N(4)-C(29)	125.4(13)
N(4)-C(29)-C(210)	126(2)	N(4)-C(29)-C(214)	118(2)
C(210)-C(29)-C(214)	116(2)	C(111)-C(110)-C(19)	117.6(11)
C(110)-C(111)-C(112)	122.4(13)	C(113)-C(112)-C(111)	120.6(12)
C(112)-C(113)-C(114)	119.3(11)	C(19)-C(114)-C(113)	119.9(12)
C(19)-C(114)-C(115)	118.8(11)	C(113)-C(114)-C(115)	121.3(10)
O(1)-C(115)-N(1)	120.8(13)	O(1)-C(115)-C(114)	123.6(12)
N(1)-C(115)-C(114)	115.5(10)	C(122)-C(117)-C(118)	116.6(13)
C(122)-C(117)-P(1)	119.1(11)	C(118)-C(117)-P(1)	124.2(11)
C(119)-C(118)-C(117)	120.4(14)	C(118)-C(119)-C(120)	119.4(14)
C(121)-C(120)-C(119)	120(2)	C(120)-C(121)-C(122)	121(2)
C(121)-C(122)-C(117)	122.0(14)	C(124)-C(123)-C(128)	117(2)
C(124)-C(123)-P(1)	114(2)	C(128)-C(123)-P(1)	129.8(13)
C(125)-C(124)-C(123)	124(3)	C(124)-C(125)-C(126)	115(4)
C(127)-C(126)-C(125)	121(4)	C(126)-C(127)-C(128)	117(2)
C(127)-C(128)-C(123)	124(2)	C(211)-C(210)-C(29)	125(2)
C(210)-C(211)-C(212)	120(2)	C(211)-C(212)-C(213)	118(2)
C(214)-C(213)-C(212)	120(2)	C(213)-C(214)-C(215)	121.3(14)
C(213)-C(214)-C(29)	121(2)	C(215)-C(214)-C(29)	118.0(13)
O(2)-C(215)-C(214)	125.4(13)	O(2)-C(215)-N(2)	118.2(14)
C(214)-C(215)-N(2)	116.2(12)	C(218)-C(217)-C(222)	123(2)
C(218)-C(217)-P(2)	124.7(11)	C(222)-C(217)-P(2)	112.6(11)
C(219)-C(218)-C(217)	121.5(14)	C(220)-C(219)-C(218)	119(2)
C(219)-C(220)-C(221)	119(3)	C(220)-C(221)-C(222)	122(4)
C(221)-C(222)-C(217)	116(2)	C(228)-C(223)-C(224)	119.1(13)
C(228)-C(223)-P(2)	126.6(11)	C(224)-C(223)-P(2)	114.1(10)
C(225)-C(224)-C(223)	118.7(14)	C(226)-C(225)-C(224)	117(2)
C(227)-C(226)-C(225)	125(2)	C(226)-C(227)-C(228)	118.6(13)
C(223)-C(228)-C(227)	120.8(13)		

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for (*S*-CSA)$_2$ • *R*-1a • *S*-1a

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

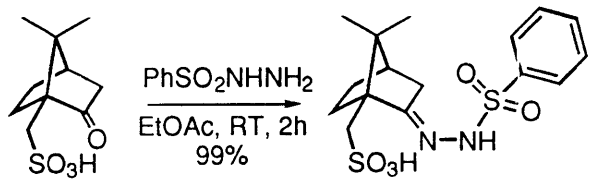
	U11	U22	U33	U23	U13	U12
S(1)	21(2)	27(3)	35(2)	4(2)	-1(2)	-2(2)
S(2)	35(2)	69(4)	37(2)	3(2)	4(2)	18(2)
P(1)	35(2)	33(3)	27(2)	11(2)	6(2)	11(2)
P(2)	34(2)	47(3)	28(2)	3(2)	2(2)	9(2)
N(1)	8(6)	22(8)	33(6)	-9(6)	8(4)	1(5)
N(2)	31(7)	35(9)	22(6)	3(6)	-4(5)	3(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (*S*-CSA)$_2$ • *R*-1a • *S*-1a

	x	y	z	U(eq)
H(1A)	8272(11)	1486(15)	1300(5)	36
H(1'A)	9048(21)	9658(29)	6284(9)	35
H(4A)	9035(17)	4647(19)	2220(7)	91
H(4B)	10448(17)	4744(19)	2182(7)	91
H(4'A)	8957(24)	4853(32)	6483(10)	156
H(5A)	9200(14)	6033(18)	1589(6)	70
H(5'A)	7544(29)	6211(34)	7004(12)	69
H(5'B)	8925(29)	6368(34)	7166(12)	69
H(7A)	11089(22)	5401(25)	1357(9)	132
H(7B)	10093(22)	5794(25)	935(9)	132
H(7'A)	6875(28)	5290(35)	6045(11)	67
H(8A)	10955(21)	3397(25)	1101(9)	135
H(8B)	10053(21)	3809(25)	653(9)	135
H(8'A)	6562(34)	7527(41)	6055(14)	237
H(8'B)	7292(34)	7222(41)	5597(14)	237
H(12B)	3357(12)	6464(16)	2204(6)	44
H(13B)	4117(12)	4843(16)	1782(5)	45
H(14A)	4159(11)	4899(15)	932(5)	35
H(15A)	3512(10)	6623(14)	504(5)	28
H(22A)	6696(12)	9536(16)	2792(6)	44
H(23A)	5903(14)	11179(18)	3211(6)	62
H(24A)	5865(14)	11089(19)	4039(6)	67
H(25A)	6538(13)	9315(17)	4478(6)	58
H(61A)	9457(17)	5196(20)	638(7)	123
H(61B)	7469(17)	5779(20)	940(7)	123
H(61C)	7242(17)	4500(20)	685(7)	123
H(61D)	10175(18)	5627(22)	5733(7)	137
H(61E)	10287(18)	7033(22)	5622(7)	137
H(61F)	9089(18)	6334(22)	5458(7)	137
H(62A)	7612(19)	3762(24)	1906(8)	156
H(62B)	6700(19)	3658(24)	1435(8)	156
H(62C)	6926(19)	4932(24)	1696(8)	156
H(62D)	10183(24)	7094(30)	6897(9)	206
H(62E)	10921(24)	7574(30)	6473(9)	206
H(62F)	10933(24)	6173(30)	6605(9)	206
H(11B)	1669(11)	12566(13)	122(4)	27
H(11C)	3312(10)	13721(13)	-17(4)	25
H(11D)	5234(11)	12992(13)	156(4)	28
H(11E)	5558(10)	11103(13)	484(4)	21
H(11F)	-29(12)	8951(15)	609(5)	61
H(11G)	592(12)	8259(15)	1069(5)	61
H(11H)	693(12)	7738(15)	537(5)	61
H(11I)	3853(12)	9279(16)	2845(5)	40
H(11J)	3952(13)	8427(16)	3625(5)	55
H(12C)	2431(13)	7097(17)	3829(6)	62
H(12D)	955(13)	6537(17)	3248(5)	53
H(12E)	886(12)	7279(15)	2471(5)	46
H(12F)	2087(62)	11275(38)	2004(96)	186
H(12G)	3116(39)	12982(50)	1785(15)	240

H(12H)	5280(26)	12804(34)	1943(10)	155
H(12I)	6170(15)	10828(18)	1894(6)	62
H(12J)	4935(12)	9169(16)	1881(5)	44
H(21A)	8809(16)	3718(20)	4871(6)	82
H(21B)	7391(17)	2373(21)	5043(7)	93
H(21C)	5341(18)	2910(21)	4911(7)	99
H(21D)	4846(15)	4921(17)	4612(6)	61
H(21E)	9073(13)	8466(17)	4049(6)	79
H(21F)	9924(13)	7338(17)	3994(6)	79
H(21G)	9820(13)	7926(17)	4514(6)	79
H(21H)	5137(16)	6859(28)	3054(41)	36
H(21I)	3876(14)	5225(17)	3096(6)	57
H(22B)	4666(26)	3270(36)	3116(10)	165
H(22C)	6773(33)	3009(43)	3205(13)	223
H(22D)	8056(20)	4676(22)	3153(8)	98
H(22F)	9112(13)	8799(16)	2555(6)	56
H(22G)	9058(14)	9569(18)	1741(6)	65
H(22H)	7634(22)	8857(16)	1179(6)	50
H(22I)	6250(22)	7515(14)	1344(5)	37
H(22J)	6216(21)	6775(14)	2144(4)	32

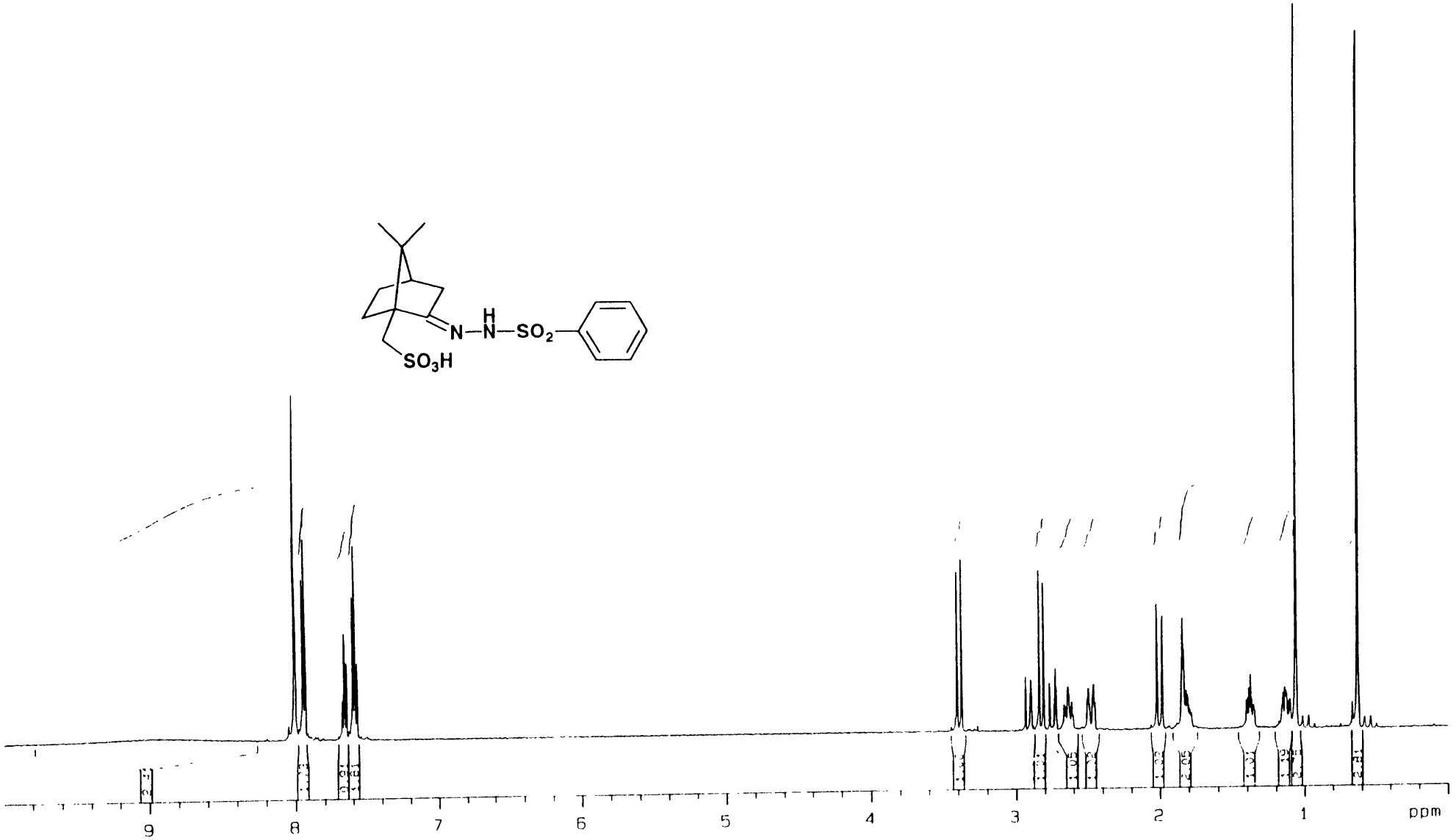
Camphorsulfonic Acid Benzenesulfonylhydrazone (CSZ, 10).



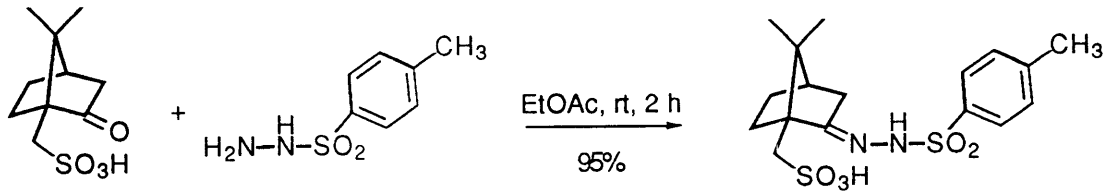
S-**CSA**
$C_{10}H_{16}O_4S$
MW: 232.29

S-**CSZ**
$C_{16}H_{22}N_2O_5S_2$
MW: 386.48

To a solution of (1*S*)-(+)-camphorsulfonic acid (10.73 g, 46.2 mmol) in ethyl acetate (170 mL) and ethanol (30 mL) was added a solution of benzenesulfonyl hydrazide (7.95 g, 46.2 mmol) in ethyl acetate (130 mL). After stirring 2h, the mixture was filtered to afford **10** as a white solid (17.8 g, 99%): mp 266-268 °C (dec.); R_f = 0.58 (silica, 1:2 methanol/ethyl acetate); FTIR (thin film, cm^{-1}) 3436, 2964, 1673, 1359, 1231, 1174, 1041; ^1H NMR (300 MHz, d_7-DMF) δ 8.30-9.80 (br s, 2H), 7.78 (dd, 2H, *J* = 1.5, 8.3 Hz), 7.49 (tt, 1H, *J* = 1.5, 7.3 Hz), 7.42 (br t, 2H, *J* = 7.6 Hz), 3.22 (d, 1H, *J* = 14.7 Hz), 2.66 (d, 1H, *J* = 15.4 Hz), 2.42-2.51 (m, 1H), 2.28-2.35 (m, 1H), 1.84 (d, 1H, *J* = 17.6 Hz), 1.60-1.70 (m, 2H), 1.18-1.25 (m, 1H), 0.93-1.00 (m, 1H), 0.89 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (75 MHz, CF_3COOH-$CDCl_3$) δ 212.31, 137.12, 135.04, 131.12, 129.10, 60.33, 55.66, 50.74, 43.79, 40.61, 30.63, 26.36, 19.60, 18.36; $[\alpha]_D^{23}$ = -9.5° (*c* = 1.01, DMF); HRMS 386.0972 (calcd for $C_{16}H_{22}N_2S_2O_5$ (M^+) 386.0970).


N—N—SO2
SO3H
9
8
7
6
5
4
3
2
1
ppm

Acid 72

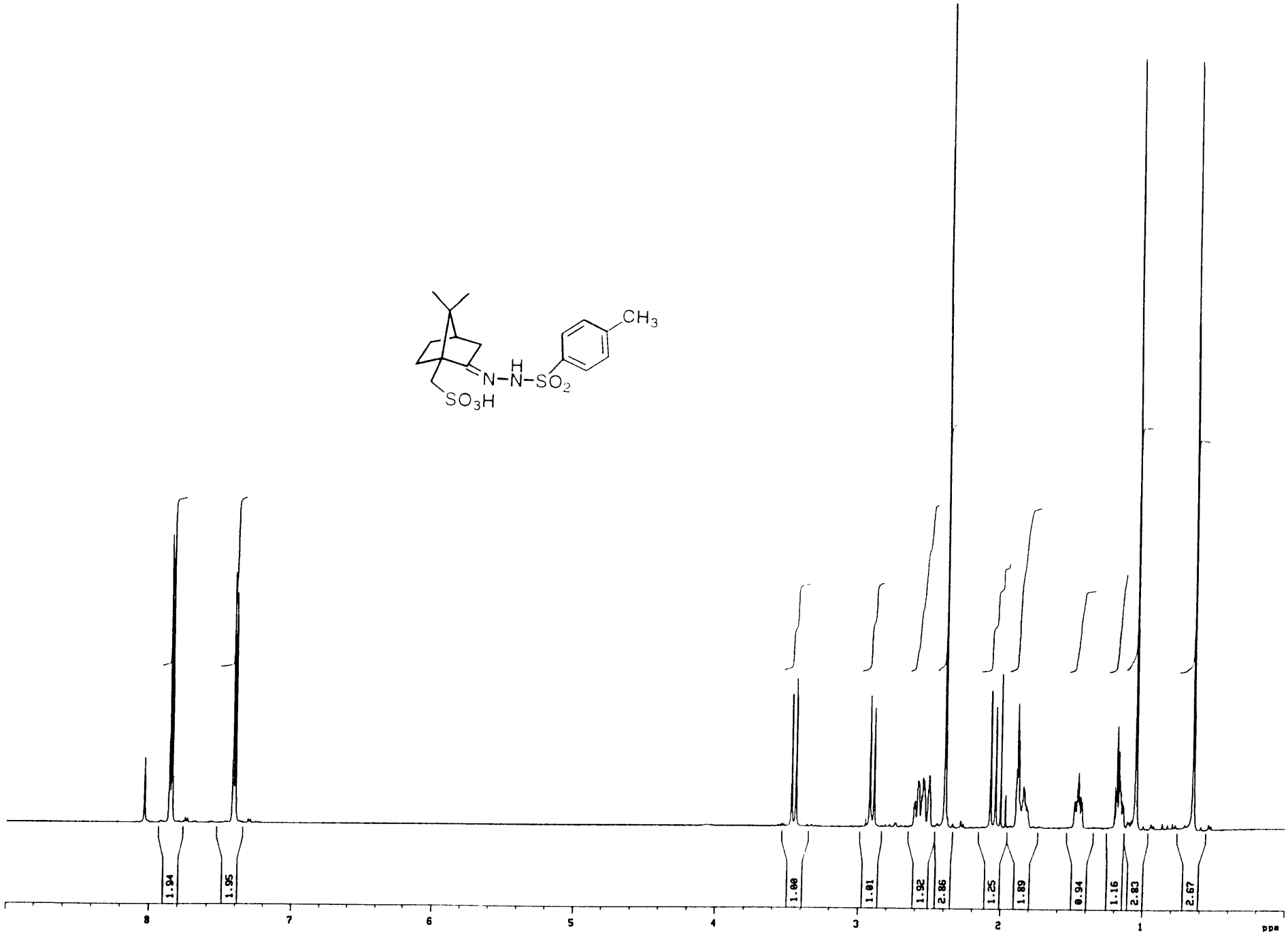


***S*-CSA**
$C_{10}H_{16}O_4S$
MW: 232.29

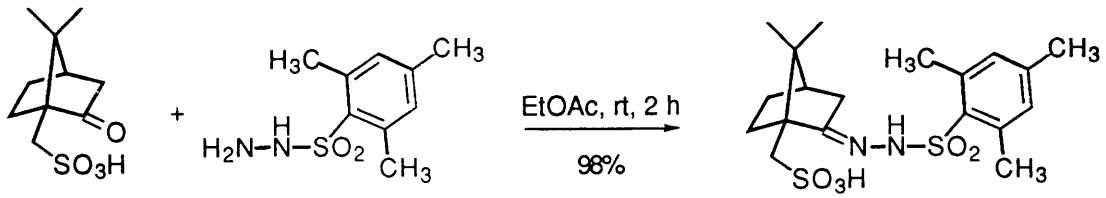
$C_7H_{10}N_2O_2S$
MW: 186.23

(*S*)-CST (**72**)
$C_{17}H_{24}N_2O_5S_2$
MW: 400.51

Compound **72** was obtained as a white solid (95%) with (1*S*)-(+)-camphorsulfonic acid and *p*-tolylsulfonyl hydrazide under conditions analogous to the reaction producing **10**: ^{1}H NMR (300 MHz, d_7-DMF) δ 7.85 (d, 2H, *J* = 8.2 Hz), 7.41 (d, 2H, *J* = 7.9 Hz), 3.46 (d, 1H, *J* = 15.0 Hz), 2.91 (d, 1H, *J* = 15.0 Hz), 2.49-2.63 (m, 1H), 2.40 (s, 3H), 2.06 (d, 1H, *J* = 18.3 Hz), 1.80-1.91 (m, 2H), 1.46 (ddd, 1H, *J* = 4.27, 9.46, 13.43 Hz), 1.14-1.21 (m, 1H), 1.06 (s, 3H), 0.66 (s, 3H).


