Synthesis and Evaluation of Planar-Chiral Paracyclophanyl Ligands and Indolo[1,2-*a*]indole Derivatives

面不斉パラシクロファン配位子ならびにインドロ[1,2-*a*]

インドール誘導体の合成と評価

February, 2019

Madhurima HAZRA

ハズラ　　マデュリマ

Synthesis and Evaluation of Planar-Chiral Paracyclophanyl Ligands and Indolo[1,2-*a*]indole Derivatives

面不斉パラシクロファン配位子ならびにインドロ[1,2-*a*]インドール誘導体の合成と評価

February, 2019

Waseda University

Graduate School of Advanced Science and Engineering

Department of Chemistry and Biochemistry

Research on Reaction Organic Chemistry

Madhurima HAZRA

ハズラ　　マデュリマ

Abstract

Optically active compounds play crucial and important roles in the pharmaceuticals, flavors, and fragrance industries resulting in significant developments in transition metal-mediated enantioselective reactions. The systematic design of chiral ligands is predominant in achieving high enantioselectivity. Various publications appeared in this field, along with a Nobel Prize in 2001. In this context, since the late 1960s, much research has been conducted on chiral bidentate phosphorus ligands in asymmetric reactions. However, enormous progress with respect to monodentate chiral phosphorus ligands was also observed during the last decade.

Chapter 1 explores different classes of chiral monodentate phosphorus ligands and their use in diverse asymmetric reactions that achieve high enantiomeric ratios.

Chapter 2 describes the synthesis of planar-chiral phosphite ligands with paracyclophane scaffold. Their efficiency was tested using two well-established asymmetric reactions.

Chapter 3 describes the synthesis of a planar-chiral phosphoramidite ligand with a paracyclophanyl scaffold and its use in two well-known asymmetric reactions to study its efficiency.

Chapter 4 introduces the indolo[1,2-*a*]indole skeleton. Various synthetic procedures are discussed.

Chapter 5 describes a novel protocol for synthesizing indolo[1,2-*a*]indole derivatives via gold-catalyzed cycloisomerization. Their photophysical properties are discussed.

Chapter 6 concludes by discussing the synthesis of a library of phosphite and phosphoramidite ligands. The synthesis and evaluation of indolo[1,2-*a*]indole derivatives is also summarized.

Contents

List of Abbreviations

AcOH	acetic acid
Ad	adamantyl
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
BSA	*N*,*O*-bis-(trimethylsilyl)acetamide
BuLi	*n*-butyllithium
ca.	circa
CAMP	cyclic adenosine monophosphate
CHDA	*trans*-1,2-diaminocyclohexane
d	day(s)
DCE	1,2-dichloroethane
DCM	dichloromethane
DME	1,2-dimethoxyethane
dig	digonal
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	ethane-1,2-diylbis(2-methoxyphenyl)phenylphosphane
DMAD	dimethyl acetylenedicarboxylate
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
DTBP	di-*tert*-butyl peroxide
ee	enantiomeric excess
EtOAc	ethyl acetate
ESI	electro spray ionization
equiv.	equivalent
Fig.	figure
HFIP	hexafluoroisopropanol
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
IR	infrared radiations

J	coupling constant
L	ligand
m	meta
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
mp	melting point
n	normal
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
N.R.	no reaction
ovn	overnight
p	para
Ph	phenyl
PTLC	preparative thin layer chromatography
sec	secondary
TADDOL	α,α,α,'α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl (as a functional group) tetramethylsilane (as a standard material)
UV	ultraviolet
xyl	3,5-xylyl

Chapter 1

General Introduction of Chiral Phosphite and Phosphoramidite Ligands

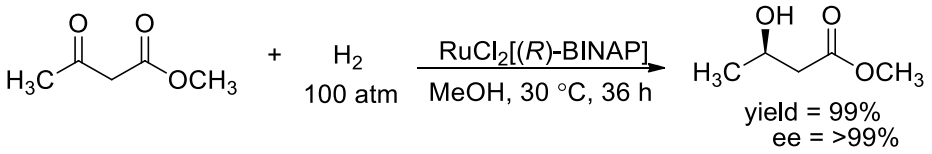
- **Background**

Importance of developing a new chiral ligand library

The increasing knowledge of transition metal catalysis has resulted in an extensive application of catalysis both in industrial and academic fields. The importance of transition metal catalysis is well represented by Nobel Prizes in 2001, 2005 and 2010 awarded to the researchers working in this field of chemistry. In particular, phosphine ligands have significantly contributed towards the evolution of transition metal-catalyzed reactions. Various ligand types and structures are reported in the literatures: mono-, bi- and polydentate achiral and chiral ligands with different steric and electronic properties. This vast ligand library is a result of the rapid evolution in the field of organometallic chemistry. Furthermore, catalytic performances of the transition metal complexes stimulate the evolutionary growth of the ligand libraries.

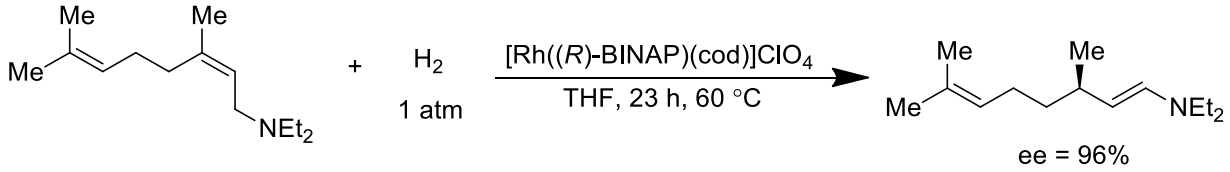
Development of the chiral ligand libraries is of utmost importance in terms of asymmetric organic transformations. Remarkable achievements have been realized in chiral transition metal-catalyzed reactions. The activity of the metal complexes can be varied by changing the electronic and/or steric properties of the ligands.

An important achievement was accomplished by Kagan in 1971 with the development of chiral bidentate phosphine DIOP.[1] This ligand resulted in the corresponding products with up to 72% ee in the enantioselective hydrogenation of acylaminocinnamic acid. Knowles synthesized DIPAMP[2] that realized an enantioselectivity of above 90% and replaced CAMP in the synthesis of L-DOPA, which resulted in the optically active drug in up to 95% ee, for which Knowles was awarded the Noble prize in chemistry in 2001.[3] The next achievement was the development of BINAP, an extremely versatile ligand, by Noyori.[4] The Ru-BINAP-catalyzed asymmetric hydrogenation of β-keto esters furnished the corresponding β-hydroxy esters with more than 99% ee (Scheme 1).



Scheme 1: Hydrogenation by Ru-BINAP-catalyst

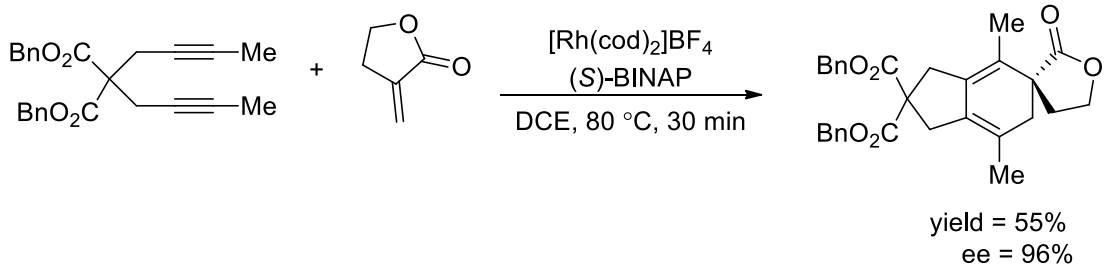
The Rh-BINAP complex was used in the asymmetric isomerization of allylic amine, which was exploited in the industrial synthesis of (-)-menthol from myrcene.[5] It achieved excellent enantioselectivity of 96% (Scheme 2). The BINAP ligand proved to be very versatile and is nowadays used in various asymmetric transition metal-catalyzed reactions (Scheme 2).



Scheme 2: Rh-BINAP-catalyzed asymmetric isomerization reaction

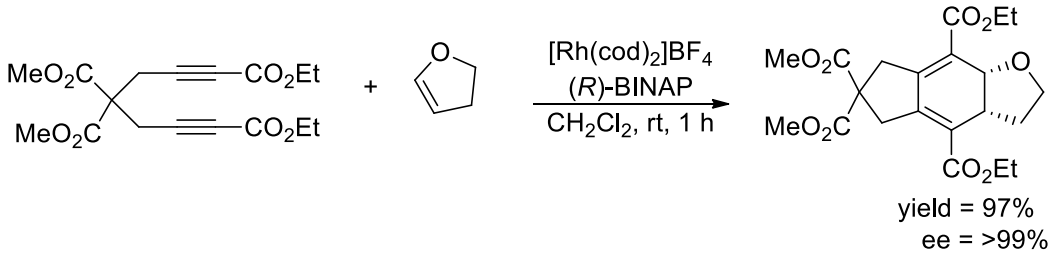
Various carbon-carbon bond forming reactions, such as cycloadditions, have been catalyzed by Rh-BINAP complexes.

In 2006, Shibata reported the first example of an asymmetric [2+2+2] cycloaddition of 1,6-diynes with electron-deficient 1,1-disubstituted alkenes catalyzed by the cationic Rh(I)-BINAP complex (Scheme 3).[6]



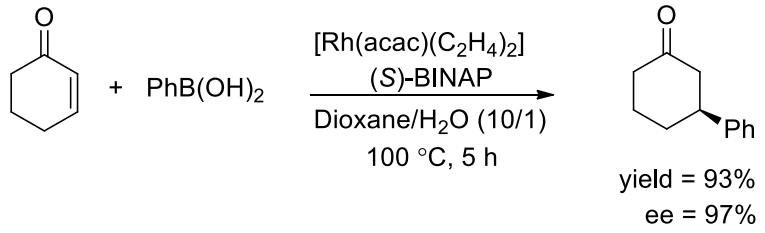
Scheme 3: Rh-BINAP-catalyzed enantioselective cycloaddition

Chiral multicyclic compounds were also synthesized using the cationic Rh (I)-BINAP complex in the asymmetric [2+2+2] cycloaddition[7] of α,ω-diynes with electron–rich unstrained unsymmetrical 1,2-disubstituted alkenes (Scheme 4).



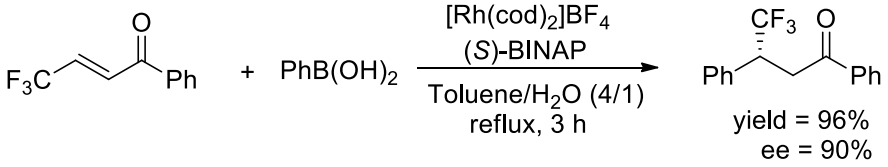
Scheme 4: Rh-BINAP-catalyzed asymmetric cycloaddition

Among various carbon-carbon bond forming reactions, the 1,4-conjugate addition of organometallic reagents to enones is widely used for the preparation of β-substituted carbonyl compound, which are important synthons in organic transformations. The asymmetric Rh-BINAP-catalyzed 1,4-conjugate addition of arylboronic acids to enones has been reported to proceed with high enantioselectivity (Scheme 5).[8]



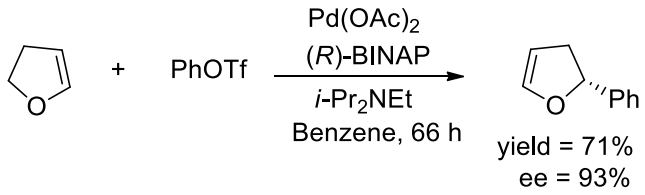
Scheme 5: Rh-BINAP-catalyzed 1,4-conjugate addition

Synthesis of enantiomerically pure compounds by using arylboronic acid is very demanding because of their stability and facile availability. For example, the Rh-catalyzed 1,4-conjugate addition of aryl groups to the electron-deficient 4,4,4-trifluoro-1-phenyl-2-buten-1-one in the presence of the Rh-BINAP catalyst is well known. (Scheme 6).[9]



Scheme 6: Rh-BINAP-catalyzed 1,4-conjugate addition

There has been considerable interest in Heck-type arylation for building carbon frameworks of biologically important organic compounds. In the catalytic arylation of 2,3-dihydrofuran using aryl triflates as arylating agents, a high enantioselectivity was achieved using the Pd-BINAP catalyst (Scheme 7).[10]



Scheme 7: Pd-catalyzed asymmetric Heck reaction

Inspired by the tremendous success achieved using BINAP as a chiral ligand in asymmetric reactions, various BINAP derivatives were synthesized to increase their catalytic efficiency and to generate a pool of ligands.[11] Such derivatization involved the replacement of phenyl groups on the phosphorus atom with different substituted phenyl groups or aliphatic groups. Variation of the substituents on the binaphthyl backbone and the partial reduction of binaphthyl backbone resulted in the H_8-BINAP family of ligands. These modifications enabled the manipulation of their electronic and steric properties. The more electron-rich H_8-BINAP contains more steric bulk and a larger dihedral angle than BINAP itself. Different atropisomeric C_2-symmetric diphosphines were also synthesized and studied extensively. Roche reported the synthesis of axially chiral diphosphine ligands, BIPHEMP and MeO-BIPHEP. Later, SEGPHOS was synthesized via an oxidative coupling, while other modifications led to the synthesis of SYNPHOS. The Zhang group developed a series of TunePhos ligands, while Burk and coworkers reported the first synthesis of BPE and DuPhos. Some of the ligands are shown below in Figure 1. The large family of diphosphine ligands not only offers a choice of different catalysts, but also provides a good opportunity to explore the catalytic processes.

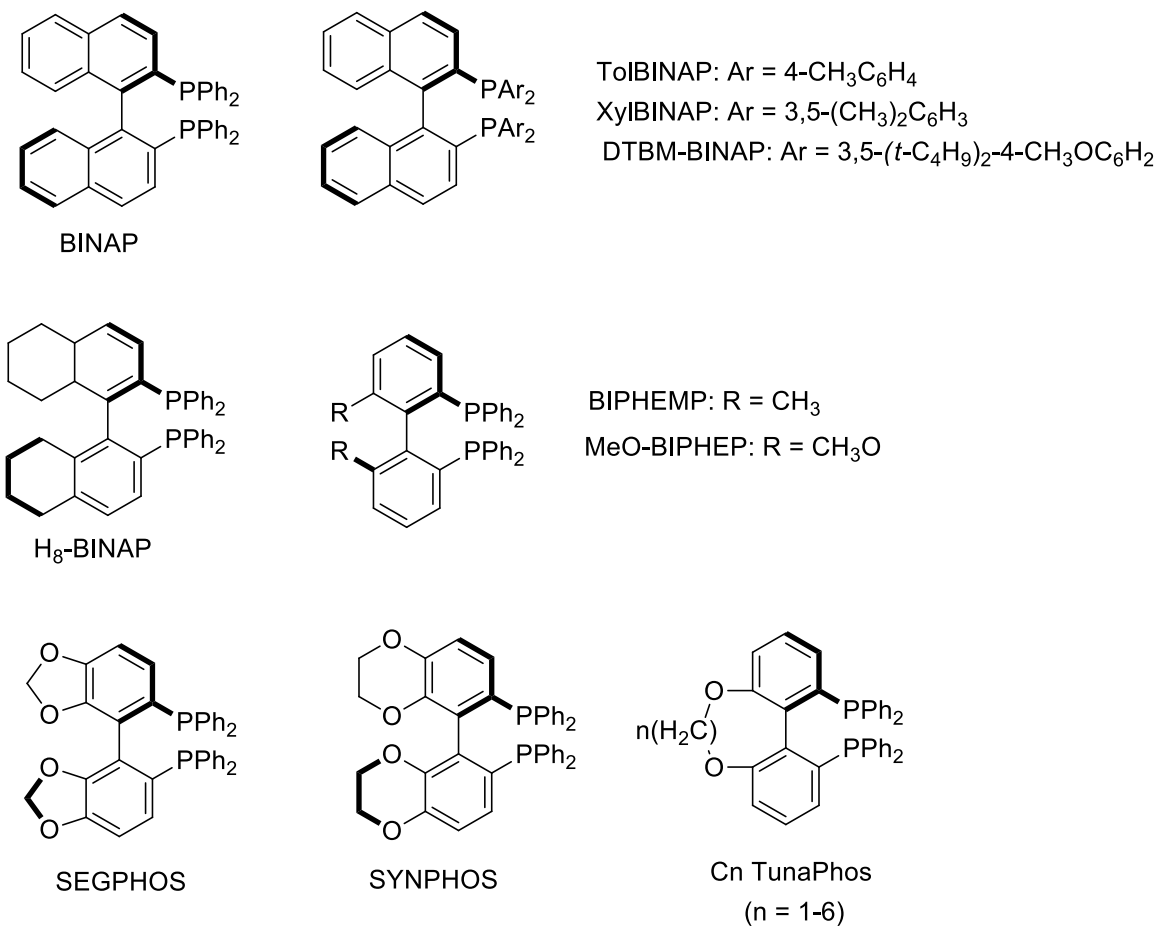
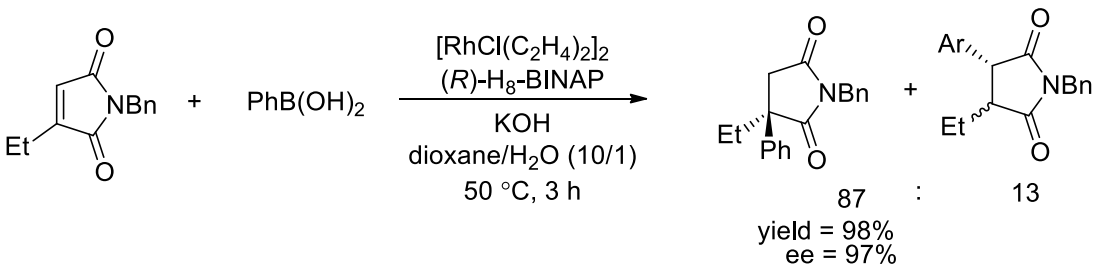


Fig. 1: (*R*)-BINAP and selected chiral biaryl diphosphines

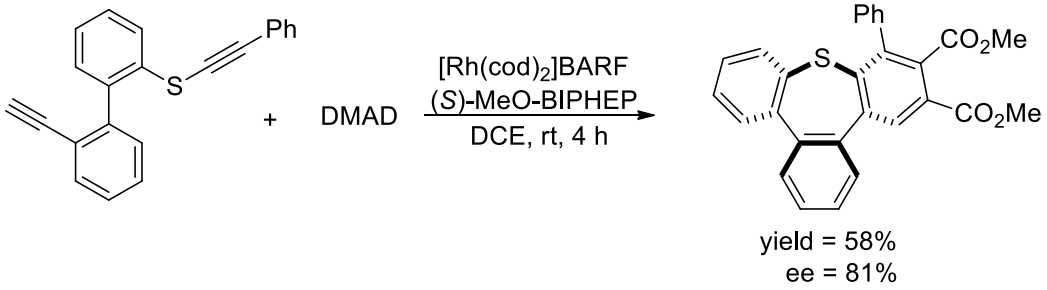
H_8-BINAP resulted in excellent enantioselectivities of the products in the Ir-catalyzed reduction of ketones, Rh-catalyzed conjugate additions to α,β-unsaturated compounds, and other metal-catalyzed cycloaddition reactions.[12]

The 1,4-addition of carbon nucleophiles to β,β-disubstituted α,β-unsaturated carbonyl compounds is a useful strategy for constructing quaternary carbon stereocenters.[13] The Rh-H_8-BINAP-catalyzed asymmetric 1,4-addition of arylboronic acids to 3-substituted maleimides afforded the desired products in high regio- and enantioselectivities (Scheme 8).



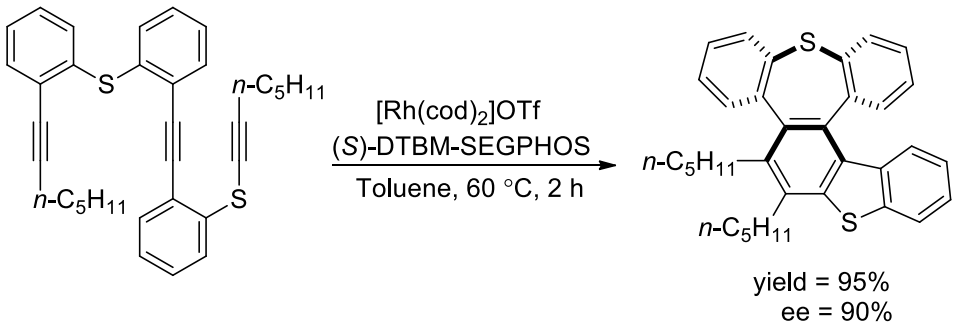
Scheme 8: Rh-catalyzed asymmetric 1,4-addition

The first catalytic synthesis of tribenzothiepin was carried out by Shibata group, with high enantioselectivity.[14] Rh-catalyzed cycloaddition was used as a novel strategy for the construction of the tribenzoheteropin framework. Intermolecular cycloaddition proceeded using the sulfur-containing cyclic system in the presence of the cationic Rh-MeO-BIPHEP catalyst (Scheme 9).



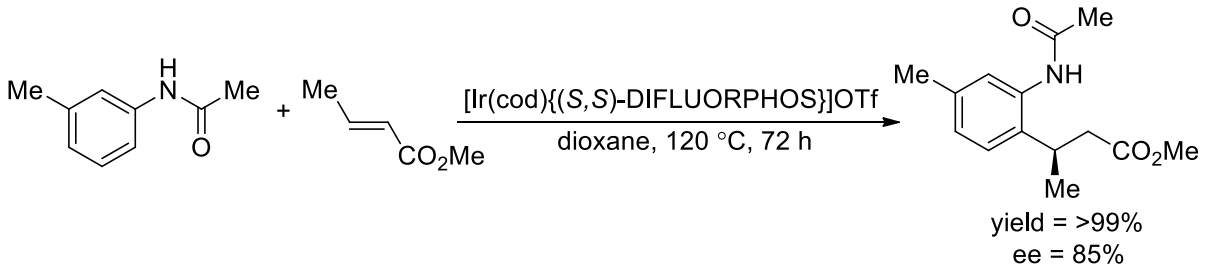
Scheme 9: Enantioselective synthesis by intermolecular cycloaddition

Shibata's group further reported an intramolecular cycloaddition of triynes using Rh-DTBM-SEGPHOS, which furnished tribenzothiepins in high yields and excellent enantiomeric excesses (Scheme 10).[15]



Scheme 10: Enantioselective intramolecular cycloaddition

Shibata's group also reported an enantioselective reaction of substituted acetanilides with β-substituted α,β-unsaturated esters using the cationic Ir-DIFLUORPHOS catalyst.[16] It was the first example of enantioselective formal C-H conjugate addition involving an sp^2 C-H bond activation to β-substituted α,β-unsaturated carbonyl compounds (Scheme 11).



Scheme 11: Enantioselective formal C-H conjugate addition

Planar-Chiral Scaffolds in Chiral Ligands

1) Solvias Ligand

Metal complexes having chiral ligands arguably are the most flexible catalysts for enantioselective transformation. In the reported literatures, large number of chiral ligands result in excellent enantioselectivities of the products in different catalytic reactions. However, organic chemists in research laboratories and industries have different perspectives. Although a vast library of chiral ligands exists, only a few of them, which are termed as "privileged ligands" by Jacobsen, are widely used for the synthesis of target molecules. There are many prerequisites for a chiral ligand to be employed by organic chemist to solve particular synthetic problems. The ready availability of the ligand increases its chances to be used in synthetic applications. For the building up of a comprehensive ligand portfolio Josiphos ligand would be a good model. Ferrocene-based ligands dominate this portfolio. Next addition to this portfolio is Walphos. Two ligand families with modularities similar to Josiphos and Walphos are Taniaphos and Mandyphos. The ligand portfolio is depicted in Figure 2. These ligands fulfil all the criteria of tunability, easy handling, scale-up, and manufacturing applications.

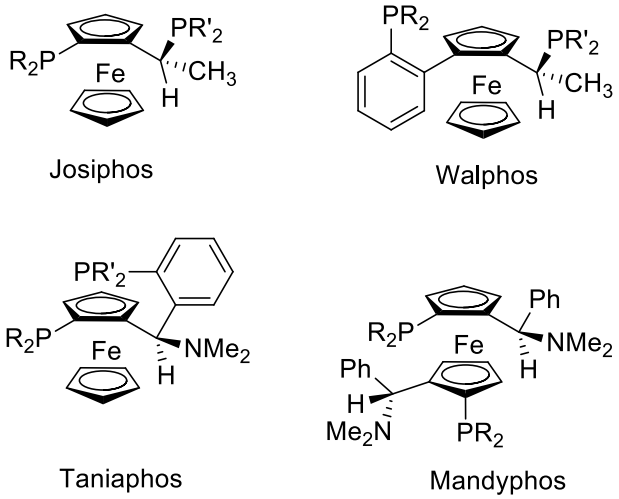
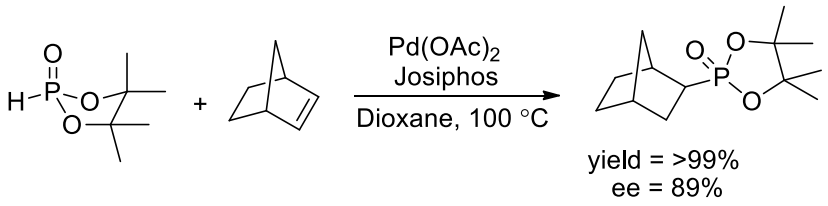


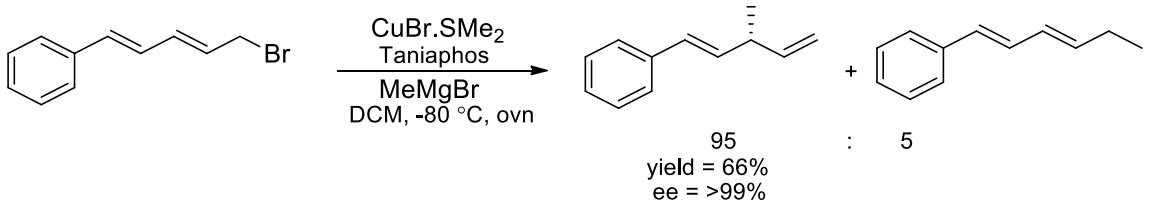
Fig. 2: Solvias ligand portfolios

A powerful method for the synthesis of enantiomerically pure heteroatom-containing compounds are the metal-catalyzed enantioselective additions of hydrogen-heteroatom bonds to alkenes. For example, the Pd-catalyzed asymmetric hydrophosphorylation of norbornenes[17] using Josiphos ligands proceeded effectively to result in the corresponding chiral phosphonates in high enantiomeric excesses (Scheme 12).



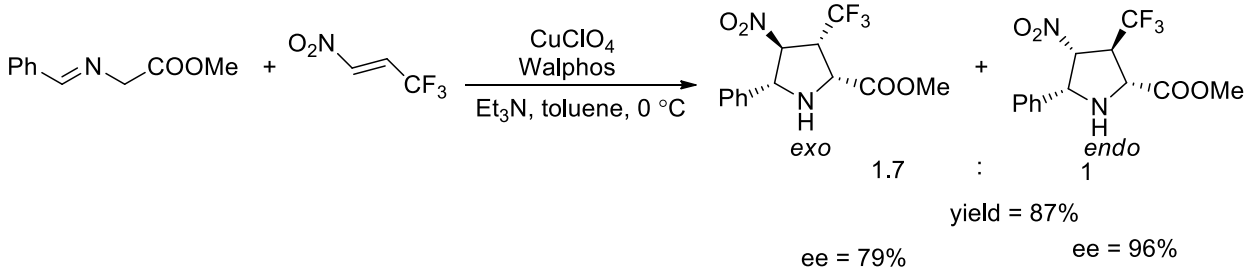
Scheme 12: Pd-catalyzed hydrophosphorylation

1,4-Dienes in natural products and polyunsaturated fatty acids have significant biological functions. A highly effective Cu-catalyzed asymmetric allylic alkylation of 1,3-dienyl bromides was developed for the enantioselective synthesis of 1,4-dienes with a methyl-substituted stereogenic carbon center.[18] Very good regio- and enantioselectivities were achieved using Taniaphos as a chiral ligand in this reaction (Scheme 13).