CH3
N–N–SO2
H
SO3H
1.94
1.95
1.00
1.01
1.92
2.86
1.25
1.89
0.94
1.16
2.83
2.67
8
7
6
5
4
3
2
1
ppm

Acid 73

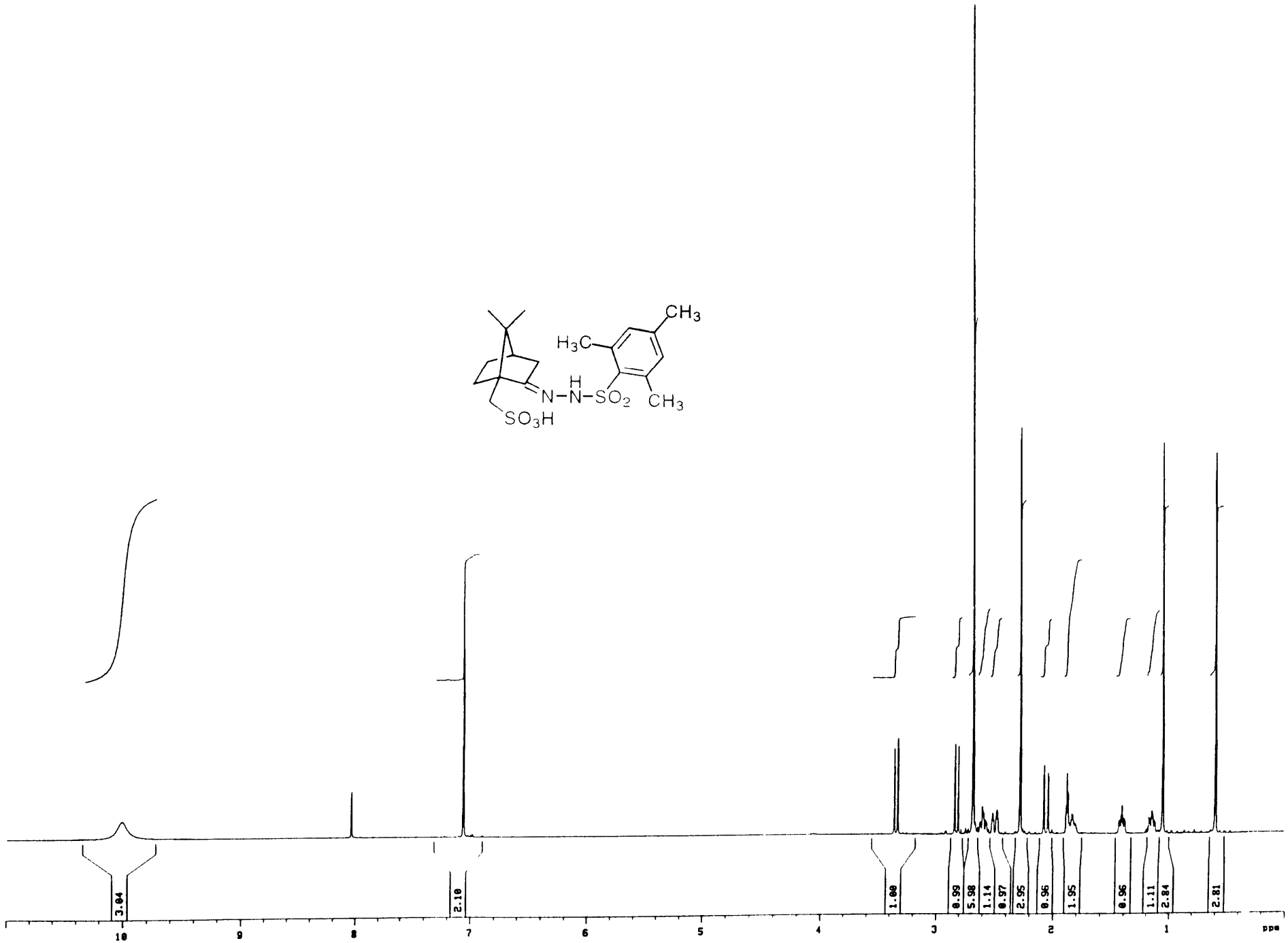


***S*-CSA**
$C_{10}H_{16}O_4S$
MW: 232.29

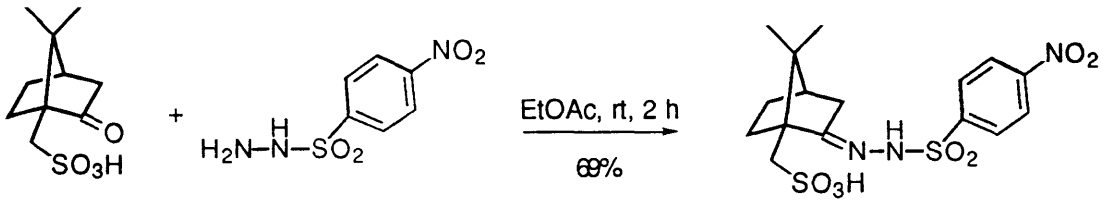
$C_9H_{14}N_2O_2S$
MW: 214.28

(*S*)-CSM (**73**)
$C_{19}H_{28}N_2O_5S_2$
MW: 428.56

Compound **73** was obtained as a white solid (98%) with (1*S*)-(+)-camphorsulfonic acid and *p*-mesitylsulfonyl hydrazide under conditions analogous to the reaction producing **10**: ^{1}H NMR (300 MHz, d$_7$-DMF) δ 10.00 (br s, 2H), 7.06 (s, 2H, 7.41 (d, 2H, *J* = 7.9 Hz), 3.35 (d, 1H, *J* = 15.0 Hz), 2.83 (d, 1H, *J* = 15.0 Hz), 2.68 (s, 6H), 2.50 (td, 1H, *J* = 3.74, 18.16 Hz), 2.28 (s, 3H), 2.06 (d, 1H, *J* = 18.01 Hz), 1.79-1.92 (m, 1H), 1.41 (ddd, 1H, *J* = 4.27, 9.46, 13.43 Hz), 1.11-1.18 (m, 1H), 1.06 (s, 3H), 0.60 (s, 3H).

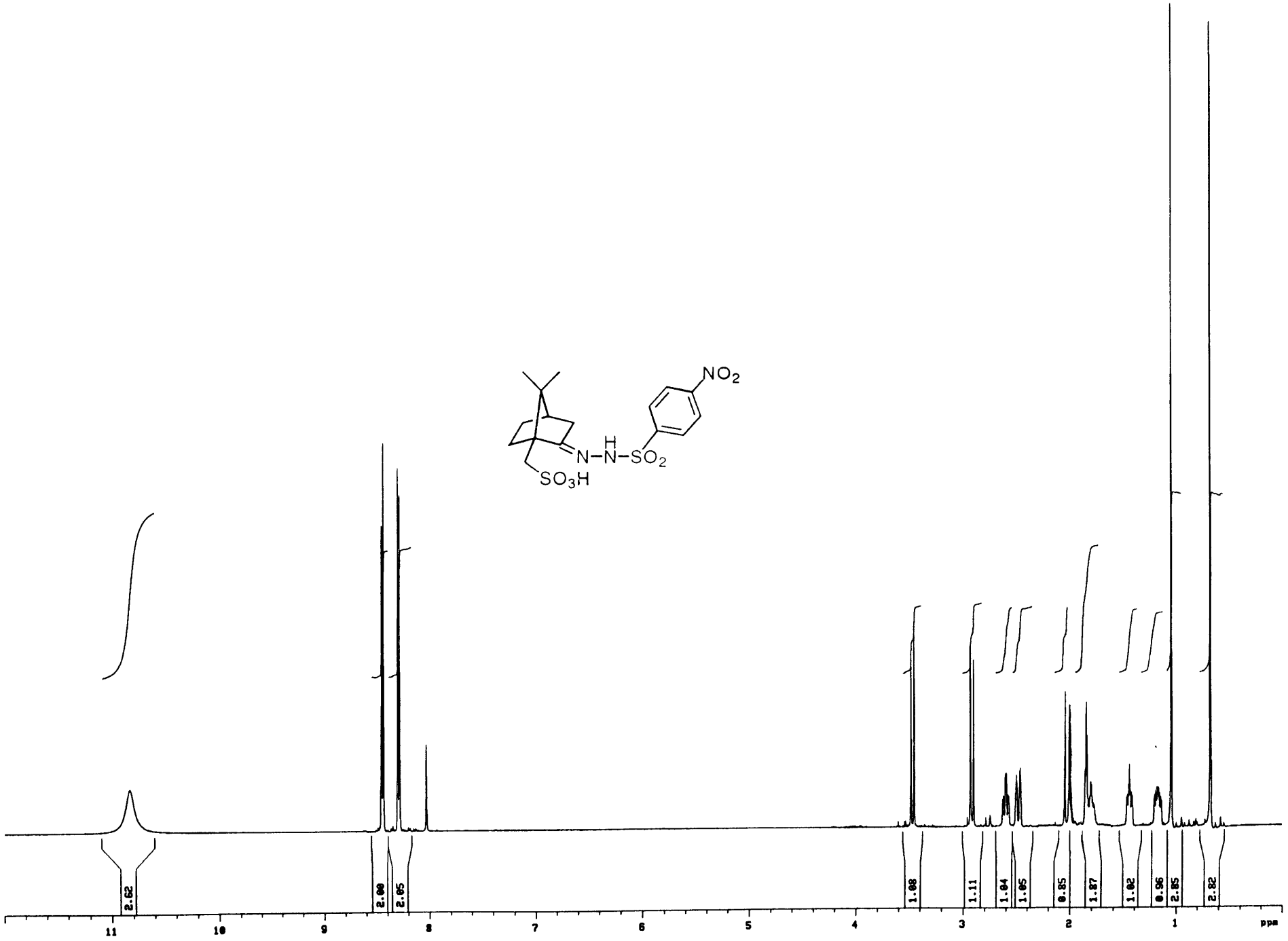

CH3
H3C
H
N–N–SO2
CH3
SO3H
3.04
2.10
1.00
0.99
5.98
1.14
0.97
2.95
0.96
1.95
0.96
1.11
2.84
2.81
10
9
8
7
6
5
4
3
2
1
ppm

Acid 74

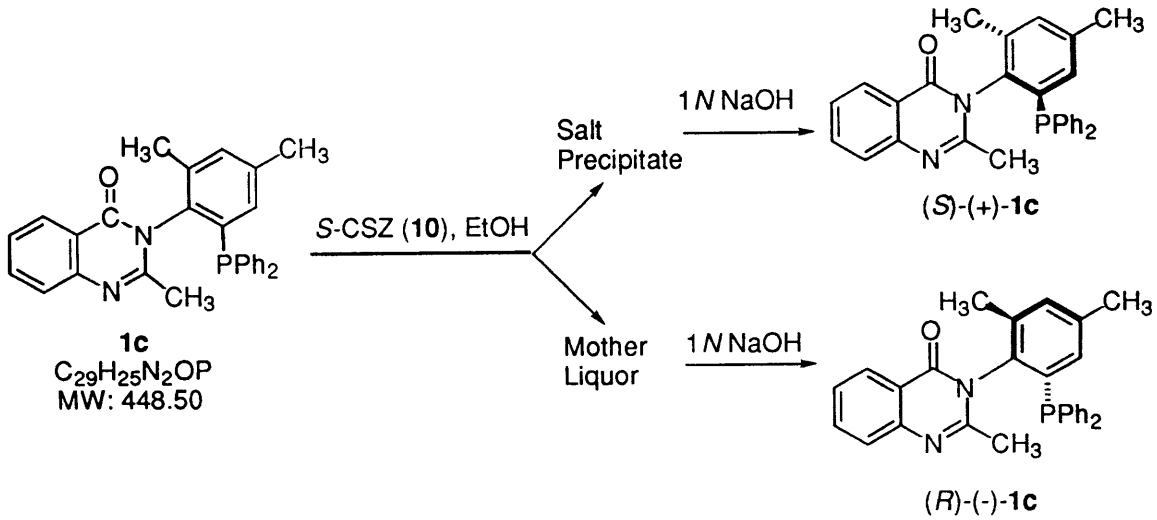


(*S*)-CSN (**74**)

Compound **74** was obtained as off-white solid (69%) with (1*S*)-(+)-camphorsulfonic acid and *p*-nitrobezenesulfonyl hydrazide under conditions analogous to the reaction producing **10**: ^{1}H NMR (300 MHz, d_7-DMF) δ 10.83 (br s, 2H), 8.45 (d, 2H, J = 8.85 Hz), 8.29 (d, 2H, J = 9.2 Hz), 3.47 (d, 1H, J = 15.0 Hz), 2.92 (d, 1H, J = 15.0 Hz), 2.60 (dt, 1H, J = 4.12, 12.59 Hz), 2.49 (td, 1H, J = 3.59, 17.85 Hz), 2.05 (d, 1H, J = 18.0 Hz), 1.45 (ddd, 1H, J = 4.27, 9.31, 13.58 Hz), 1.15-1.21 (m, 1H), 1.05 (s, 3H), 0.66 (s, 3H).


NO2
N–N–SO2
SO3H
2.62
2.00
2.05
1.08
1.11
1.04
1.05
0.85
1.87
1.20
0.96
2.82
2.82
11
10
9
8
7
6
5
4
3
2
1
ppm

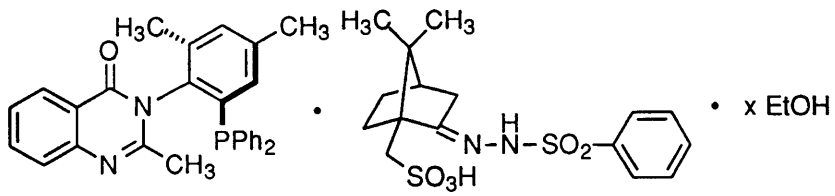
Resolution of 1c Using Resolving Agent 10.



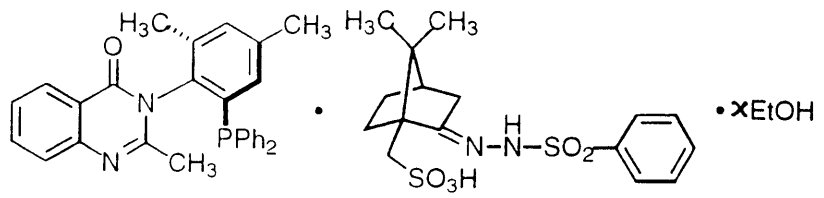
In a 200 mL, round-bottom flask 21.6 g (56.0 mmol, 1.00 equiv.) of acid **10** was dissolved in 1200 mL of ethanol at reflux, and 25.1 g (56.0 mmol, 1.00 equiv.) of racemic **1c** was added. The clear solution was cooled slowly to 0 °C, and kept at 0 °C overnight. The crystals were filtered, washed with ethanol (3 × 20 mL), and air-dried to afford 22.4 g (96 %) of white (*S*)-**1c**·**10** salt. Trituration of this salt in ethyl acetate (100 mL) and filtration freed the ligand. Acid **7** was recovered as white solid. After washing with aqueous sodium bicarbonate (2 × 30 mL) and recrystallization, the ethyl acetate solution afforded optically pure (+)-**1c** (9.05g, 73%): mp 167-169 °C; $[\alpha]_D^{23}$ = +186° (*c* = 0.90, $CHCl_3$) (>99.5 % ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.25 mL/min, λ = 295 nm, , t_R = 31.8 min).

The ethanolic mother liquor was concentrated to dryness. The residue was triturated, neutralized and crystallized as above to give 9.05 g of white prisms (72%): mp 166 - 167 °C; $[\alpha]_D^{23}$ = -193° (*c* = 0.90, $CHCl_3$) (>99.5% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.25 mL/min, λ = 295 nm, t_R = 36.7 min).

NMR data for salt (*S*)-(+)-1c·10·xEtOH:

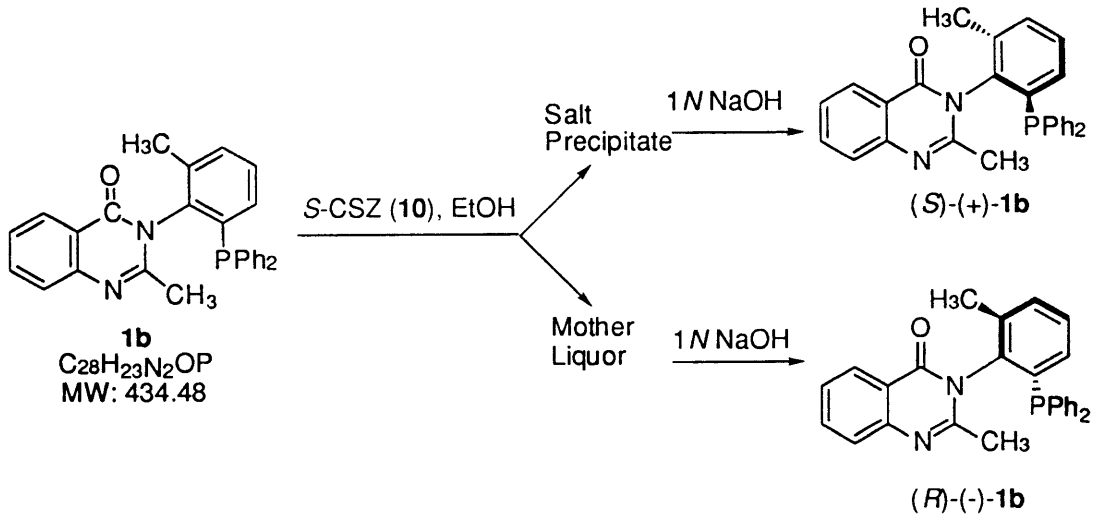


^{1}H NMR (500 MHz, d$_7$-DMF) δ 8.3-9.8 (br s, 2 H), 8.07 (d, 1 H, *J* = 8.2 Hz), 7.95-8.00 (m, 3 H), 7.90 (d, 1 H, *J* = 8.2 Hz), 7.66-7.71 (m, 1 h), 7.59-7.65 (m, 3H), 7.48-7.52 (m, 3H), 7.38-7.45(m, 3 H), 7.29-7.36 (m, 3 H), 7.16 (t, 2 H, *J* = 7.3 Hz), 7.04 (br s, 1 H), 3.45 (d, 1 H, *J* = 15.0 Hz), 2.87 (d, 1 H, *J* = 15.3 Hz), 2.68-2.76 (m, 1 H), 2.53 (dt, 1 H, *J* = 17.6, 3.6 Hz), 2.33 (s, 3 H), 2.21 (s, 3 H), 2.19 (s, 3 H), 2.04 (d, 1 H, *J* = 18.0 Hz), 1.81-1.90 (m, 2 H), 1.40-1.48 (m, 1 H), 1.12-1.20 (m, 1 H), 1.10 (s, 3 H), 0.65 (s, 3 H); ^{13}C NMR (125 MHz, d$_7$-DMF) δ 172.6, 161.3, 157.8, 145.9, 140.9, 140.6, 139.4, 139.2, 137.42, 137.39, 137.1, 137.0, 136.74, 136.66, 136.4, 136.1, 136.0, 135.2, 135.1, 134.7, 134.4, 134.2, 133.9, 130.7, 130.2, 130.1, 130.0, 129.6, 129.5, 128.8, 128.5, 127.9, 126.2, 121.3, 57.7, 54.9, 50.0, 44.8, 28.5, 27.8, 23.31, 23.28, 21.5, 20.3, 19.8, 19.3, 18.05, 18.03.


H3C
CH3
O
N
PPh2
N
CH3
H3C
CH3
N-N-SO2
H
SO3H
•xEtOH

10
9
8
7
6
5
4
3
2
1
ppm
48.69
33.48
17.94
22.62
16.93
50.04
19.40
20.60
98.35
36.07
115.96
18.03
49.74

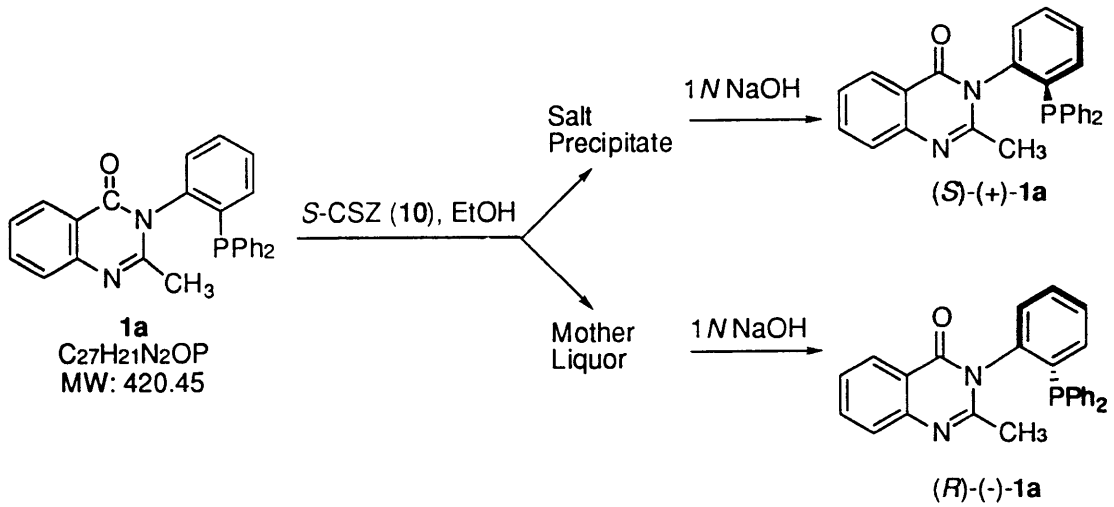
Resolution of 1b Using Resolving Agent 10.



Compound **1b** was resolved analogously to that described for **1c**, starting from racemic **1b** (2.33 g, 5.36 mmol) and acid **10** (2.08 g, 5.39 mmol) in 120 mL of ethanol. The white (*S*)-**1b**·CSZ salt provided 0.862 g of white prisms (74%): mp 143-145 °C; $[\alpha]_D^{23}$ = + 172° (*c* = 0.93, $CHCl_3$) (>99.5 % ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 1.00 mL/min, λ = 295 nm, , t_R = 18.8 min).

The ethanolic mother liquor afforded 1.07 g of white prisms (91%): mp 142-144 °C; $[\alpha]_D^{23}$ = -176° (*c* = 0.97, $CHCl_3$) (>99.5% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 1.00 mL/min, λ = 295 nm, t_R = 22.9 min).

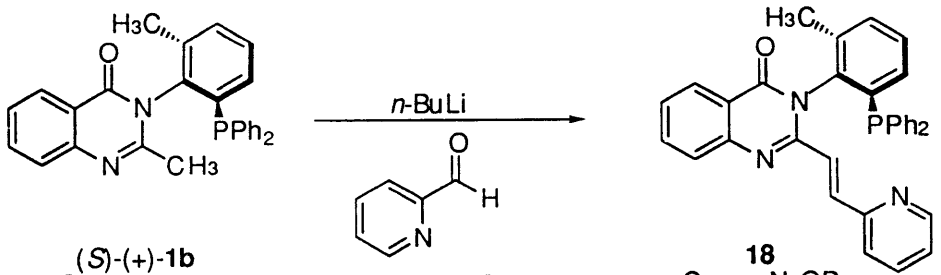
Resolution of 1a Using Resolving Agent 10.



Compound **1a** was resolved analogously to that described for **1c**, starting from racemic **1a** (2.44 g, 5.81 mmol) and acid **10** (2.27 g, 5.88 mmol) in 140 mL of ethanol. The white (*S*)-**1a**·CSZ salt provided 0.935 g of white prisms (77%): mp 142-144 °C; $[\alpha]_D^{23}$ = +229° (*c* = 1.29, $CHCl_3$) (>99.5% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 94:6 hexane/2-propanol, flow rate 1.00 mL/min, λ = 295 nm, t_R = 11.9 min).

The ethanolic mother liquor afforded 1.06 g of white prisms (87%): mp 138-141 °C; $[\alpha]_D^{23}$ = -245° (*c* = 1.31, $CHCl_3$) (97% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 94:6 hexane/2-propanol, flow rate 1.00 mL/min, λ = 295 nm, t_R = 14.8 min).

Ligand 18.



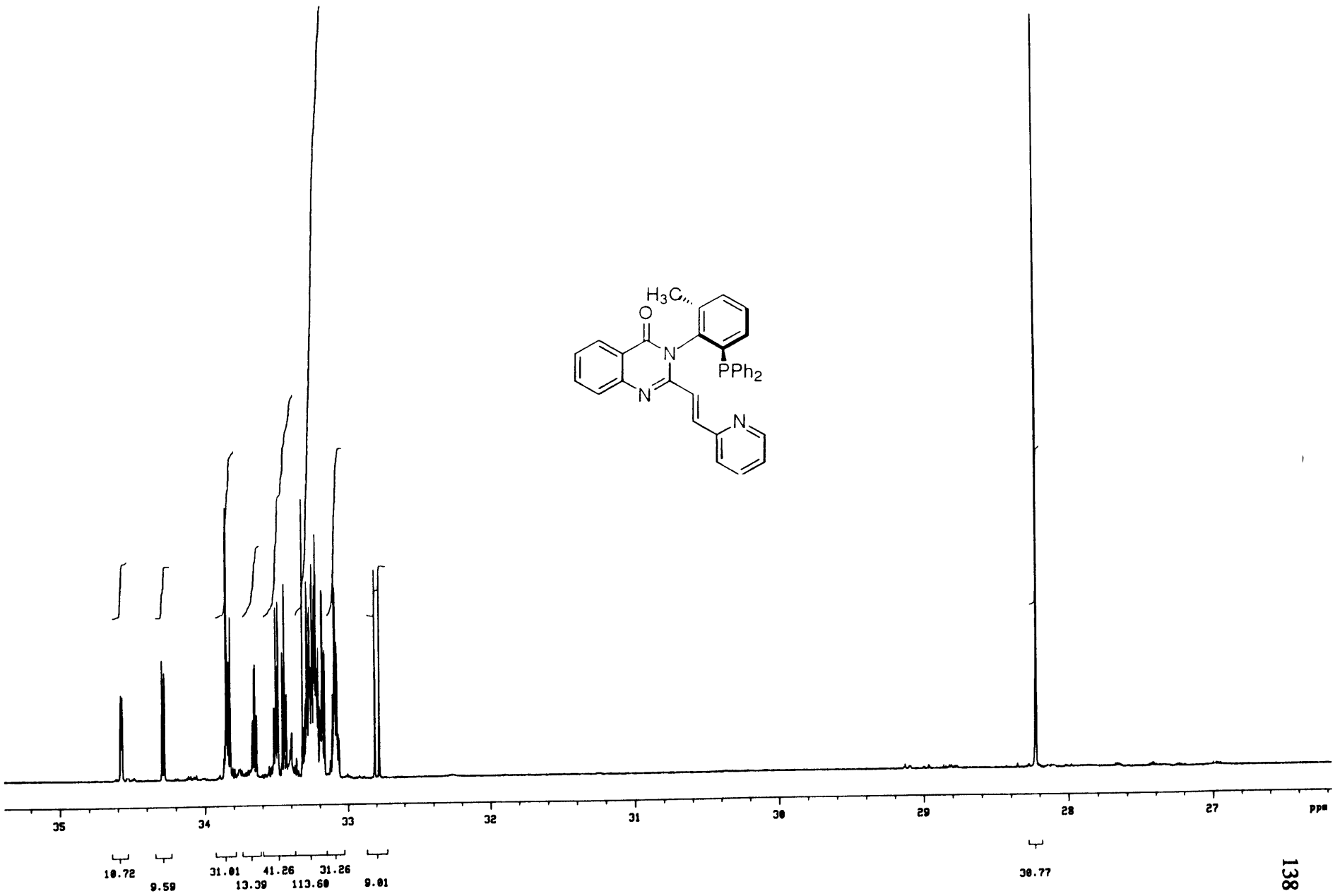
(*S*)-(+)-**1b**
$C_{28}H_{23}N_2OP$
MW: 434.48

C_6H_5NO
MW: 107.11

18
$C_{34}H_{26}N_3OP$
MW: 523.57

To a cold (-78 °C), magnetically stirred solution of ligand (*S*)-(+)-**1b** (298.7 mg, 0.687 mmol) in THF (10 mL) was added dropwise 0.825 mmol of *n*-BuLi (1.5 M in hexanes). The resulting dark red solution was stirred at -78 °C for 20 min, then allowed to warm up and stay at -15 °C for 20 min before cooled back to -78 °C. Neat 2-pyridinecarboxaldehyde was added dropwise. The resulting yellow solution was slowly warmed up to room temperature while stirring, quenched with cold saturated NH_4Cl, and diluted with ethyl acetate. The separated aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue on silica gel (1:3 ethyl acetate/hexane) followed by crystallization (1:3 ethyl acetate/hexanes) provided 280.7 mg (78%) of ligand **18** as off-white needles: mp 99-101 °C; *Rf* = 0.22 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3052, 1680, 1580, 1551, 1470, 1432, 1346, 1338, 777, 742, 696; $[\alpha]_D^{23}$ = -113° (*c* = 1.27, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (dd, 1H, *J* = 1.46, 4.88 Hz), 8.23 (d, 1H, *J* = 7.81 Hz), 7.75-7.81 (m, 3H), 7.58 (dt, 1H, *J* = 1.71, 7.69 Hz), 7.31-7.46 (m, 4H), 7.01-7.25 (m, 12?H), 6.75 (d, 1H, *J* = 15.14 Hz), 2.16 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 161.35 (C4), 159.03?, 153.65, 151.66, 149.83, 148.01, 140.72 (d, *J* = 25.28 Hz), 138.93, 137.66 (d, *J* = 13.2 Hz), 136.61 (d, *J* = 3.08 Hz), 136.31, 136.16 (d, *J* = 10.35 Hz), 135.26 (d, *J* = 12.15 Hz), 134.45, 134.31, 134.06, 133.60, 133.37, 132.49, 129.74, 128.74, 128.56, 128.38,

128.26, 127.59, 127.43, 126.55, 124.14, 123.52, 123.38, 121.33, 18.48. $^{31}P\{^{1}H\}$ NMR (121.4 MHz, $CDCl_3$): -16.91 (s); HRMS: 523.18143 (calcd for $C_{34}H_{26}N_3OP$ 523.18135).


H3C
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N
PPh2
N
N
35
34
33
32
31
30
29
28
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ppm
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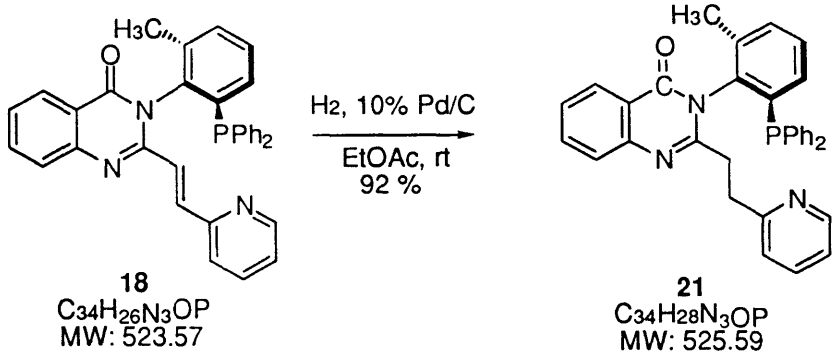
31.01
13.39
41.26
113.60
31.26
9.01
30.77

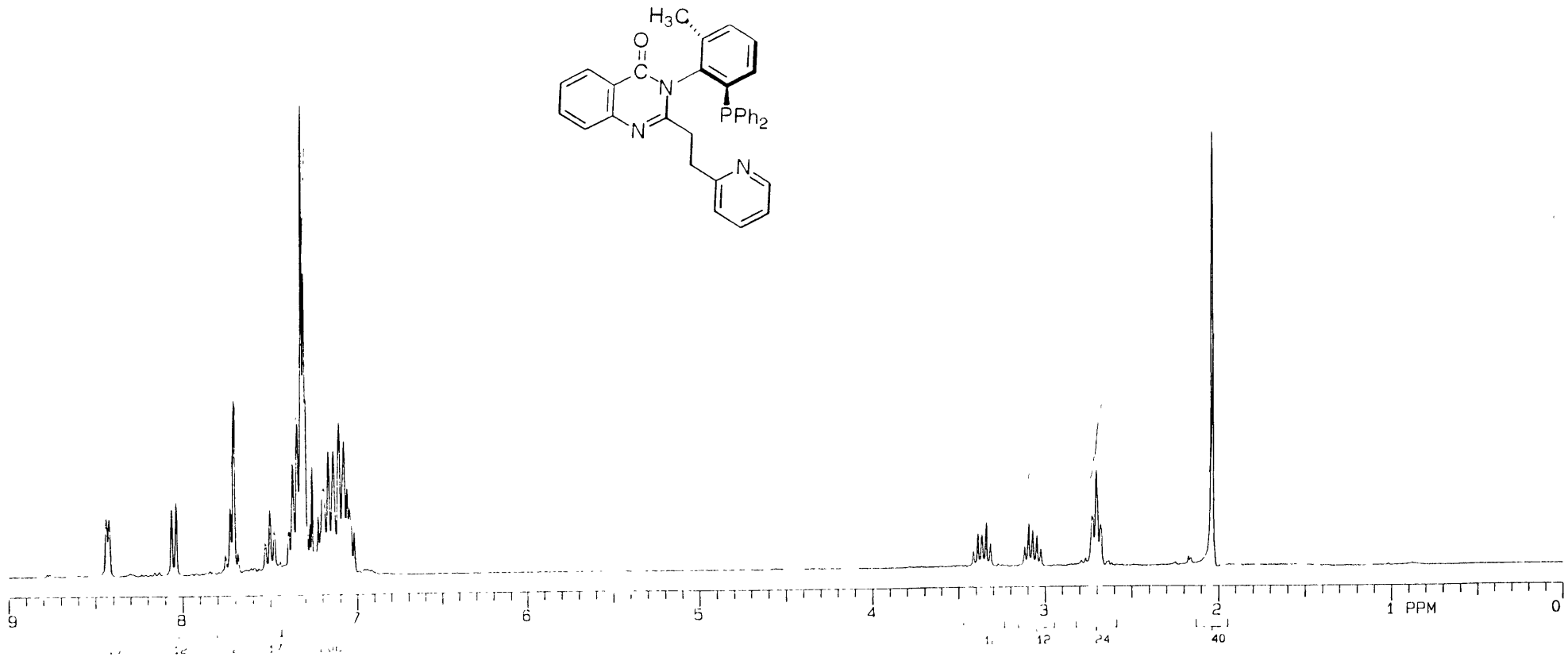
Ligand 21.



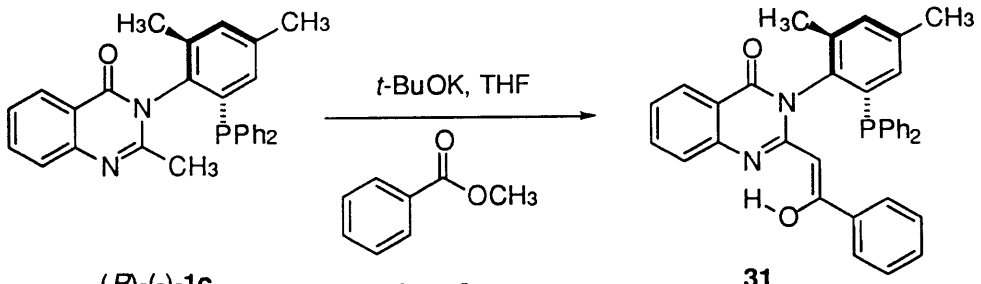
18
$C_{34}H_{26}N_3OP$
MW: 523.57

21
$C_{34}H_{28}N_3OP$
MW: 525.59

A solution of ligand **18** (200.0 mg, 0.382 mmol) in toluene and 60 mg of palladium on carbon (10%) were added to a hydrogenation flask. The mixture was stirred under hydrogen (40 psi) for 4 hours. The excess of toluene was evaporated. The residue was purified by flash chromatography to yield 184.7 mg (92%) of ligand **21** as a white solid: Rf = 0.21 (silica, 1:2 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, 1H, J = 1.46, 4.71 Hz), 8.43 (d, 1H, J = 7.65 Hz), 7.01-7.76 (m, 19H), 3.36 (ddd, 1H, J = 7.45, 7.45, 14.46 Hz), 3.08 (ddd, 1H, J = 6.89, 6.89, 14.70 Hz), 2.71 (t, 1H, J = 7.25 Hz), 2.70 (t, 1H, J = 7.25 Hz), 2.04 (s, 3H, CH_3).


H3C
O
C
N
N
PPh2
N
9
8
7
6
5
4
3
2
1 PPM
0
12
24
40

Ligand 31.

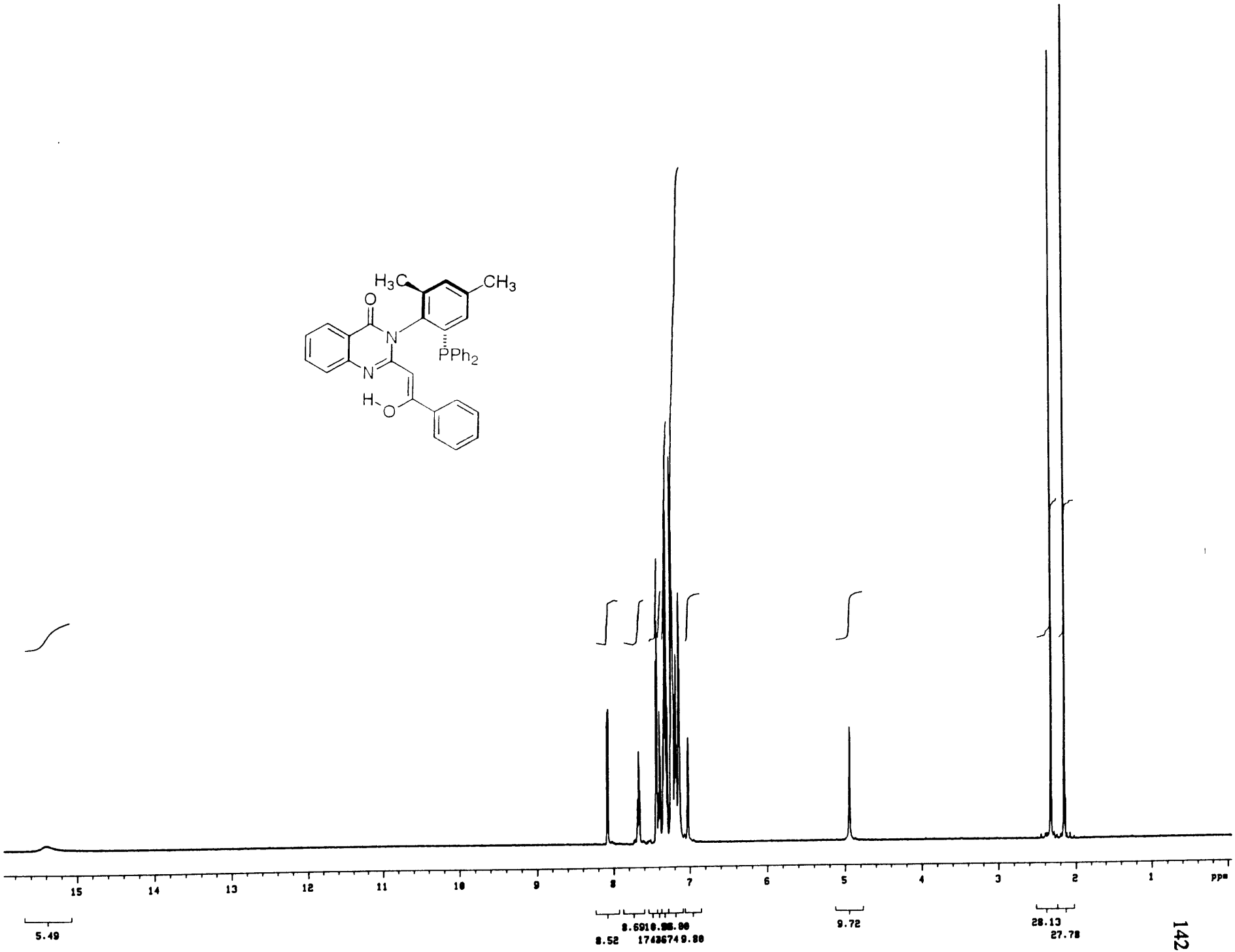


(*R*)-(-)-**1c**
$C_{29}H_{25}N_2OP$
MW: 448.50

$C_8H_8O_2$
MW: 136.15

31
$C_{36}H_{29}N_2O_2P$
MW: 552.61

The solution of ligand (*R*)-(-)-**1c** (800.0 mg, 1.78 mmol), *t*-BuOK (240.2 mg, 2.14 mmol), and methyl benzoate (0.28 mL, 2.25 mmol) in THF (20 mL) was heated to reflux for 18 h. The reaction mixture was concentrated and purified by flash chromatography to yield 946.3 mg (96%) of ligand **31** as a white solid: mp 163-165 °C; R_f = 0.43 (silica, 1:2 ethyl acetate/hexane); $[\alpha]_D^{23}$ = +275° (*c* = 0.56, $CHCl_3$); FTIR (thin film, cm^{-1}) 3051, 1696 (C=O), 1614, 1577, 1549, 1515, 1370, 1222, 1025, 741, 693, 626; ^1H NMR (300 MHz, $CDCl_3$) δ 15.41 (s, 1H, O*H*), 8.071 (br t, 2H, *J* = 8.0 Hz), 7.675 (br d, 1H, *J* = 7.7 Hz), 7.10-7.62 (m, 17H), 7.034 (br s, 1H), 4.934 (s, 1H), 2.331 (s, CH_3), 2.155 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 185.97, 159.92 (C4), 154.81 (C2), 139.84, 139.81, 139.41, 137.37, 137.25, 136.95, 136.80, 136.74, 136.27, 136.30, 136.03, 135.94, 135.52, 134.40, 134.34, 134.17, 133.81, 133.31, 133.16, 132.96, 130.95, 130.16, 129.67, 129.14, 128.63, 128.57, 128.46, 128.40, 128.39, 128.36, 128.25, 126.89, 123.97, 117.38, 116.77, 81.64, 21.58, 17.81 (d, *J* = 2.23 Hz); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -17.15 ppm (s); HRMS: 552.19648 (calcd for $C_{36}H_{29}N_2O_2P$ 552.19664).