Scheme 13: Cu-catalyzed asymmetric allylic alkylation

Fluorine-containing amino acids are significant components due to their biological activities. A catalytic asymmetric cycloaddition reaction with azomethine ylides was developed from chiral Walphos ligand and copper(I) perchlorate.[19] This reaction provides a simple approach to obtain optically active *exo* 3-(trifluoromethyl)proline derivatives in high yields and enantiomeric excesses (Scheme 14).

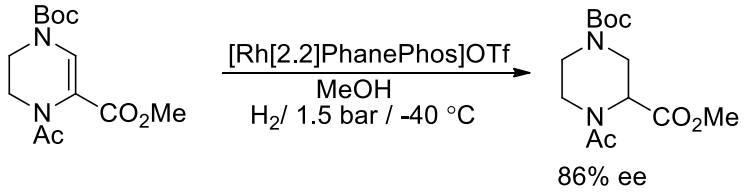


Scheme 14: Cu-catalyzed asymmetric [3+2] cycloaddition

2) Cyclophane Ligand

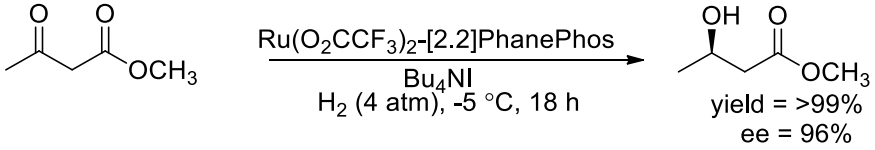
The demand for optically active compounds is significant and chiral phosphines play an important role in asymmetric catalysis for the synthesis of such compounds. Phosphines with central or axial chirality are common, while phosphines with planar chirality are less studied. The presence of an alternative chiral scaffold i.e, planar chirality, opens up new possibilities. Ferrocene derivatives such as JosiPhos contain a chiral center in addition to the planar chirality hence, separation of the influence of each of these two chiral elements is difficult. In this context, planar-chiral cyclophanes attract considerable attention due to their structural and electronic properties. The most common cyclophane is [2.2]paracyclophane, in which a molecule consisting of two eclipsing aryl rings is held together at the *para* position by two ethylene moieties. Unusual electronic properties originate due to the close

proximity of the benzene rings. The first successfully synthesized chiral phosphine ligand possessing the [2.2]paracyclophane scaffold is PhanePhos. It is the most commonly studied and versatile cyclophanyl ligands. The first use of PhanePhos was made in the hydrogenation of tetrahydropyrazine[20] at low temperature, that resulted in the corresponding product with 86% ee (Scheme 15). Previously employed standard phosphine ligands BINAP and Et-DUPHOS required harsh conditions and resulted in moderate ee of the products (56% with BINAP and 50% with Et-DUPHOS).



Scheme 15: Rh-catalyzed hydrogenation

In the Ru-catalyzed hydrogenation of β-keto esters, PhanePhos was also employed as a chiral ligand. An excellent enantioselectivity of 96% was achieved in the presence of NBu_4I at low temperature.[21] In contrast, BINAP derivatives gave poor results under similar conditions (Scheme 16).



Scheme 16: Ru-catalyzed hydrogenation

Asymmetric synthesis and the uses of planar-chiral [2.2]paracyclophane-based ligands are less explored when compared to the planar-chiral ferrocenyl compounds. In the development of new methodologies for the synthesis of optically pure derivatives, the chemistry of [2.2]paracyclophane is often used. To investigate their applications in catalysis, organic chemists have developed some interest in the synthesis of a variety of [2.2]paracyclophanes and successfully expanded the tool-box (Figure 3).

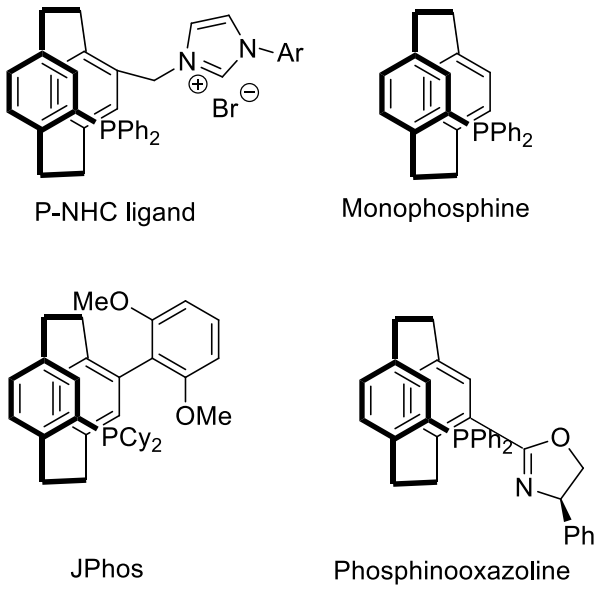
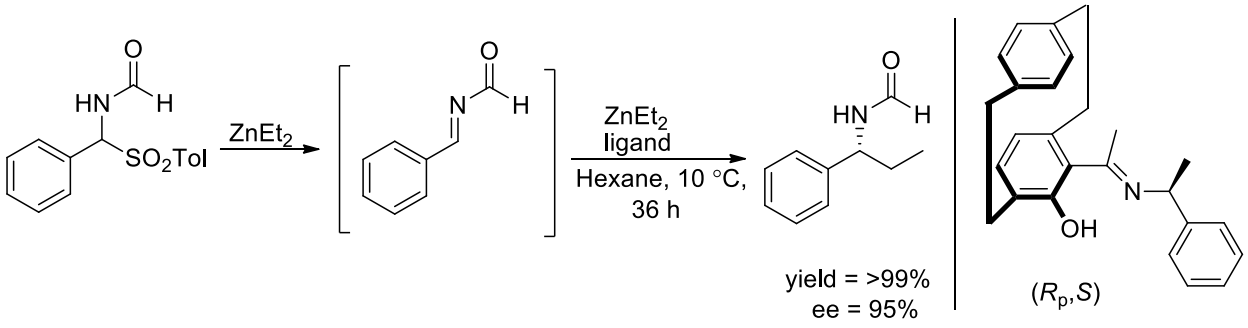


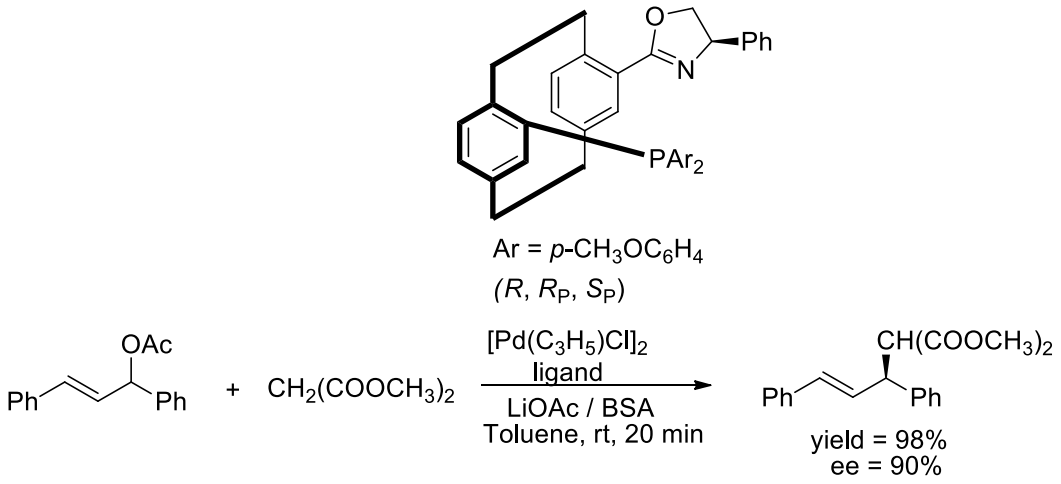
Fig. 3: Different types of [2.2]paracyclophane-based ligands

The enantioselective addition of organometallic reagents to C=N bonds is one of the important reactions for the preparation of chiral amines in homogeneous catalysis. Addition of dialkylzinc to imines[22] was reported in the presence of the [2.2]paracyclophane-based *N,O*-ligand (Scheme 17).



Scheme 17: Enantioselective addition of diethylzinc addition to imines

Planar-chiral *P,N*-[2.2]paracyclophane ligands were synthesized and studied in the asymmetric Pd-catalyzed allylic alkylation.[23] *P,N*-Ligands realized a high reactivity and led to the completion of the reaction within 20 min and gave the chiral product in an almost quantitative yield and high ee (Scheme 18).



Scheme 18: Pd-catalyzed allylic alkylation

[2.2]Paracyclophane ligands as novel cytostatics

By the derivatization of [2.2]paracyclophane with tunable polar groups, a selective drug can be obtained. [2.2]Paracyclophanyl gold(I) complex has recently been explored as a substitute for therapeutically well-known cisplatin (Figure 4).[24]

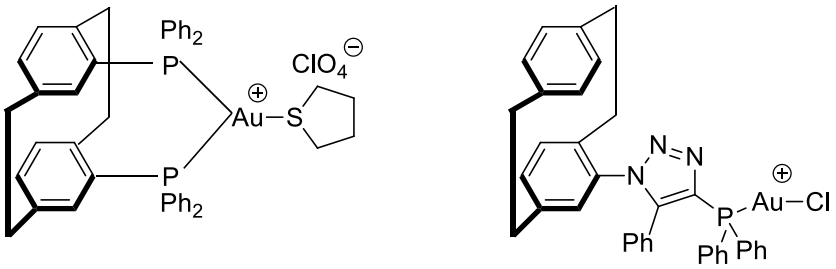
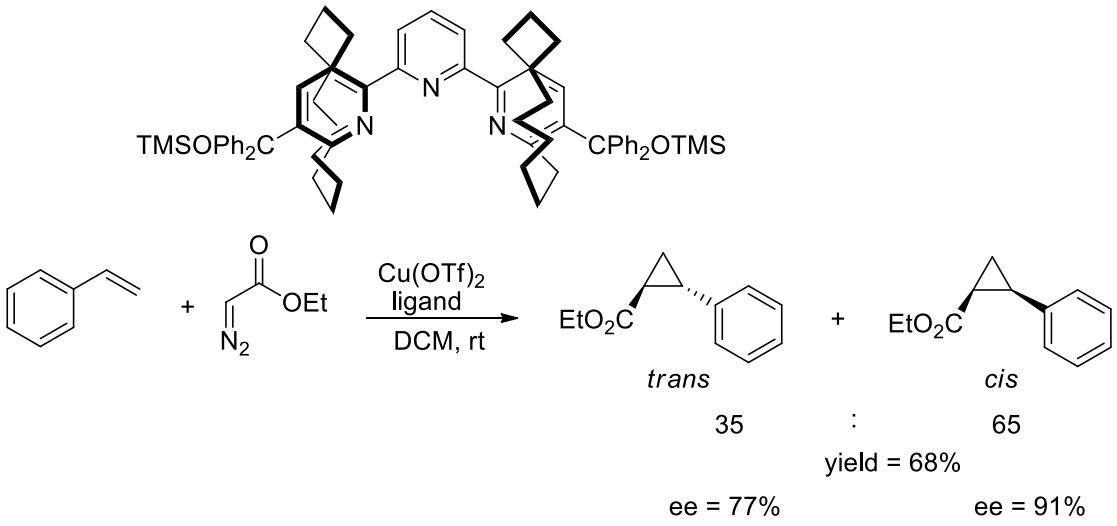


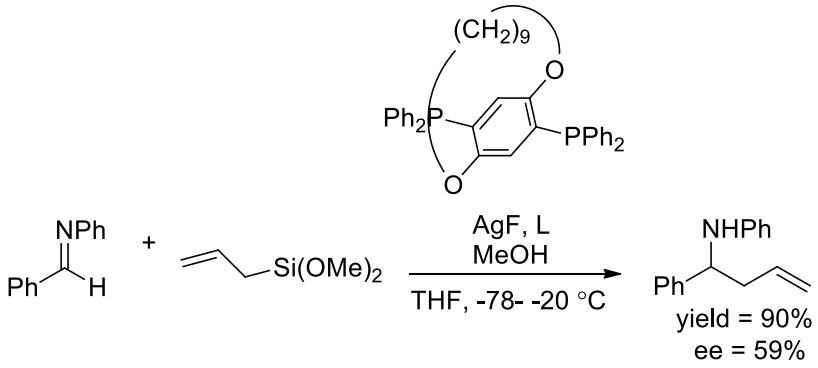
Fig. 4: Paracyclophane gold(I) complexes as cytostatics

Besides [2.2]paracyclophanes, pyridinophane backbones also have the planar chirality. Kanomata has studied the stereocontrolled synthesis of parapyridinophanes. An enantioselective cyclopropanation[25] was explored using a Cu catalyst in the presence of C_2-symmetric planar-chiral bridged terpyridines. Moderate diastereomeric excess and high enantiomeric excess were achieved (Scheme 19).



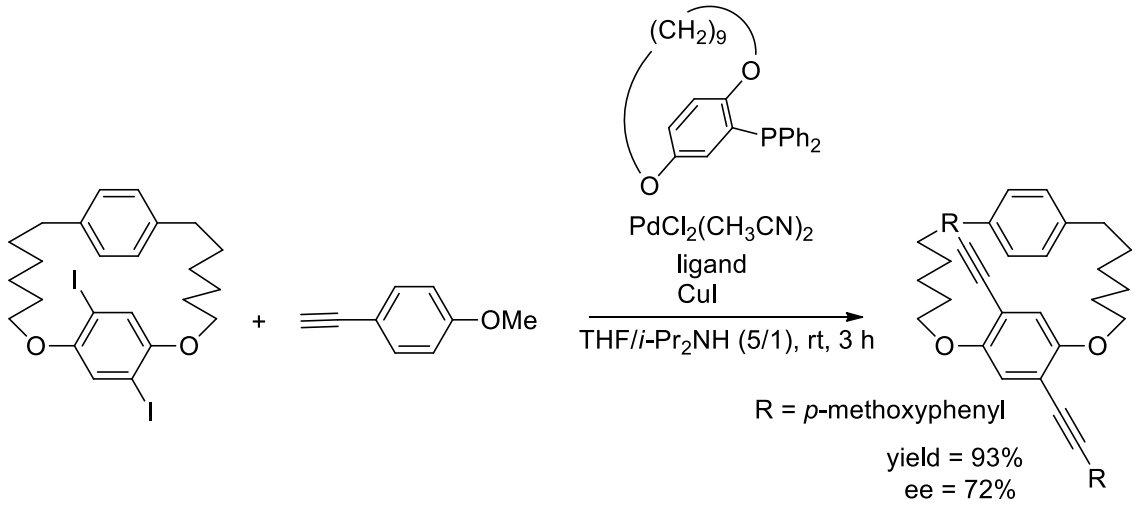
Scheme 19: Cu-catalyzed enantioselective cyclopropanation

Besides these examples, asymmetric synthesis of planar-chiral paracyclophanes was reported by Shibata's group. Enantioselective *ortho*-lithiation of paracyclophane was carried out to obtain planar-chiral paracyclophanes in good to excellent enantioselectivities. Synthetic applications as chiral ligands in asymmetric reactions were tested after synthesizing corresponding monophosphino and diphosphino paracyclophanes. Silver-catalyzed allylation of arylamine[26] with the planar-chiral paracyclophanyl phosphine resulted in moderate enantiomeric excess of the corresponding product (Scheme 20).



Scheme 20: Ag-catalyzed enantioselective allylation of imine

Next, enantioselective double Sonogashira coupling[27] of diiodoparacyclophane was realized with paracyclophanyl phosphine as chiral ligand, which resulted in the product with good enantioselectivity (Scheme 21).



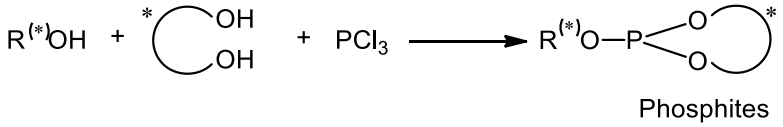
Scheme 21: Enantioselective Sonogashira coupling

- **Purpose of The Research in These Chapters**

As mentioned above, planar-chiral paracyclophane is an attractive privileged chiral source that has a major role in the field of asymmetric catalysis. New ligands are always required for new reactions. Furthermore, facile methods for the synthesis of ligand and the stabilities of the synthesized ligands are foremost essential, and hence, generation of a ligand library is very useful.

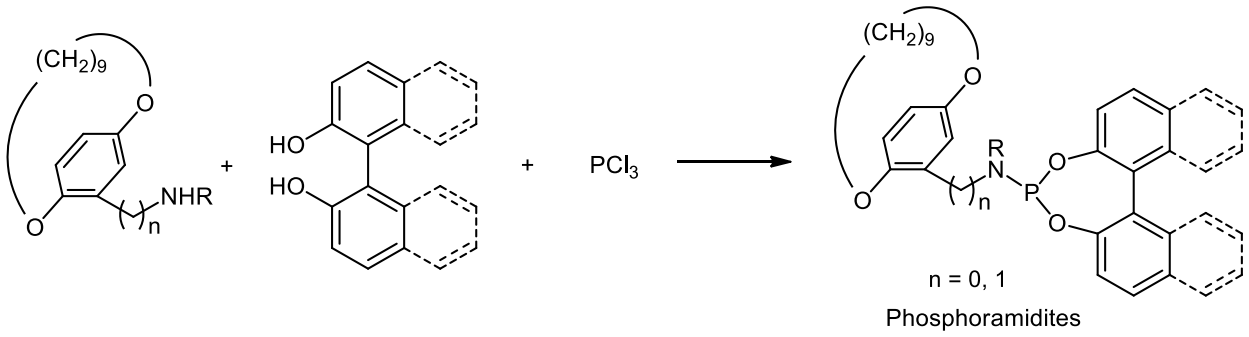
In this thesis, the author describes two new approaches for the synthesis of planar-chiral paracyclophanyl-phosphite/phosphoramidite ligands and examines their performance in two benchmark asymmetric reactions. These ligands are versatile and allow a fine tuning of substituents. They are stable under ambient conditions and thus are easy to handle.

Chapter 2 describes the synthesis of planar-chiral paracyclophanyl phosphite ligands (Scheme 22). They were prepared in two steps from a chiral alcohol and a chiral diol. They were tested in two standard asymmetric reactions to check their efficiency.



Scheme 22: Outline review for synthesis of paracyclophanyl phosphites

Chapter 3 describes the synthesis of planar-chiral paracyclophanyl phosphoramidite ligands (Scheme 23). A versatile ligand library was built; each ligand was obtained in three steps from a chiral amine and a chiral diol. The efficiency of the ligands was tested in two well-known asymmetric reactions.



Scheme 23: Outline review for synthesis of paracyclophanyl phosphoramidites

- **References**

1. Dang, T.-P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481-481.

2. Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567-2568.

3. Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999-2007.

4. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc*. **1987**, *109*, 5856-5858.

5. Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc*. **1984**, *106*, 5208-5217.

6. Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc*. **2006**, *128*, 13686-13687.

7. Aida, Y.; Sugiyama, H.; Uekusa, H.; Shibata, Y.; Tanaka, K. *Org. Lett*. **2016**, *18*, 2672-2675.

8. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580.

9. Boz, E.; Haslak, Z. P.; Tuzun, N. S.; Konuklar, F. A. S. *Organometallics* **2014**, *33*, 5111-5119.

10. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 1417-1419.

11. Gillespie, J. A.; Zuidema, E.; van Leeuwan, P.W. M. N.; Kamer, P. C. J. *Phosphorus (III) ligands in homogeneous catalysis: Design and Synthesis*, Wiley 2012.

12. (a) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem*. **2001**, *66*, 6852-6856. (b) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628-5629.

13. Shintani, R.; Duan, W.-L.; Hayashi, T.; *J. Am. Chem. Soc*. **2006**, *128*, 5628-5629.

14. Tahara, Y.; Matsubara, R.; Mitake, A.; Sato, T.; Kanyiva, K. S.; Shibata, T. *Angew. Chem. Int. Ed*. **2016**, *55*, 4552-4556.

15. Mitake, A.; Fusamae, T.; Kanyiva, K. S.; Shibata, T. *Eur. J. Org. Chem*. **2017**, 7266-7270.

16. Shibata, T.; Michino, M.; Kurita, H.; Tahara, Y.; Kanyiva, K. S. *Chem. Eur. J.* **2017**, *23*, 88-91.

17. Xu, Q.; Han, L.-B. *Org. Lett*. **2006**, *8*, 2099-2101.

18. Huang, Y.; Fananas-Mastral, M.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun*. **2013**, *49*, 3309-3311.

19. Li, Q.; Ding, C.-H.; Li, X.-H.; Weissensteiner, W.; Hou, X.-L. *Synthesis*, **2012**, *44*, 265-271.

20. Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc*. **1997**, *119*, 6207-6208.

21. Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1998**, *39*, 4441-4444.

22. Dahmen, S.; Brase, S. *J. Am. Chem. Soc*, **2002**, *124*, 5940-5941.

23. Wu, X-W.; Yuan, K.; Sun, W.; Zhang, M. J.; Hou, X.-L. *Tetrahedron: Asymmetry* **2003**, 107-112.

24. Bestgen, S.; Seidl, C.; Weisner, T.; Zimmer, A.; Falk, M.; Koberle, B.; Austeri, M.; Paradies, J.; Brase, S.; Schepers, U.; Roesky, P. W. *Chem. Eur. J*. **2017**, *23*, 6315-6322.

25. Mugishima, N.; Kanomata, N.; Akutsu, N.; Kubota, H. *Tetrahedron Lett*. **2015**, *56*, 1898-1903.

26. Kanda, K.; Hamanaka, R.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 1407-1416.

27. Kanda, K.; Oshima, S.; Shizuno, T.; Hamanaka, R.; Fukai, M.; Shibata, T. *Heterocycles* **2014**, *88*, 1355-1370.

Chapter 2

Synthesis of Planar-Chiral Paracyclophanyl Phosphite Ligands and Their Application to Asymmetric Reactions

• Background

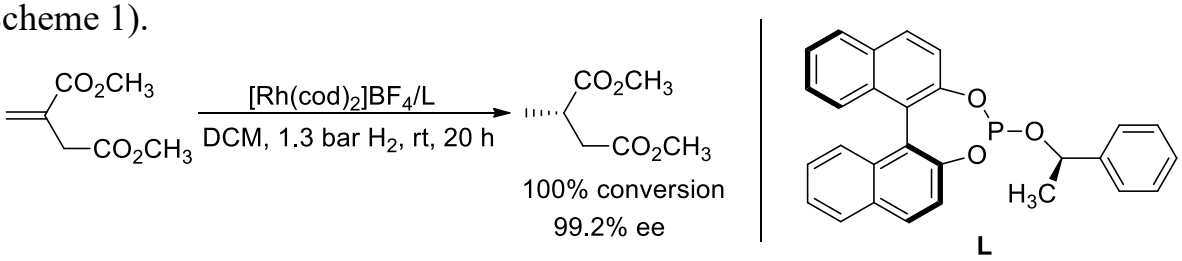
Several natural building blocks have been widely used to develop chiral ligand libraries. However, the availability of both (*R*)-and (*S*)-BINOLs in optically pure forms has directed the synthetic community toward the synthesis of chiral ligands and new materials. BINOL derivatives are currently considered as favourable backbones of chiral ligands and are used in various catalytic asymmetric carbon-carbon bond forming reactions including allylic alkylation, conjugate addition, and Diels-Alder reaction.[1] Moreover, chiral phosphorus ligands with binaphthyl scaffold have earned the status of "privileged ligands" due to their wide use in asymmetric transformations. A diverse family of chiral phosphorus ligands with various chemical properties is prepared by introducing heteroatoms including phosphites and phosphoramidites.

Phosphite Ligands

Phosphites are attractive chiral ligands for developing several catalytic asymmetric reactions. Phosphites are generally easy to prepare from readily available chiral or achiral alcohols, less sensitive to air, and stable under ambient conditions. In the last decade, there has been continuing interest in chiral monodentate phosphorus ligands due to their excellent performances in catalytic asymmetric reactions including hydrogenation and allylic substitution. Facile structural variation of monodentate ligands by straightforward synthesis is highly advantageous. In recent years, many ligand libraries of BINOL-based monodentate phosphites were developed. During the ligand design, several modifications were performed by varying either the alcohol unit or the substituent at the binaphthyl moiety. A two-step procedure was generally involved in synthesizing monodentate phosphite ligands. Selected examples of asymmetric applications of monodentate phosphites are mentioned below.

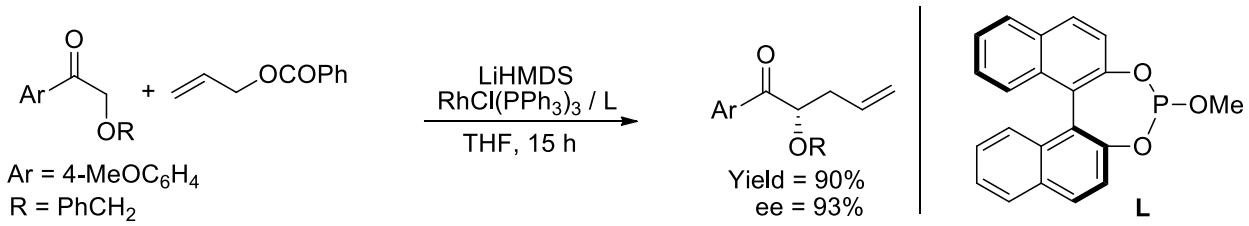
Examples of Chiral Phosphite Ligands:

The first highly enantioselective Rh-catalyzed hydrogenation involving a chiral monophosphate ligand was reported by Reetz in 2000.[2] A BINOL-based monophosphite with a chiral alcohol moiety proved to be an excellent ligand (Scheme 1).



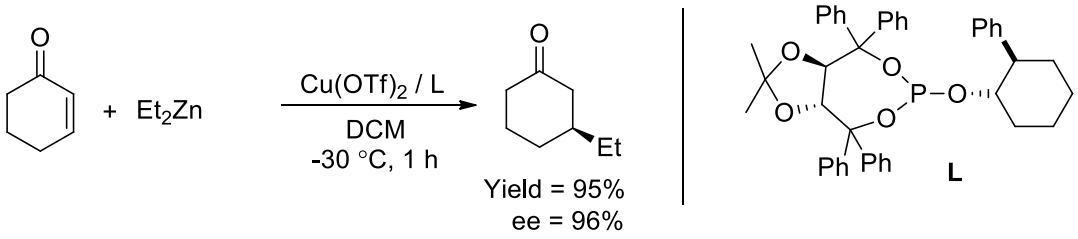
Scheme 1: Hydrogenation by monodentate phosphite ligand

Evans *et al*. reported a highly enantioselective allylic alkylation of acyclic α-alkoxy aryl ketones using a Rh-catalyst derived from Wilkinson's complex and a chiral monodentate phosphite.[3] This was the first enantioselective Rh-catalyzed allylic substitution with a prochiral nucleophile. Its ability to transform aryl ketones illustrates the potential application of this transformation to target-directed synthesis (Scheme 2).