H3C
CH3
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N
PPh2
N
H
O
15
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13
12
11
10
9
8
7
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5
4
3
2
1
ppm
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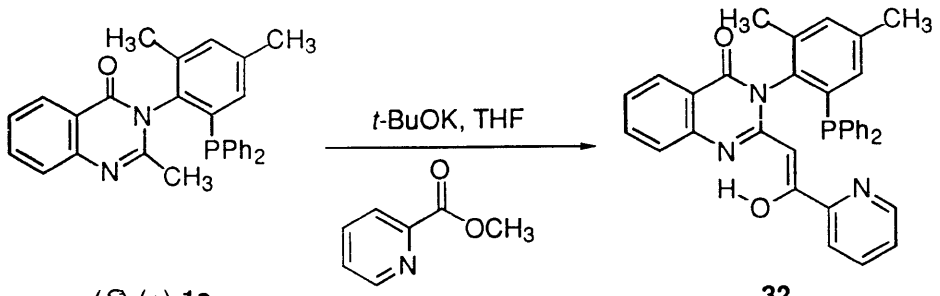
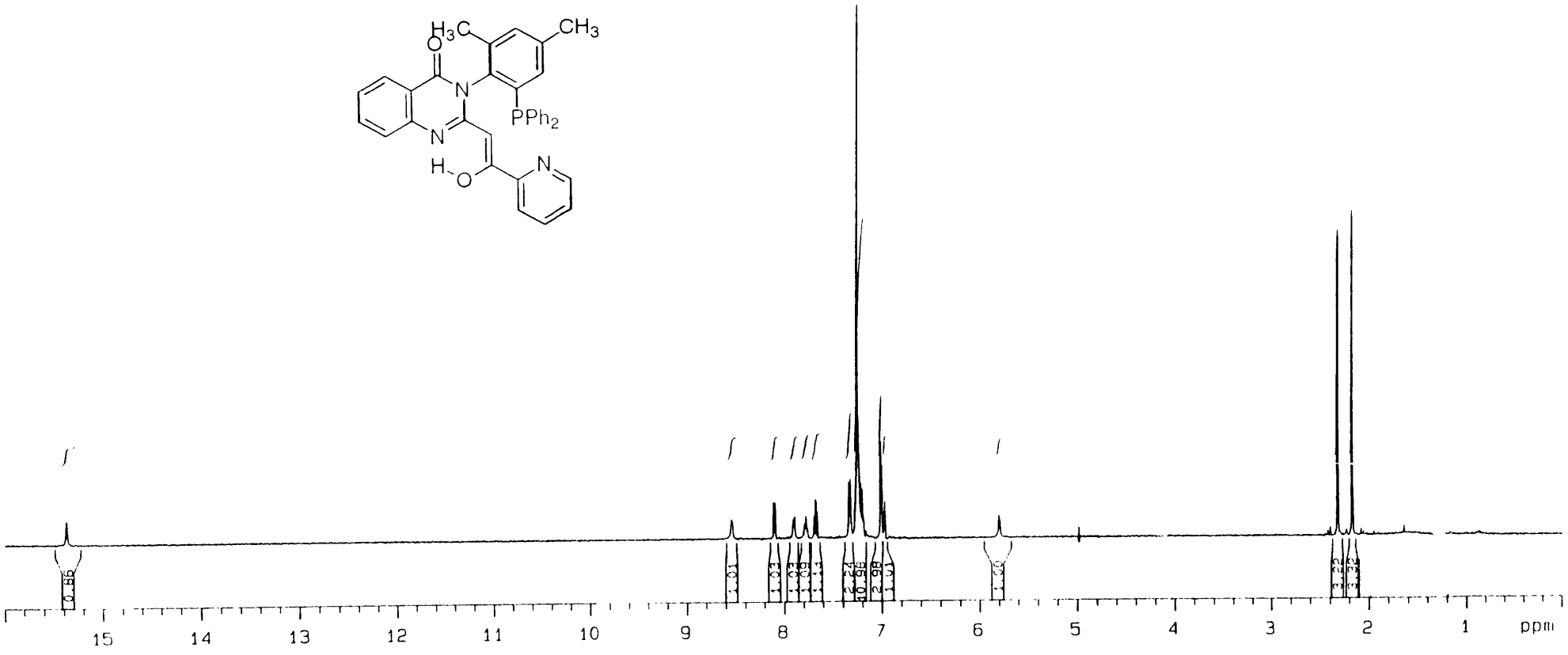
8.52
9.72
28.13
27.78

Ligand 32.



The solution of ligand (*S*)-(+)-**1c** (829.2 mg, 1.85 mmol), *t*-BuOK (249.0 mg, 2.22 mmol), and ethyl picolinate (0.31 mL, 2.23 mmol) in THF (20 mL) was heated to reflux for 3 h. The reaction mixture was concentrated and purified by flash chromatography to yield 991.0 mg (97%) of ligand **32** as a white solid: Rf = 0.23 (silica, 1:2 ethyl acetate/hexane); $[\alpha]_D^{23}$ = -205° (c = 1.02, $CHCl_3$); FTIR (thin film, cm^{-1}) 3051, 1695 (C=O), 1614, 1584, 1567, 1549, 1512, 1376, 1226, 1079, 768, 744, 695; ^1H NMR (500 MHz, $CDCl_3$) δ 15.41 (s, 1H), 8.50 (dd, 1H, J = 0.73, 4.76 Hz), 8.11 (dd, 1H, J = 1.28, 7.87 Hz), 7.96 (td, 1H, J = 1.10, 8.06 Hz), 7.76 (dt, 1H, J = 1,83, 7.69 Hz), 7.68 (ddd, 1H, J = 1.47, 7.33, 8.06 Hz), 7.34 (d, 2H, J = 7.78 Hz), 7.21-7.32 (m, 8H), 6.97-7.05 (m, 4H), 5.88 (s, 1H), 2.33 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 183.74, 159.80, 155.21, 155.12, 148.59, 139.77, 139.61, 137.10, 137.04, 136.84, 136.74, 136.58, 136.44, 136.17, 136.13, 136.05, 135.41, 134.54, 133.97, 133.89, 133.69, 133.58, 133.34, 128.57, 128.39, 128.32, 128.30, 128.25, 128.22, 128.16, 128.13, 128.10, 125.04, 124.05, 121.25, 117.36, 116.91, 81.97, 21.74, 18.10; $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): -16.90 (s); HRMS (EI) calcd for $C_{28}H_{23}N_2OP$ 553.1919, found 553.1917.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1.03
1.03
1.09
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1.66
3.32
3.32
3.32
15
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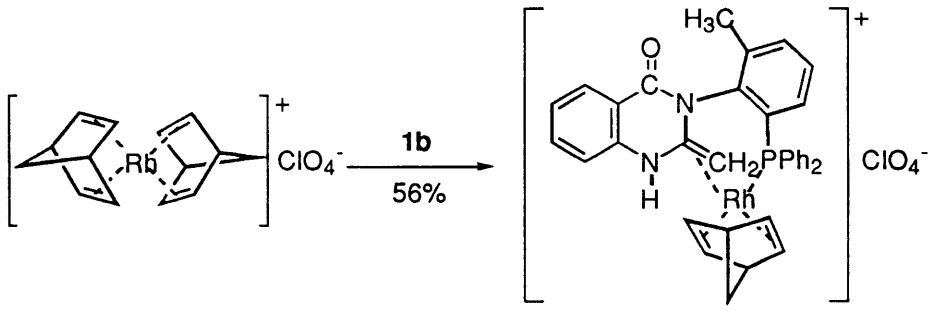
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Rhodium Complex 25b



24

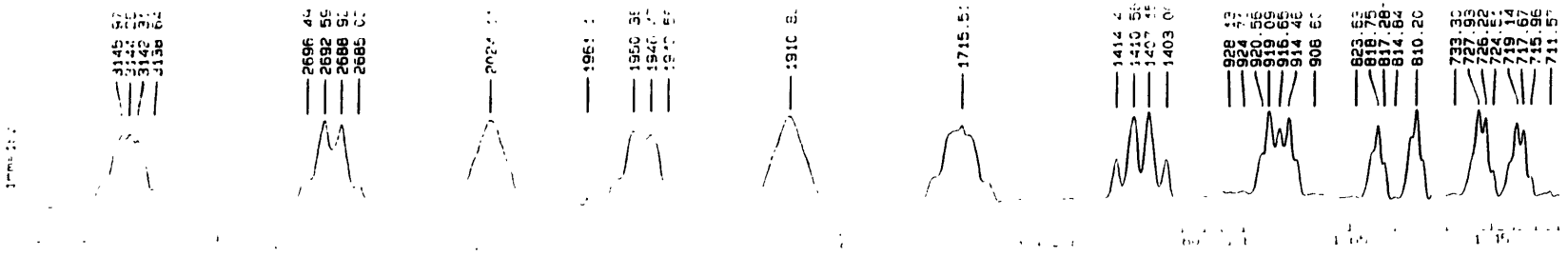
$C_{14}H_{16}ClO_4Rh$
MW 386.64

25b

$C_{35}H_{31}ClN_2O_5PRh$
MW 728.98

A CH_2Cl_2 solution of Rh complex **24** (155.0 mg, 0.40 mmol)) and ligand **1b** (174.0 mg, 0.40 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 kept at 0 °C for two days. The product **25b** was collected as yellow powder (228.6 mg, 56%) by filtration under a stream of nitrogen over $MgSO_4$ followed by solvent evaporation: FTIR ($CDCl_3$, cm^{-1}) 3378, 3063, 2983, 2930, 1677, 1604, 1566; ^1H NMR (300 MHz, $CDCl_3$) 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, 1H, J = 3.9 Hz), 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 (75 MHz, $CDCl_3$) δ_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, 129.76, 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. $^{31}P\{^{1}H\}$ NMR (121.4 MHz, $CDCl_3$): δ 30.3 (d, $J_{Rh\text{-}P}$ = 172.6 Hz).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1403
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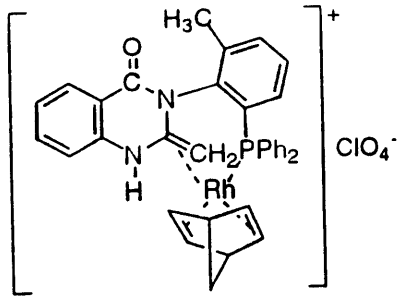
717
715
711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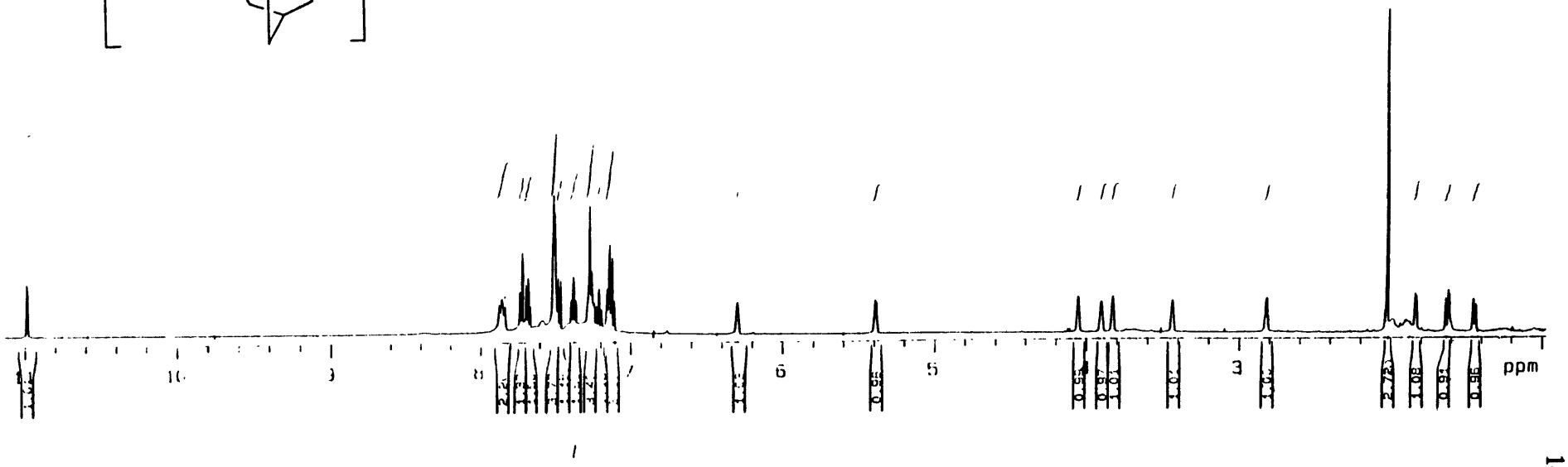
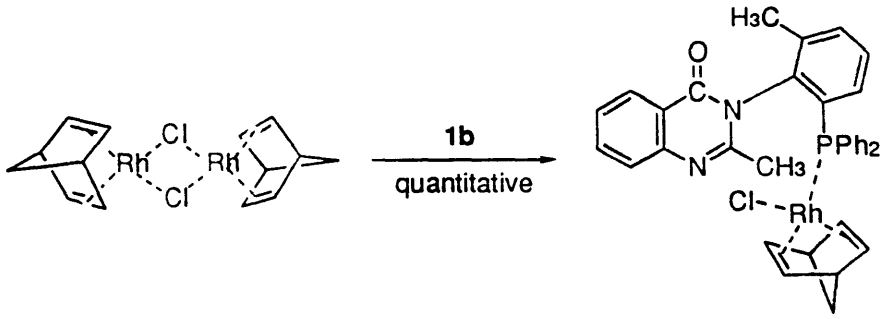

ppm

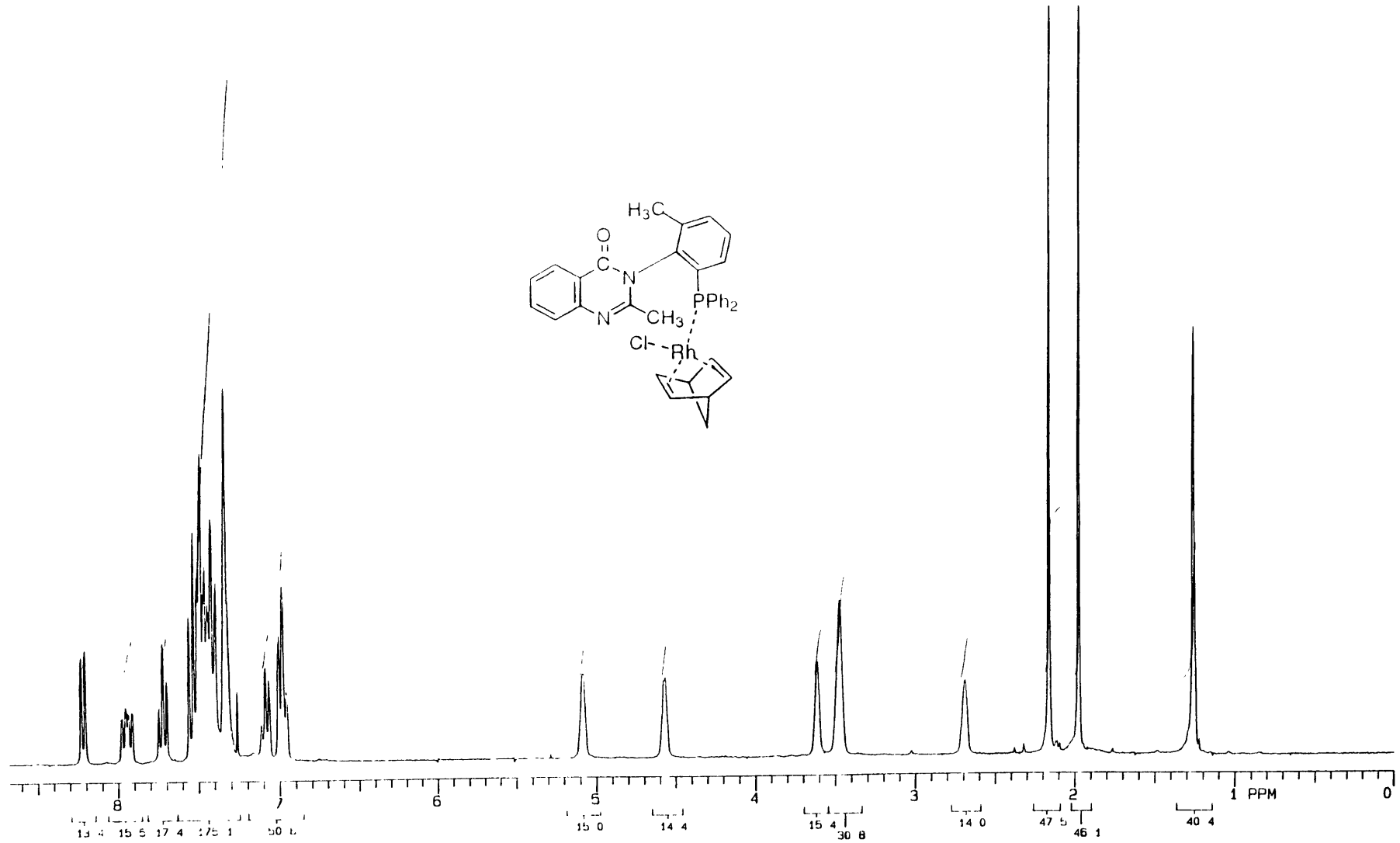
Rhodium Complex 27.



26
$C_{14}H_{16}ClO_4Rh$
MW 461.00

27
$C_{35}H_{31}ClN_2OPRh$
MW 664.98

Complex **27** was obtained in quantitative yield base on ^1H NMR analysis by mixing ligand **1b** (38.5 mg, 0.089 mmol.) with complex **26** (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).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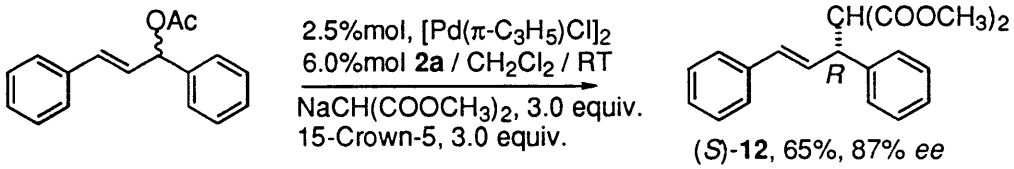
PPh2
N
CH3
Cl
Rh
8
7
6
5
4
3
2
1 PPM
0
15 0
14 4
15 4
30 8
14 0
47 5
46 1
40 4

Catalytic Reactions.

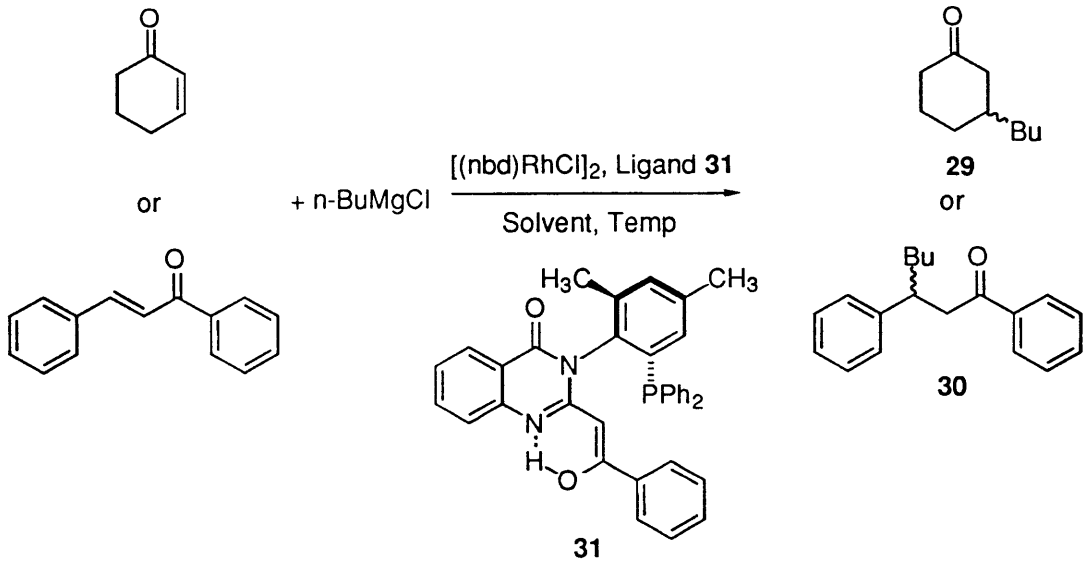
Palladium-Catalyzed Asymmetric Allylic Alkylation.

Substrate 1,3-diphenyl-2-propen-1-yl acetate was synthesized according to literature procedure.[51]



A representative experimental procedure for asymmetric allylic alkylation is as follows (Table 3, entry 6): A mixture of [Pd(π-ally)Cl]$_2$ (3.7 mg, 0.010 mmol) and (*S*)-(-)-**18** (12.8 mg, 0.0248 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 30 min. A solution of substrate 1,3-diphenyl-2-propen-1-yl acetate (100.9 mg, 0.40 mmol) in CH_2Cl_2 (1 mL) was added followed by a solution of dimethyl malonate (0.137 mL, 1.20 mmol), NaH (28.8 mg, 1.2 mmol), and 15-crown-5 (0.238 mL, 1.2 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 36 h. After the solvent was evaporated in vacuo, column chromatography on silica gel (1:10 ethyl acetate/hexane with 1% Et_3N) gave 84.3 mg (65%) of product. The optical purity was determined to be 87% ee by HPLC analysis (Daicel Chiralcel OD column, flow rate 0.2 mL/min, 98:2 hexane/2-propanol, λ = 295 nm).

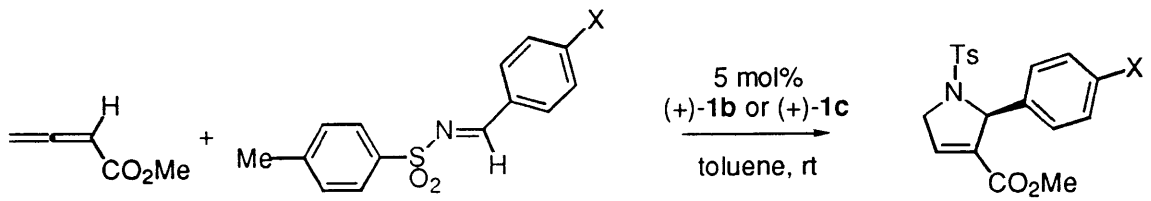
Rh complex Catalyzed Conjugate Addition.



A representative experimental procedure for rhodium-catalyzed conjugate addition is as follows (Table 4, entry 3): A mixture of $[(nbd)RhCl]_2$ (16.3 mg, 0.035 mmol) and (*S*)-(-)-**31** (39.1 mg, 0.071 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 15 min. To the resulting yellow solution was added 0.04 mL of *n*-BuMgCl (2 M in ether) followed by a solution of 2-cyclohexen-1-one (136.5 mg, 1.42 mmol) in CH_2Cl_2 (2 mL). To the above mixture was added 0.71 mL of *n*-BuMgCl (0.04 mL, 2 M in ether) dropwise. The reaction mixture was stirred at 0 °C for 2 h before quenched with cold saturated aqueous NH_4Cl, and diluted with ether. The separated aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue on silica gel (1:5 ether/hexane) provided 168.65 mg as clear oil with strong smell. The optical purity was determined to be 9.0% ee by ^{13}C NMR analysis of the cyclic aminal formed by mixing product with (*R*,*R*)-1,2-diphenylethylenediamine in the NMR tube.[67]

[3+2] Cycloaddition

Methyl 2,3-butadienoate and *N*-sulfonimines were prepared following reported methods.[103]



39 **40**: X = H; **41**: X = OCH_3 **42**: X = H; **43**: X = OCH_3

A representative experimental procedure is as follows (Table 5, entry 2):

A solution of methyl 2,3-butadienoate (107.9 mg, 1.10 mmol), *N*-toluenesulfonyl benzaldimine (259.3 mg, 1.00 mmol), and ligand (*S*)-(+)-**1c** (22.4 mg, 0.05 mmol) in toluene was stirred at room temperature for four days to afford cycloaddition product **42** in 69% yield and 11% ee (determined by ^{1}H NMR analysis using chiral shift reagent Eu(hfc)$_3$, and by HPLC using a Chiralcel OJ column. 75:25 Hexane:*i*-PrOH, 1.0 mL/min, 34.9 min (major), 49.8 min (minor); $[\alpha]_D^{23}$ = -21.3° (*c* = 5.88, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2H, *J* = 8.30 Hz), 7.20-7.25 (m, 5H), 7.14 (d, 2H, *J* = 8.30 Hz), 6.77 (q, 1H, *J* = 1.95 Hz), 5.73 (td, 1H, *J* = 1.71, 5.86 Hz), 4.50 (td, 1H, *J* = 2.44, 17.09 Hz), 4.38 (ddd, 1H, *J* = 1.83, 5.74, 17.21 Hz), 3.58 (s, 3H), 2.36 (s, 3H).

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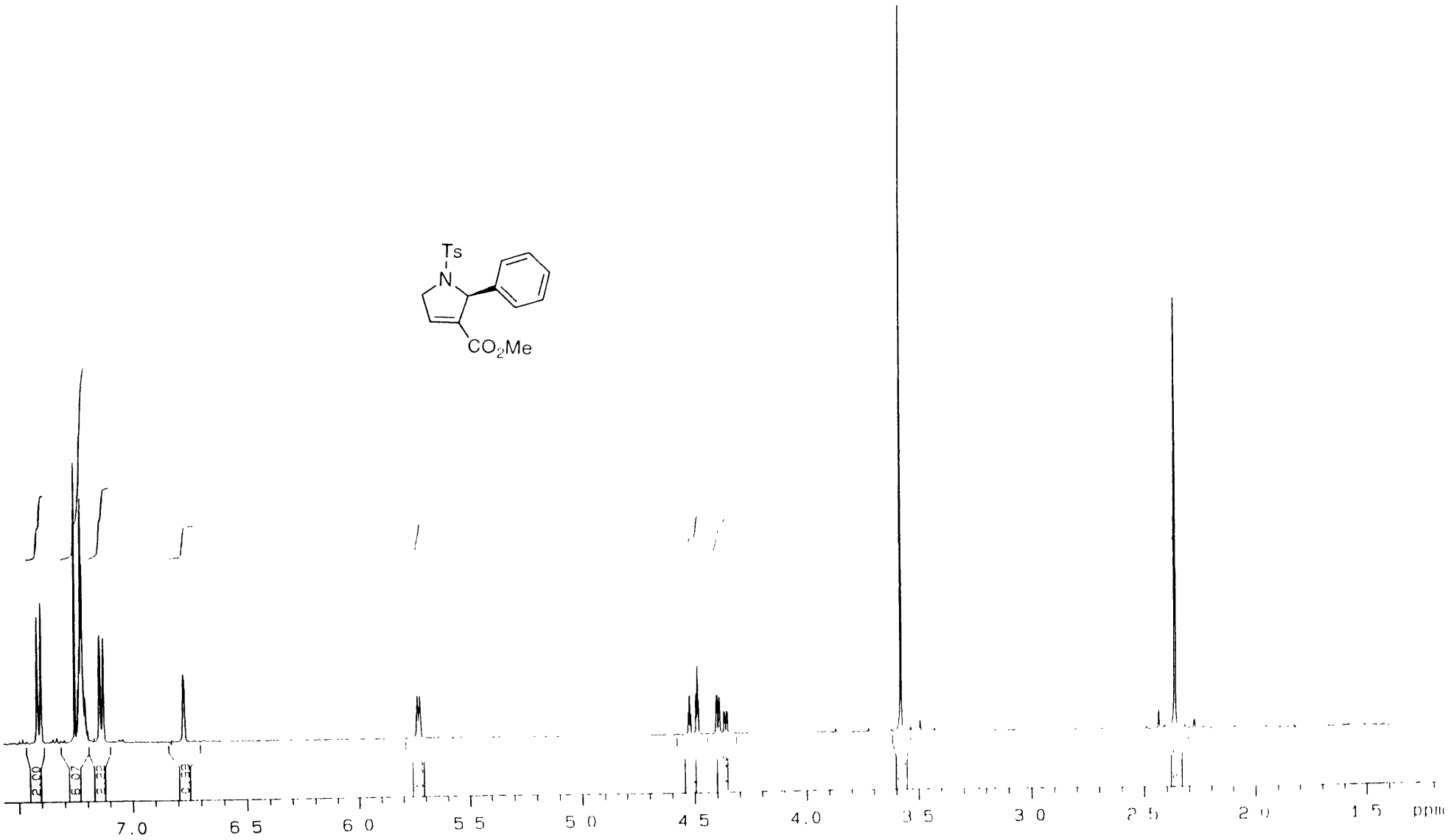
[103] For methyl 2,3-butadienoate: Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, *62*, 202. For *N*-sulfonimines: (a) Davis, F. A.; Lamendola, J. Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R. Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000-2004. (b) Trost, B. M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468-6470.

Product **43** was obtained from methyl 2,3-butadienoate (107.9 mg, 1.10 mmol), *N*-toluenesulfonyl benzaldimine (289.4 mg, 1.00 mmol), and ligand (*S*)-(+)-**1c** (22.4 mg, 0.05 mmol) under conditions analogous to the reaction producing **42**: 63%, 11.5% ee (determined by ^{1}H NMR analysis using chiral shift reagent Eu(hfc)$_3$, $[\alpha]_D^{23}$ = -22.1° (*c* = 1.01, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2H, *J* = 8.30 Hz), 7.15 (d, 2H, *J* = 7.82 Hz), 7.13 (d, 2H, *J* = 8.64 Hz); 6.72-6.79 (m, 3H); 5.70 (td, 1H, *J* = 1.71, 5.21 Hz); 4.48 (td, 1H, *J* = 2.44, 17.11 Hz); 4.36 (ddd, 1H, *J* = 1.96, 5.74, 17.21 Hz); 3.78 (s, 3H); 3.59 (s, 3H); 2.37 (s, 3H).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N
CO2Me
2.00
6.07
2.35
2.35
7.0
6.5
6.0
5.5
5.0
4.5
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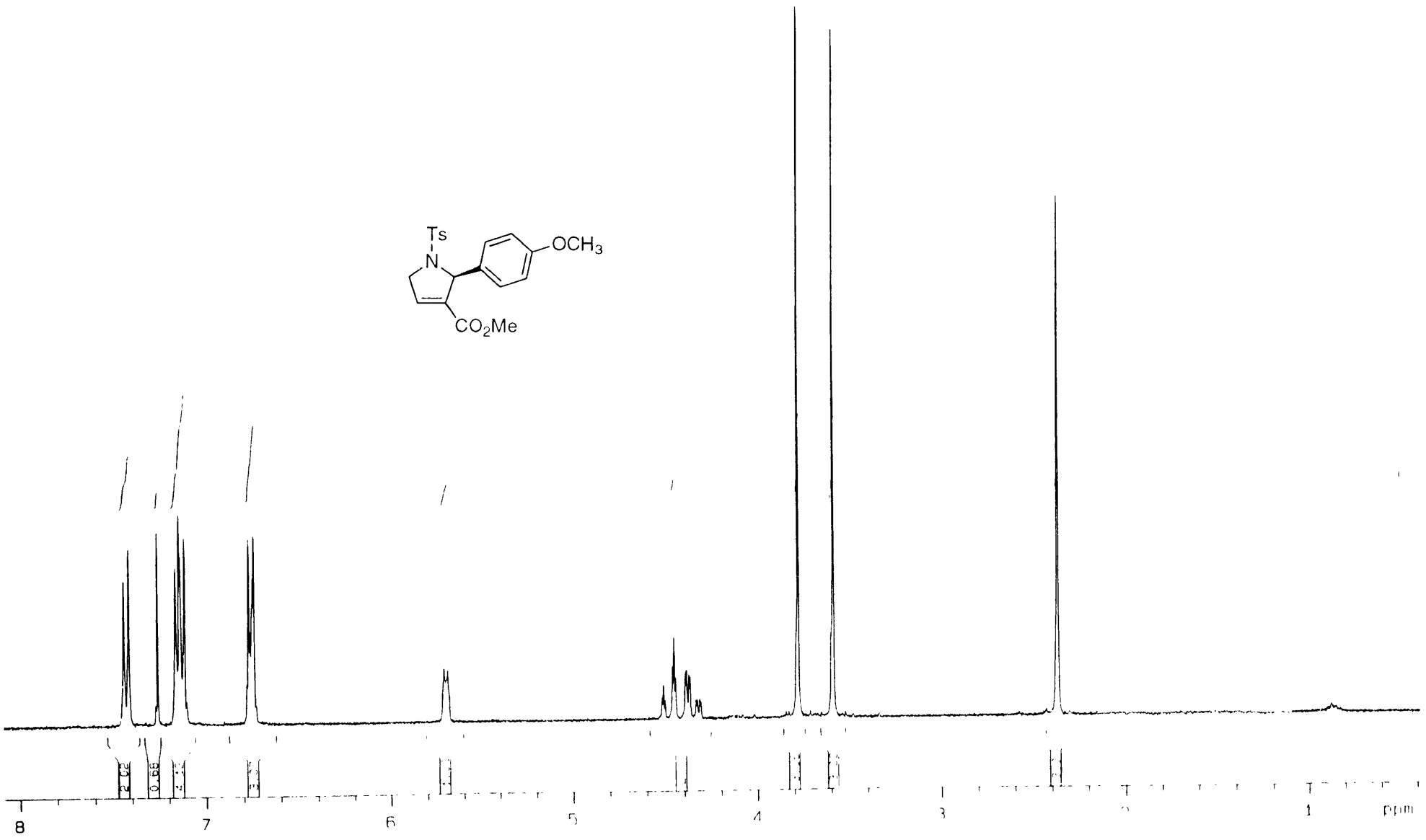
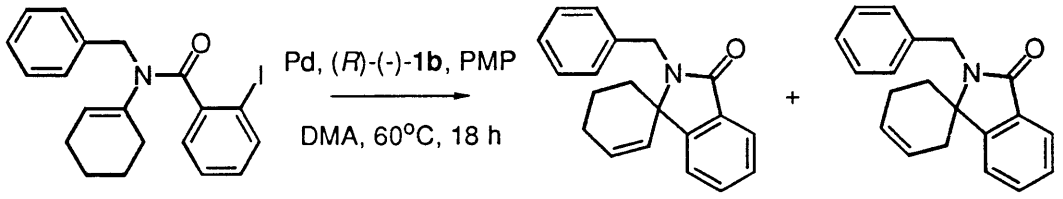
3.5
3.0
2.5
2.0
1.5
ppm


Ts
N
OCH3
CO2Me
8
7
6
5
4
3
2
1
ppm

Intramolecular Heck Reaction



58
$C_{20}H_{20}INO$
MW: 417.29

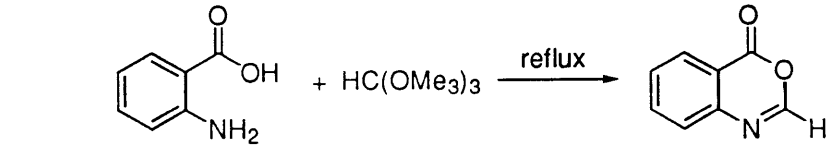
59
$C_{20}H_{19}NO$
MW: 289.38

60
$C_{20}H_{19}NO$
MW: 289.38

A representative experimental procedure is as follows (Table 6, entry 7):

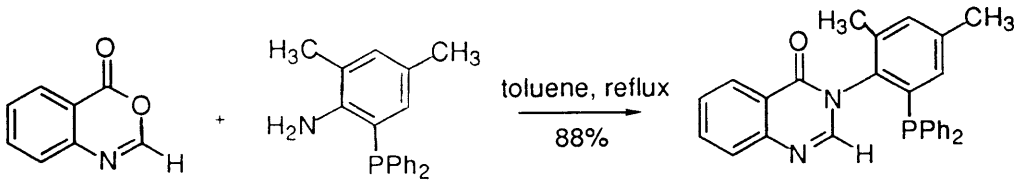
A mixture of $Pd(OAc)_2$ (6.1 mg, 0.027 mmol) and (*R*)-(-)-**1b** (47.0 mg, 0.108 mmol) in *N*,*N*-dimethylacetamide (DMA, 3 mL) was stirred at room temperature for 1 h. A solution of substrate **58** (112.8 mg, 0.27 mmol) and 1,2,2,6,6-pentamethylpiperidine (PMP, 0.24 mL, 1.35 mmol) in DMA (5 mL) was added. The resulting mixture was stirred at 60 °C for 18 h, diluted with ether (20 mL), and then washed with aqueous saturated $NaHCO_3$ (10 mL). The aqueous layer was further extracted with ether (2x10 mL), and the combined extracts were washed with brine (10 mL) and dried ($MgSO_4$). Removal of solvent followed by column chromatography on silica gel (1:8 ethyl acetate/hexane) gave 48.5 mg (62%) of **59** (26.3% ee) and 24.2 mg(31%) of **60** (19% ee). The ^1H NMR spectroscopic data of compound **59** and **60** are identical to the reported ones.[78b]

3-[4',6'-Dimethyl-2'-(diphenylphosphino)phenyl)-4(3*H*)-quinazolinone (1d).



3
$C_7H_7NO_2$
MW: 137.14

71
$C_8H_5NO_2$
MW: 147.13



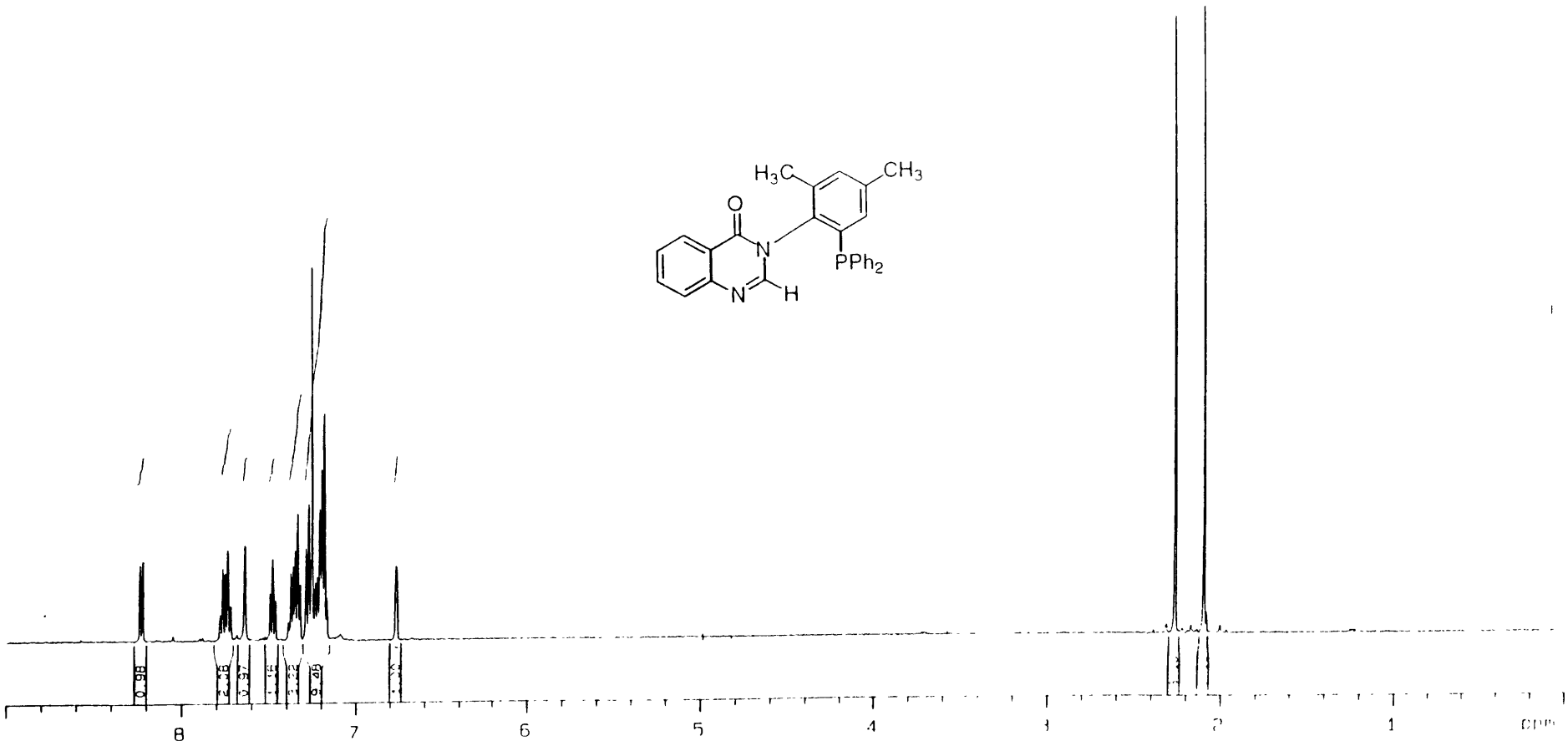
71
$C_8H_5NO_2$
MW: 147.13

4c
$C_{20}H_{20}NP$
MW: 305.36

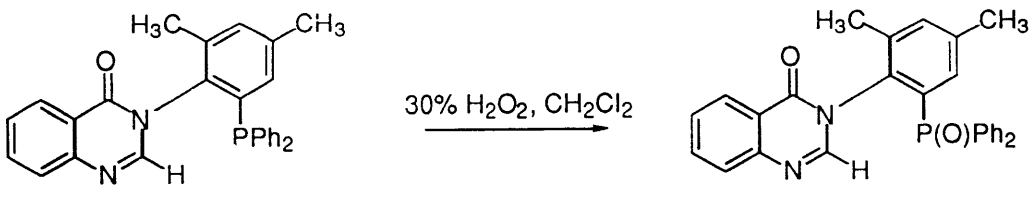
1d
$C_{28}H_{23}N_2OP$
MW: 434.476

A mixture of anthranilic acid (27.0 g, 0.197 mol) and trimethyl orthoformate (75.0 mL, 0.686 mol) was heated at reflux for 3 h. The excess of orthoformate and the resulting methanol were removed by distillation. To the crude hygroscopic 4*H*-3,1-benzoxazin-4-one (**71**) was added a solution of phosphine **4c** (20.0 g, 0.0655 mol) in toluene. The mixture was heated to reflux for 6 h. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ to remove anthranilic acid followed by brine. The separated organic layer was dried ($MgSO_4$), and evaporated followed by crystallization (8:1 acetone/water) to afford 25.0 g (88%) of ligand HQ as white needles: mp 140-142 °C; *Rf* = 0.38 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3049, 1686, 1607, 1471, 1434, 1289, 1272, 909, 775, 744, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, 1H, *J* = 1.4, 7.9 Hz), 7.76 (ddd, 1H, *J* = 1.5, 6.8, 8.3 Hz), 7.70 (dd, 1H, *J* = 1.8, 8.2 Hz), 7.62 (d, 1H, *J* = 1.6 Hz), 7.47 (ddd, 1H, *J* = 1.7, 6.7, 7.9 Hz), 7.17-7.40 (m, 11H), 6.80 (dd, 1H, *J* = 2.2, 3.2 Hz), 2.27 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) 160.29, 148.14 , 146.86 (d, J = 2.3 Hz), 139.79, 137.99, 137.80, 137.21, 137.09, 136.45 (d, J = 2.75 Hz), 135.32, 135.24, 134.52, 134.40, 134.35, 134.05, 133.89, 133.01, 132.87, 129.54, 129.17, 128.99, 128.92, 128.86, 128.49, 128.43, 127.54, 127.41, 127.19, 122.71, 21.45, 18.03 (d, $^4J_{CP}$ = 1.8 Hz, C6'*Me*); $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): -15.1 (s); HRMS 434.15476 (calcd for $C_{28}H_{23}N_2OP$ 434.15480)