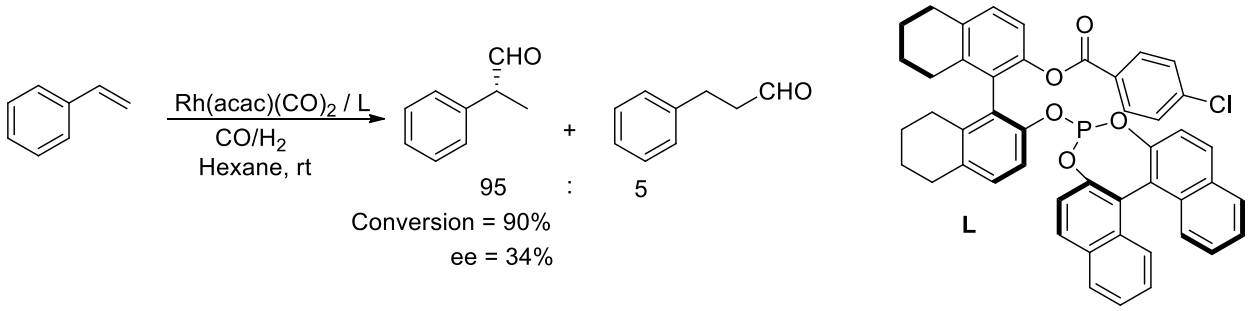
Scheme 2: Rh-catalyzed allylic alkylation

A new series of monodentate phosphites based on TADDOL was synthesized and these operated as efficient chiral ligands in Cu-catalyzed 1,4-conjugate addition (Scheme 3).[4]



Scheme 3: Cu-catalyzed 1,4-conjugate addition

A new series of phosphites based on axially chiral monoesterified H_8-BINOL and BINOL was synthesized. In the Rh-catalyzed asymmetric hydroformylation of styrene,[5] these ligands showed excellent chemoselectivity for branched aldehydes, but with low enantioselectivity (Scheme 4).



Scheme 4: Rh-catalyzed asymmetric hydroformylation of styrene

Purpose of This Chapter

As mentioned above, asymmetric reactions with chiral phosphite ligands represent an important tool for obtaining various optically active compounds. Thus, the author predicted that enantioselective synthesis of planar-chiral paracyclophanyl phosphite would be important in generating a new chiral ligand library.

In this chapter, the author describes the enantioselective synthesis of planar-chiral paracyclophanyl phosphites as shown in Fig.1. Synthesized ligands were used in enantioselective Pd-catalyzed allylic alkylation and Rh-catalyzed 1,4-addition to test their efficiency.

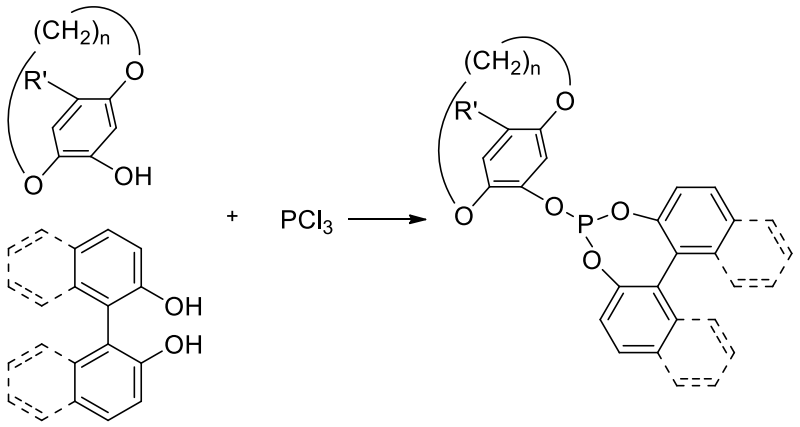


Fig. 1: Outline review for the synthesis of planar-chiral paracyclophanyl phosphites

- **Results and Discussion**

Chiral phosphites were generally synthesized by reacting achiral or chiral alcohols and BINOL or biphenol with phosphorus trichloride (Fig. 2).

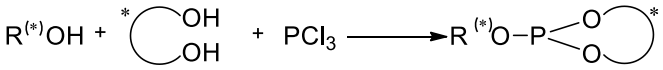
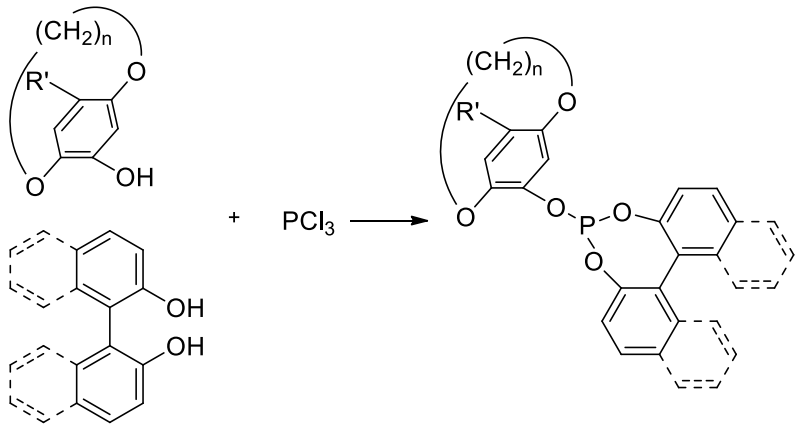


Fig. 2: Outline review for the synthesis of chiral phosphites

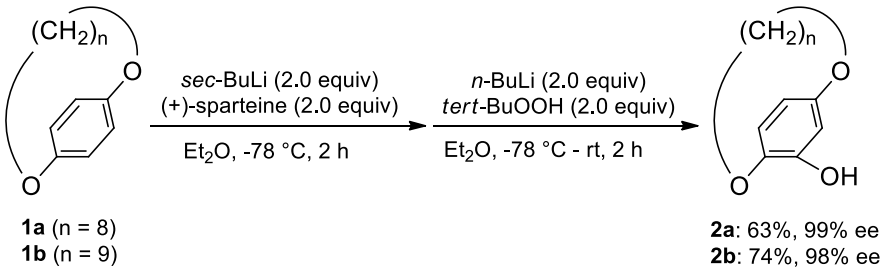
Herein, chiral alcohols ($R^{(*)}OH$) and BINOL were used, which would cooperatively induce high enantioselectivity.[6] A combination of planar-chiral 1,*n*-dioxa[*n*]paracyclophane possessing a hydroxyl group and BINOL as a backbone was used for the reactions of a new library of phosphites (Scheme 5). A substituent (R') at the *para*-position is considered to regulate the paracyclophane scaffold sterically and/or electronically.



Scheme 5: Synthesis of planar-chiral paracyclophanyl phosphites

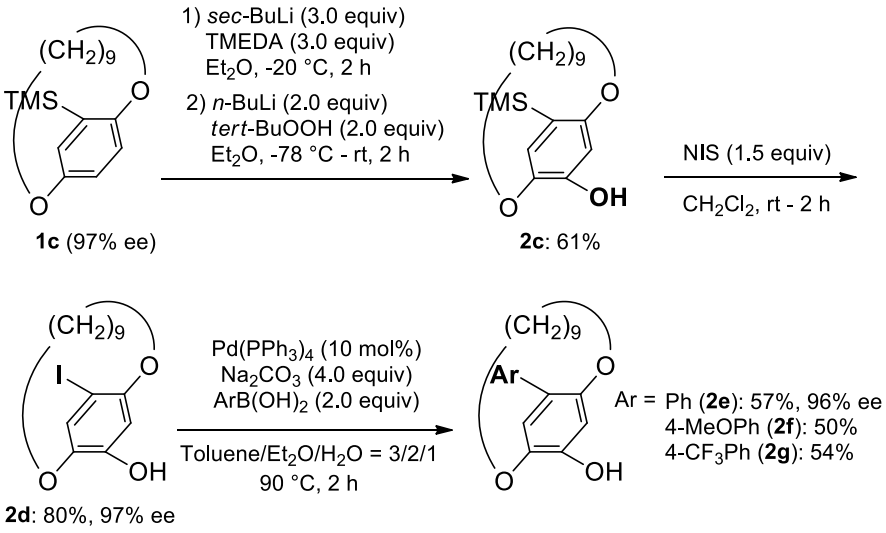
Synthesis of substituted paracyclophanyl alcohols

To introduce a hydroxyl group to 1,*n*-dioxa[*n*]paracyclophanes, a lithium salt of *tert*-butyl hydroperoxide was selected as an electrophile.[7] The reaction of aryllithium synthesized from 1,*n*-dioxa[*n*]paracyclophanes **1a** (n = 8), *sec*-BuLi, and (+)-sparteine afforded planar-chiral hydroxyl derivative **2a**. Under the same reaction conditions, **2b** (n = 9) was prepared from **1b**. Excellent enantioselectivity was obtained in both transformations (Scheme 6).



Scheme 6: Synthesis of paracyclophanyl alcohols

Moreover, the author prepared a para-substituted paracyclophanyl alcohol from TMS-substituted paracyclophane **1c**. *Para*-selective lithiation was performed under literature conditions.[8] A reaction with the lithium salt of *tert*-butyl hydroperoxide[9] afforded paracyclophanyl alcohol **2c** in good yield. A subsequent reaction with NIS furnished iodo-substituted paracyclophanyl alcohol **2d** as a vital synthetic intermediate in good yield. The retention of an enantiomeric excess of **2d** was confirmed. *Para*-arylated paracyclophanyl alcohols **2e**-**2g** were prepared by Suzuki coupling under literature conditions.[10] Retention of an enantiomeric excess was verified using compound **2e** (96% ee) (Scheme 7). It was slightly decreased.

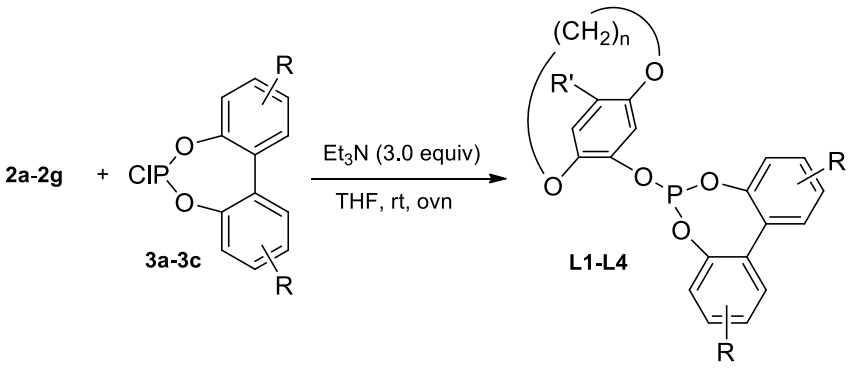


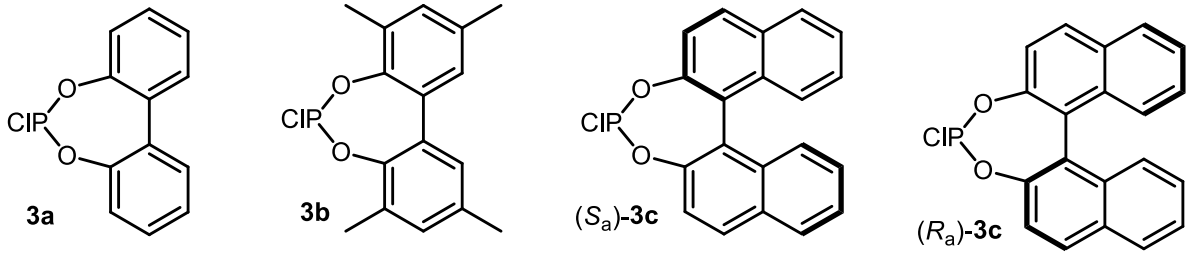
Scheme 7: Synthesis of aryl-substituted paracyclophanyl alcohols

Synthesis of planar-chiral paracyclophanyl phosphites

The author subsequently synthesized planar-chiral paracyclophanyl phosphites starting from paracyclophanyl alcohol (Table 1). The reaction of **2a** with 2,2'-biphenylene phosphorochloridite **3a** in the presence of triethylamine afforded the desired planar-chiral phosphite **L1** (Entry 1).[11] The reaction with **2b** similarly afforded planar-chiral phosphite **L2** (Entry 2). Bulky phosphite **L3** containing tetramethyl groups on the biphenyl backbone was also prepared from **2b** in moderate yield (Entry 3). These ligands were stable in air. The reaction with axially chiral 2,2'-binaphthyl phosphorochloridites **3c** furnished (S_a)-**L4** and (R_a)-**L4** (Entries 4 and 5). While phosphite (S_a)-**L4** was sufficiently stable to be isolated, its diastereomer (R_a)-**L4** was unstable and easily hydrolyzed even during isolation by Florisil® column chromatography. It was subsequently obtained as a mixture of phosphite (R_a)-**L4** and alcohol **2b** (Entries 4 and 5). *Para*-substituted paracyclophanyl phosphite **L2**(TMS) was also prepared from TMS-substituted paracyclophanyl alcohol **2c** in good yield (Entry 6). Other *para*-substituted paracyclophanyl phosphites including **L2**(Ph), **L2**(MeOPh), and **L2**(CF_3Ph) were prepared from **2e**-**2g** according to the same protocol (Entries 7-9).

Table 1: Synthesis of planar-chiral phosphites





Entry	Alcohol **2**	**3**	Phosphites	Yield (%)
1	**2a**	**3a**	**L1**	66
2	**2b**	**3a**	**L2**	89
3	**2b**	**3b**	**L3**	56
4	**2b**	(S_a)-**3c**	(S_a)-**L4**	98
5	**2b**	(R_a)-**3c**	(R_a)-**L4**	ca.80[a]
6	**2c**	**3a**	**L2**(TMS)	83
7	**2e**	**3a**	**L2**(Ph)	69
8	**2f**	**3a**	**L2**(MeOPh)	58
9	**2g**	**3a**	**L2** (CF_3Ph)	37

[a] The total yield of phosphite (R_a)-**L4** and monool **2b**.

Thermal Stability

The thermal stability of paracyclophanyl alcohol **2b** was investigated by heating in DCE for two hours at different temperatures. An enantiomeric excess of 98% was retained even at 60 ˚C. However, it decreased to 88% ee at 80 ˚C. Therefore, paracyclophanyl alcohol **2b** is sufficiently stable up to 60 ˚C and *para*-substituted paracyclophanyl alcohols **2c** and **2e**-**2g** are considered more stable than **2b**.

The reactions of paracyclophanyl alcohols and phosphorochloridites were performed at room temperature (Table 1), thus, the enantiomeric excess of phosphite ligands can be considered equivalent to that of original paracyclophanyl alcohols.

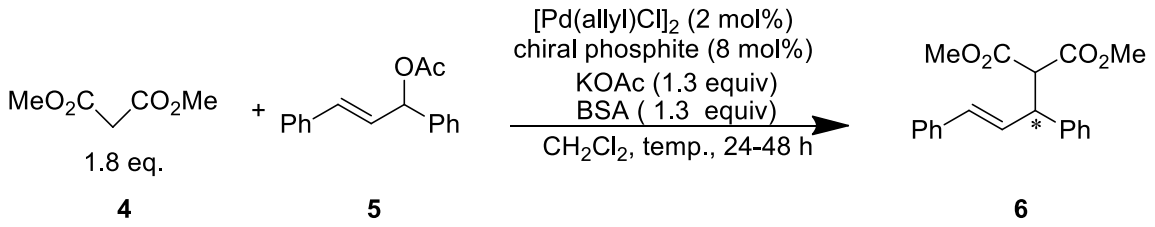
Application

These phosphite ligands were employed as chiral ligands in two standard reactions: Pd-catalyzed allylic alkylation and Rh-catalyzed 1,4-addition.

Enantioselective allylic alkylation

The author initially investigated the synthesized planar-chiral phosphites in enantioselective Pd-catalyzed allylic alkylation (Table 2).[6] The reaction between dimethyl malonate (**4**) and (*E*)-1,3-diphenylallyl acetate (**5**) proceeded almost quantitatively when using phosphite **L1** or **L2** (Entries 1 and 2). The enantiomeric excess of compound **6** was moderate. An observed decrease in the enantiomeric excess was probably caused by steric hindrance and the (*S*)-**6** was the major enantiomer regardless of the absolute configuration of the axial chirality of the phosphite (Entries 4 and 5). Furthermore, the enantiomeric excess was almost the same as that obtained using a ligand without axial chirality. These results showed that enantioinduction was governed by the planar-chirality of the 1,*n*-dioxa[*n*]paracyclophane scaffold. The author tested *para*-substituted paracyclophanyl phosphites, but the enantioselectivity was not improved (Entries 6-9). The author further screened the reaction temperature. At lower temperature, the enantioselectivity gradually increased and the enantiomeric excess of compound **6** was 73% at -60 ˚C, albeit in low yield due to the low conversion (Entry 12). But no reaction proceeded at -78 ˚C (Entry 13).

Table 2: Enantioselective Pd-catalyzed allylic alkylation



Entry	Phosphite	Temp. (˚C)	Yield (%)[b]	Ee (%)[c]
1	**L1**	rt	>99	49 (*S*)
2	**L2**	rt	98	42 (*S*)
3	**L3**	rt	>99	8 (*R*)
4	(S_a)-**L4**	rt	69	42 (*S*)
5	(R_a)-**L4**[a]	rt	>99	43 (*S*)
6	**L2**(TMS)	rt	>99	31 (*S*)
7	**L2**(Ph)	rt	>99	33 (*S*)
8	**L2**(MeOPh)	rt	>99	26 (*S*)
9	**L2**(CF_3Ph)	rt	>99	43 (*S*)
10	**L2**	0	>99	55 (*S*)
11	**L2**	-40	>99	66 (*S*)
12	**L2**	-60	31	73 (*S*)
13	**L2**	-78	N.R.	-

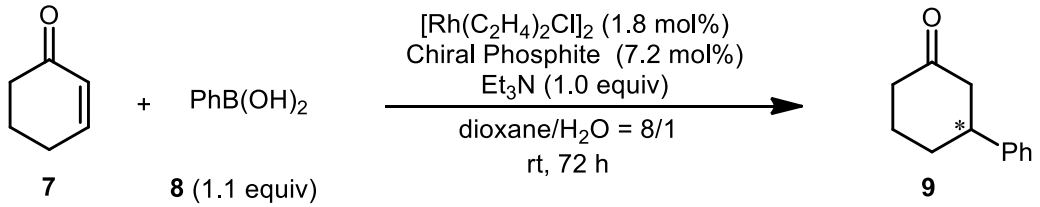
[a] A mixture of phosphite (R_a)-**L4** and monool **2b** was used. [b] Isolated yield. [c] Ee was determined by HPLC analysis using Daicel Chiralcel OD-3 (eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min). The absolute configuration of the major isomer was described in the parentheses.

Enantioselective Rh-catalyzed 1,4-addition

The author employed the planar-chiral paracyclophanyl phosphites as chiral ligands in Rh-catalyzed 1,4-addition of cyclohex-2-enone (**7**) with phenylboronic acid (**8**) (Table 3).[12] The different structures of phosphites **L1** and **L2** with different ansa chain lengths affected the catalytic activity. With ligand **L1** (n=8), the reaction did not proceed at all, while with ligand **L2**, it proceeded with moderate yield and enantioselectivity (Entries 1 and 2). Generally, cyclophanes possessing a shorter ansa chain are more rigid, namely more bulky. Probably Rh-catalyzed 1,4-addition is sensitive to steric bulkiness and more bulky ligand deterred the reaction. With

bulky phosphite **L3**, the reaction did not proceed possibly due to steric hindrance (Entry 3). Diastereomers (S_a)-**L4** and (R_a)-**L4** gave contrasting results (Entries 4 and 5). While compound **9** was obtained in low yield and enantiomeric excess by using (S_a)-**L4**, no reaction occurred when using (R_a)-**L4** probably due to contamination by monool **2b**. When *para*-substituted paracyclophanyl phosphites were examined, **L2**(TMS) gave the best enantioselectivity of all the ligands and phenylated product **9** was obtained in moderate yield (Entries 6-9).

Table 3: Enantioselective Rh-catalyzed 1,4-addition



7 **8** (1.1 equiv) **9**

Entry	Phosphite	Yield (%)	Ee (%)
1	**L1**	NR	-
2	**L2**	49	36 (*S*)
3	**L3**	NR	-
4	(S_a)-**L4**	36	16 (*S*)
5	(R_a)-**L4**[a]	NR	-
6	**L2** (TMS)	66	40 (*S*)
7	**L2** (Ph)	18	31 (*S*)
8	**L2** (MeOPh)	19	37 (*S*)
9	**L2** (CF_3Ph)	67	30 (*S*)

[a] A mixture of phosphite (R_a)-**L4** and monool **2b** was used. [a] Isolated yield. [b] Ee was determined by HPLC analysis using Daicel Chiralcel OD-3 (eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min). The absolute configuration of the major isomer was described in the parentheses.

Enantioselective Induction

When ligands **L1** and **L2** possessing only planar-chirality were investigated in Pd-catalyzed allylic alkylation, moderate enantioselectivity was achieved. Conversely, ligands (S_a)- and (R_a)-**L4** possessing both planar and axial chiralities exhibited almost the same enantioselectivity. Therefore, it can be deduced that the enantioselectivity was governed by the planar chirality derived from paracyclophane. The axial chirality of the BINOL moiety minimally affected this reaction. Various *para*-substituted planar-chiral ligands were screened and they showed moderate enantioselectivity. Ligand **L2** showed moderate enantioselectivity for 1,4-addition. When (S_a)-**L4** was screened, it induced low enantioselectivity. Low enantioselectivity was probably due to steric repulsion of paracyclophane moiety which was far from the substrate. Therefore, the enantioselectivity was governed by the planar-chirality of paracyclophane. The substituent at the *para*-position slightly affected the enantioselectivity and the highest enantioselectivity was achieved with TMS-substituted paracyclophane.

- ## Conclusion

The author synthesized planar-chiral paracyclophanes with a hydroxy group through enantioselective *ortho*-lithiation and converted them to paracyclophanyl phosphites by reaction with 2,2'-biarylene phosphorochloridites. A ligand library was prepared by varying the substituents at the paracyclophane moiety or using BINOL and biphenol as backbones. Most of these ligands were stable in air. The obtained phosphites were used as chiral ligands in Pd-catalyzed allylic alkylation and Rh-catalyzed 1,4-addition. Moderate enantioselectivity was achieved in both reactions and enantioinduction was governed by the planar chirality of paracyclophane.

- **Experimental Section**

General: ^{1}H NMR spectra were recorded on JEOL ECX-500 (500 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. ^{13}C NMR spectra were obtained by JEOL ECX-500 (125 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.16 ppm in $CDCl_3$). $CDCl_3$ was used as a NMR solvent. High-resolution mass spectra (HRMS) were measured on an ESI (Electro Spray Ionization)-Orbitrap mass spectrometer method. Optical rotations were measured on a JASCO DIP-1000 polarimeter. IR was measured in JASCO FT/IR-4100ST. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in our laboratory, Flash column chromatography was performed over silica gel 200-300. All reactions were performed under argon atmosphere. All reagents were purchased from Wako, Kanto, Aldrich and TCI and used without further purification.

Experimental procedure of enantioselective synthesis of paracyclophanes 2b

A cyclohexane solution of *sec*-butyllithium (0.99 M, 1 mL, 1.0 mmol) was added dropwise to an ethereal solution (5.0 mL) of 1,*n*-dioxaparacyclophane (*n* = 11 (**1b**), 1.0 mmol) and (+)-sparteine (0.23 mL, 1.0 mmol) at -78 °C and the reaction was stirred for 2 h. In another vacuum dried Schlenk tube, dropwise addition of *n*-BuLi (1.54 M, 0.98 ml, 1.5 mmol) to a solution of *tert*-butyl hydroperoxide (5.5 M, 0.30 ml, 1.5 mmol) in Et_2O (5.0 ml) was carried out at -78 °C and stirred for 30 min. This solution was transferred to the previous reaction mixture via cannula and warmed to ambient temperature. It was quenched with 1 M HCl (20 ml) aqueous solution and extracted with dichloromethane (3×10 ml). The organic layer was washed with brine and dried over Na_2SO_4. It was evaporated under reduced pressure and resultant residue was purified through flash column chromatography.

12-Hydroxy-1,10-dioxa[10]paracyclophane (2a): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as white solid (74.4 mg, 63%). mp 43 °C; IR (CH_2Cl_2) 3380.6, 2933.2, 2869.6, 1596.8, 1492.6, 1139.7, 860.1 cm^{-1}; ^{1}H NMR δ 6.94 (d, *J* = 8.9 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 6.57 (dd, *J* = 2.7, 8.9 Hz, 1H), 5.83 (s, 1H), 4.28-4.24 (m, 1H), 4.20-4.12 (m, 3H), 1.73-1.58 (m, 2H), 1.54-1.46 (m, 1H), 1.39-1.31 (m, 1H), 0.94-0.64 (m, 8H); ^{13}C NMR δ 155.0, 150.1, 139.7, 120.9, 113.8, 108.9, 73.2, 72.0, 28.2, 28.1, 26.6, 24.7, 24.5 (A pair of peaks at the aliphatic region is overlapping); HRMS(ESI, positive): *m/z* calcd. for $C_{14}H_{21}O_3$: 237.1485; found: 237.1486; $[\alpha]^{28}_{D}$ = 92.2 (*c* 0.85, $CHCl_3$, 99% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane,

flow rate: 1.0 mL/min, retention time: 9.1 min for major isomer and 13.7 min for minor isomer).

13-Hydroxy-1,11-dioxa[11]paracyclophane (2b): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as white solid (185.1 mg, 74%). mp 56 °C; IR (CH_2Cl_2) 3338.2, 2929.3, 2850.3, 1592.9, 1504.2, 1245.8, 835.0 cm^{-1}; ^1H NMR δ 6.95 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 6.59 (dd, *J* = 2.9, 8.8 Hz, 1H), 5.89 (s, 1H), 4.32-4.26 (m, 1H), 4.23-4.12 (m, 3H), 1.70-1.57 (m, 4H), 1.08-0.78 (m, 10H); ^{13}C NMR δ 156.0, 149.0, 141.0, 119.7, 112.1, 108.0, 72.5, 71.5, 30.1, 30.1, 27.8, 26.1, 26.0, 25.6, 25.2; HRMS(ESI, positive): *m/z* calcd. for $C_{15}H_{23}O_3$: 251.1642; found: 251.1642; $[\alpha]^{29}_D$ = 54.6 (*c* 0.94, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8.3 min for major isomer and 13.3 min for minor isomer).

13-Hydroxy-16-(trimethylsilyl)-1,11-dioxa[11]paracyclophane (2c): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as white solid (144.4 mg, 61%). mp 118 °C; IR (CH_2Cl_2) 3374.8, 2933.2, 2858.0, 1589.1, 1492.6, 1407.8, 1253.5, 1147.4, 1047.2, 842.7 cm^{-1}; ^1H NMR δ 6.99 (s, 1H), 6.61 (s, 1H), 5.82 (s, 1H), 4.37-4.27 (m, 2H), 4.17-4.07 (m, 2H), 1.72-1.62 (m, 3H), 1.15-0.79 (m, 10H), 0.72-0.61 (m, 1H), 0.26 (s, 9H); ^{13}C NMR δ 160.9, 150.1, 140.3, 125.8, 121.2, 104.0, 73.4, 69.5, 30.3, 29.7, 28.1, 26.8, 26.2, 25.7, 25.3, -0.10; HRMS (ESI, positive): *m/z* calcd. for $C_{18}H_{30}NaO_3Si$ (M+Na): 345.1856; found: 345.1857; $[\alpha]^{28}_D$ = 54.0 (*c* 1.00, $CHCl_3$).