H3C
CH3
O
N
PPh2
N
H
0.98
2.46
0.97
1.15
1.22
0.95
3.44
8
7
6
5
4
3
2
1
ppm

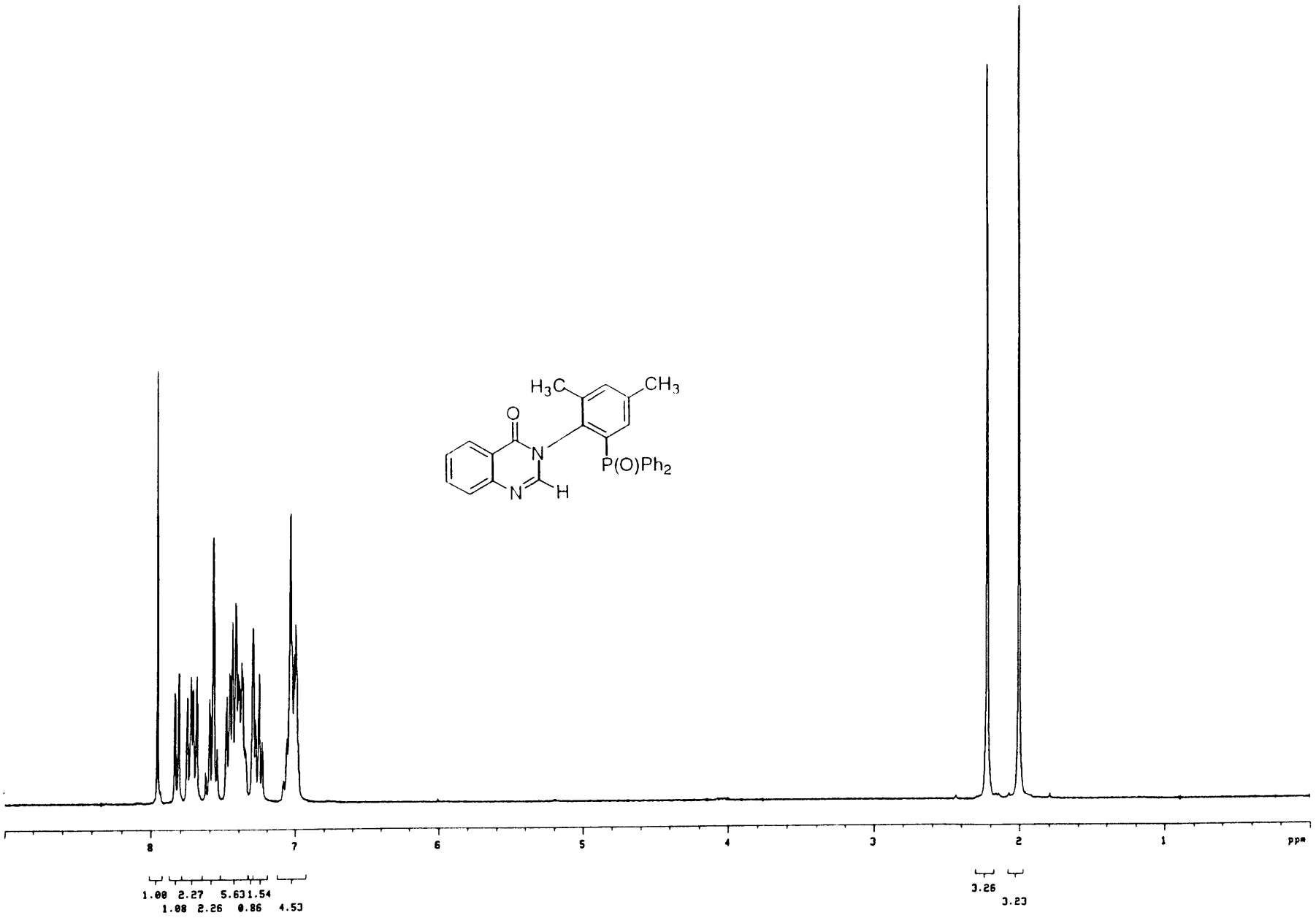
Phosphine oxide 75.



1d
$C_{28}H_{23}N_2OP$
Mol. Wt.: 434.48

75
$C_{28}H_{23}N_2O_2P$
Mol. Wt.: 450.48

To a solution of ligand **1d** (2.00 g, 4.6 mmol) in CH_2Cl_2 (10 mL) was added 2 mL of 30 wt. % aqueous H_2O_2 dropwise. The reaction mixture was stirred at room temperature for 30 min, diluted with CH_2Cl_2 (10 mL), and washed with brine (10 mL). The separated organic layer was dried ($MgSO_4$) and evaporated to afford 2.03 g (98%) of **75** as white solid: mp 225-227 °C; Rf = 0.37 (silica, ethyl acetate); FTIR (thin film, cm^{-1}) 3054, 1684, 1609, 1472, 1438, 1272, 1189, 1116, 722, 697; ^1H NMR δ 8.02.96 (s, 1H), 7.89 (dd, 1H, J = 1.22, 7.58 Hz), 7.74-7.83 (m, 2H), 7.59-7.70 (m, 2H), 7.40-7.57 (5H), 7.28-7.40 (m, 2H), 7.02-7.16(m, 4H), 2.32 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ_c 159.88, 147.89, 146.96, 139.47, 139.31, 138.54, 138.44, 136.69, 136.64, 135.85, 134.07, 132.85, 132.72, 132.41, 132.18, 132.03, 131.91, 131.60, 131.22, 131.08, 130.78, 130.22, 128.60, 128.44, 127.95, 127.78, 127.25, 126.79, 126.50, 121.82, 21.21, 17.76; ^{31}P $\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): δ_p 26.67 ppm; HRMS (FAB, 3-Nitrobenzyl alcohol) 450.1495 (calcd for $C_{28}H_{23}N_2O_2P$ 450.1497).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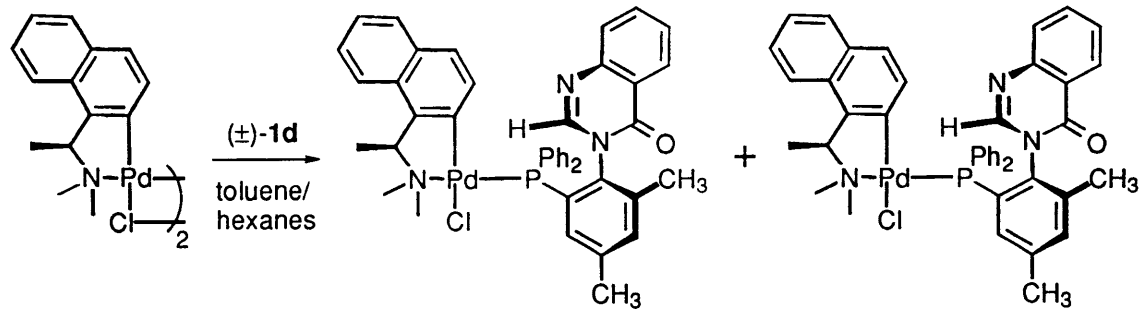
CH3
O
N
P(O)Ph2
N
H
8
7
6
5
4
3
2
1
ppm
1.00 2.27 5.63 1.54
1.08 2.26 0.86 4.53
3.26
3.23

Resolution of Ligand 1d Using (-)-Di-μ-chloro-bis[(*S*)-dimethyl-(1-naphthylethyl)aminato-C^2, *N*]dipalladium(II) (78).



(*S*)-**78**
$C_{28}H_{32}Cl_2N_2Pd_2$
MW: 680.29

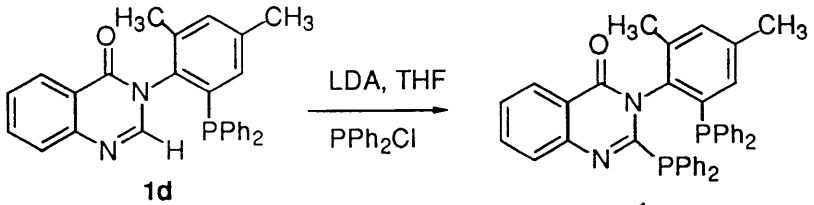
(*S,R*)-**79**
$C_{42}H_{39}ClN_3OPPd$
MW: 914.76

(*S,R*)-**80**
$C_{42}H_{39}ClN_3OPPd$
MW: 914.76

To a solution of complex **78** (0.500 g, 0.735 mmol) in toluene (60 mL) was added **1d** (1.28 g, 2.94 mmol) and the solution was stirred for 4 hours at ambient temperature. The mixture was treated with hexane (50 mL) and stored at 0 °C overnight. The yellow wax of (*S, R*)-**79** was separated from the mother liquor, treated with ethylenediamine (0.197 mL, 1.72 mmol) in CH_2Cl_2 (20 mL), followed by filtration and crystallization from CH_2Cl_2/hexanes (1:6) solvent mixture to give 0.179 g (28%) of free ligand (*R*)-(-)-**1d** as white needles: mp 168-170 °C; $[\alpha]_D^{23}$ = -189° (*c* = 1.09, $CHCl_3$), (99% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.50 mL/min, λ = 295 nm, t_R = 32.4 min).

The mother liquor was concentrated followed by crystallization from CH_2Cl_2/hexanes (1:6) solvent mixture to afford 0.154 g of (*S*)-(+)-**1d** (24%): mp 169.5-170.5 °C; $[\alpha]_D^{23}$ = +204° (*c* = 1.01, $CHCl_3$), (>99.5% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.50 mL/min, λ = 295 nm, t_R = 17.8 min).

2-Diphenylphosphino-3-[4',6'-dimethyl-2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1e).

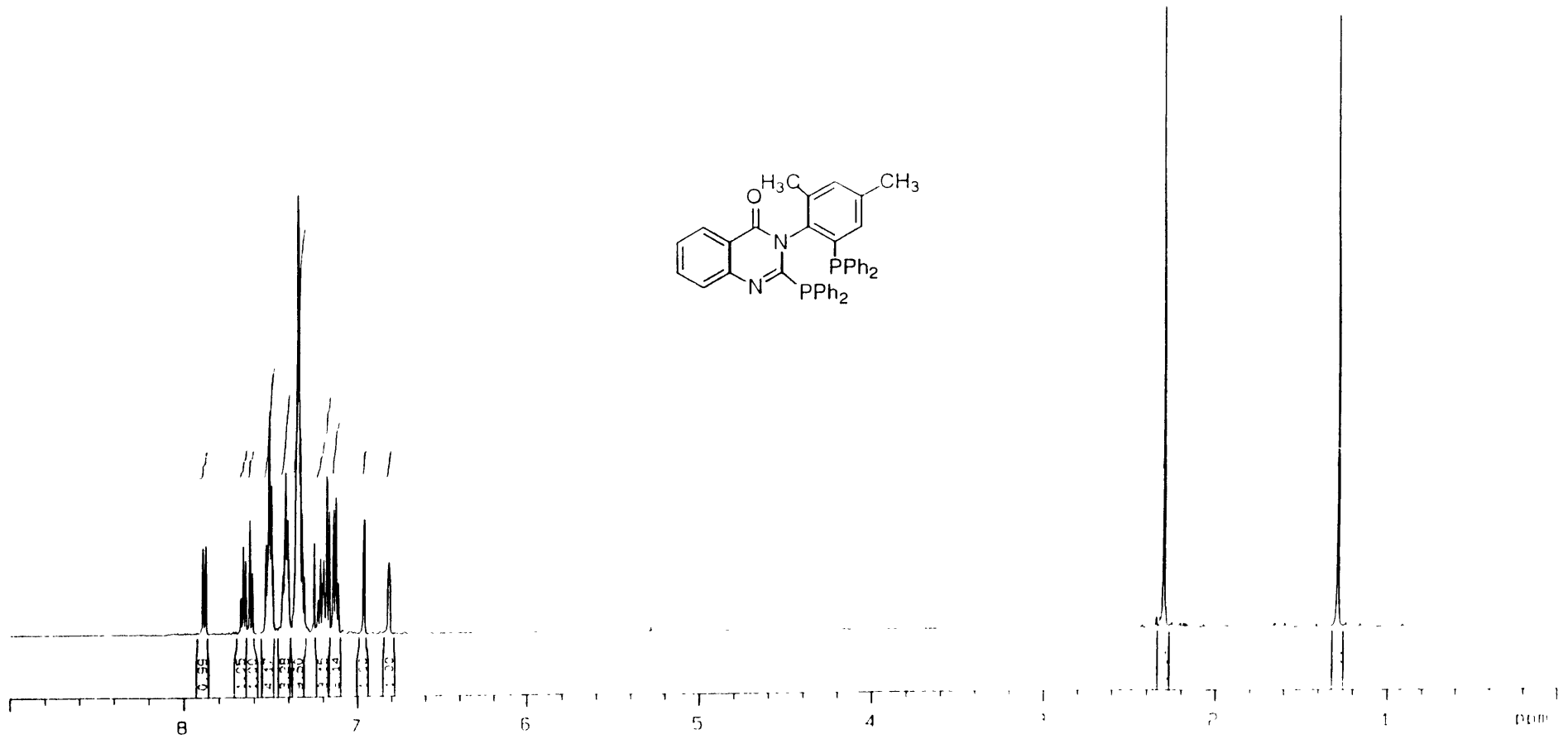


1d
$C_{28}H_{23}N_2OP$
Mol. Wt.: 434.48

1e
$C_{40}H_{32}N_2OP_2$
Mol. Wt.: 618.65

To a cold (-78 °C), magnetically stirred solution of ligand **1d** (3.00 g, 6.9 mmol) in THF (30 mL) was added dropwise 8.25 mL of LDA (1.0 M). After stirring at the same temperature for 0.5 h, the resulting orange solution was treated with 1.49 mL of PPh_2Cl (8.3 mmol). The reaction mixture was stirred for another one hour before allowed to warm up slowly to room temperature, quenched with a cold saturated ammonium chloride solution, and diluted in CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), passed through a short silica gel column, and evaporated. Crystallization from CH_2Cl_2 /hexane afforded 3.75 g (88%) of ligand 1e as white needles: mp 238-241 °C; *Rf* = 0.58 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3051, 1687, 1542, 1468, 1434, 1246, 1193, 742, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, 1H, *J* = 1.5, 7.8 Hz), 7.77 (ddd, 1H, *J* = 1.5, 7.1, 8.1 Hz), 7.62 (dd, 1H, *J* = 1.2, 8.1 Hz), 7.46-7.55 (m, 4H), 7.30 - 7.45 (m, 12H), 7.10 - 7.38 (m, 5H), 6.97 (d, 1H, *J* = 1.5 Hz), 6.82 (dd, 1H, *J* = 2.0, 3.4 Hz), 2.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 162.49 (d, *J* = 8.2 Hz), 160.66, 147.68 (d, *J* = 1.8 Hz) , 139.56, 138.29 (dd, *J* = 2.0, 3.6 Hz), 137.83 (dd, *J* = 4.6, 10.1 Hz), 137.20 (dd, *J* = 3.7, 21.5 Hz), 136.50, 136.40, 136.31, 136.27, 136.20, 135.07, 134.89, 134.43 (dd, *J* = 2.4, 9.6 Hz), 133.93, 133.91, 133.86, 133.78, 133.76, 133.34 (dd, *J* = 2.3, 18.3 Hz), 132.67, 132.60, 132.43 (dd, *J* = 6.0,

11.9 Hz), 130.62, 129.20, 128.82, 128.75, 128.64, 128.59, 128.31, 128.21, 128.15, 127.99, 127.97, 127.93, 126.96, 126.77, 121.52, 120.14, 21.62, 17.00 (d, $^4J_{CP}$ = 2.3 Hz, C6'*Me*); ^{31}P {^1H} NMR (202.3 MHz, $CDCl_3$): -2.16 (d, *J* = 71.38 Hz), -12.70 (d, *J* = 71.38 Hz); HRMS 618.19810 (calcd for $C_{40}H_{32}N_2OP_2$ 618.19899)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CH3
N
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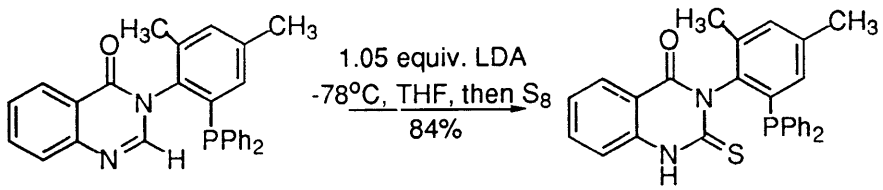
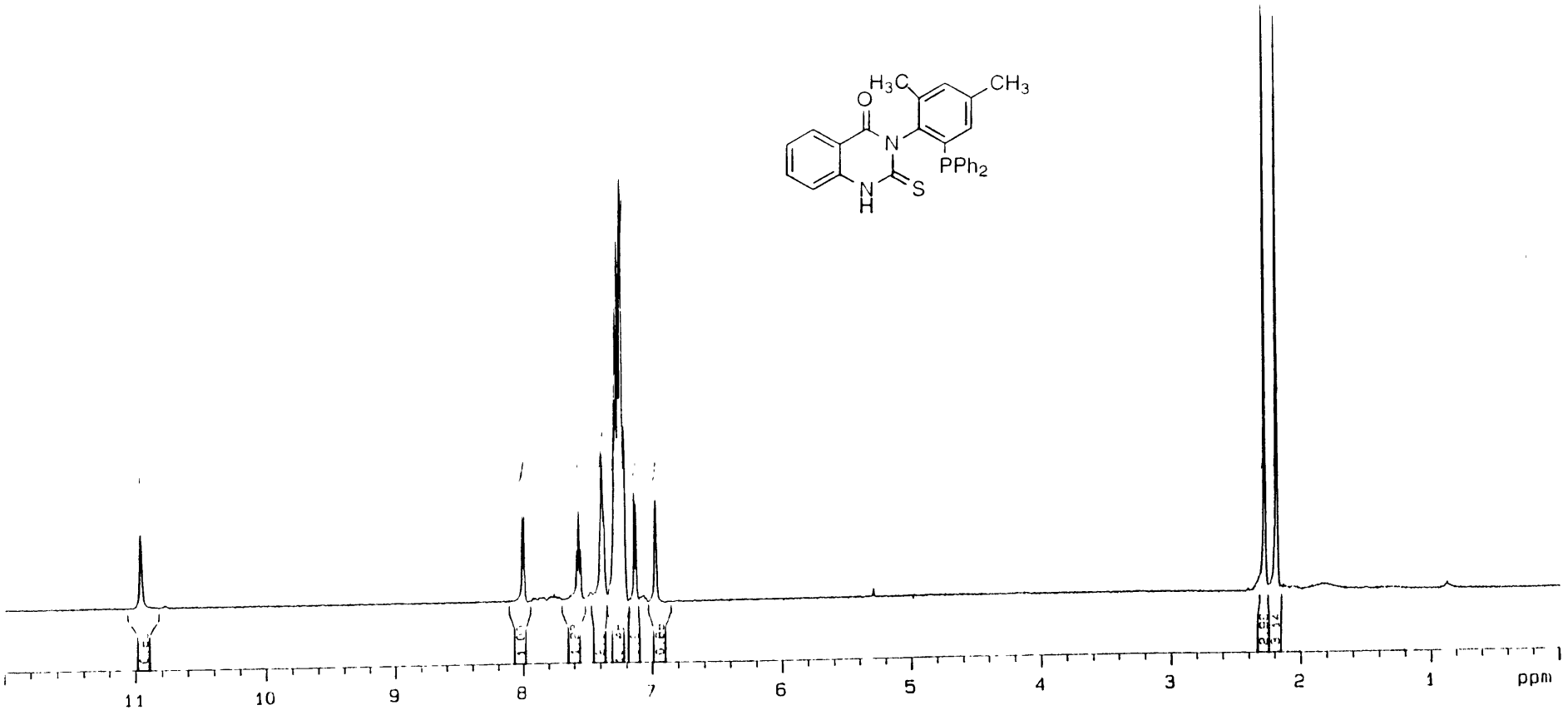
N
PPh2
8
7
6
5
4
2
1
ppm

(2-Mercapto-3-[4',6'-dimethyl-2'-(diphenylphosphino)phenyl]-4(3*H*)-quinazolinone (1f).