13-Hydroxy-16-iodo-1,11-dioxa[11]paracyclophane (2d): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as brown oil (135.5 mg, 80%). IR (CH_2Cl_2) 3401.8, 2929.3, 2850.3, 1575.6, 1479.1, 1288.2, 1151.3, 877.5 cm^{-1}; ^1H NMR δ 7.37 (s, 1H), 6.69 (s, 1H), 5.84 (s, 1H), 4.36-4.13 (m, 4H), 1.87-1.55 (m, 4H), 1.11-0.79 (m, 10H); ^{13}C NMR δ 155.1, 149.3, 142.7, 128.8, 107.6, 78.0, 73.1, 72.2, 30.5, 30.1, 28.2, 26.0, 26.0, 25.6, 24.9; HRMS (ESI, positive): *m/z* calcd. for $C_{15}H_{21}INaO_3$ (M+Na): 399.0428; found: 399.0429; $[\alpha]^{29}_D$ = -0.24 (*c* 1.17, $CHCl_3$, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4.6×250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 ml/min, retention time: 11.3 min for major isomer and 17.8 min for minor isomer).

13-Hydroxy-16-phenyl-1,11-dioxa[11]paracyclophane (2e): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as yellow oil (53.0 mg, 57%). IR (CH_2Cl_2) 3527.2, 2921.6, 2850.3, 1592.9,

1486.9, 1284.4, 1135.9, 902.5, 702.0 cm^{-1}; ^1H NMR δ 7.55-7.53 (dd, *J* = 1.3, 8.4 Hz, 2H), 7.42-7.39 (m, 2H), 7.32-7.29 (dd, *J* = 1.3, 7.3 Hz, 1H), 7.04 (s, 1H), 6.78 (s, 1H), 5.83 (s, 1H), 4.37-4.27 (m, 2H), 3.97-3.92 (m, 1H), 3.71-3.66 (m, 1H), 1.85-1.61 (m, 2H), 1.52-1.33 (m, 2H), 1.28-0.96 (m, 6H), 0.88-0.71 (m, 4H); ^{13}C NMR δ 152.1, 147.9, 142.1, 138.4, 129.2, 129.2, 128.2, 128.2, 126.7, 126.6, 120.2, 109.5, 72.2, 71.0, 30.7, 29.7, 28.0, 26.0, 25.9, 25.6, 25.4; HRMS(ESI, positive): *m/z* calcd. for $C_{21}H_{26}NaO_3$ (M+Na): 349.1774; found: 349.1774; $[\alpha]^{20}_D$ = 5.04 (*c* 1.17, $CHCl_3$, 96% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 9.0 min for major isomer and 11.4 min for minor isomer).

13-Hydroxy-16-(4-methoxyphenyl)-1,11-dioxa[11]paracyclophane (2f): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as yellow oil (51.4 mg, 50%). IR (CH_2Cl_2) 3523.1, 3056.6, 2921.6, 2850.3, 1589.1, 1504.2, 1461.8, 1232.3, 1143.6, 1101.2, 952.7, 825.4, 694.3, 644.1 cm^{-1}; ^1H NMR δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.01 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 1H), 5.89 (s, 1H), 4.36-4.26 (m, 2H), 3.96-3.91 (m, 1H), 3.85 (s, 3H), 3.73-3.68 (m, 1H), 1.84-1.60 (m, 2H), 1.52-1.33 (m, 2H), 1.28-0.92 (m, 6H), 0.90-0.67 (m, 4H); ^{13}C NMR δ 158.5, 151.9, 147.5, 142.1, 130.9, 130.2, 130.2, 126.3, 120.0, 113.7, 113.7, 109.5, 72.1, 70.9, 55.2, 30.8, 29.7, 28.0, 26.0, 25.9, 25.6, 24.5; HRMS(ESI, positive): *m/z* calcd. for $C_{22}H_{28}NaO_4$ (M+Na): 379.1880; found: 379.1880; $[\alpha]^{18}_D$ = -6.46 (*c* 1.02, $CHCl_3$).

13-Hydroxy-16-(4-trifluoromethylphenyl)-1,11-dioxa[11]paracyclophane (2g): it was isolated by flash column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as yellow oil (66.2 mg, 54%). IR (CH_2Cl_2) 3380.6, 2933.2, 2865.7, 1618.0, 1504.2, 1330.6, 1126.22, 846.6, 729.0 cm^{-1}; ^1H NMR δ 7.65 (s, 4H), 7.05 (s, 1H), 6.80 (s, 1H), 5.88 (s, 1H), 4.39-4.27 (m, 2H), 4.04-3.98 (m, 1H), 3.76-3.70 (m, 1H), 1.82-1.61 (m, 2H), 1.51-1.33 (m, 2H), 1.26-0.68 (m, 10H); ^{13}C NMR δ 152.4, 148.7, 142.2, 142.0, 129.4, 129.4, 128.6 (q, *J* = 32.48 Hz), 125.2, 125.1, 125.1, 120.1, 109.2, 72.3, 71.4, 30.7, 29.7, 27.9, 26.0, 25.9, 25.5, 24.5 (A peak derived from CF_3 is missing); ^{19}F NMR δ -62.09; HRMS(ESI, positive): *m/z* calcd. for $C_{22}H_{25}F_3NaO_3$ (M+Na): 417.1648; found: 417.1647; $[\alpha]^{19}_D$ = 16.9 (*c* 0.67, $CHCl_3$).

Typical experimental procedure for the synthesis of phosphite ligands (L1 –L4):

To a THF (1.5 ml) solution of alcohol **2a** (0.15 mmol), triethylamine (0.45 mmol) and 2,2'-biarylene phosphorochloridite **3** (prepared by mixing the corresponding biaryl diol (0.20 mmol) and PCl_3 (0.28 mmol) at 75 °C for overnight) were added and stirred at room temperature for overnight. The resulting solution was filtered

through filter paper using dichloromethane and was evaporated to dryness at room temperature.

6-(1,10-Dioxa[10]paracyclophan-12-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L1): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (44.6 mg, 66%). IR (CH_2Cl_2) 2933.2, 2858.0, 1602.6, 1504.2, 1249.7, 1186.0, 1151.3, 1097.3, 906.4, 860.1 cm^{-1}; ^1H NMR δ 7.49 (dd, *J* = 1.8, 8.1 Hz, 2H), 7.41-7.36 (m, 2H), 7.32-7.28 (m, 3H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 9.3, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.78 (dd, *J* = 2.7, 8.6 Hz, 1H), 4.34-4.20 (m, 2H), 4.18-4.10 (m, 2H), 1.60-1.49 (m, 4H), 0.93-0.48 (m, 8H); ^{13}C NMR δ 154.4, 149.2 (d, *J* = 5.0 Hz), 149.0 (d, *J* = 4.8 Hz), 145.3 (d, *J* = 6.5 Hz), 143.5, 143.4, 131.3 (d, *J* = 3.8 Hz), 131.1 (d, *J* = 2.6 Hz), 129.9, 129.2, 125.5 (d, *J* = 1.0 Hz), 125.3 (d, *J* = 1.2 Hz), 123.8, 122.3 (d, *J* = 1.7 Hz), 122.2 (d, *J* = 1.2 Hz), 117.3 (d, *J* = 1.4 Hz),115.0, 115.0, 72.4, 71.4, 28.3, 27.3, 26.4, 26.3, 24.9, 23.7; ^{31}P NMR (200 MHz) δ 147.9; HRMS(ESI, positive): *m/z* calcd. for $C_{26}H_{27}NaO_5P$ (M+Na): 473.1488; found: 473.1490; $[\alpha]^{26}_D$ = 20.4 (*c* 0.92, $CHCl_3$).

6-(1,11-Dioxa[11]paracyclophan-13-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L2): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (62.8 mg, 89%). IR (CH_2Cl_2) 2929.3, 2858.0, 1598.7, 1496.5, 1432.9, 1238.1, 1147.4, 1093.4, 910.2, 867.8 cm^{-1}; ^1H NMR δ 7.50 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.41-7.36 (m, 2H), 7.33-7.28 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 1.0, 2.8 Hz, 1H), 6.84-6.81 (m, 1H), 4.36-4.26 (m, 1H), 4.24-4.10 (m, 3H), 1.74-1.55 (m, 4H), 1.12-0.76 (m, 10H); ^{13}C NMR δ 156.1, 149.2, 149.1, 149.0, 149.0, 144.7 144.7 (d, *J* = 1.0 Hz), 130.0 (d, *J* = 1.2 Hz), 129.2 (d, *J* = 1.2 Hz), 125.4 (d, *J* = 1.2 Hz), 125.3 (d, *J* = 1.2 Hz), 123.2, 122.3 (d, *J* = 1.2 Hz), 122.2 (d, *J* = 1.2 Hz), 116.5, 116.5 114.2, 114.1, 72.1, 71.5, 30.2, 29.6, 27.7, 26.1, 26.0, 25.9, 25.2; ^{31}P NMR (200 MHz) δ 146.5; HRMS(ESI, positive): *m/z* calcd. for $C_{27}H_{29}NaO_5P$ (M+Na): 487.1645; found: 487.1645;$[\alpha]^{26}_D$= 30.8 (*c* 1.30, $CHCl_3$).

6-(1,11-Dioxa[11]paracyclophan-13-yloxy)-2,4,8,10-tetramethyldibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L3): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (43.7 mg, 56%). IR (CH_2Cl_2) 2950.6, 2896.6, 1745.3, 1483.0, 1245.8, 1211.1, 1151.3, 1037.5, 833.1 cm^{-1}; ^1H NMR δ 7.12-7.07 (m, 4H), 6.84-6.79 (m, 3H), 4.33-4.28 (m, 1H), 4.21-4.09 (m, 3H), 2.44 (s, 3H), 2.41 (s, 3H), 2.37 (d, *J* = 3.4, 6H), 1.72-1.61 (m, 4H), 1.09-0.79 (m, 10H); ^{13}C NMR δ 156.2, 145.4 (d, *J* = 5.4 Hz), 144.7 (d, *J* = 3.2 Hz), 134.4 (d, *J* = 3.3 Hz), 134.2 (d, *J* = 1.2

Hz), 131.6 (d, J = 3.9 Hz), 131.3, 131.2, 131.0 (d, J = 2.7 Hz), 130.5 (d, J = 2.0 Hz), 130.2 (d, J = 1.2 Hz), 128.2 (d, J = 1.2 Hz), 128.1 (d, J = 1.2 Hz), 123.3, 116.2, 113.9, 113.8, 72.5, 71.6, 30.4, 29.6, 27.9, 26.4, 26.3, 26.1, 25.4, 21.0 (d, J = 1.2 Hz), 17.1, 16.8; ^{31}P NMR (200 MHz) δ 144.9; HRMS(ESI, positive): *m/z* calcd. for $C_{31}H_{37}NaO_5P$ (M+Na): 543.2271; found: 543.2272; $[\alpha]^{26}_D$ = 3.56 (*c* 1.26, $CHCl_3$).

4-(1,11-Dioxa[11]paracyclophan-13-yloxy)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine ((S_a)-L4): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as foamy white solid (100.8 mg, 98%). mp 90 °C; IR (CH_2Cl_2) 2929.3, 2850.3, 1592.9, 1500.4, 1465.6, 1232.3, 1189.9, 1151.3, 952.7, 838.9, 740.5, 702.0 cm^{-1}; ^{1}H NMR δ 8.00-7.91 (m, 4H), 7.55 (dd, J = 9.1, 9.1 Hz, 2H), 7.47-7.38 (m, 4H), 7.30-7.24 (m, 2H), 7.07 (d, J = 8.6 Hz, 1H), 6.88-6.81 (m, 2H), 4.33- 4.28 (m, 1H), 4.21-4.15 (m, 3H), 1.72-1.59 (m, 4H), 1.05-0.78 (m, 10H); ^{13}C NMR δ 156.0, 147.8 (d, J = 4.6 Hz), 147.0 (d, J = 2.4 Hz), 144.8 (d, J = 2.9 Hz), 144.7, 144.6, 132.8 (d, J = 1.7), 132.6 (d, J = 1.7 Hz), 131.6, 131.3, 130.4, 129.7, 128.4, 128.3, 127.1, 127.0, 126.3, 126.1, 125.2, 125.0, 123.2, 122.1, 121.8 (d, J = 1.7), 116.6, 114.1, 114.1, 72.1, 71.5, 30.2, 29.6, 27.7, 26.2, 26.0, 25.9, 25.2; ^{31}P NMR (200 MHz) δ 148.9; HRMS(ESI, positive): *m/z* calcd. for $C_{35}H_{33}NaO_5P$ (M+Na): 587.1958; found: 587.1957; $[\alpha]^{25}_D$ = 175.9 (*c* 0.68, $CHCl_3$).

4-(1,11-Dioxa[11]paracyclophan-13-yloxy)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine ((R_a)-L4): the compound was obtained as a mixture of (R_a)-**L4** and **2b**, and could not be isolated because of its instability. The title compound was obtained as foamy white solid (85.1 mg, ca. 80%). Mp 70 °C; IR (CH_2Cl_2) 3396.0, 2935.1, 2858.0, 1567.8, 1486.9, 1280.5, 1189.9, 1151.3, 902.5, 771.4 cm^{-1}; ^{1}H NMR δ 8.01-7.96 (m, 4H), 7.60-6.57 (m, 11H), 4.35- 4.12 (m, 4H), 1.72-1.55 (m, 4H), 1.09-0.76 (m, 10H); ^{13}C NMR δ 156.0, 147.8 (d, J = 4.6 Hz), 147.0 (d, J = 2.4 Hz), 144.8 (d, J = 2.9 Hz),144.7, 144.6, 132.8 (d, J = 1.7 Hz), 132.6 (d, J = 1.7 Hz), 131.6, 131.3, 130.4, 129.7, 128.4, 128.3, 127.1, 127.0, 126.3, 126.1, 125.2, 125.0, 123.2, 122.1, 121.8 (d, J = 1.7 Hz), 116.6, 114.1, 114.1, 72.1, 71.5, 30.2, 29.6, 27.7, 26.2, 26.0, 25.9, 25.2; ^{31}P NMR (200 MHz) δ 1467.3; HRMS(ESI, positive): *m/z* calcd. for $C_{35}H_{33}NaO_5P$ (M+Na): 587.1958; found: 587.1959;

6-(16-(Trimethylsilyl)-1,11-dioxa[11]paracyclophan-13-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L2(TMS)): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (67.0 mg, 83%). IR (CH_2Cl_2) 2925.5, 2865.7, 1606.4, 1500.4, 1429.0, 1429.7, 1193.7, 1157.1, 1087.7, 970.0, 910.2, 860.1, 740.5 cm^{-1}; ^{1}H NMR δ 7.51-7.28 (m, 7H), 7.22-7.20 (m, 1H), 7.12 (m, 1H), 6.77 (s, 1H), 4.35-4.29 (m, 2H), 4.20-4.11 (m, 2H), 1.78-1.45 (m, 4H), 1.11-0.57 (m, 10H), 0.29 (s, 9H);

^{13}C NMR δ 160.7, 149.1 (dd, *J* = 4.8, 11.6 Hz), 145.5 (d, *J* = 6.0 Hz), 143.2 (d, *J* = 3.3 Hz), 131.3 (d, *J* = 3.3 Hz), 131.2 (d, *J* = 3.0 Hz), 130.0, 130.0, 129.2, 129.1, 129.1, 126.2 (d, *J* = 1.2 Hz), 125.4, 125.3, 122.4 (d, *J* = 1.5 Hz), 122.2 (d, *J* = 1.2 Hz), 110.0, 110.0, 72.3, 69.6, 29.6, 29.5, 27.8, 26.5, 26.5, 26.2, 24.7, -0.4; ^{31}P NMR (200 MHz) δ 146.3; HRMS(ESI, positive): *m/z* calcd. for $C_{30}H_{37}INaO_5PSi$ (M+Na): 559.2040; found: 559.2040; $[\alpha]^{25}_D$ = 23.3 (c 0.66, $CHCl_3$).

6-(16-Phenyl-1,11-dioxa[11]paracyclophan-13-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L2(Ph)): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (56.0 mg, 69%). IR (CH_2Cl_2) 2925.5, 2854.1, 1606.4, 1490.7, 1442.4, 1241.9, 1178.3, 1139.7, 1033.7, 910.2, 835.0, 769.5, 736.7, 702.0, 599.8, 516.8 cm^{-1}; ^{1}H NMR δ 7.57-7.50 (m, 4H), 7.45-7.24 (m, 9H), 7.18 (s, 1H), 6.98 (s, 1H), 4.42-4.26 (m, 2H), 4.00-3.78 (m, 2H), 1.90-1.63 (m, 2H), 1.49-1.33 (m, 2H), 1.11-0.74 (m, 10H); ^{13}C NMR δ152.2, 149.2 (d, *J* =4.9 Hz), 149.0 (d, *J* = 4.9 Hz), 145.5 (d, *J* = 3.3 Hz), 143.4 (d, *J* = 5.8 Hz), 137.9, 131.3 (d, *J* = 3.0 Hz), 131.1 (d, *J* = 2.7 Hz), 130.9, 130.3, 130.2, 130.0, 129.3, 129.2, 128.3, 127.1, 126.8, 125.5, 125.3, 123.7, 122.4, 122.2, 121.7 (d, *J* = 4.0 Hz), 115.7 (d, *J* = 6.4 Hz), 71.9, 71.4, 30.1, 29.9, 27.8, 26.1, 26.0, 25.6, 25.3; ^{31}P NMR (200 MHz) δ 144.9; HRMS(ESI, positive): *m/z* calcd. for $C_{33}H_{33}NaO_5P$ (M+Na): 563.1958; found: 563.1959; $[\alpha]^{21}_D$ = 10.3 (*c* 0.69, $CHCl_3$).

6-(16-(4-Methoxyphenyl)-1,11-dioxa[11]paracyclophan-13-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L2(MeOPh)): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (33.0 mg, 58%). IR (CH_2Cl_2) 2929.3, 2854.1, 1619.9, 1500.4, 1245.8, 1178.3, 1132.0, 1066.4, 907.0, 838.9, 769.5 cm^{-1}; ^{1}H NMR δ 7.52-7.23 (m, 10H), 7.15 (s, 1H), 7.07-6.94 (m, 3H), 4.41-4.25 (m, 2H), 3.86 (s, 3H), 3.99-3.67 (m, 2H), 1.87-1.33 (m, 4H), 0.74-1.10 (m, 10H); ^{13}C NMR δ 158.9, 152.2, 149.3 (d, *J* = 5.0 Hz), 149.2 (d, *J* = 4.8 Hz), 145.7 (d, *J* = 2.9 Hz), 143.1 (d, *J* = 6.0 Hz), 131.5, 131.5, 131.3, 131.3, 130.7 (d, *J* = 1.2 Hz), 130.5, 130.4, 130.1 (d, *J* = 1.4 Hz), 129.4, 129.3, 125.6 (d, *J* = 0.96 Hz), 125.5, 123.5, 122.5 (d, *J* = 1.4 Hz), 122.4 (d, *J* = 1.2 Hz), 115.9, 115.9, 113.9, 113.8, 72.0, 71.4, 55.4, 30.3, 30.1, 28.0, 26.2, 26.1, 25.7, 25.4; ^{31}P NMR (200 MHz) δ 147.6; HRMS(ESI, positive): *m/z* calcd. for $C_{34}H_{35}NaO_6P$ (M+Na): 593.2063; found: 593.2063; $[\alpha]^{26}_D$ = 2.21 (*c* 0.71, $CHCl_3$).

6-(16-(4-(Trifluoromehtyl)phenyl)-1,11-dioxa[11]paracyclophan-13-yloxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (L2(CF_3Ph)): it was isolated by Florisil® column chromatography (hexane/ethyl acetate = 4/1). The title compound was obtained as colorless oil (33.4 mg, 37%). IR (CH_2Cl_2) 2929.3, 2850.3, 1490.7, 1241.9, 1211.1, 1147.4, 1101.2, 885.2, 864.0, 813.8 cm^{-1}; ^{1}H NMR δ 7.68-7.65 (m,

4H), 7.53-7.17 (m, 8H), 7.17-6.79 (m, 2H), 4.42-4.26 (m, 2H), 4.05-3.70 (m, 2H), 1.88-1.64 (m, 2H), 1.50-1.32 (m, 2H), 1.20-0.71 (m, 10H); ^{13}C NMR δ 152.5, 149.2, 149.0 (d, J = 5.2 Hz), 145.5 (d, J = 2.4 Hz), 144.3, 144.3, 141.4, 131.3 (d, J = 3.1 Hz), 131.1 (d, J = 2.2 Hz), 130.0, 129.6, 129.2, 125.5, 125.4, 125.2, 125.2, 123.6, 122.3, 122.2, 115.5, 115.4, 72.0, 71.7, 30.0, 29.8, 27.8, 26.1, 26.0, 26.0, 25.6, 25.2 (A peak derived from CF_3 is missing); ^{31}P NMR (200 MHz) δ 144.5; ^{19}F NMR (470 MHz) δ -62.2; HRMS(ESI, positive): *m/z* calcd. for $C_{34}H_{32}F_3NaO_5P$ (M+Na): 631.1832; found: 631.1829; $[\alpha]^{23}_D$ = 19.0 (*c* 0.67, $CHCl_3$).

Experimental procedure for enantioselective alkylation in Table 2

In a schlenk tube, $[Pd(allyl)Cl]_2$ catalyst (2.0 mol%) and the ligand (8.0 mol%) was dissolved in DCM (0.9 ml) and stirred for 40 min at the desired temperature. (*E*)-1,3-Diphenylallyl acetate (**5**) (0.03ml, 0.15mmol) was added and stirred for another 15 min. Dimethyl malonate (**4**) (0.03ml, 1.8 equiv) was added followed by addition of BSA (1.3 equiv) and KOAc (1.3 equiv), then stirred at the desired temperature for 24-48 h. The reaction mixture was diluted by DCM, filtered and evaporated. The crude mixture was purified by PTLC. The absolute configuration of product **6** was determined by comparison of the sign of optical rotation with that in the literature.[13]

Experimental procedure for 1,4-addition in Table 3

In a schlenk tube, Rh catalyst (1.8 mol%) and the ligand (7.2 mol%) was added followed by addition of cyclohex-2-enone (**7**) (9.7 µl, 0.1 mmol), phenylboronic acid (**8**) (12.8mg, 1.05 equiv) and stirred for 5 min. Et_3N (1.0 mol%) was added followed by addition of dioxane/H_2O (8/1) and stirred at room temperature for 72 h. The reaction mixture was evaporated and crude product was purified by PTLC. The absolute configuration of product **9** was determined by comparison of the sign of optical rotation with that in the literature.[14]

- **References**

1. Chen, Y.; Yekta, S.; Yudin, A. K.; *Chem. Rev*. **2003**, *103*, 3155-3212.

2. Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed*. **2000**, *39*, 3889–3890.

3. Evans, P. A.; Clizbe, E. A.; Lawler, M. J.; Oliver, S. *Chem. Sci*. **2012**, *3*, 1835–1838.

4. Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869-7872.

5. Tian, M.; Pang, Z.-b.; Li, H.-f.; Wang, L.-l. *Tetrahedron: Asymmetry* **2017**, *28*, 330–337.

6. (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 2054-2056; (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197-6201.

7. Julia, M.; Jalmes, V. P.-S.; Plé, K.; Verpeaux, J.-N. *Bull. Soc. Chim. Fr.* **1996**, *133*, 15-24.

8. Kanda, K; Hamanaka, R; Endo, K; Shibata, T. *Tetrahedron* **2012**, *68*, 1407-1416.

9. Kawaguchi, K.; Nakano, K.; Nozaki, K. *J. Org. Chem*. **2007**, *72*, 5119-5128.

10. Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, j. G.; Minnaard, A. J.; Feringa, B. L. *J.Org. Chem*. **2004**, *69*, 8045-8052.

11. Lyubimov, S. E.; Zhuravskii, R. P.; Rozenberg, V. I.; Safronov, A. S.; Petrovskii, P. V.; Davankov, V. A. *Russ. Chem. Bull., Int. Ed*. **2008**, *57*, 137-201.

12. Gavrilov, K. N.; Zheglov, S. V.; Gavrilova, M. N.; Novikov, I. M.; Maksimova, M. G.; Groshkin, N. N.; Rastorguev, E. A.; Davankov, V. A. *Tetrahedron* **2012**, *68*, 1581-1589.

13. Benetskiy, E. B.; Bolm, C. *Tetrahedron: Asymmetry* **2011**, *22*, 373-378.

14. Muhlhauser, T.; Savin, A.; Frey, W.; Baro, A.; Schneider, A. J.; Doteberg, H.-G.; Bauer, F.; Kohn, A.; Laschat, S. *J. Org. Chem.* **2017**, *82*, 13468-13480.

Chapter 3

Synthesis of Planar-Chiral Paracyclophanyl Phosporamidite Ligands and Their Application to Asymmetric Reactions

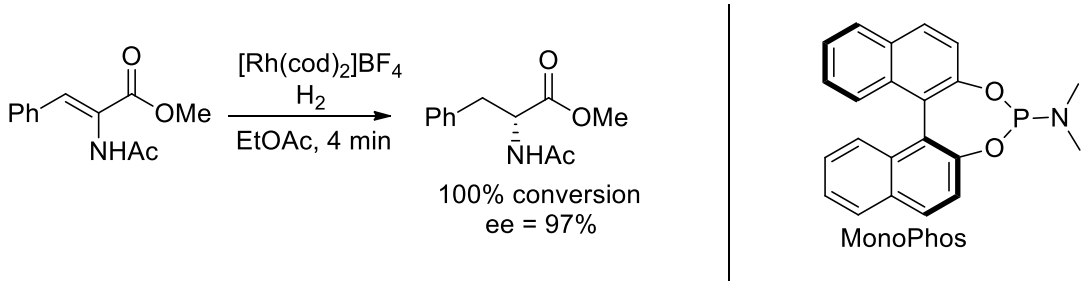
- # Background

Asymmetric catalysis with transition metal complexes is a basis for extensive stereoselective transformations. Its success lies in the design of vital chiral ligands. Chiral ligand design involves inexpensive ligands and catalysts that are easily prepared and allow fine tuning for specific chemical transformations. There is a high demand for expansion of the catalytic tool box and for catalysts that can be optimized for enantioselective synthetic steps that avoid tedious procedures. Another important issue is practicability. During the past few decades, most studies relied on multidentate chiral ligands. The bidentate chiral ligand DIOP developed by Kagan and Dang in 1971 began the era of bidentate ligands. Following its commercial success in L-DOPA synthesis, the superiority of bidentate ligands was established. During these years, many applications of monodentate ligands emerged. Monodentate chiral phosphoramidites were then introduced in 1994.[1] In 1996/1997, a vital breakthrough appeared in the synthesis of asymmetric copper-catalyzed conjugate addition with high enantioselectivity.[2] This was the start of the new millennium for monodentate chiral ligands. During the last decade, various asymmetric transformations were found to work well with monodentate chiral ligands. The research groups of Reetz, Pringle, Feringa and deVries independently reported using monodentate phosphoramidite ligands for hydrogenation attaining high enantioselectivity. Phosphoramidites offered excellent and versatile performances in asymmetric hydrogenation. Phosphoramidites were easily prepared by reaction with the appropriate amine in the presence of base. They are extremely stable and versatile, and allow rapid fine-tuning by varying the substituents.

Examples of chiral phosphoramidite ligands

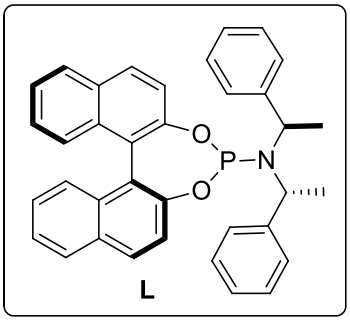
Chiral phosphoramidite ligands have been used in several reactions including hydrogenation, allylic alkylation, and conjugate addition.

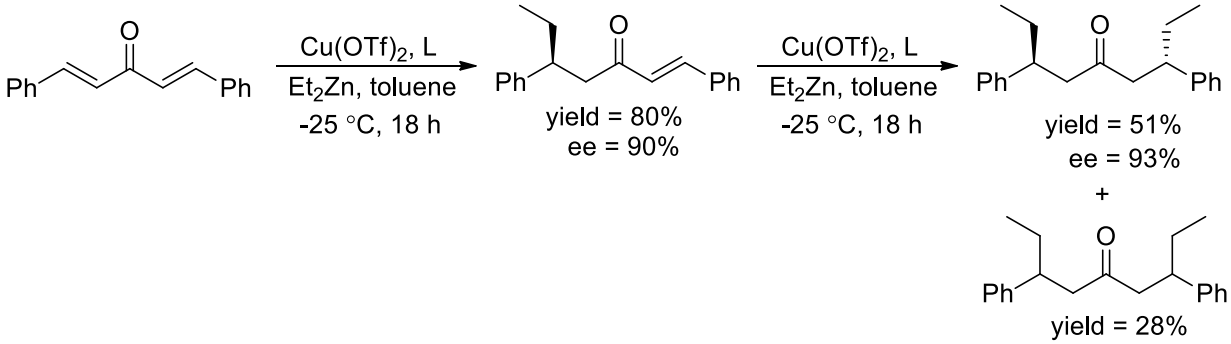
The most often studied and effective transition metal-catalyzed reactions is the enantioselective hydrogenation of functionalized prochiral olefins. Here, monodentate phosphoramidites are reported as new ligands for enantioselective Rh-catalyzed olefin hydrogenation (Scheme 1).[3]



Scheme 1: Rh-catalyzed asymmetric hydrogenation

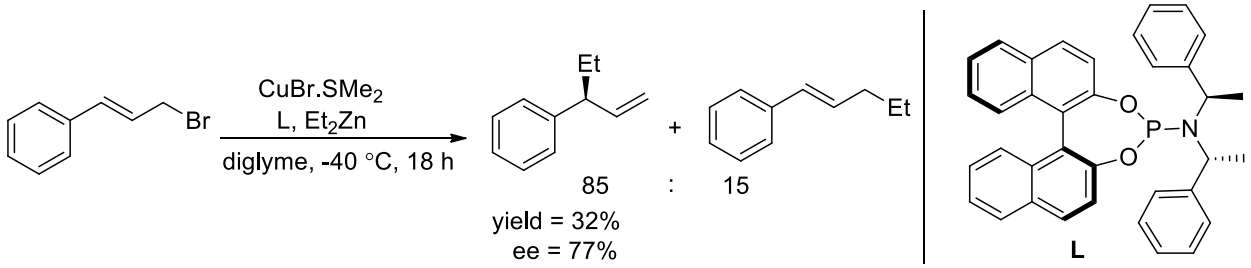
Conjugate addition of organometallic reagents to α,β-unsaturated systems is a key transformation in synthetic organic chemistry. The enantioselective Cu/phosphoramidite-catalyzed 1,4-addition of dialkylzinc reagents to acyclic dienones is described. The obtained product can be further functionalized by a second conjugate addition, but with modest diastereoselectivity (Scheme 2).[4]





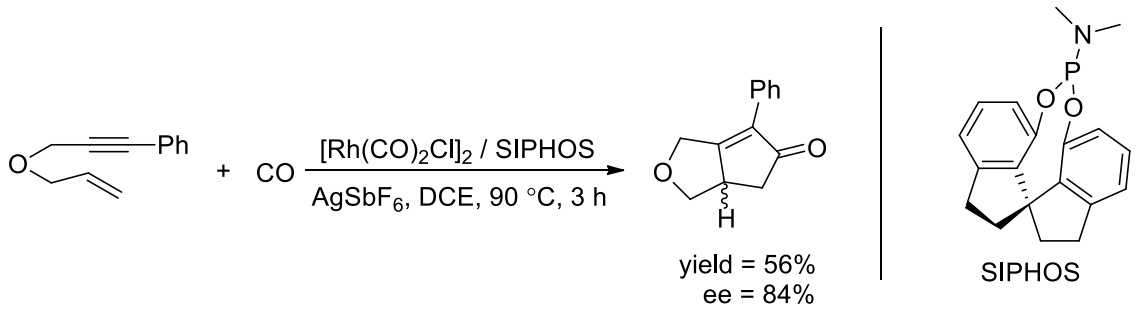
Scheme 2: Cu-catalyzed conjugate addition

Feringa *et al*. disclosed Cu-catalyzed allylic substitution with phosphoramidite as ligand in 2001. They described asymmetric allylic alkylation of cinnamyl halides with dialkylzinc reagents. Although the branched/linear ratio and yields were moderate, the branched product exhibited 77% ee (Scheme 3).[5]



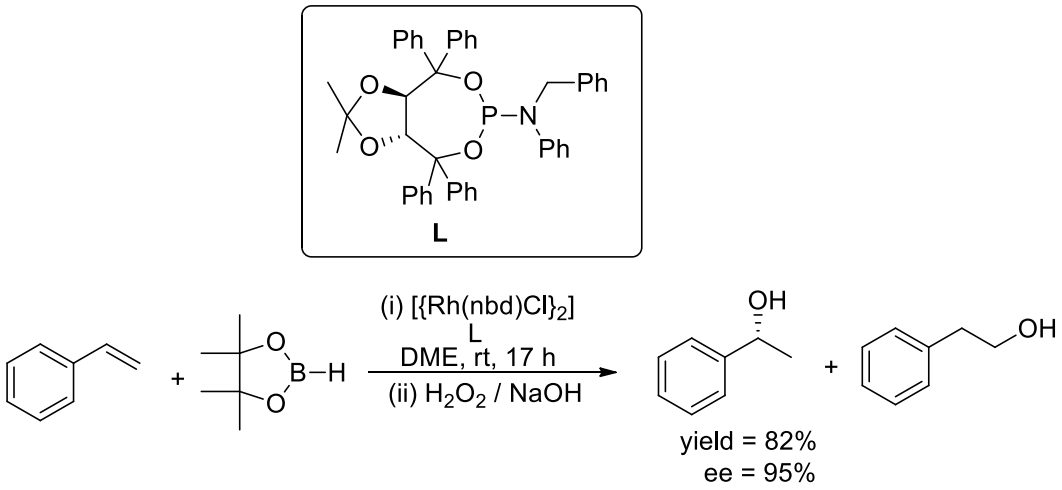
Scheme 3: Cu-catalyzed allylic alkylation

Zhou *et al*. described a Rh-catalyzed enantioselective intramolecular Pauson-Khand reaction employing a chiral monophosphoramidite. In this reaction, an *in situ* catalyst obtained from $[Rh(CO)_2Cl]_2$, SIPHOS, the spiro-monophosphoramidite ligand and $AgSbF_6$ was found productive for a series of 1,6-enynes affording the cocyclized products with good enantiomeric excess (Scheme 4).[6]



Scheme 4: Rh-catalyzed enantioselective Pauson-Khand reaction

Rh-catalyzed hydroboration presents a extremely versatile method for enantioselective functionalization of olefins. A Rh/phosphoramidite-catalyzed hydroboration of styrenes with pinacolborane was reported by Takacs *et al*.[7] By employing TADDOL-derived phosphoramidites possessing a sterically crowded amine moiety, the corresponding chiral benzyl alcohols were achieved with excellent yields and enantiomeric excess after oxidation. Although, it was found that only moderate to good regioselectivity was achieved (Scheme 5).



Scheme 5: Rh-catalyzed asymmetric hydroboration of styrenes

Purpose of this chapter

As mentioned above, phosphoramidites have rapidly emerged as highly potent ligands in enantioselective transition metal catalysis. Their versatility is arguably evident from their numerous reactions. The most attractive feature of this type of ligand is that they are easily accessible from cheap starting materials, and thus their structures can be readily optimized for specific transformations.

They are easily prepared by reacting with the appropriate amine in the presence of base. They are extremely versatile and allow rapid fine tuning by varying their substituents. Therefore, a library of ligands can be easily prepared for specific transformations. They are also extremely stable. Thus, the author describes the synthesis of chiral phosphoramidites in Fig.1.

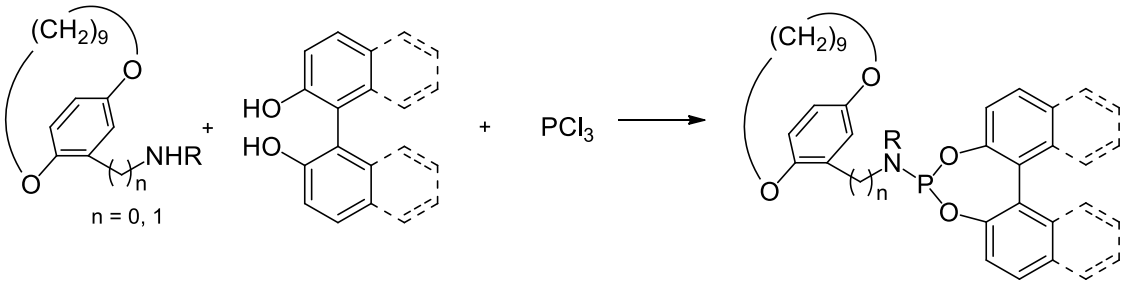


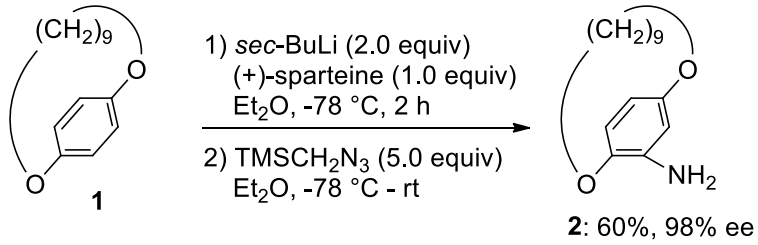
Fig. 1: Outline synthesis of phosphoramidites

The obtained phosphoramidites were used in benchmark reactions such as allylic substitution and conjugate addition to test their efficiency.

- **Results and Discussion**

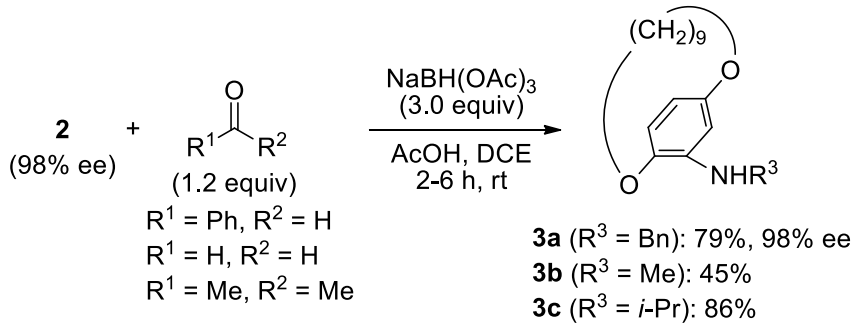
Synthesis of planar-chiral paracyclophanylamine

The author synthesized a new family of chiral phosphoramidite ligands via three steps. In the presence of (+)-sparteine, enantioselective *ortho*-lithiation[8] of 1,11-dioxa[11]paracyclophane (**1**) was performed, subsequent quenching with trimethylsilylmethyl azide[9] then furnished planar-chiral paracyclophanylamine **2** in excellent enantiomeric excess. (Scheme 6).



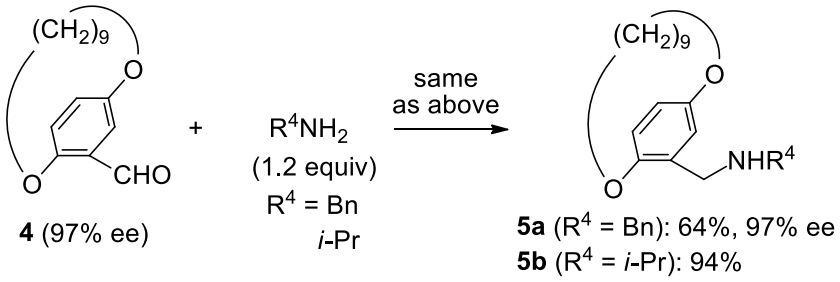
Scheme 6: Synthesis of planar-chiral paracyclophanylamine

The planar chirality of primary amine **2** was exploited in the reductive amination of carbonyl compounds with sodium triacetoxyborohydride, which furnished secondary paracyclophanylamines **3a**-**3c** (Scheme 7).



Scheme 7: Synthesis of secondary paracyclophanylamines

Moreover, the planar-chirality of aldehyde **4**[10] was used for reductive amination by benzylamine and isopropylamine under the reaction conditions described above to give secondary paracyclophanylmethylamines **5a** and **5b** (Scheme 8). The retention of enantiomeric excess of the reductive amination was established by compounds **3a** and **5a** (Scheme 8).



Scheme 8: Synthesis of secondary paracyclophanylmethylamines

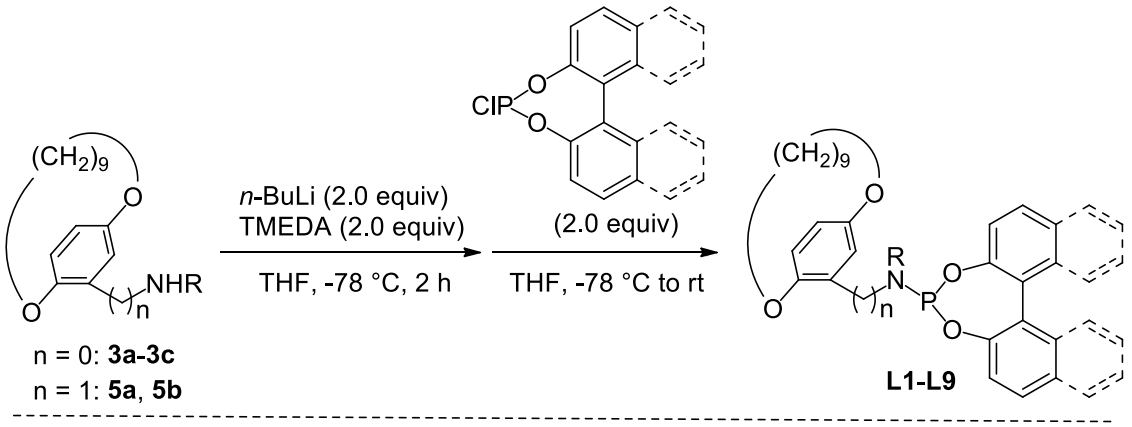
Thermal stability

The thermal stabilities of paracyclophanylamines and paracyclophanylmethylamines were determined. Paracyclophanylamines were slightly more stable than paracyclophanylmethylamines under heated conditions. At room temperature, the ee of **3a** was measured as 98%. After heating **3a** in DCE solvent for two hours at 40 ˚C, the ee decreased only slightly to 97%. However, when it was heated at 60 ˚C for two hours, the enantioselectivity decreased to 89%. Therefore, paracyclophanylamines can tolerate heating up to 40 ˚C but destabilize at 60 ˚C. However, when the author heated **5a** for two hours at 40 ˚C, the ee decreased to 72% from 97% at room temperature. Therefore, paracyclophanylmethylamines cannot withstand heating at even 40 ˚C. Thus, based on the ee decreases, paracyclophanylamines are more stable than paracyclophanylmethylamines.

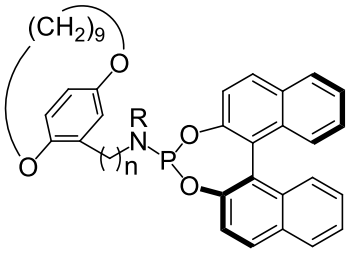
The reaction of paracyclophanylamines and paracyclophanylmethylamines with phosphorochloridites were performed at -78 °C to room temperature; thus, the enantiomeric excess of phosphoramidite ligands can be considered equivalent to that of original paracyclophanylamines and paracyclophanylmethylamines.

Synthesis of phosphoramidites

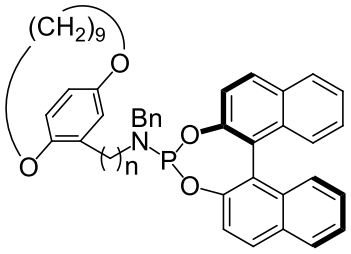
With *n*-butyllithium, lithiation of these secondary amines in the presence of TMEDA proceeded, and this was followed by treatment with *in situ* prepared 2,2'-biarylene phosphorochloridites (Scheme 9). *n*-Butyllithium was added in slightly excess amount because starting material was not consumed completely. The reaction of paracyclophanylamine **3a** with axially chiral 2,2'-binaphthyl phosphorochloridites afforded the corresponding (R_a)-**L1** and (S_a)-**L1**. These ligands have both planar and axial chiralities. Diastereomeric (R_a)-**L2** and (S_a)-**L2** were obtained from paracyclophanylmethylamine **5a**. These ligands also exhibited planar and axial chiralities. The *N*-methyl and *N*-isopropyl counterparts (R_a)-**L3** and (R_a)-**L4** were also synthesized from **3b** and **3c**. When **3a**, **5a**, and **5b** were reacted with achiral 2,2'-biphenylene phosphorochloridite, **L5**-**L7** were obtained. The retention of enantiomeric excess of **L6** was ascertained. **L8** and **L9**, i.e, tetramethyl-substituted biphenylene-derived ligands were also synthesized using a similar procedure to that described above. These phosphoramidites were purified by silica gel preparative chromatography to afford foamy solids, which were stable at room temperature; therefore, due to their ease of handling, they could easily be applied to catalytic asymmetric reactions.



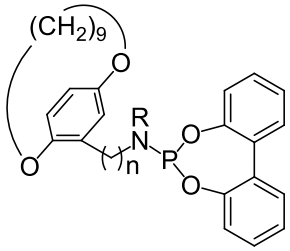
n = 0: **3a-3c**
n = 1: **5a**, **5b**



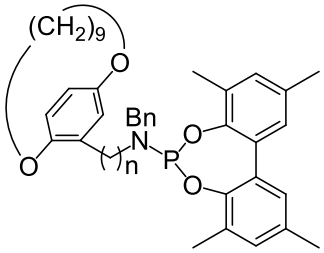
(R_a)-**L1** (n = 0, R = Bn): 41%
(R_a)-**L2** (n = 1, R = Bn): 36%
(R_a)-**L3** (n = 0, R = Me): 30%
(R_a)-**L4** (n = 0, R = *i*-Pr): 20%



(S_a)-**L1** (n = 0): 65%
(S_a)-**L2** (n = 1): 45%



L5 (n = 0, R = Bn): 70%
L6 (n = 1, R = Bn): 47%, 96% ee
L7 (n = 1, R = *i*-Pr): 30%



L8 (n = 0): 55%
L9 (n = 1): 39%

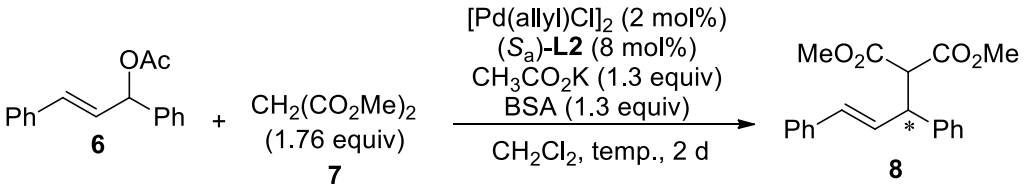
Scheme 9: Synthesis of phosphoramidites

After synthesizing these planar-chiral phosphoramidites, ligands **L1**-**L9** were employed in two standard reactions, Pd-catalyzed allylic substitution and Cu-catalyzed conjugate addition.

Pd-catalyzed allylic substitution

The author conducted enantioselective allylic alkylation reaction according to (Table 1).[11] The allylated product **8** was obtained by reacting dimethyl malonate (**7**) with (*E*)-1,3-diphenylallyl acetate (**6**) in low to excellent yield. Variations in stereoselectivity and enantioselectivity were observed depending on the ligand structure. Initially, temperature screening was performed with the (S_a)-**L2** ligand (Table 1).

Table 1: Enantioselective Pd-catalyzed allylic alkylation of malonate



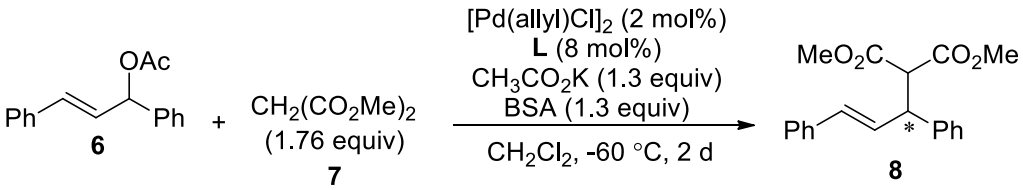
Entry	Temp.(˚C)	Yield (%)[a]	Ee (%)[b]
1	rt	90	22 (*R*)
2	-20	73	21 (*R*)
3	-40	77	32 (*R*)
4	-60	74	67 (*R*)
5	-78	N.R.	-

[a] Isolated yield. [b] Ee was determined by HPLC analysis using Daicel Chiralcel OD-3 (eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min). The absolute configuration of the major isomer was described in the parentheses.

The highest enantioselectivity was obtained at -60 ˚C. Thus, all the reactions were conducted at -60 ˚C (Table 2). The major enantiomer (*R*)-**8** was obtained from the diastereomeric pair (R_a)-**L1** and (S_a)-**L1**, which contain both planar and axial chiralities. These results indicate that the stereoselectivity was mainly determined by the planar-chiral paracyclophane moiety (Entries 1 and 2). However, the BINOL moiety was also important for enantioselective induction, as phosphoramidite ligands **L5** and **L8**, obtained from 2,2'-biphenol and tetramethyl-substituted 2,2'-

biphenol backbones, afforded low enantioselectivity (Entries 7 and 10). Conversely, the diastereomeric pair, paracyclophanylmethylamine-based (R_a)-**L2** and (S_a)-**L2**, showed opposite stereoselectivities, indicating that the axial chirality of the BINOL backbone predominantly controlled the stereoselectivity. (Entries 3 and 4). Notably, ligand **L6** possessing only planar chirality showed the highest enantioselectivity of 70%. Furthermore, **L7** and **L9**, i.e, paracyclophanylmethylamine-based ligands, resulted in low enantioselectivities due to steric bulkiness (Entries 9 and 11). These results indicate that in the phosphoramidite ligand, the planar-chiral dioxaparacyclophane was an effective chiral scaffold. The choice of substituent on the nitrogen atom and the 2,2'-biphenylene diol backbone were also important.

Table 2: Enantioselective Pd-catalyzed allylic alkylation of malonate



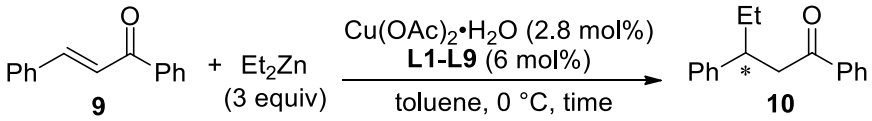
Entry	Ligand	Yield (%)[a]	Ee (%)[b]
1	(R_a)-**L1**	49	48 (*R*)
2	(S_a)-**L1**	76	39 (*R*)
3	(R_a)-**L2**	75	62 (*S*)
4	(S_a)-**L2**	74	67 (*R*)
5	(R_a)-**L3**	81	12 (*S*)
6	(R_a)-**L4**	36	10 (*R*)
7	**L5**	97	6 (*R*)
8	**L6**	82	**70** (*R*)
9	**L7**	86	51 (*R*)
10	**L8**	23	15 (*R*)
11	**L9**	50	8 (*R*)

[a] Isolated yield. [b] Ee was determined by HPLC analysis using Daicel Chiralcel OD-3 (eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min). The absolute configuration of the major isomer was described in the parentheses.

Cu-catalyzed conjugate addition

The author studied ligands **L1**-**L9** in Cu-catalyzed asymmetric conjugate addition of chalcone (**9**) with diethylzinc.[12] The ethylated product **10** was afforded in moderate to quantitative yield (Table 3). Contrary to the Pd-catalyzed allylic alkylation, the opposite enantiomers of the alkylated product **10** were obtained from the diastereomeric pair (R_a)-**L1** and (S_a)-**L1** and the enantioselectivity was completely different (Entries 1 and 2). Low enantioselectivity was observed on treating with the diastereomeric pair of paracyclophanylmethylamine-based ligands, (R_a)-**L2** and (S_a)-**L2** (Entries 3 and 4). The potential for a substituent on the nitrogen atom was important as the methyl group showed the best enantioselectivity of 64% among paracyclophanylamine-based ligands containing BINOL as a backbone (Entries 1, 5 and 6). Conversely, with the ligand having an achiral 2,2'-biphenol as a backbone, moderate enantioselectivity was induced by an isopropyl group on the nitrogen atom (Entries 5-9). Thus, a slight change in the structure of the phosphoramidite ligands resulted in a different degree of enantioselective induction by the cooperative effect of three substituents at the nitrogen center.

Table 3: Enantioselective Cu-catalyzed conjugate addition

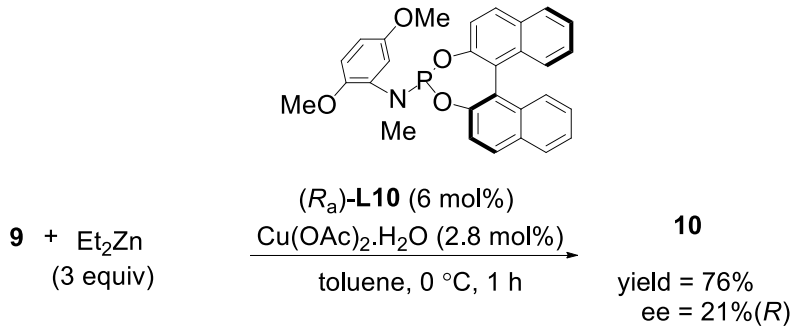


Entry	Ligand	Time (h)	Yield (%)[a]	Ee (%)[b]
1	(R_a)-**L1**	1.5	>99	44 (*R*)
2	(S_a)-**L1**	1.0	>99	18 (*S*)
3	(R_a)-**L2**	3.0	>99	6 (*S*)
4	(S_a)-**L2**	1.0	>99	17 (*R*)
5	(R_a)-**L3**	1.5	91	**64** (*R*)
6	(R_a)-**L4**	2.0	>99	7 (*S*)
7	**L5**	3.0	>99	4 (*R*)
8	**L6**	5.5	70	19 (*R*)
9	**L7**	1.5	89	50 (*R*)
10	**L8**	5.5	88	14 (*R*)
11	**L9**	5.5	63	4 (*R*)

[a] Isolated yield. [b] Ee was determined by HPLC analysis using Daicel Chiralcel OD-3 (eluent: 0.5% 2-propanol in hexane, flow rate: 1.0 mL/min). The absolute configuration of the major isomer was described in the parentheses.

Control experiment without planar chirality

When ligand (*R*a)-**L10** with no planar-chiral paracyclophane moiety was used in a Cu-catalyzed conjugate addition, not only the yield but also the enantioselectivity decreased. This highlights the importance of the planar chiral paracyclophane moiety in enantioinduction.