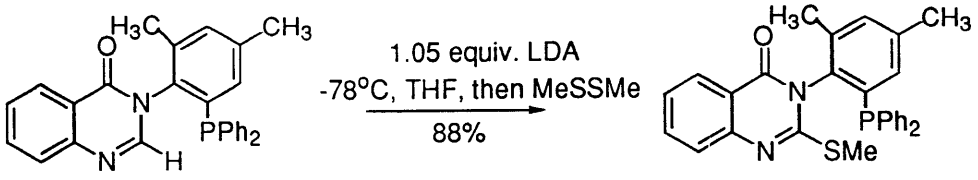


1d **1f**

To a cold (-78 °C), magnetically stirred solution of ligand **1d** (3.00 g, 6.9 mmol) in THF (30 mL) was added dropwise 7.25 mL of LDA (1.0 M). After stirring at the same temperature for 0.5 h, the resulting orange solution was treated with 0.227 g of S_8 (7.1 mmol). The reaction mixture was stirred for another one hour before allowed to warm up slowly to room temperature, quenched with a cold saturated ammonium chloride solution, and diluted in CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), passed through a short silica gel column, and evaporated. Crystallization from CH_2Cl_2 /hexane afforded 2.71 g (84%) of ligand **1f** as white needles: mp: >300 °C; R_f = 0.43 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film, cm^{-1}) 3248, 3037, 1701, 1666, 1618, 1528, 1484, 1396, 1199, 743, 694; ^1H NMR (300 MHz, $CDCl_3$) δ 10.96 (br s, 1H), 7.99 (dd, 1H, J = 1.0, 7.8 Hz), 7.60 (tdd, 1H, J = 1.5, 7.3, 8.3 Hz), 7.35 - 7.42 (m, 2H), 7.16 - 7.52 (m, 10H), 7.14 (d, 1H, J = 8.3 Hz), 6.96 (dd, 1H, J = 2.0, 3.9 Hz), 2.28 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 176.68 (d, J = 1.25 Hz), 160.30 (d, J = 1.00 Hz), 141.20, 140.99, 139.67, 139.64, 137.71, 137.63, 137.20, 137.12, 136.90, 136.79, 136.50, 136.46, 136.19, 134.83, 134.81, 134.29, 134.13, 134.02, 133.87, 133.85, 129.18, 129.16, 128.96, 128.883, 128.876, 128.825, 125.422, 116.73, 115.64, 21.69, 18.23 (d, $^4J_{CP}$ = 2.75 Hz, C6'*Me*); ^{31}P NMR{^1H} NMR (202.3 MHz, $CDCl_3$): δ -17.0 (s); HRMS 466.12644 (calcd for $C_{28}H_{23}N_2OPS$ 466.12687).


H3C
CH3
O
N
PPh2
N
H
S
11
10
9
8
7
6
5
4
3
2
1
ppm

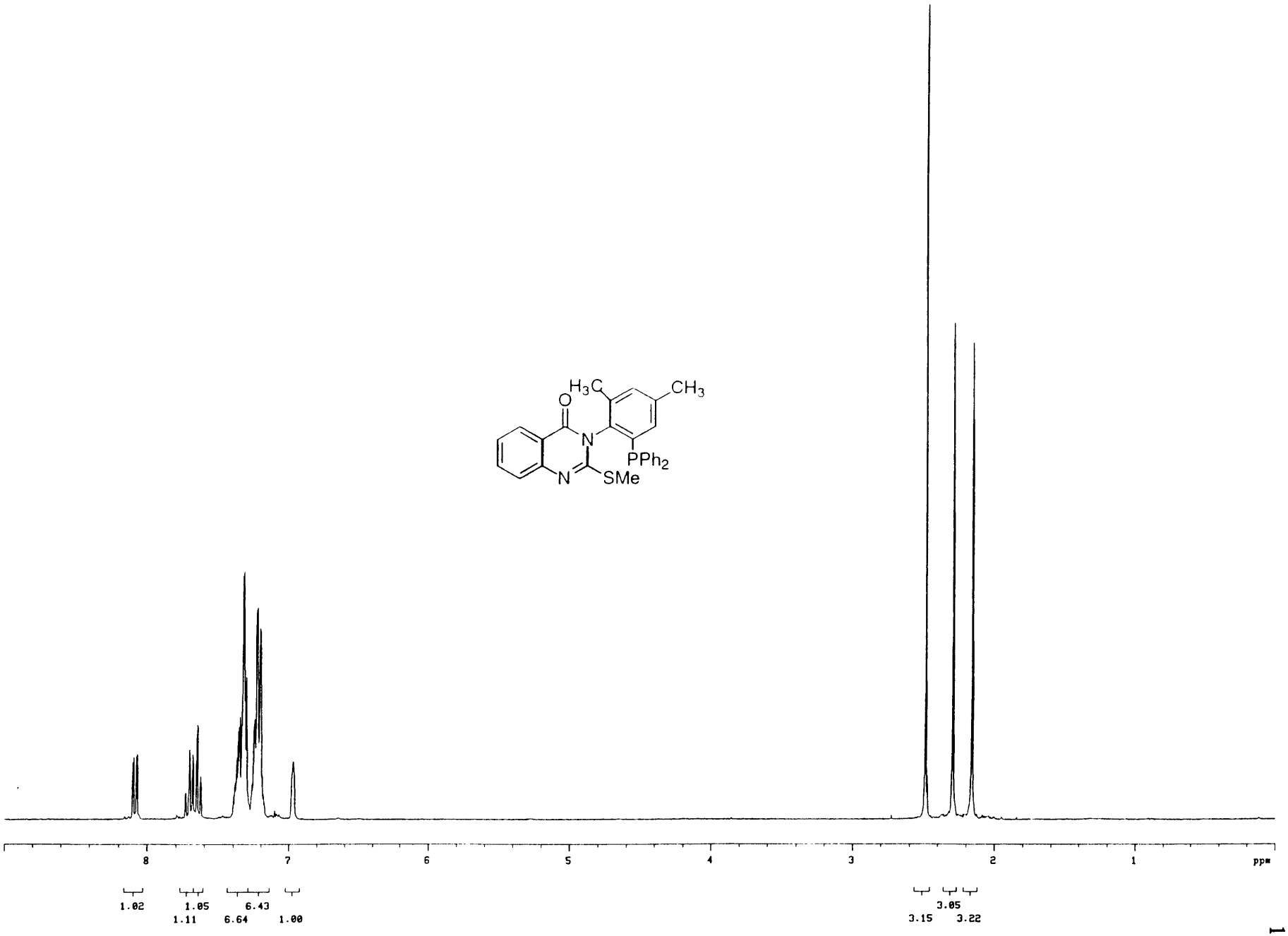
Ligand 1g.



1d
$C_{28}H_{23}N_2OP$
Mol. Wt.: 434.48

1g
$C_{29}H_{25}N_2OPS$
Mol. Wt.: 480.56

To a cold (-78 °C), magnetically stirred solution of ligand **1d** (3.50 g, 6.9 mmol) in THF (30 mL) was added dropwise 8.86 mL of LDA (1.0 M). After stirring at the same temperature for 0.5 h, the resulting orange solution was treated with 0.762 mL of methyl disulfide (8.3 mmol). The reaction mixture was stirred for another one hour before allowed to warm up slowly to room temperature, quenched with a cold saturated ammonium chloride solution, and diluted in CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), passed through a short silica gel column, and evaporated. Crystallization from ether afforded 3.40 g (88%) of ligand **1g** as white needles: mp 130-132 °C; R_f = 0.55 (silica, 1:2 ethyl acetate/hexane); FTIR (thin film) 3052, 1684, 1546, 1467, 769, 743, 695; ^{1}H NMR d 8.10 (dd, 1H, J = 1.46, 7.81 Hz), 7.72 (ddd, 1H, J = 1.46, 6.84, 8.30), 7.66 (dd, 1H, J = 1.46, 8.30), 7.15-7.42 (m, 12 H), 6.99 (dd, 1H, J = 1.46, 3.42), 2.51 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H); ^{13}C NMR δ_C 161.09, 158.33, 148.18, 140.22, 138.06, 137.95, 137.46, 137.26, 137.23, 137.19, 136.69, 136.61, 136.18, 136.05, 134.45, 134.05, 134.00, 133.99, 133.92, 133.89, 133.76, 133.38, 128.73, 128.63, 128.43, 128.37, 128.35, 128.30, 127.56, 126.29, 125.47, 119.86, 21.59, 17.95 (d, J = 2.3 Hz), 15.36; ^{31}P{^{1}H} NMR (202.3 MHz, $CDCl_3$): δ -16.72 ppm; HRMS calcd: 480.142524, measured: (FAB, 3-Nitrobenzyl alcohol) 480.14240.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PPh2
N
SMe
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7
6
5
4
3
2
1
ppm
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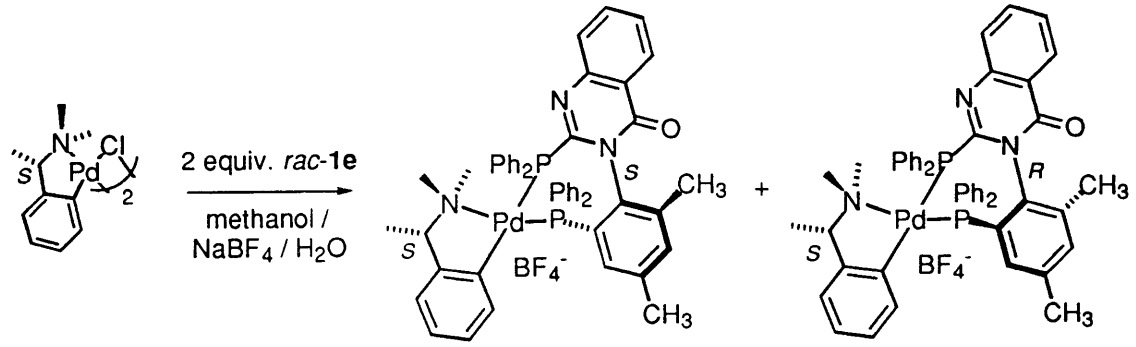
1.11
6.43
6.64
1.00
3.05
3.15
3.22

Resolution of Ligand 1e



(*S*)-**7**
$C_{20}H_{28}Cl_2N_2Pd_2$
MW: 580.17

(*S*, *S*)-**85**
$C_{50}H_{46}N_3OP_2PdBF_4$
MW: 960.10

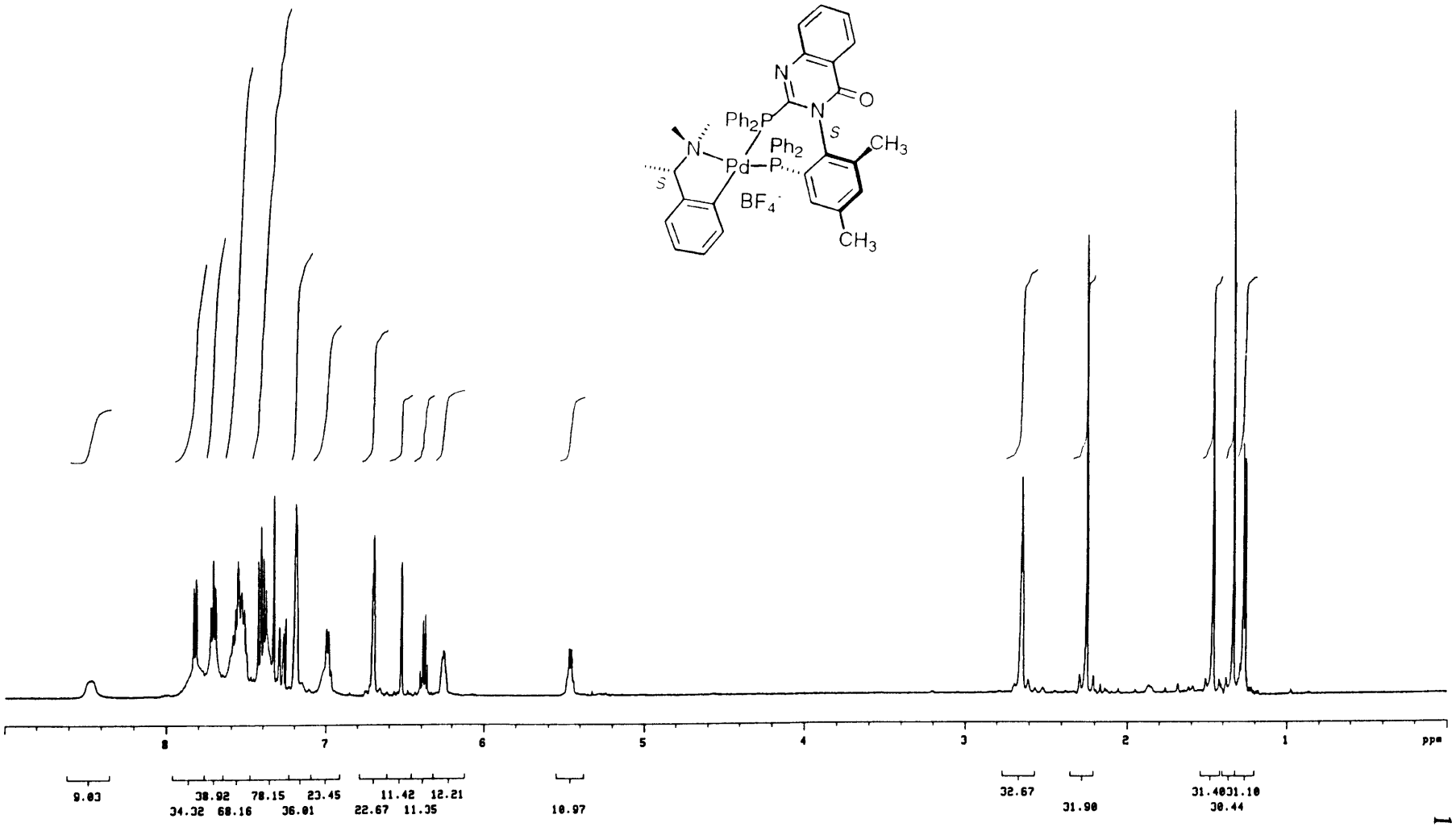
(*S*, *S*)-**86**
$C_{50}H_{46}N_3OP_2PdBF_4$
MW: 960.10

A suspension of complex **7** (0.234 g, 0.403 mmol) and ligand **1e** (0.50 g, 0.808 mmol) in methanol (20 mL) was stirred at ambient temperature to give a clear, almost colorless, solution. A solution of $NaBF_4$ (89.0 mg, 0.811 mmol) in water (6 mL) was added dropwise to the above clear solution. The resulting white slurry was stirred for 4 h. The precipitate was then collected, washed with 50% aqueous methanol and diethyl ether. Crystallization from benzene gave 0.352 g of complex **85** (91%) as colorless bricks: mp 207 °C (dec.); Rf = 0.44 (silica, ethyl acetate); $[\alpha]_D^{23}$ = -316.9° (c = 1.00, $CHCl_3$); FTIR (thin film, cm^{-1}) 3048.5, 2919.2, 1692.5, 1547.9, 1437.6, 1057.1, 748.1, 694.9, 495.9; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35-8.57 (br s, 1H), 7.25-7.87 (m, 19H), 7.16-7.23(m, 3H), 6.94-7.05 (m, 2H), 6.67-6.74 (m, 2H), 6.53 (s, 1H), 6.39 (q, 1H, J = 7.66 Hz), 6.26 (br s, 1H), 5.47 (q, 1H, J = 6.41 Hz), 2.65 (t, 3H, J = 3.67 Hz), 2.25 (s, 3H), 1.47 (d, 3H, J = 2.12 Hz), 1.34 (s, 3H), 1.27 (d, 3H, J = 6.52 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.30, 165.24, 164.47, 164.42, 159.63 , 151.96, 151.94, 151.49, 149.95. 149.93, 146.09, 145.99, 141.34, 141.26, 139.97, 139.92, 137.79, 137.17, 137.07, 136.46, 136.20, 135.46, 135.16, 135.14, 134.96, 134.19, 133.60, 133.53, 132.74, 132.72, 132.63, 132.61, 131.47, 131.06, 131.04, 130.59, 130.54, 130.21, 130.16, 129.07, 128.23, 128.15, 128.10, 128.01, 127.77, 127.75, 127.65, 127.29, 127.22,

126.71, 126.42, 126.38, 126.31, 125.08, 124.07, 124.02, 122.91, 122.53, 121.17, 120.89, 120.58, 73.12, 49.40, 40.50 (d, J = 2.25 Hz), 21.22, 19.19 (d, J = 1.38 Hz), 9.24; ^{31}P NMR (121.4 MHz): δ 35.37 (d, J = 40.4 Hz), 19.17 (d, J = 41.2 Hz); HRMS calcd for $C_{50}H_{46}N_3OP_2PdBF_4$ (M^+): 959.217419. calcd for $C_{50}H_{46}N_3OP_2Pd^+$ 872.21509. measured: (FAB, 3-Nitrobenzyl alcohol) 872.21483.

Treatment of the above complex (*S*,*S*)-**86** (0.352 g, 0.367 mmol) with ethylenediamine (0.041 mL, 0.613 mmol) in CH_2Cl_2 (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Crystallization from ethyl acetate/hexanes (1:3) solvent mixture gave 0.193 g of free ligand (85%) (*S*)-(-)-**1e** as white bricks: mp 238-240 °C; $[\alpha]_D^{23}$ = -21.2° (*c* = 1.20, $CHCl_3$), (98% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.50 mL/min, λ = 295 nm, t_R = 17.8 min).

The aqueous mother liquor was and treated with ethylenediamine in a similar fashion, followed by crystallization from ethyl acetate/hexanes (1:3) solvent mixture to afford 0.198 g of (*R*)-(+)-**1e** (79%, based on the total amount of (*R*)-(+)-**1e**) as white bricks: mp 238-240 °C; $[\alpha]_D^{23}$ = +16.8° (*c* = 1.46, $CHCl_3$); (90% ee based on chiral HPLC analysis, Daicel Chiralcel OD, 98:2 hexane/2-propanol, flow rate 0.50 mL/min, λ = 295 nm, t_R = 19.4 min).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S
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Ph2
N
Pd
P
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BF4-
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CH3
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7
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4
3
2
1
ppm
9.03
38.92
34.32
68.16
78.15
36.01
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10.97
32.67
31.90
31.40
31.10
30.44

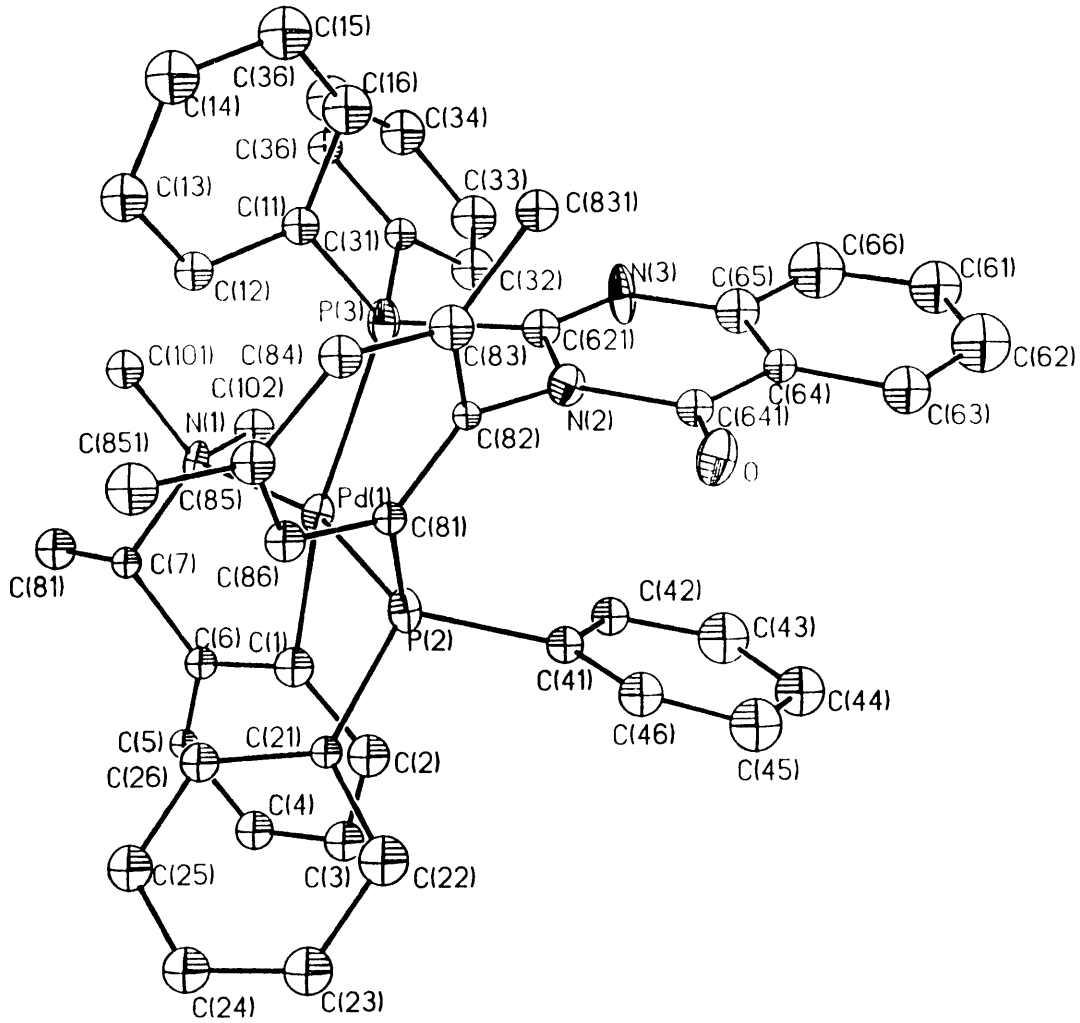

Figure C. ORTEP plot of complex (*S*,*R*)-**85**. The counter anion (BF_4^-) has been omitted for clarity.