Scheme 10: Control Experiment

Cooperative effect of chiralities

The cooperative effect of chiralities was observed in a conjugate addition reaction. When a ligand containing either axial or planar chirality was used, a decrease in enantioselectivity was observed (Entry 7 and scheme 10). However, when a ligand possessing both axial and planar chirality was used, the enantioselectivity was good (Entry 5). This illustrates the cooperative effect of both planar and axial chirality. The structure of the amine moiety is crucial, but the BINOL also significantly influenced the enantioinduction. Because of steric repulsion, the paracyclophane moiety was far from the substrate. This was confirmed by the low enantiomeric excess of ligand containing only planar chirality (Entry 7). There are no reports describing the enantioinduction mechanism. A matched-mismatched combination may occur. In addition to the BINOL backbone, the choice of substituents at the nitrogen center was also important. The cooperative effect of three substituents at the nitrogen center was important for enantioselective induction.

- **Conclusion**

A chiral library of phosphoramidite ligands was synthesized with planar chirality on the nitrogen atom. These were easily prepared with the appropriate amines in the presence of base. Substituents at the nitrogen atom were varied. BINOL and biphenol backbone were employed. A combination of planar and axially chiral ligands was synthesized. Their efficiency was examined in two well-known reactions, Pd-catalyzed allylic alkylation and Cu-catalyzed conjugate addition. These ligands are easy tuned and easy to handle. Therefore, they are not difficult to preserve. They are also moisture stable. They afforded moderate to good enantioselectivity in Pd-catalyzed allylic alkylation and Cu-catalyzed conjugate addition. The cooperative effect of both planar and axial chiralities was examined in copper-catalyzed conjugate addition.

- **Experimental Section**

General

Unless otherwise noted, all materials were purchased from commercial suppliers and used as received. Anhydrous solvents were stocked on activated molecular sieves 4Å under argon atmosphere, and degassed by argon bubbling prior to use. All reactions were carried out under argon atmosphere in oven-dried glassware with a magnetic stirring bar.

^{1}H NMR spectra were recorded on JEOL AL-400 (400 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet, brs, broad singlet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL AL-400 (100 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). ^{31}P NMR spectra were obtained by JEOL AL-400 (200 MHz) spectrometers and H_3PO_4 was used as an external standard (0.00 ppm). $CDCl_3$ was used as a NMR solvent. High-resolution mass spectra (HRMS) were measured on ESI (Electrospray ionization) method at a JEOL GC-mate II. IR was measured in JASCO FT/IR-4100ST. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in our laboratory. Flash column chromatography was performed over silica gel 200-300.

Experimental procedure for the preparation of amine 2

In a two-neck flask purged with argon, a solution of 1,11-dioxa[11]paracyclophane (**1**) (0.5 mmol) in Et_2O (0.5 ml) was added followed by (+)-sparteine (1 equiv) and the resulting solution was cooled to -78 °C. *sec*-BuLi (0.98 M) (2 equiv) was added dropwise and stirred at -78 °C for 2 h. A solution of trimethylsilylmethyl azide (5 equiv) in Et_2O (0.6 mL) was added dropwise and the reaction mixture was warmed to ambient temperature. The reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (10 ml × 3). The organic layer was washed with brine and dried with Na_2SO_4. The solution was evaporated and purified.

13-Amino-1,11-dioxa[11]paracyclophane (2): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as yellow viscous oil (75.8 mg, 60%). ^{1}H NMR (ppm) δ 6.90-6.88 (m, 1H), 6.45-6.43 (m, 2H), 4.26-4.15 (m, 4H), 3.87 (brs, 2H), 1.71-1.61 (m, 4H), 1.03-0.90 (m, 10H); ^{13}C NMR (ppm) δ 155.7, 141.5, 140.0, 120.6, 110.0, 108.2, 71.4, 71.3, 30.2, 30.0, 27.9, 26.1, 26.1, 25.7, 25.4; IR (cm^{-1}) 3365, 2924, 2851, 2362, 1617, 1506, 1457, 1198, 1163, 982; HRMS(ESI, positive): *m/z* calcd. for $C_{15}H_{24}NO_2$ $[M+H]^+$: 250.1802; found: 250.1802. $[\alpha]_D^{23}$ = +38.6 (*c* 0.57, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4 x 250mm, 254nm UV detector, rt, eluent: 40% EtOAc in hexane, flow rate: 0.5 mL/min, retention time: 10.2 min for minor isomer and 11.0 min for major isomer).

General experimental procedure for reductive amination

To a two-neck flask purged with argon, a solution of appropriate amine (0.1 mmol) and aldehyde (1.2 equiv) in 1,2-dichloroethane (0.3 mL) was added followed by $NaBH(OAc)_3$ (3 equiv) and AcOH (0.02 mL). The reaction mixture was stirred till the completion of reaction. A saturated aqueous solution of K_2CO_3 was added to the reaction mixture and extracted with dichloromethane (10 ml × 3). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness.

13-Benzylamino-1,11-dioxa[11]paracyclophane (3a): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as yellow viscous oil (12.5 mg, 79%).^{1}H NMR (ppm) δ 7.40-7.30 (m, 4H), 7.25-7.23 (m, 1H), 6.84 (dd, *J* = 4.8, 3.8 Hz, 1H), 6.34-6.32 (m, 1H), 6.28-6.27 (m, 1H), 4.77 (brs, 1H), 4.34-4.12 (m, 4H), 4.06-4.04 (m, 2H), 1.61-1.47 (m, 4H), 0.95-0.74 (m, 10H); ^{13}C NMR (ppm) δ 155.9, 141.9, 141.1, 139.5, 128.5, 127.4, 127.1, 119.4, 107.8, 104.3, 71.6, 71.4, 47.9, 30.2, 30.1, 27.9, 26.2, 26.1, 25.8, 25.6 (two pair of peaks are overlapped at aromatic region); IR (cm^{-1}) 2924, 2852, 2362, 2340, 1603, 1516, 1456, 1182, 977, 697,419; HRMS(ESI, positive): *m/z* calcd. for $C_{22}H_{29}NNaO_2$ $[M+Na]^+$: 362.2090; found: 362.2091. $[\alpha]_D^{25}$ = +63.2 (*c* 0.76, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4 x 250mm, 254nm UV detector, rt, eluent: 10% EtOAc in hexane, flow rate: 1 mL/min, retention time: 8.3 min for minor isomer and 10.7 min for major isomer).

13-Methylamino-1,11-dioxa[11]paracyclophane (3b): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as yellow viscous oil (11.7 mg, 45%). ^{1}H NMR (ppm) δ 6.90-6.87 (m,

1H), 6.40-6.35 (m, 2H), 4.34 (brs, 1H), 4.26-4.15 (m, 4H), 2.88 (d, *J* = 2.5 Hz, 3H), 1.69-1.61 (m, 4H), 1.04-0.90 (m, 10H); ^{13}C NMR (ppm) δ 156.1, 143.4, 141.3, 119.3, 107.3, 103.6, 71.6, 71.4, 30.5, 30.3, 30.0, 28.0, 26.1, 26.1, 25.8, 25.4; IR (cm^{-1}) 3426, 2923, 2852, 2362, 1606, 1518, 1457, 1186, 981, 447, 419; HRMS(ESI, positive): *m/z* calcd. for $C_{16}H_{26}NO_2$ $[M+H]^+$: 264.1958; found: 264.1958. $[\alpha]_D^{26}$ = +88.2 (*c* 1.32, $CHCl_3$).

13-Isopropylamino-1,11-dioxa[11]paracyclophane (3c): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as pale yellow viscous oil (24.8 mg, 86%). ^{1}H NMR (ppm) δ 6.85-6.83 (m, 1H), 6.32-6.30 (m, 2H), 4.24-4.10 (m, 5H), 3.57 (brs, 1H), 1.65-1.60 (m, 4H), 1.25-1.20 (m, 6H), 1.03-0.87 (m, 10H); ^{13}C NMR (ppm) δ 156.0, 141.3, 141.0, 119.5, 106.8, 104.0, 71.6, 71.4, 43.6, 30.4, 30.1, 27.9, 26.1, 26.1, 25.8, 25.4, 23.0, 22.9; IR (cm^{-1}) 3419, 2924, 2853, 2363, 1605, 1516, 1458, 1187, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{18}H_{30}NO_2$ $[M+H]^+$: 292.2270; found: 292.2271. $[\alpha]_D^{25}$ =+98.4 (*c* 0.57, $CHCl_3$).

13-(Benzylamino)methyl-1,11-dioxa[11]paracyclophane (5a): it was isolated by PTLC (hexane/ethyl acetate = 3/1). The title compound was obtained as yellow viscous oil (21.5 mg, 64%). ^{1}H NMR (ppm) δ 7.35-7.30 (m, 4H), 7.26-7.24 (m, 1H), 7.02-7.00 (m, 1H), 6.99-6.94 (m, 2H), 4.22-4.17 (m, 4H), 4.06 (d, *J* = 13.7 Hz, 1H), 3.83-3.74 (m, 2H), 3.63 (d, *J* = 13.7 Hz, 1H), 2.02 (brs, 1H), 1.68-1.58 (m, 4H), 0.96-0.73 (m, 10H); ^{13}C NMR (ppm) δ 154.5, 152.6, 140.3, 133.0, 128.3, 128.1, 126.8, 121.6, 120.0, 119.7, 71.7, 71.1, 52.9, 48.5, 30.0, 29.8, 27.7, 26.2, 26.0, 25.8, 25.2 (two pairs of peaks are overlapped at aromatic region); IR (cm^{-1}) 2925, 2854, 2361, 1491, 1456, 1199, 1150, 979, 824, 736, 698; HRMS(ESI, positive): *m/z* calcd. for $C_{23}H_{32}NO_2$ $[M+H]^+$: 354.2425; found: 354.2428. $[\alpha]_D^{26}$ = +13.0 (*c* 0.85, $CHCl_3$, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 x 250mm, 254nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 16.4 min for major isomer and 24.0 min for minor isomer).

13-(Isopropylamino)methyl-1,11-dioxa[11]paracyclophane (5b): it was isolated by PTLC (hexane/ethyl acetate = 3/1). The title compound was obtained as yellow viscous oil (32.1 mg, 94%). ^{1}H NMR (ppm) δ

6.97 (d, *J* = 2.4 Hz, 2H), 6.94-6.92 (m, 1H), 4.22-4.17 (m, 4H), 4.03 (d, *J* = 13.5 Hz, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 2.79-2.77 (dd, *J* = 5.9, 2.7 Hz, 1H), 1.66-1.61 (m, 4H), 1.43 (brs, 1H), 1.07 (d, *J* = 5.6 Hz, 6H), 0.97-0.67 (m, 10H); ^{13}C NMR (ppm) δ 154.5, 152.6, 133.5, 121.5, 119.9, 119.5, 71.7, 71.1, 47.4, 46.7, 30.1, 29.9, 27.8, 26.2, 26.0, 25.8, 25.3, 23.0, 22.7. IR (cm^{-1}) 3853, 3749, 3735, 3649, 2924, 2853, 2361, 1490, 1457, 1193; HRMS(ESI, positive): *m/z* calcd. for $C_{19}H_{32}NO_2$ $[M+H]^+$: 306.2425; found: 306.2428. $[\alpha]_D^{28}$ = +8.8 (*c* 0.61, $CHCl_3$).

General procedure for the synthesis of phosphoramidite ligands (L1-L9)

In a Schlenk tube evacuated and purged with argon (3 times), a solution of appropriate planar-chiral amine (**3a-3c**, **5a** and **5b**) (0.1 mmol) in THF (0.5 mL) and TMEDA (2 equiv) were added and cooled to -78 °C. A hexane solution of *n*-BuLi (1.54 M, 2 equiv) was added dropwise to the solution, and the reaction mixture was stirred for 2 h at -78 °C. A THF solution (0.6 mL) of commercially available chlorodioxaphosphepin (2 equiv) or *in situ* prepared 2,2′-biarylene phosphorochloridite [prepared by mixing the corresponding biaryl diol (0.20 mmol) and PCl_3 (0.28 mmol) at 75 °C overnight] was added dropwise at -78 °C and warmed to room temperature overnight. The resulting solution was filtered through filter paper using dichloromethane and was evaporated to dryness.

(*R*$_a$)-*N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((*R*$_a$)-L1): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as foamy white solid (26.4 mg, 41%). Mp: 124-128 °C; ^{1}H NMR (ppm) δ 8.04-7.90 (m, 4H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.45-7.36 (m, 4H), 7.27-7.24 (m, 3H), 7.06-7.04 (m, 4H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.53 (s, 1H), 4.56-4.51 (m, 1H), 4.43-4.35 (m, 2H), 4.23 (dd, *J* = 14.4, 3.4 Hz, 1H), 3.97-3.88 (m, 2H), 1.82-1.77 (m, 2H), 1.45-1.42 (m, 2H), 0.95-0.80 (m, 8H), 0.72-0.71 (m, 2H); ^{13}C NMR (ppm) δ 154.8, 150.0, 149.2, 142.5, 139.6, 138.5, 137.9, 134.8, 132.8, 132.6, 131.5, 130.8, 130.3, 129.1, 128.3, 127.9, 127.1, 127.0, 126.8, 126.1, 124.9, 124.7, 124.2, 124.1, 122.6, 122.2, 122.1, 122.0, 121.6, 118.3, 71.4, 50.3, 30.1, 29.4, 27.6, 26.5, 25.9, 25.8, 25.3 (a pair of peak at aliphatic region is overlapped.); ^{31}P (ppm) δ 140.3. IR (cm^{-1}) 3749, 3735, 3649, 2921, 2361, 2343, 1734, 1363, 1229, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{42}H_{40}NNaO_4P$ $[M+Na]^+$: 676.2584; found: 676.2587. $[\alpha]_D^{23}$ = -193.7 (*c* 0.91, $CHCl_3$).

(S_a)-*N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((S_a)-L1): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as foamy white solid (41.6 mg, 65%). Mp: 126-130 °C; ^{1}H NMR (ppm) δ 7.98 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 6.6 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.46-7.33 (m, 5H), 7.25-7.12 (m, 7H), 6.91 (brs, 2H), 6.79 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 15.3 Hz, 1H), 4.39-4.21 (m, 3H), 4.13-4.03 (m, 2H), 1.76-1.50 (m, 4H), 1.00-0.79 (m, 10H); ^{13}C NMR (ppm) δ 155.1, 149.8, 149.8, 149.7, 149.0, 138.3, 135.7, 135.5, 132.8, 132.6, 131.4, 130.6, 130.4, 129.8, 128.4, 128.3, 128.2, 127.9, 127.1, 127.0, 126.6, 126.1, 126.0, 124.9, 124.5, 122.0, 121.9, 121.0, 120.9, 118.1, 71.5, 70.8, 49.8, 30.3, 29.6, 27.7, 26.6, 26.3, 25.1, 25.3; ^{31}P (ppm) δ 140.7. IR (cm^{-1}) 2924, 2854, 2361, 1601, 1508, 1457, 1223, 966, 813, 445; HRMS(ESI, positive): *m/z* calcd. for $C_{42}H_{40}NNaO_4P$ $[M+Na]^+$: 676.2584; found: 676.2587. $[\alpha]_D^{23}$ = -61.9 (*c* 0.51, $CHCl_3$).

(R_a)-*N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-ylmethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((R_a)-L2): it was isolated by PTLC (hexane/ethyl acetate = 3/1). The title compound was obtained as foamy white solid (25.2 mg, 36%). Mp: 113-117 °C; ^{1}H NMR (ppm) δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.35-7.30 (m, 3H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.25-7.18 (m, 5H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.10-7.03 (m, 2H), 6.92 (brs, 1H), 4.51 (dd, *J* = 15.3, 10.3 Hz, 1H), 4.20-4.08 (m, 4H), 4.05 (dd, *J* = 15.3, 4.4 Hz, 1H), 3.69 (dd, *J* = 18.7, 15.4 Hz, 1H), 3.38 (dd, *J* = 15.3, 5.9 Hz, 1H), 1.72-1.46 (m, 4H), 0.93-0.68 (m, 10H); ^{13}C NMR (ppm) δ 154.0, 153.3, 149.8, 149.5, 138.0, 132.8, 132.5, 131.4, 130.7, 130.7, 130.1, 130.0, 128.4, 128.3, 128.2, 127.0, 127.0, 126.9, 126.0, 125.9, 124.7, 124.5, 124.1, 124.1, 122.7, 122.4, 122.2, 121.9, 120.3, 120.1, 72.0, 71.0, 47.3, 44.8, 30.0, 29.6, 27.8, 26.2, 26.1, 26.0, 25.2; ^{31}P (ppm) δ 147.0. IR (cm^{-1}) 2924, 2852, 2361, 2329, 1490, 1457, 1230, 1200, 936, 822, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{43}H_{42}NNaO_4P$ $[M+Na]^+$: 690.2739; found: 690.2744. $[\alpha]_D^{26}$ = -113.0 (*c* 1.06, $CHCl_3$).

(S_a)-*N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-ylmethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((S_a)-L2): it was isolated by PTLC (hexane/ethyl acetate = 3/1). The title compound was obtained as foamy white solid (32.8 mg, 45%). Mp: 114-118 °C; ^{1}H NMR (ppm) δ 7.98 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.93 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.84-7.81 (m, 2H), 7.56-7.53 (m, 1H), 7.44-7.31 (m, 8H), 7.27-7.26 (m, 2H), 7.21-7.13 (m, 3H), 6.86-6.77 (m, 2H), 4.62-4.55 (m, 1H), 4.35-4.28 (m, 1H), 4.20-4.12 (m, 1H), 3.83-3.67 (m, 4H), 3.50-3.44 (m, 1H), 1.65-1.56 (m, 3H), 0.82-0.12 (m, 11H); ^{13}C NMR (ppm) δ 155.0, 152.3, 149.8, 149.7, 149.2, 138.3, 132.8, 132.5, 131.3, 130.8, 130.7, 130.2, 130.1, 128.9, 128.4, 128.2, 128.1, 127.5, 127.0, 126.9, 126.1, 125.9, 124.8, 124.5, 122.5, 122.0, 121.6, 120.5, 119.6, 119.2, 71.5, 71.3, 50.6, 42.5, 30.2, 29.3, 27.3, 25.4, 25.2, 24.5 (a pair of peak at aliphatic region is overlapped); ^{31}P (ppm) δ 148.7. IR (cm^{-1}) 2929, 2362, 2343, 2328, 1507, 1489, 1230, 421; HRMS(ESI, positive): *m/z* calcd. for $C_{43}H_{42}NNaO_4P$ $[M+Na]^+$: 690.2740; found: 690.2744. $[\alpha]_D^{24}$ = +174.5 (*c* 1.10, $CHCl_3$).

(R_a)-*N*-(1,11-Dioxa[11]paracyclophan-13-yl)-*N*-methyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((R_a)-L3): it was isolated by PTLC (toluene only). The title compound was obtained as foamy white solid (17.1 mg, 30%). Mp: 110-115 °C; ^{1}H NMR (ppm) δ 7.99 (dd, *J* = 8.8, 8.8 Hz, 2H), 7.94 (dd, *J* = 8.1, 3.3 Hz, 2H), 7.59 (dd, *J* = 12.0, 8.8 Hz, 2H), 7.46-7.41 (m, 3H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.31-7.29 (m, 1H), 7.27 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.90-6.87 (m, 2H), 4.46-4.41 (m, 1H), 4.34-4.30 (m, 1H), 4.18-4.14 (m, 2H), 2.73 (s, 3H), 1.78-1.77 (m, 1H), 1.71-1.65 (m, 2H), 1.05-0.84 (m, 11H); ^{13}C NMR (ppm) δ 155.7, 149.3, 149.1, 132.8, 132.6, 131.5, 130.7, 130.4, 130.1, 128.3, 128.3, 127.0, 126.1, 124.9, 124.7, 124.2, 124.0, 124.0, 122.7, 122.2, 119.1, 119.0, 117.8, 117.6, 71.6, 71.4, 34.9, 30.3, 29.6, 27.7, 26.3, 26.1, 26.0, 25.3 (two pairs of peaks in the aromatic region are overlapped); ^{31}P (ppm) δ 144.0. IR (cm^{-1}) 2924, 2362, 2328, 1746, 1734, 1539, 1507, 1456, 1229, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{36}H_{36}NNaO_4P$ $[M+Na]^+$: 600.2274; found: 600.2274. $[\alpha]_D^{28}$ = -124.7 (*c* 0.43, $CHCl_3$).

(R_a)-*N*-(1,11-Dioxa[11]paracyclophan-13-yl)-*N*-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine ((R_a)-L4): it was isolated by PTLC (hexane/ethyl acetate = 5/1). The

title compound was obtained as foamy white solid (12.4 mg, 20%). Mp: 116-120 °C; ^{1}H NMR (ppm) δ 8.0-7.89 (m, 4H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.42-7.35 (m, 4H), 7.26-7.24 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.65 (s, 1H), 4.50-4.37 (m, 2H), 3.99 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 1H), 3.58-3.53 (m, 1H), 1.87-1.83 (m, 1H), 1.72-1.66 (m, 1H), 1.42-1.20 (m, 2H), 0.99-0.85 (m, 8H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.80-0.66 (m, 2H); ^{13}C NMR (ppm) δ 179.8, 178.8, 154.1, 151.7, 150.1, 149.8, 132.9, 132.7, 131.4, 130.8, 130.1, 129.8, 128.9, 128.4, 128.3, 127.7, 127.1, 127.1, 126.0, 125.9, 124.7, 124.4, 122.6, 122.3, 120.4, 119.9, 71.7, 71.2, 53.4, 30.2, 29.7, 29.6, 27.7, 26.6, 26.0, 25.6, 22.9, 21.5; ^{31}P (ppm) δ 144.4. IR (cm^{-1}) 2926, 2360, 2339, 1735, 1540, 1509, 1490, 1363, 1231, 948, 517, 458, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{38}H_{40}NNaO_4P$ $[M+Na]^+$: 628.2584; found: 628.2587. $[\alpha]_D^{30}$ = -142.5 (*c* 0.87, $CHCl_3$).

***N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-yl)dibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L5):** it was isolated by PTLC (toluene only). The title compound was obtained as foamy white solid (38.9 mg, 41%). Mp: 68-74 °C; ^{1}H NMR (ppm) δ 7.48-7.46 (m, 2H), 7.36-7.26 (m, 6H), 7.11-7.05 (m, 5H), 6.97-6.93 (m, 1H), 6.78-6.72 (m, 2H), 4.61-4.35 (m, 4H), 4.12-4.06 (m, 2H), 1.72-1.61 (m, 3H), 0.92-0.78 (m, 11H); ^{13}C NMR (ppm) δ 155.1, 151.9, 150.9, 149.9, 138.2, 135.3, 135.1, 131.3, 130.6, 129.9, 129.8, 129.5, 129.3, 129.0, 128.0, 126.8, 125.0, 124.6, 122.5, 122.2, 122.1, 121.5, 121.4, 118.1, 71.6, 71.3, 49.8, 30.4, 29.6, 27.8, 26.5, 26.1, 25.9, 25.4; ^{31}P (ppm) δ 141.0. IR (cm^{-1}) 2924, 2852, 2361, 1493, 1474, 1457, 1436, 1246, 1192, 1166, 885; HRMS(ESI, positive): *m/z* calcd. for $C_{34}H_{36}O_4NNaP$ $[M+Na]^+$: 576.2280; found: 576.2274. $[\alpha]_D^{24}$ = -90.5 (*c* 0.53, $CHCl_3$).

***N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-ylmethyl)dibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L6):** it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as foamy white solid (26.5 mg, 47%). Mp: 65-70 °C; ^{1}H NMR (ppm) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.39-7.36 (m, 5H), 7.34-7.24 (m, 4H), 7.22-7.16 (m, 3H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.91-6.90 (m, 2H), 4.41-4.35 (m, 1H), 4.29-4.24 (m, 1H), 4.20-4.15 (m, 1H), 4.13-3.93 (m, 4H), 3.89-3.86 (m, 1H), 1.71-1.54 (m, 3H), 1.16-1.09 (m, 1H), 0.88-0.75 (m, 3H), 0.56-0.51 (m, 7H); ^{13}C NMR (ppm) δ 154.8, 152.5, 151.9, 151.8, 138.3, 131.4, 131.4, 130.4, 130.4, 129.7, 129.5, 129.3, 129.0, 128.6,

128.3, 127.2, 124.7, 124.2, 122.2, 121.7, 120.2, 120.1, 119.5, 71.8, 71.1, 49.4, 43.3, 30.1, 29.7, 27.6, 25.8, 25.6, 25.6, 25.0 (a pair of peaks in the aromatic region is overlapped); ^{31}P (ppm) δ 149.1. IR (cm^{-1}) 2927, 2361, 2341, 1734, 1541, 1489, 1436, 1191, 884, 772, 447, 419; HRMS(ESI, positive): *m/z* calcd. for $C_{35}H_{38}NNaO_4P$ $[M+Na]^+$: 590.2430; found: 590.2431. $[\alpha]_D^{20}$ = -8.7 (*c* 0.61, $CHCl_3$).

***N*-(1,11-Dioxa[11]paracyclophan-13-ylmethyl)-*N*-isopropyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L7):** it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as foamy white solid (15.4 mg, 30%). Mp: 130-134 °C; ^{1}H NMR (ppm) δ 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.23-7.17 (m, 5H), 6.80 (d, *J* = 1.6 Hz, 2H), 4.26-4.19 (m, 1H), 4.17-4.13 (m, 2H), 4.04-3.97 (m, 2H), 3.85 (ddd, *J* = 12.0, 6.6, 3.1 Hz, 1H), 3.69-3.61 (m, 1H), 1.65-1.58 (m, 1H), 1.56-1.48 (m, 1H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.27-1.23 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.10-1.05 (m, 1H), 0.81-0.74 (m, 2H), 0.52-0.39 (m, 8H); ^{13}C NMR (ppm) δ 154.8, 152.6, 152.6, 151.4, 133.5, 130.3, 130.3, 129.9, 129.5, 129.3, 128.9, 124.7, 124.0, 122.4, 121.7, 120.2, 119.7, 118.9, 71.7, 71.2, 49.2, 41.3, 30.2, 29.7, 27.5, 25.8, 25.6, 25.5, 25.0, 23.2, 23.0; ^{31}P (ppm) δ 151.3. IR (cm^{-1}) 2924, 2852, 2362, 1488, 1435, 1247, 1191, 1095, 1036, 888, 847, 765, 419; HRMS(ESI, positive): *m/z* calcd. for $C_{31}H_{38}NNaO_4P$ $[M+Na]^+$: 542.2432; found: 542.2431. $[\alpha]_D^{28}$ = +86.9 (*c* 0.84, $CHCl_3$).

***N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-yl)-2,4,8,10-tetramethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L8):** it was

isolated by PTLC (toluene only). The title compound was obtained as foamy white solid (33.2 mg, 55%). Mp: 82-86 °C; ^{1}H NMR (ppm) δ 7.14-7.11 (m, 3H), 7.09-7.05 (m, 6H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.80-6.77 (m, 2H), 4.67 (d, *J* = 14.4 Hz, 1H), 4.42 (dd, *J* = 14.4, 2.2 Hz, 1H), 4.24 (dd, *J* = 5.1, 5.1 Hz, 2H), 4.20-4.07 (m, 2H), 2.47 (s, 3H), 2.46 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H), 1.65-1.58 (m, 2H), 1.39-1.37 (m, 2H), 0.96-0.83 (m, 4H), 0.80-0.67 (m, 6H); ^{13}C NMR (ppm) δ 154.9, 149.3, 149.2, 148.1, 148.0, 146.5, 137.8, 135.6, 135.4, 133.8, 132.8, 131.2, 131.1, 129.8, 129.6, 128.1, 127.8, 126.8, 122.0, 120.1, 120.0, 117.3, 71.4, 71.2, 48.5, 30.0, 29.1, 27.4, 26.3, 25.9, 25.6, 25.2, 20.9, 20.8, 17.0, 16.7; ^{31}P (ppm) δ 134.7. IR (cm^{-1}) 2923, 2852, 1600, 1494, 1478, 1457, 1409, 1245, 1213, 1193, 1154, 1120, 1065, 857, 759, 699, 593, 476, 418; HRMS(ESI, positive): *m/z* calcd. for $C_{38}H_{44}O_4NNaP$ $[M+Na]^+$: 632.2897; found: 632.2900. $[\alpha]_D^{27}$ = -123.3 (*c* 0.56, $CHCl_3$).

***N*-Benzyl-*N*-(1,11-dioxa[11]paracyclophan-13-ylmethyl)-2,4,8,10-tetramethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L9):** it was isolated by PTLC (hexane/ethyl acetate = 5/1). The title compound was obtained as white solid (24.5 mg, 39%). Mp: 76-80 °C; ^{1}H NMR (ppm) δ 7.37 (d, *J* = 6.8 Hz, 2H), 7.31 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.27-7.26 (m, 1H), 7.14 (s, 1H), 7.01-6.98 (m, 3H), 6.92-6.90 (m, 3H), 4.24-4.20 (m, 1H), 4.15-3.97 (m, 5H), 3.92 (d, *J* = 14.7, Hz, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 2.04 (s, 3H), 1.29-1.27 (m, 3H), 0.82-0.52 (m, 11H); ^{13}C NMR (ppm) δ 154.8, 152.7, 149.6, 147.9, 146.7, 138.1, 133.2, 132.6, 131.3, 130.9, 130.9, 130.8, 130.0, 129.9, 129.2, 128.2, 127.8, 127.7, 127.2, 120.3, 119.5, 99.9, 71.6, 71.4, 30.2, 29.7, 27.7, 25.9, 25.6, 25.5, 25.2, 20.8, 20.8, 16.5, 16.5. (two pairs of peaks are overlapped at aliphatic region). ^{31}P (ppm) δ 143.0. IR (cm^{-1}) 2923, 2851, 2362, 2338, 1735, 1489, 1363, 1214, 1194, 854, 420; HRMS(ESI, positive): *m/z* calcd. for $C_{39}H_{46}NNaO_4P$ $[M+Na]^+$: 646.3054; found: 646.3057. $[\alpha]_D^{25}$ = +24.1 (*c* 1.27, $CHCl_3$).

***N*-(2,5-dimethoxyphenyl)-*N*-methyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (L10):** it was isolated by PTLC (toluene only). The title compound was obtained as foamy white solid (13.9 mg, 29%). Mp: 89-92 °C; ^{1}H NMR (ppm) *δ* 7.97-7.89 (m, 4H), 7.56-7.53 (m, 2H), 7.45-7.33 (m, 4H), 7.28-7.22 (m, 2H), 6.88-6.84 (m, 2H), 6.72-6.69 (m, 1H), 3.89-3.87 (m, 3H), 3.75-3.73 (m, 3H), 2.59-2.57 (m, 3H); ^{13}C NMR (ppm) *δ* 153.9, 150.2, 150.1, 149.5, 135.2, 135.0, 132.9, 131.4, 130.8, 130.2, 129.9, 128.3, 128.2, 127.0, 126.9, 126.0, 124.0,

124.0, 122.7, 122.2, 122.0, 115.0, 114.9, 113.4, 111.1, 99.9, 56.6, 55.7, 35.0; ^{31}P (ppm) δ 144.7. IR (cm^{-1}) 2927, 1614, 1587, 1500, 1460, 1327, 1269, 1221, 1063, 937, 820; HRMS(ESI, positive): *m/z* calcd. for $C_{29}H_{25}NO_4P$ $[M+H]^+$: 482.1517; found: 482.1516. $[\alpha]_D^{32.} = -72.1$ (*c* 0.77, $CHCl_3$).

Experimental procedure for enantioselective alkylation in Table 2

In a schlenk tube, $[Pd(allyl)Cl]_2$ catalyst (2.0 mol%) and the ligand (8.0 mol%) was dissolved in DCM (0.9 ml) and stirred for 40 min at the desired temperature. (*E*)-1,3-Diphenylallyl acetate (**6**) (0.03ml, 0.15mmol) was added and stirred for another 15 min. Dimethyl malonate (**7**) (0.03ml, 1.8 equiv) was added followed by addition of BSA (1.3 equiv) and KOAc (1.3 equiv), then stirred at the desired temperature for 24-48 h. The reaction mixture was diluted by DCM, filtered and evaporated. The crude mixture was purified by PTLC. The absolute configuration of product **8** was determined by the comparison of the sign of optical rotation with that in the literature.[13]

Experimental procedure for conjugate addition in Table 3

In a schlenk tube, Cu catalyst (2.8 mol%) and the ligand (6 mol%) were dissolved in toluene (0.8 ml) and stirred for 1 h at 0 °C. (*E*)-Chalcone (**9**) (20.8 mg, 0.1 mmol) was added followed by dropwise addition of diethylzinc (3 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1-6 h, then quenched with saturated NH_4Cl solution. The solution was extracted with Et_2O (×3 times) and washed with saturated brine solution. The reaction mixture was dried over Na_2SO_4 and evaporated. Crude product was purified by PTLC. The absolute configuration of product **10** was determined by the comparison of the sign of optical rotation with that in the literature.[14]

- **References**

1. Hulst, R; de Vries, N. K; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699-708.

2. (a) de Vries, A. H; Meetsma, A; Feringa, B. L. *Angew. Chem. Int. Ed*. **1996**, *35*, 2374-2376; (b) Feringa, B. L; Pineschi, M; Arnold, L. A; Imbos, R, de Vries, A. H. M. *Angew. Chem. Int. Ed*. **1997**, *36*, 2620-2623.

3. Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*. **2000**, *122*, 11539-11540.

4. Sebesta, R.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2007**, *349*, 1931-1937.

5. Malda, H.; Van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169-1171.

6. Fan, B.-M.; Xie, J.-H.; Li, S.; Tu, Y.-Q.; Zhou, Q.-L. *Adv. Synth. Catal*. **2005**, *347*, 759 –762.

7. Moteki, S. A.; Wu, D.; Chandra, K. L.; Reddy, D. S.; Takacs, J. M. *Org. Lett.* **2006**, *8*, 3097-3100.

8. Balaraman, E.; Swamy, K. C. K. *Tetrahedron: Asymmetry* **2007**, *18*, 2037-2048.

9. Nishiyama, K.; Tanaka, N. *J. Chem. Soc., Chem Commun*. **1983**, 1322–1323.

10. (a) Kanda, K.; Endo, K.; Shibata, T. *Org. Lett*. **2010**, *12*, 1980–1983; (b) Kanda, K.; Hamanaka, R.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 1407–1416.

11. Gavrilov, K. N.; Shiryaev, A. A.; Chuchelkin, I. V.; Zheglov, S. V.; Rastorguev, E. A.; Davankov, V. A.; Borner, A. *Tetrahedron: Asymmetry* **2012**, *23*, 1052–1057.

12. (a) Yu, H.; Xie, F.; Ma, Z.; Liu, Y.; Zhang, W. *Org. Biomol. Chem*. **2012**, *10,* 5137–5142; (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc*. **2002**, *124*, 5262–5263.

13. Benetskiy, E. B.; Bolm, C.; *Tetrahedron: Asymmetry* **2011**, *22*, 373-378.

14. Tauchman, J.; Cisarova, I.; Stepnicka, P. *Eur. J. Org. Chem*. **2010**, 4276-4287.

Chapter 4

Introduction of Indolo[1,2-*a*]indole Derivatives

• Background

Diverse biological and pharmacological properties were exhibited by nitrogen-containing heterocycles. Particularly, the foundation for many well-known medicinally active compounds[1] is an indole core. For medicinal chemists,[2] convenient methods for constructing indole-fused skeletons are extremely valuable. Significant attention was devoted to studying diverse synthetic analogues of indole. To synthesize new drugs, new methodologies for synthesizing indole derivatives are essential.[3] Among these compounds, there is particular interest in indoloindoles, in which indole fragments are fused to have in common carbon atoms of the pyrrole ring (for example, 5*H*,10*H*-indolo[3,2-*b*]indole (**1**)), carbon and nitrogen atoms of the pyrrole rings (for example, 10*H*-indolo[1,2-*a*]indole (**2**)), or carbon atoms of the benzene ring (for example, 1*H*,6*H*-indolo[7,6-*g*]indole (**3**) and 3*H*, 8*H*,-indolo[4,5-*e*]indole (**4**))[4] (Fig. 1).

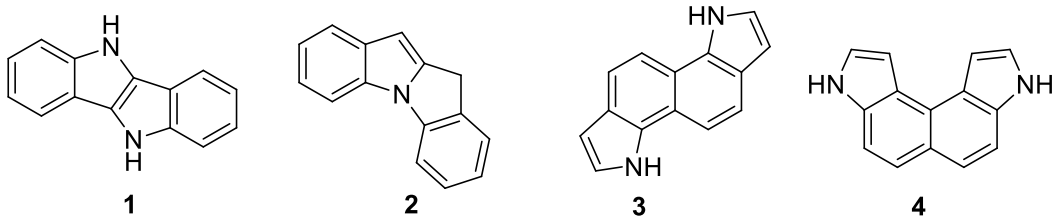


Fig 1: Various types of indoloindoles

Indoloindoles are particularly known as chromogenic and fluorogenic indicators. They are also well-known as materials for organic electroluminescent devices[5] and for electronic devices,[6] such as organic integrated circuits, organic field-effect transistors, organic solar cells, and organic light-emitting diode (Fig. 2).

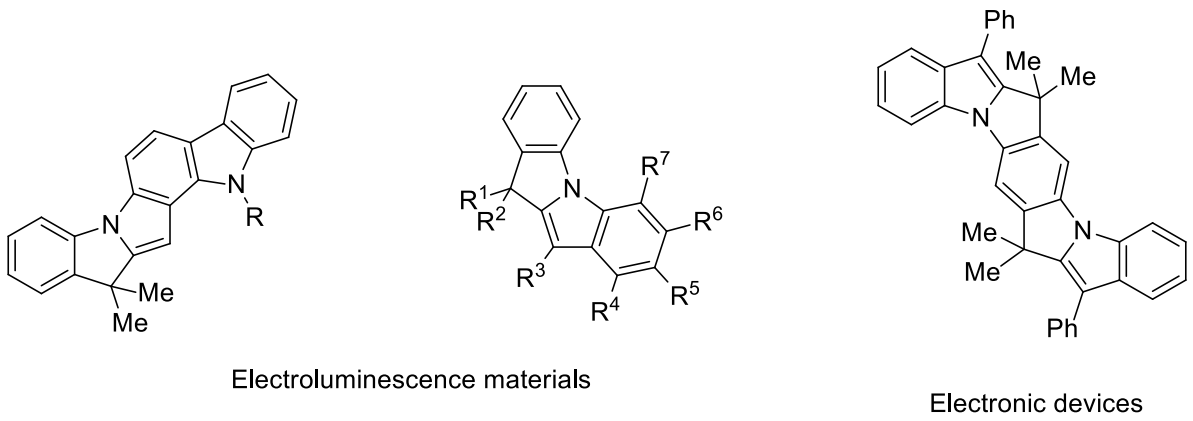
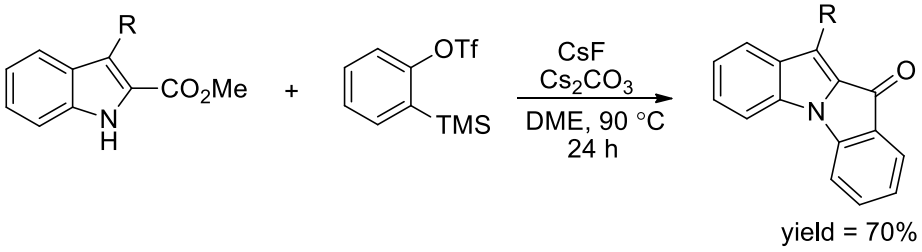


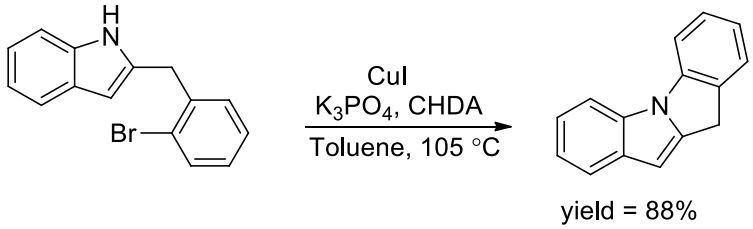
Fig 2. Compounds used in electroluminescence and electronic devices

The first non-catalytic approach to synthesizing indoloindolone was described by Larock's group. The novel indoloindolone ring system was obtained by reacting methyl indole-2-carboxylates and arynes.[7] It tolerates appreciable functionality and has broader substrate scope. It afforded a high yield and the reaction proceeded under mild conditions (Scheme 1).



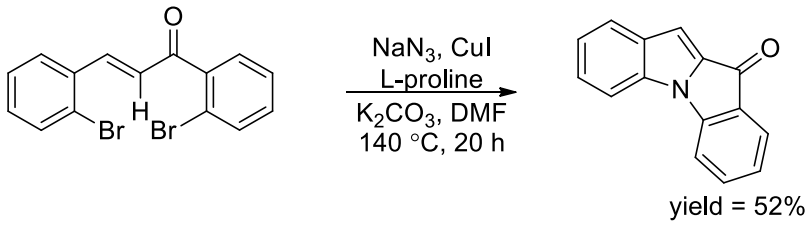
Scheme 1: [3+2] annulation reaction

Dominguez reported a new synthetic route to develop indolo[1,2-*a*]indole derivatives. The key step in this strategy was C_{aryl}-N bond formation. This represented the first Cu-catalyzed intramolecular C-H arylation of indole via C-H functionalization (Scheme 2).[8]



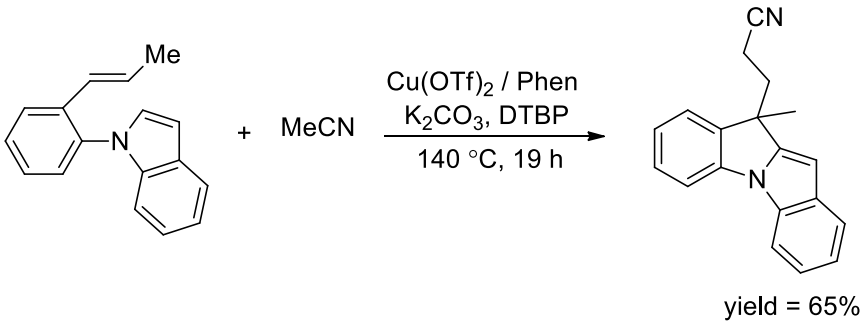
Scheme 2: Preparation of indolo[1,2-*a*]indole

Ramana developed a tetracyclic indoloindolone core from 2,2'-bis-bromochalcones by using Cu catalyst. This reaction formed three C-N bonds in one pot; namely, Cu-catalyzed S_NAr with azide, C-H bond insertion by nitrene, and an intramolecular Ullmann reaction (Scheme 3).[9]



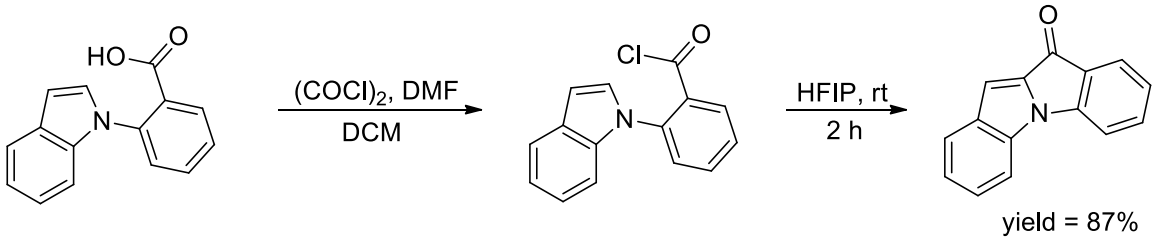
Scheme 3: Synthesis of indoloindolone

Cu-mediated selective dual C-H bond cleavage was reported by Ji. This novel approach provided highly functionalized pyrroloindole derivatives. Both a quaternary center and a five-membered ring were formed in this reaction (Scheme 4).[10]



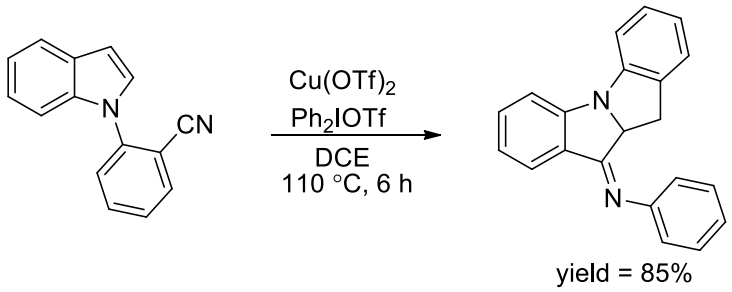
Scheme 4: Cu-mediated indoloindole synthesis

An intramolecular Friedel-Crafts acylation was presented for synthesizing an indoloindolone scaffold using HFIP (Scheme 5).[11]



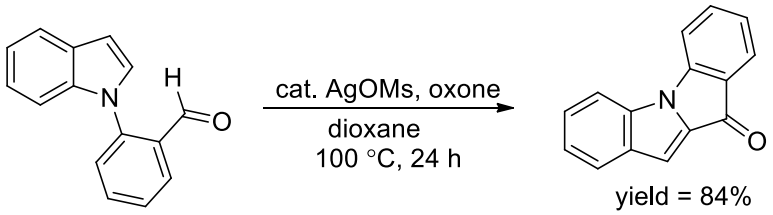
Scheme 5: Protocol for indoloindolone synthesis

An effective synthetic strategy was developed for synthesizing fused indoles of [1,2-*a*]indol-10-imines through a $Cu(OTf)_2$-catalyzed intramolecular cyclization by reacting *N*-(2-cyanophenyl)indoles in the presence of diaryliodonium triflate salts under mild conditions (Scheme 6).[12]



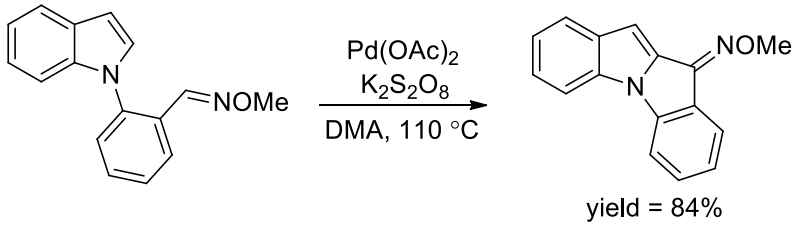
Scheme 6: Cu-catalyzed annulation

A method for a highly selective indoloindolone scaffold through a Ag-catalyzed C-H bond functionalization was reported. This involves direct oxidative coupling between aldehyde C-H and aromatic C-H bonds. A direct annulation of *N*-(2-formylaryl)indoles was developed for synthesizing a medicinally important indole-fused indolone moiety (Scheme 7).[13]



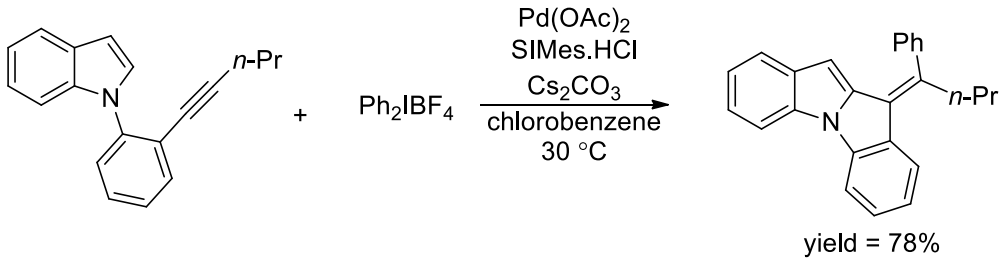
Scheme 7: Synthesis of indoloindolone

A strategy for synthesizing indolo[1,2-*a*]indoles[14] was reported by Roy involving sequential Pd-catalyzed indole-*N*-arylated aldoxime annulation (Scheme 8).



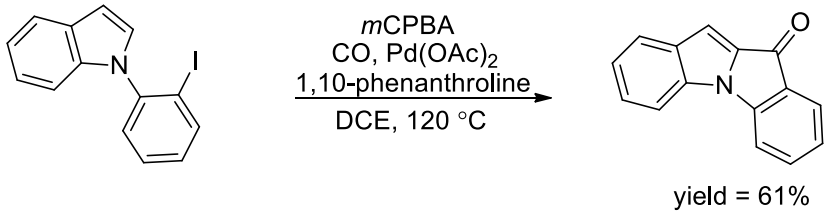
Scheme 8: Pd-catalyzed synthesis of indolo[1,2-*a*]indoles

A novel protocol for Pd-catalyzed indole C-H activation, carbopalladation to alkyne moiety, and arylation with diaryliodonium salts was reported by Greaney.[15] Functionalized indole alkenes were synthesized in excellent yield with *Z*-alkene selectivity (Scheme 9).



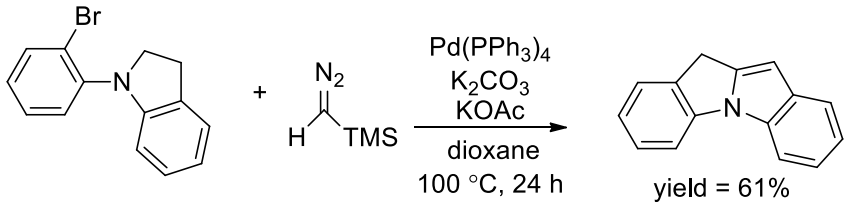
Scheme 9: Synthesis of tetrasubstituted olefin moiety

An efficient strategy was developed for synthesizing indole-fused indolone via Pd-catalyzed cyclocarbonylation of cyclic diaryliodoniums prepared from iodoarene and *m*CPBA (Scheme 10).[16]



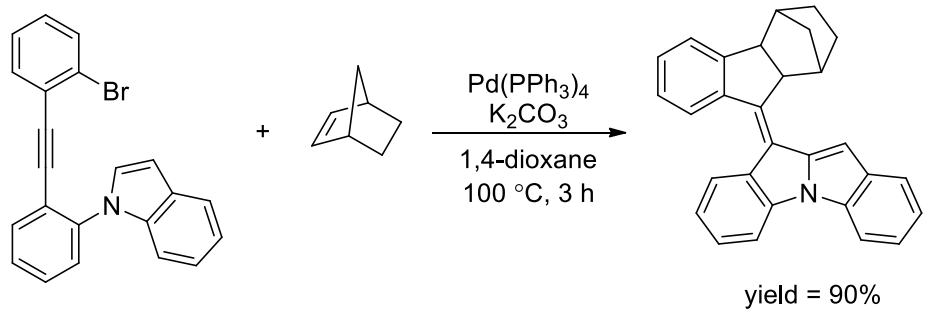
Scheme 10: Synthesis of indole-fused indolone

Wang reported Pd-catalyzed formal [4+1] annulation. This involved formation of two carbon-carbon bonds at a carbenic center. The key steps were migratory insertion of a metal carbene and C(sp^2)-H bond functionalization (Scheme 11).[17]



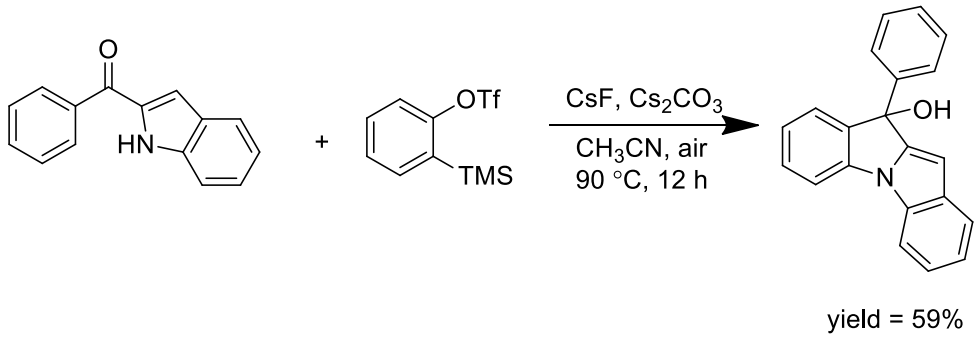
Scheme 11: Pd-catalyzed synthesis of indolo[1,2-*a*]indole

Perumal described a highly regio- and stereocontrolled strategy for the preparation of tetrasubstituted olefins via a Pd-catalyzed process.[18] This involves double carbopalladation and C-H bond activation (Scheme 12).



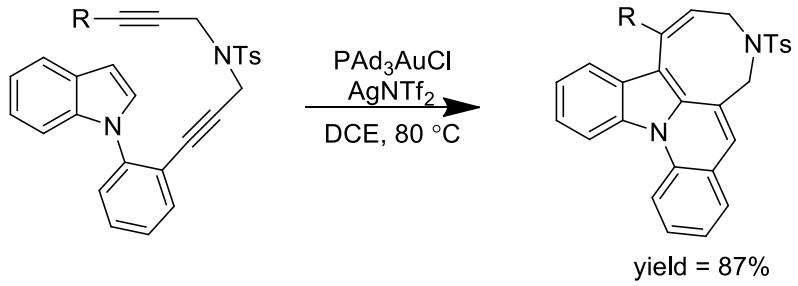
Scheme 12: Synthesis of tetrasubstituted alkene

An efficient strategy was described for synthesizing indole-fused indoles using aryne and base under transition-metal-free conditions (Scheme 13).[19]



Scheme 13: Synthesis of indoloindoline derivatives

An eight-membered ring synthesis for fused indolo-quinoline was described by Shi. A Au-catalyzed cycloisomerization involves two-fold hydroarylation with indole (Scheme 14).[20]



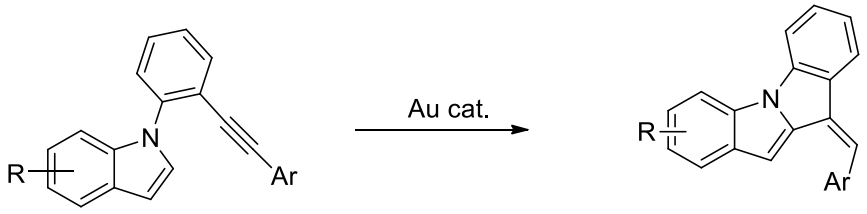
Scheme 14: Synthesis of Au-catalyzed indoloquinoline

- **Purpose of The Research in This Chapter**

As mentioned above, indoloindoles are attractive scaffolds for potential biological activity. They are also used as indicators and in electroluminescence and electronic devices, such as organic solar cells and organic field effect transistors.

The author described various methods for synthesizing indoloindoles. Most of the strategies involved Pd- or Cu-catalyzed processes. Only one method used Au-catalyzed cycloisomerization for the preparation of an eight-membered-fused indolo-quinoline as an *endo* product.

Against this background, chapter 5 discusses the synthesis of indoloindoles through Au-catalyzed cycloisomerization. This provided a 5-*exo*-dig cycloisomerized product. Photophysical properties were also discussed including UV-VIS, fluorescence spectroscopy, and fluorescence quantum yield.