Table C1. Crystal Data and Structure Refinement for complex **85**.

A. Crystal data

Empirical formula	$C_{50}H_{46}BF_4N_3OP_2Pd$	
Formula weight	960.10	
Temperature	183 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 15.6576(3) Å	$\alpha = 90°$
	b = 16.1037(4) Å	$\beta = 90°$
	c = 19.6933(3) Å	$\gamma = 90°$
Volume, Z	4965.6 (2) $Å^3$, 4	
Density (calcd)	1.286 Mg/m^3	
Absorption coefficient	0.490 mm^{-1}	
F(000)	1972	
Crystal morphology	colorless, prismatic	
Crystal size	0.18 x 0.12 x 0.08 mm	

B. Data Collection and Reduction

Diffractometer	Siemens SMART/CCD
Crystal-Detector distance	6.0 cm
Scan type	ω Scans
Scan angle	0.30°
θ range for data collection	1.63 to 20.00°
Limiting indices	$-17 \leq h \leq 10$, $-17 \leq k \leq 17$, $-21 \leq l \leq 18$
Reflections collected	14973
Independent reflections	4640 (R_{int} = 0.1514)
Absorption correction	None

C. Structure Solution and Refinement

Refinement method	Full-matrix least-squares on F^2
No. of data/ restraints / parameters	4637 / 0 / 305
Goodness of fit on F^2	1.061
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0816, wR_2 = 0.1829
R indices (all data)	R_1 = 0.0932, wR_2 = 0.1982
Absolute structure parameter	0.05 (7)
Extinction coefficient	0.0003 (2)
Largest diff. peak and hole	0.567 and -0.760 eÅ^{-3}

Notes:

$R_1 = \Sigma \| |F_0| - |F_c| \| / \Sigma |F_0|$

$wR_2 = \{ \Sigma [w (F_0^2 - F_c^2)^2 / [\Sigma (F_0^2)^2] \}^{1/2}$

Weighting scheme

calcd $w = 1 / [\sigma^2(F_0^2) + (0.0316P)^2 + 2.9688P]$ where $P = (F_0^2 + 2F_c^2) / 3$

Refinement on F^2 for ALL reflections. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors are based on F, with F set to zero for negative F_0^2. The observed criterion for $F^2 > 2\sigma(F^2)$ is used only for calculating R_1 and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table C2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 85. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Pd(1)	-7075(1)	-4080(1)	-436(1)	21(1)
P(2)	-6389(3)	-4730(2)	-1291(2)	24(1)
P(3)	-8470(3)	-4592(3)	-788(2)	27(1)
O	-7419(7)	-6788(6)	-2472(5)	36(3)
N(1)	-7499(7)	-3128(6)	281(5)	19(3)
N(2)	-7949(8)	-5847(7)	-1705(5)	26(3)
N(3)	-8646(9)	-6276(7)	-708(6)	36(4)
C(1)	-5918(9)	-3857(9)	49(8)	33(4)
C(2)	-5236(9)	-4401(10)	105(8)	36(4)
C(3)	-4545(9)	-4193(9)	520(7)	33(4)
C(4)	-4596(10)	-3481(10)	879(7)	32(4)
C(5)	-5278(8)	-2942(9)	871(7)	18(3)
C(6)	-5937(8)	-3127(8)	445(8)	22(3)
C(7)	-6720(8)	-2583(8)	350(7)	20(3)
C(11)	-9100(8)	-4068(10)	-1437(6)	25(3)
C(12)	-8770(10)	-3370(9)	-1745(7)	26(4)
C(13)	-9222(10)	-2984(10)	-2276(8)	38(4)
C(14)	-9987(12)	-3332(11)	-2473(10)	46(4)
C(15)	-10319(10)	-4038(12)	-2186(8)	47(4)
C(16)	-9875(10)	-4408(10)	-1657(8)	42(5)
C(21)	-5426(8)	-4200(8)	-1541(6)	17(3)
C(22)	-4713(10)	-4601(11)	-1824(8)	42(4)
C(23)	-4007(10)	-4112(11)	-2032(7)	40(4)
C(24)	-4009(10)	-3294(10)	-1936(8)	37(4)
C(25)	-4669(10)	-2882(10)	-1664(7)	37(4)
C(26)	-5365(9)	-3332(9)	-1470(7)	26(4)
C(31)	-9174(8)	-4695(9)	-54(7)	20(3)
C(32)	-8949(10)	-5215(9)	491(8)	39(4)
C(33)	-9413(10)	-5221(11)	1102(8)	45(5)
C(34)	-10104(10)	-4675(11)	1144(9)	45(5)
C(36)	-9840(8)	-4148(10)	17(7)	24(3)
C(36)	-10307(10)	-4147(12)	641(7)	47(5)
C(41)	-6122(8)	-5827(9)	-1173(6)	24(3)
C(42)	-6288(8)	-6165(8)	-532(7)	27(4)
C(43)	-6107(10)	-6984(10)	-390(10)	51(5)
C(44)	-5744(11)	-7481(11)	-898(8)	46(5)
C(45)	-5563(11)	-7110(11)	-1521(9)	49(5)
C(46)	-5802(10)	-6324(9)	-1688(8)	34(4)
C(61)	-8665(11)	-8515(11)	-606(9)	53(5)
C(62)	-8222(11)	-8728(13)	-1182(9)	63(6)
C(63)	-7881(11)	-8143(9)	-1617(7)	40(4)
C(64)	-8069(8)	-7308(8)	-1473(6)	20(3)
C(65)	-8495(10)	-7076(10)	-879(8)	37(4)
C(66)	-8815(11)	-7689(11)	-441(11)	62(5)
C(81)	-7043(9)	-4668(8)	-2083(6)	18(3)
C(81)	-6827(9)	-1945(10)	943(7)	37(4)
C(82)	-7735(8)	-5186(8)	-2183(6)	13(3)
C(83)	-8287(9)	-5108(9)	-2758(8)	31(4)

Table C2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 85. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(84)	-8088(9)	-4429(8)	-3175(7)	27(4)
C(85)	-7424(9)	-3869(9)	-3088(7)	29(4)
C(86)	-6904(9)	-4014(10)	-2509(6)	27(4)
C(101)	-8200(9)	-2644(9)	-4(8)	30(4)
C(102)	-7759(10)	-3504(10)	917(7)	36(4)
C(621)	-8383(9)	-5692(9)	-1095(7)	26(4)
C(641)	-7771(10)	-6692(9)	-1919(7)	24(4)
C(831)	-9020(9)	-5658(9)	-2883(7)	27(4)
C(851)	-7266(10)	-3177(9)	-3536(8)	40(4)
B	-7117(18)	-1376(15)	-1842(11)	52(6)
F(1)	-6985(10)	-1911(10)	-1303(7)	133(6)
F(2)	-6434(10)	-1262(12)	-2196(7)	147(7)
F(3)	-7784(10)	-1681(11)	-2167(7)	129(6)
F(4)	-7300(13)	-663(12)	-1602(13)	213(10)

Table 3. Bond lengths [Å] and angles [°] for 85.

Pd(1)-C(1)	2.08(2)	Pd(1)-N(1)	2.187(10)
Pd(1)-P(2)	2.254(4)	Pd(1)-P(3)	2.435(4)
P(2)-C(21)	1.802(13)	P(2)-C(41)	1.83(2)
P(2)-C(81)	1.869(13)	P(3)-C(31)	1.825(14)
P(3)-C(11)	1.821(14)	P(3)-C(621)	1.878(14)
O-C(641)	1.23(2)	N(1)-C(102)	1.45(2)
N(1)-C(101)	1.46(2)	N(1)-C(7)	1.51(2)
N(2)-C(621)	1.40(2)	N(2)-C(641)	1.45(2)
N(2)-C(82)	1.46(2)	N(3)-C(621)	1.28(2)
N(3)-C(65)	1.35(2)	C(1)-C(2)	1.39(2)
C(1)-C(6)	1.41(2)	C(2)-C(3)	1.40(2)
C(3)-C(4)	1.35(2)	C(4)-C(5)	1.38(2)
C(5)-C(6)	1.36(2)	C(6)-C(7)	1.52(2)
C(7)-C(81)	1.57(2)	C(11)-C(12)	1.38(2)
C(11)-C(16)	1.40(2)	C(12)-C(13)	1.41(2)
C(13)-C(14)	1.38(2)	C(14)-C(15)	1.37(2)
C(15)-C(16)	1.39(2)	C(21)-C(22)	1.40(2)
C(21)-C(26)	1.41(2)	C(22)-C(23)	1.42(2)
C(23)-C(24)	1.33(2)	C(24)-C(25)	1.34(2)
C(25)-C(26)	1.36(2)	C(31)-C(36)	1.37(2)
C(31)-C(32)	1.40(2)	C(32)-C(33)	1.41(2)
C(33)-C(34)	1.40(2)	C(34)-C(36)	1.34(2)
C(36)-C(36)	1.43(2)	C(41)-C(46)	1.39(2)
C(41)-C(42)	1.40(2)	C(42)-C(43)	1.38(2)
C(43)-C(44)	1.40(2)	C(44)-C(45)	1.39(2)
C(45)-C(46)	1.36(2)	C(61)-C(62)	1.37(2)
C(61)-C(66)	1.39(2)	C(62)-C(63)	1.38(2)
C(63)-C(64)	1.41(2)	C(64)-C(65)	1.40(2)
C(64)-C(641)	1.40(2)	C(65)-C(66)	1.40(2)
C(81)-C(86)	1.36(2)	C(81)-C(82)	1.38(2)
C(82)-C(83)	1.43(2)	C(83)-C(84)	1.40(2)
C(83)-C(831)	1.47(2)	C(84)-C(85)	1.39(2)
C(85)-C(86)	1.42(2)	C(85)-C(851)	1.44(2)
B-F(4)	1.27(3)	B-F(2)	1.29(3)
B-F(3)	1.32(3)	B-F(1)	1.38(2)

C(1)-Pd(1)-N(1)	81.2(5)	C(1)-Pd(1)-P(2)	90.5(4)
N(1)-Pd(1)-P(2)	162.1(3)	C(1)-Pd(1)-P(3)	166.2(4)
N(1)-Pd(1)-P(3)	98.5(3)	P(2)-Pd(1)-P(3)	93.31(14)
C(21)-P(2)-C(41)	107.5(6)	C(21)-P(2)-C(81)	101.8(6)
C(41)-P(2)-C(81)	106.4(6)	C(21)-P(2)-Pd(1)	112.6(4)
C(41)-P(2)-Pd(1)	117.5(4)	C(81)-P(2)-Pd(1)	109.8(4)
C(31)-P(3)-C(11)	105.7(6)	C(31)-P(3)-C(621)	102.3(7)
C(11)-P(3)-C(621)	104.5(7)	C(31)-P(3)-Pd(1)	110.3(5)
C(11)-P(3)-Pd(1)	121.9(5)	C(621)-P(3)-Pd(1)	110.2(5)
C(102)-N(1)-C(101)	110.1(10)	C(102)-N(1)-C(7)	113.1(10)
C(101)-N(1)-C(7)	109.4(10)	C(102)-N(1)-Pd(1)	110.5(8)
C(101)-N(1)-Pd(1)	110.8(8)	C(7)-N(1)-Pd(1)	102.8(7)
C(621)-N(2)-C(641)	120.6(12)	C(621)-N(2)-C(82)	122.2(11)
C(641)-N(2)-C(82)	116.9(10)	C(621)-N(3)-C(65)	119.7(12)
C(2)-C(1)-C(6)	119.9(13)	C(2)-C(1)-Pd(1)	126.8(11)
C(6)-C(1)-Pd(1)	112.4(10)	C(1)-C(2)-C(3)	119.5(14)
C(4)-C(3)-C(2)	117.7(14)	C(3)-C(4)-C(5)	125.1(14)
C(6)-C(5)-C(4)	117.2(13)	C(5)-C(6)-C(1)	120.5(12)
C(5)-C(6)-C(7)	124.2(12)	C(1)-C(6)-C(7)	115.3(12)

Table 3. Bond lengths [Å] and angles [°] for 85.

N(1)-C(7)-C(6)	109.2(10)	N(1)-C(7)-C(81)	111.3(10)
C(6)-C(7)-C(81)	111.9(11)	C(12)-C(11)-C(16)	120.5(13)
C(12)-C(11)-P(3)	118.9(10)	C(16)-C(11)-P(3)	120.4(12)
C(11)-C(12)-C(13)	119.9(14)	C(14)-C(13)-C(12)	118(2)
C(15)-C(14)-C(13)	123(2)	C(14)-C(15)-C(16)	118(2)
C(15)-C(16)-C(11)	120(2)	C(22)-C(21)-C(26)	116.2(13)
C(22)-C(21)-P(2)	123.8(11)	C(26)-C(21)-P(2)	119.9(10)
C(21)-C(22)-C(23)	119(2)	C(24)-C(23)-C(22)	121(2)
C(23)-C(24)-C(25)	123(2)	C(24)-C(25)-C(26)	118(2)
C(25)-C(26)-C(21)	123.6(14)	C(36)-C(31)-C(32)	119.7(13)
C(36)-C(31)-P(3)	118.7(11)	C(32)-C(31)-P(3)	120.5(11)
C(31)-C(32)-C(33)	121.9(14)	C(34)-C(33)-C(32)	117(2)
C(36)-C(34)-C(33)	123(2)	C(31)-C(36)-C(36)	118.4(14)
C(34)-C(36)-C(36)	121(2)	C(46)-C(41)-C(42)	120.2(14)
C(46)-C(41)-P(2)	123.1(11)	C(42)-C(41)-P(2)	116.6(10)
C(43)-C(42)-C(41)	121(2)	C(42)-C(43)-C(44)	119(2)
C(43)-C(44)-C(45)	118(2)	C(46)-C(45)-C(44)	124(2)
C(45)-C(46)-C(41)	117(2)	C(62)-C(61)-C(66)	121(2)
C(61)-C(62)-C(63)	123(2)	C(62)-C(63)-C(64)	117(2)
C(65)-C(64)-C(63)	121.6(13)	C(65)-C(64)-C(641)	119.6(13)
C(63)-C(64)-C(641)	118.7(13)	N(3)-C(65)-C(64)	123.1(14)
N(3)-C(65)-C(66)	117(2)	C(64)-C(65)-C(66)	120(2)
C(61)-C(66)-C(65)	118(2)	C(86)-C(81)-C(82)	120.2(12)
C(86)-C(81)-P(2)	117.9(11)	C(82)-C(81)-P(2)	121.0(9)
C(81)-C(82)-C(83)	122.2(12)	C(81)-C(82)-N(2)	122.0(11)
C(83)-C(82)-N(2)	115.8(11)	C(84)-C(83)-C(82)	113.5(13)
C(84)-C(83)-C(831)	123.0(13)	C(82)-C(83)-C(831)	123.5(13)
C(85)-C(84)-C(83)	126.9(13)	C(84)-C(85)-C(86)	115.0(13)
C(84)-C(85)-C(851)	123.7(13)	C(86)-C(85)-C(851)	121.3(13)
C(81)-C(86)-C(85)	122.0(14)	N(3)-C(621)-N(2)	122.4(13)
N(3)-C(621)-P(3)	118.6(11)	N(2)-C(621)-P(3)	118.6(11)
O-C(641)-C(64)	127.8(13)	O-C(641)-N(2)	117.4(12)
C(64)-C(641)-N(2)	114.6(12)	F(4)-B-F(2)	105(2)
F(4)-B-F(3)	110(3)	F(2)-B-F(3)	117(2)
F(4)-B-F(1)	108(2)	F(2)-B-F(1)	112(2)
F(3)-B-F(1)	105(2)		

Table C4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 85. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Pd(1)	32(1)	20(1)	11(1)	-2(1)	-1(1)	3(1)
P(2)	37(3)	20(2)	16(2)	-1(2)	2(2)	-2(2)
P(3)	40(3)	20(2)	21(2)	2(2)	4(2)	1(2)
O	55(8)	29(7)	24(6)	-9(5)	3(5)	8(5)
N(1)	36(7)	13(6)	8(7)	0(5)	1(5)	6(5)
N(2)	31(7)	25(7)	21(6)	-10(6)	3(6)	2(7)
N(3)	69(10)	14(7)	25(8)	-7(6)	24(7)	-5(7)
F(1)	128(12)	161(15)	110(11)	72(10)	-36(10)	-34(12)
F(2)	115(13)	231(21)	93(11)	24(12)	-3(10)	-43(13)
F(3)	115(12)	186(16)	87(9)	7(10)	-38(9)	-81(12)
F(4)	156(17)	147(18)	335(28)	-95(19)	-9(18)	72(14)

Table C5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 85.

	x	y	z	U(eq)
H(3B)	-8925(9)	-6157(7)	-332(6)	43
H(2A)	-5238(9)	-4911(10)	-138(8)	44
H(3A)	-4057(9)	-4542(9)	549(7)	40
H(4A)	-4123(10)	-3340(10)	1160(7)	39
H(5A)	-5289(8)	-2461(9)	1151(7)	22
H(7A)	-6649(8)	-2265(8)	-83(7)	24
H(12A)	-8237(10)	-3150(9)	-1599(7)	32
H(13A)	-9006(10)	-2499(10)	-2491(8)	46
H(14A)	-10300(12)	-3069(11)	-2825(10)	55
H(15A)	-10841(10)	-4267(12)	-2346(8)	57
H(16A)	-10096(10)	-4891(10)	-1444(8)	50
H(22A)	-4703(10)	-5187(11)	-1875(8)	50
H(23A)	-3529(10)	-4369(11)	-2242(7)	48
H(24A)	-3518(10)	-2987(10)	-2066(8)	44
H(25A)	-4653(10)	-2296(10)	-1609(7)	44
H(26A)	-5834(9)	-3045(9)	-1275(7)	31
H(32A)	-8470(10)	-5572(9)	445(8)	47
H(33A)	-9264(10)	-5578(11)	1467(8)	54
H(34A)	-10443(10)	-4676(11)	1544(9)	54
H(36A)	-9988(8)	-3778(10)	-340(7)	28
H(36C)	-10767(10)	-3769(12)	701(7)	57
H(42A)	-6530(8)	-5823(8)	-189(7)	33
H(43A)	-6226(10)	-7209(10)	46(10)	62
H(44A)	-5626(11)	-8052(11)	-820(8)	55
H(45A)	-5255(11)	-7424(11)	-1848(9)	59
H(46A)	-5751(10)	-6123(9)	-2140(8)	41
H(61A)	-8872(11)	-8940(11)	-315(9)	64
H(62A)	-8148(11)	-9300(13)	-1285(9)	76
H(63A)	-7536(11)	-8297(9)	-1993(7)	48
H(66A)	-9126(11)	-7544(11)	-44(11)	75
H(81A)	-7339(9)	-1607(10)	864(7)	56
H(81B)	-6325(9)	-1583(10)	963(7)	56
H(81C)	-6886(9)	-2244(10)	1374(7)	56
H(84A)	-8446(9)	-4344(8)	-3558(7)	33
H(86A)	-6446(9)	-3644(10)	-2416(6)	32
H(10D)	-8017(9)	-2392(9)	-433(8)	45
H(10E)	-8363(9)	-2206(9)	316(8)	45
H(10F)	-8690(9)	-3008(9)	-87(8)	45
H(10A)	-7283(10)	-3826(10)	1105(7)	54
H(10B)	-8248(10)	-3871(10)	838(7)	54
H(10C)	-7921(10)	-3068(10)	1239(7)	54
H(83A)	-9039(9)	-6090(9)	-2533(7)	40
H(83B)	-8961(9)	-5917(9)	-3331(7)	40
H(83C)	-9549(9)	-5333(9)	-2868(7)	40
H(85A)	-6765(10)	-2868(9)	-3376(8)	59
H(85B)	-7765(10)	-2809(9)	-3538(8)	59
H(85C)	-7162(10)	-3382(9)	-3996(8)	59