Scheme 15: Outline of Au-catalyzed cycloisomerization

- **References**

1. Gil, C; Brase, S. J. *Comb. Chem*. **2009**, *11*, 175–197.

2. Horton, D. A; Bourne, G. T; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893–930.

3. Rowinsky, E. C.; Donehover, R. C.; In DeVita, V. T. Jr.; Hellman, S.; Rosenberg, S. A. Eds., 5th ed.; *Cancer Principles and Practice of Oncology*; Lippincott-Raven:Philadelphia, **1997**, *467*.

4. Samsoniya, Sh. A.; Trapaidze, M. V. *Russ. Chem. Rev.* **2007**, *76*, 313–326.

5. Sungmoo, K.; Hyungchan, B.; Youngmi, B.; Jinyong, S.; Hocheol, P.; Jun, C. L.; Young Bae, K.; Hyung, T. *PCT Int. Appl*. **2014**, WO 2014081134 A1 20140530.

6. Teresa, M.-F.; Christof, P.; Irina, M. *PCT Int. Appl*. **2012**, WO 2012139692 A120121018.

7. Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 44003-4008.

8. Barbero, N.; SanMartin, R.; Dominguez, E. *Tetrahedron Lett.* **2009**, *50*, 2129-2131.

9. Kulkarni, A. M.; Srinivas, K.; Deshpande, M. V.; Ramana, C. V. *Org. Chem. Front*. **2016**, *3*, 43-46.

10. Chu, X.-Q.; Xing, Z.-H.; Meng, H.; Xu, X.-P.; Ji, S.-J. *Org. Chem. Front*. **2016**, *3*, 165-169.

11. Motiwala, H. F.; Vekariya, R. H.; Aube, J. *Org. Lett*. **2015**, *17*, 5484-5487.

12. Zhang, L.; Wang, Y.; Zheng, L.; Guo, B.; Hua, R. *Tetrahedron* **2017**, *73*, 395-402.

13. Wang, X.; Li, Z.; Cao, S.; Rao, H. *Adv. Synth. Catal*. **2016**, *358*, 2059-2065.

14. Hazra, S.; Mondal, B.; Narayan De, R.; Roy, B. *RSC Adv*. **2015**, *5*, 22480-22489.

15. Saurez, L. L.; Greaney, M. F. *Chem. Commun*. **2011**, *47*, 7992-7994.

16. Liu, L.; Qiang, J.; Bai, S.; Li, Y.; Miao, C.; Li, J. *Appl. Organometal. Chem.* **2017**, *31*, 3817.

17. Xu, S.; Chen, Ri.; Fu, Z.; Zhou, Q.; Zhang, Y.; Wang, J. *ACS Catal*. **2017**, *7*, 1993-1997.

18. Naveen, K.; Nikson, S. A.; Perumal, P. T. *Adv. Synth. Catal*. **2017**, *359*, 2407-2413.

19. Li, B.; Mai, S.; Song, Q. *Org. Chem. Front*. **2018**, *5*, 1639-1642.

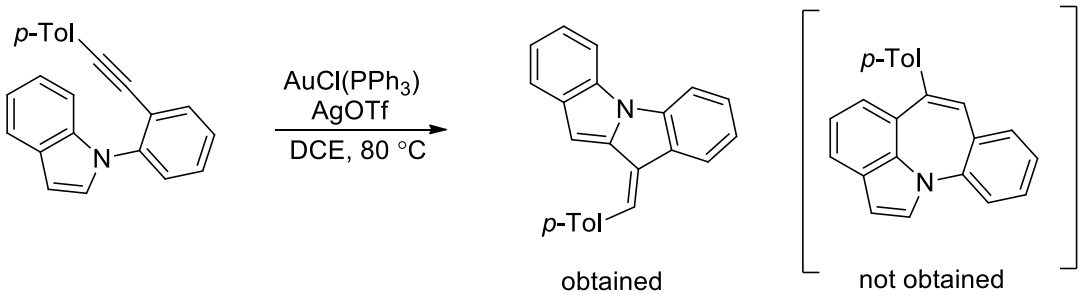
20. Liu, R.; Wang, Q.; Wei, Y.; Shi, M. *Chem. Commun*. **2018**, *54*, 1225-1228.

Chapter 5
Synthesis of Indolo[1,2-*a*]indole Derivatives and Their Photophysical Properties

- **Background**

Cycloisomerization is an atom economical process and an efficient protocol for the preparation of cyclic compounds.[1] Among various transformations, cycloisomerization initiated by activation of the alkyne moiety using transition metal catalyst, especially gold catalyst, is most well-known.

Shibata's group recently reported Au(I)-catalyzed reaction for the construction of medium ring system.[2] During the investigation of substrate scope, the reaction of *N*-(2-(arylethynyl)phenyl)indole proceeded at the undesired C2 position instead of C7 position of the indole ring, which afforded nitrogen-containing tetracyclic compound as 5-*exo*-*dig* product (Scheme 1).[2a]

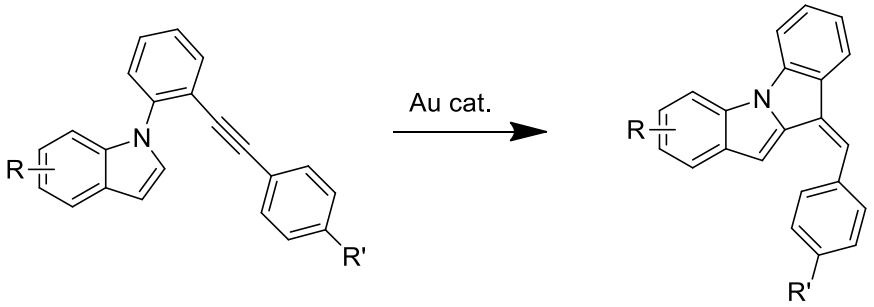


Scheme 1: Preliminary result of an indole substrate

Purpose of This Chapter

As mentioned above, *N*-(2-(arylethynyl)phenyl)indole realized 5-*exo*-*dig*-selective cycloisomerization and indoloindole skeleton was constructed, which is an important class of scaffold as described in Chapter 4.

The author focused on the synthesis of indolo-indoles through Au-catalyzed cycloisomerization. Various substituents were available including electron-donating and electron-deficient groups. Substituents were also varied on the indole ring. Photophysical properties, such as UV-VIS absorption and fluorescence spectra, and fluorescence quantum yield, were measured.

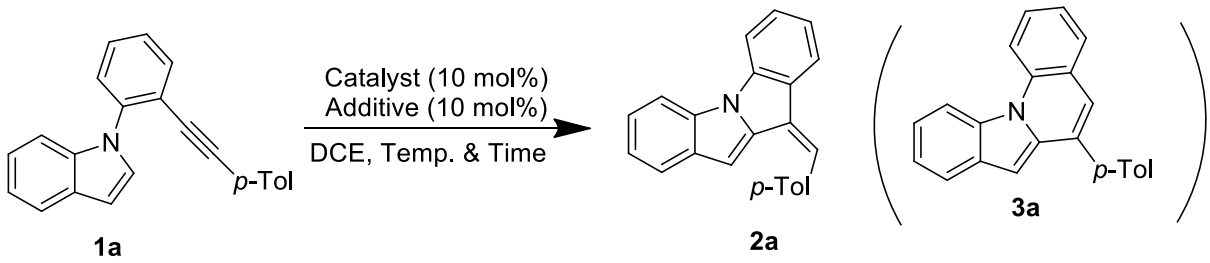


Scheme 2: Outline synthesis of indoloindoles

- **Results and Discussion**

The author screened the reaction conditions for the intramolecular cyclo-isomerization of *N*-(2-(*p*-tolylethynyl)phenyl)indole (**1a**) in DCE (Table 1). A cationic Au(I) catalyst prepared by the combination of $AuCl(PPh_3)$ and silver salts was used and AgOTf afforded of 5-*exo*-*dig* product **2a** in moderate yield without forming 6-*endo*-*dig* product **3a**[3] (Entries 1-3). The cationic Pt(II) and Pd(II) afforded **2a**, in lower yields (Entries 4 and 5). AgOTf and trifluoromethanesulfonic acid could also promote the cycloisomerization, but the reaction gave many inseparable products, and the isolated yields were low (Entries 6 and 7). When electron-deficient phosphine ligands with cationic Au(I) catalyst were used, the reaction progressed even at room temperature, but alkyne **1a** was not completely consumed and the yield of **2a** was lower at higher reaction temperature than Entry 3 (Entries 8 and 9). Hence, the author decided Entry 3 as the best conditions.

Table 1: Screening of reaction conditions



Entry	Catalyst	Additive	Temp. and Time	Yield of **2a** (%)
1	$AuCl(PPh_3)$	AgOTf	rt, 24 h	21
2	$AuCl(PPh_3)$	AgOTf	60 °C, 24 h	33
3	$AuCl(PPh_3)$	AgOTf	80 °C, 24 h	58
4[a]	$PtCl_2(PPh_3)_2$	AgOTf	r.t., 1 h, then 60 °C, 24 h	45
5[a]	$PdCl_2(PPh_3)_2$	AgOTf	60 °C, 24 h	18
6	AgOTf	none	80 °C, 3 h	22
7[b]	TfOH	none	r.t., 1 h, then 60 °C, 1 h	19
8	$AuCl[P(4\text{-}F_3CC_6H_4)]$	AgOTf	r.t., 5 h, then 80 °C, 24 h	56
9	$AuCl[P(C_6F_5)_3]$	AgOTf	r.t., 1 h, then 80 °C, 2 h	29

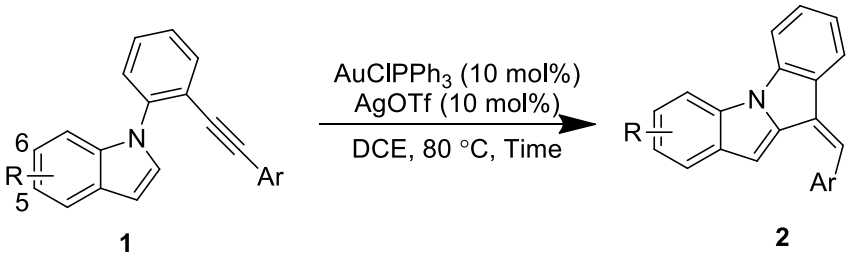
[a] AgOTf (20 mol %) was used. [b] TfOH (30 mol%) was used.

Substrate Scope

The author examined the reaction of *N*-(2-(arylethynyl)phenyl)indoles **1b**-**1e**, which possessed different substituents at the position *para*- to the arene moiety, under the ideal reaction conditions (Table 2, Entries 1-4). Compared with the phenyl group, the electron-rich *p*-anisyl group afforded the highest yield of 76% (Entries 1 and 2). While electron-deficient aryl group could also be available, the yield was lower (Entries 3 and 4). The starting material was not consumed completely and the

reaction was slow in case of electron-deficient group. Concerning the substituents on the indole ring, the author conducted the cycloisomerization of 5- and 6-substituted indoles and get the tetracyclic products (Entries 5-7). For each and everyone entry, 5-*exo-dig* cycloadducts were obtained as a *Z*-isomer and no 6-*endo-dig* cycloadducts were found.

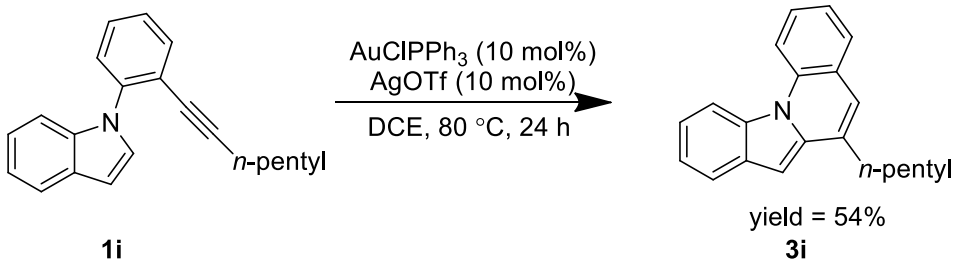
Table 2: Substrate scope



Entry	R	Ar	Time	Yield (%)
1	H	Ph (**1b**)	24	71 (**2b**)
2	H	4-$MeOC_6H_4$ (**1c**)	6	76 (**2c**)
3	H	4-FC_6H_4 (**1d**)	6	55 (**2d**)
4	H	4-$CF_3C_6H_4$ (**1e**)	24	50 (**2e**)
5	5-MeO	4-$MeOC_6H_4$ (**1f**)	6	67 (**2f**)
6	6-Me	4-$MeOC_6H_4$ (**1g**)	6	61 (**2g**)
7	6-F	4-$MeOC_6H_4$ (**1h**)	6	60 (**2h**)

Endo Selectivity

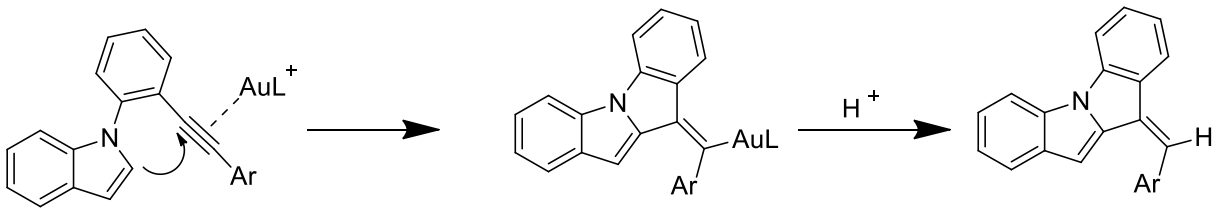
While alkynes with aryl group afforded 5-*exo-dig* cycloadducts, an alkyne with alkyl group gave 6-*endo-dig* cycloadduct selectively (Scheme 3). The reason for the *endo* selectivity is that electron-donating alkyl group increases electron density at the distal position. As a result, nucleophilic addition by indole moiety proceeds at the other end of the alkyne moiety to give *endo* product.[3]



Scheme 3: *Endo*-selective product

Reason for the *Z*-selectivity in the products

In general, *trans*-alkenyl gold complexes as intermediates were formed from the nucleophilic Markovnikov attack to activated alkynes. This type of activation mode is often observed in Au-catalyzed cycloisomerization.[4]



Scheme 4: Mechanism for *Z*-selectivity

Photophysical Properties

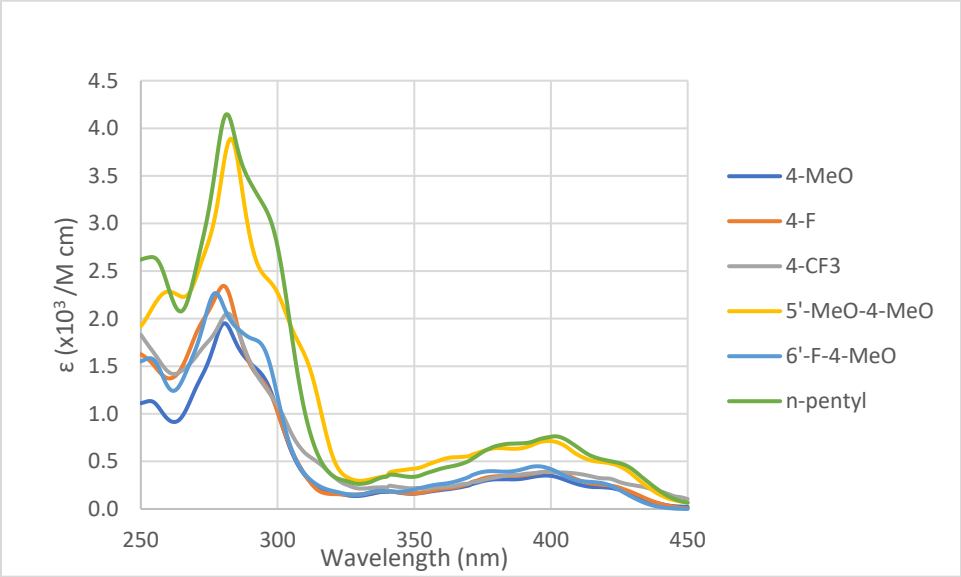
The author evaluated the photophysical properties of the obtained compounds by UV-VIS absorption and fluorescence spectroscopies (Table 3). These compounds emitted fluorescence in the visible range of 400-600 nm. There was not much effects by *para*-substituent on aryl group. An electron-withdrawing trifluoromethylphenyl group (**2e**: $\lambda_{max(em)}$ = 511 nm) showed a red shift compared to the phenyl group (**2b**: $\lambda_{max(em)}$ = 492 nm), whereas 4-tolyl (**2a**: $\lambda_{max(em)}$ = 487 nm) and 4-anisyl group (**2c**: $\lambda_{max(em)}$ = 484 nm) induced a blue-shift (Entries 1-3 and 5). The 5-position on the indoloindole skeleton was more sensitized from the 6 position when compared with fluorescence maxima of **2c** and **2f-2h** (Entries 3, 6-8). Electron-donating methyl group exhibited fluorescence at 487 nm, but electron-withdrawing fluoro group exhibited fluorescence at 478 nm (Entries 7 and 8). For the absorption spectra the effect of substituents were less for example, the maximum absorption wavelength ($\lambda_{max(abs)}$) of **2** were found around 395-404 nm. Electron-withdrawing group on the scaffold showed lower absorbance than electron-donating group (Entries 6-8). Most of these compounds exhibited emissions below 500 nm except **2e**. The reason might be due to insufficient conjugation of the aryl group with indoloindole scaffold. The effect of substituents on both of aryl and indole rings were little in the fluorescence quantum yield. The 6-*endo-dig* product gave lower fluorescence quantum yield than the aryl substituted 5-*exo-dig* product.

Table 3: Photophysical properties

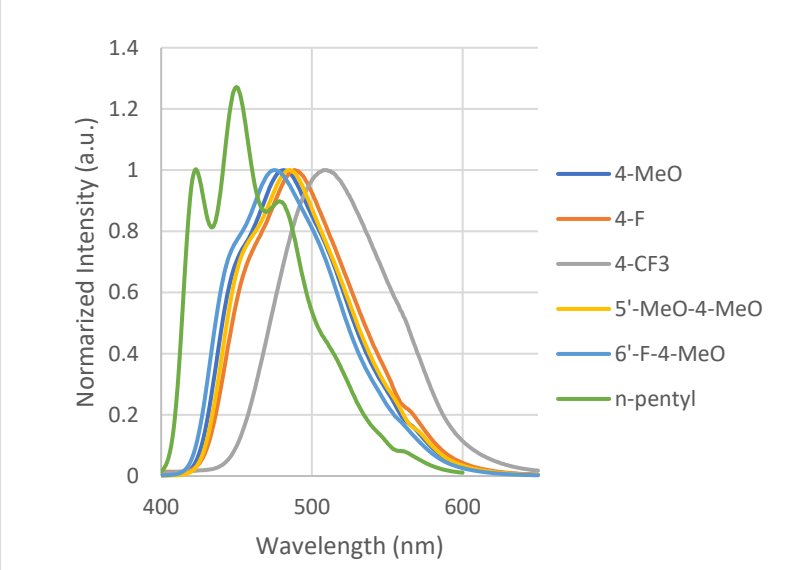
Entry	Comp.	$\lambda_{max(abs)}$ (nm) [ε (x10^3 cm^{-1})][a,b]	$\lambda_{max(em)}$ (nm)[a,b,c]	Φ[a,b,c]
1	**2a**	255 (1.2), 280 (1.6), 401 (0.3)	487	0.67
2	**2b**	280 (2.5), 399 (0.3)	492	0.23
3	**2c**	238 (1.4), 282 (1.9), 398 (0.3)	484	0.64
4	**2d**	245 (1.8), 280 (2.2), 400 (0.4),	491	0.60
5	**2e**	242 (2.1), 282 (2.0), 395 (0.4)	511	0.42
6	**2f**	234 (2.6), 283 (3.8), 401 (0.7)	487	0.49
7	**2g**	253 (2.6), 281 (4.1), 404 (0.8)	491	0.66
8	**2h**	251 (1.6), 277 (2.3), 397 (0.5)	478	0.67
9	**3i**	256 (2.6), 283 (4.1), 401 (0.8)	452	0.30

(a)Measured in CH_2Cl_2. (b) **2a** 1.9x10^{-6} M; **2b** 1.7x10^{-6} M; **2c** 3.0x10^{-6} M; **2d** 1.5x10^{-6} M; **2e** 1.6x10^{-6} M; **2f** 1.9x10^{-6} M; **2g** 2.4x10^{-6} M; **2h** 3.3x10^{-6} M; **3i** 1.2x10^{-6} M. (c) Excitation wavelength: **2a**: 280 nm; **2b**: 280 nm; **2c**: 282 nm, **2d**: 280 nm; **2e**: 282 nm**; 2f**: 283 nm; **2g**: 281 nm; **2h**: 277 nm; **3i** 278 nm.

UV-VIS spectra



Fluorescence Spectra



- **Conclusion**

The author has developed a simple protocol for the synthesis of indoloindole derivatives by Au-catalyzed cycloisomerization. While aryl-substituted alkynes afforded 5-*exo*-*dig* products, an alkyl-substituted alkyne provided 6-*endo*-*dig* product. The author has also measured photophysical properties, such as UV-VIS absorption and fluorescence spectrocopies, and fluorescence quantum yield. On the UV-VIS spectra the effect of substituents were little. Fluorescence was observed at the visible region of 400-600 nm. Moderate quantum yield was generally achieved.

- **Experimental Section**

General

Unless otherwise noted, all materials were purchased from commercial suppliers and used as received. Anhydrous solvents were stocked on activated molecular sieves 4Å under argon atmosphere, and degassed by argon bubbling prior to use. All reactions were carried out under argon atmosphere in oven-dried glassware with a magnetic stirring bar.

^{1}H NMR spectra were recorded on JEOL AL-400 (400 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet, brs, broad singlet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL AL-400 (100 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). ^{19}F NMR spectra were obtained by JEOL ECX-500 (470 MHz) spectrometers and referenced to the fluorine resonance of external standard: trifluoroacetic acid (-76.5 ppm). High-resolution mass spectra (HRMS) were measured on ESI (Electrospray ionization) method at a JEOL GC-mate II. UV-vis spectra were measured on a JASCO V-630 photometer. Fluorescence spectra were taken on a JASCO FP-8200 spectrofluorometer and quantum yields were determined with an integrating sphere (diameter 10 cm). Absolute PL quantum yield was measured by Hamamatsu Photonics C9920-02 spectrometer. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in our laboratory. Flash column chromatography was performed over silica gel 200-300. Gold complexes and silver salts were weighed and handled under an argon atmosphere in globe box at room temperature.

General procedures for the cycloisomerization in Table 2 : $AuCl(PPh_3)$ (0.0050 mmol), AgOTf (0.0050 mmol), and *N*-(2-alkynylphenyl)indoline derivatives **1** (0.050 mmol) were placed in a Schlenk tube under an argon atmosphere in globe box, which was then evacuated and backfilled with argon (×3). To the reaction vessel was added anhydrous DCE (0.50 mL), then the solution was stirred at 80 °C (bath temperature). The reaction mixture was cooled to room temperature, and the solution was passed through cotton filtration. After removal of solvent, the crude products were purified by PTLC to give **2a-h**.

1-(2-(Phenylethynyl)phenyl)-1*H*-indole (1b): it was isolated by PTLC (hexane only). The title compound was obtained as yellow viscous oil (78.1 mg, 85%). ^{1}H NMR δ 7.71 (dd, *J* = 7.3, 1.8 Hz, 2H), 7.53-7.47 (m, 3H), 7.42-7.36 (m, 2H), 7.26-7.15 (m, 5H), 7.08 (dd, *J* = 7.6, 1.8, Hz, 2H), 6.71 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR δ 140.9, 136.7, 133.5, 131.6, 129.3, 129.0, 128.6, 128.3, 127.3, 127.2, 122.9, 122.2, 121.0, 120.3, 111.2, 103.0, 94.7, 86.4 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{16}N$ ($[M+H]^+$) 294.1277, found 294.1277.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-1*H*-indole (1c): it was isolated by PTLC (hexane/ethyl acetate = 99/1). The title compound was obtained as brown viscous oil (93.2 mg, 92%). ^{1}H NMR δ 7.72-7.67 (m, 2H), 7.51-7.36 (m, 5H), 7.22-7.15 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.75-6.67 (m, 3H), 3.67 (s, 3H); ^{13}C NMR δ 159.9, 140.7, 136.7, 133.2, 133.0, 129.3, 128.8, 127.3, 127.1, 122.1, 121.4, 120.9, 120.3, 114.9, 114.0, 111.3, 102.9, 94.9, 85.2, 55.4 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{18}NO$ ($[M+H]^+$) 324.1383, found 324.1383.

1-(2-((4-Fluorophenyl)ethynyl)phenyl)-1*H*-indole (1d): it was isolated by PTLC (hexane/ethyl acetate = 99/1). The title compound was obtained as brown viscous oil (82.9 mg, 85%). ^{1}H NMR δ 7.69 (d, *J* = 8.7 Hz, 2H), 7.50-7.34 (m, 5H), 7.19-7.17 (m, 2H), 7.01-7.00 (m, 2H), 6.91-6.87 (m, 2H), 6.70-6.68 (m, 1H); ^{13}C NMR δ 163.9 (d, *J* = 249.4 Hz), 140.9, 136.7, 133.5, 133.3, 133.2, 129.2, 128.9 (d, *J* = 12.9 Hz), 127.4 (d, *J* = 16.8 Hz), 122.2, 121.0, 120.9, 120.2, 118.9, 118.8, 115.7 (d, *J* = 22.0 Hz), 111.2, 103.0, 93.7, 86.1; ^{19}F NMR δ -110.4. HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{15}FN$ ($[M+H]^+$) 312.1183, found 312.1183.

1-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)-1*H*-indole (1e): it was isolated by PTLC (hexane/ethyl acetate = 99/1). The title compound was obtained as brown viscous oil (78.1 mg, 69%). ^{1}H NMR δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.58-7.44 (m, 6H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.20-7.16 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.72 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR δ 141.3, 136.6, 133.5, 131.6, 129.9, 129.0, 128.9, 127.4, 127.2, 125.3 (q, *J* = 4.1 Hz), 125.0, 122.2, 121.0, 120.3, 111.2, 103.1, 93.1, 88.6 (three pairs of peaks at the aromatic region are overlapped); ^{19}F NMR δ -62.8; HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{15}F_3N$ ($[M+H]^+$) 362.1150, found 362.1151.

5-Methoxy-1-(2-((4-methoxyphenyl)ethynyl)phenyl)-1*H*-indole (1f): it was isolated by PTLC (hexane/ethyl acetate = 95/5). The title compound was obtained

as yellow viscous oil (66.8 mg, 66%). ^{1}H NMR δ 7.68 (d, *J* = 7.3 Hz, 1H), 7.58-7.41 (m, 3H), 7.38-7.34 (m, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.18 (s, 1H), 7.08 (d, *J* = 2.3 Hz, 2H), 6.87 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.63-6.61 (m, 1H), 3.89 (s, 3H), 3.71 (s, 3H); ^{13}C NMR δ 159.9, 154.6, 140.7, 133.3, 133.1, 131.9, 129.9, 129.5, 128.8, 127.1, 126.9, 121.1, 115.0, 114.0, 112.2, 112.0, 102.8, 102.6, 94.7, 85.2, 56.1, 55.4 ; HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{19}NNaO_2$ ($[M+Na]^+$) 376.1308, found 376.1308.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-6-methyl-1*H*-indole (1g): it was isolated by PTLC (hexane/ethyl acetate = 99/1). The title compound was obtained as brown viscous oil (71.3 mg, 70%). ^{1}H NMR δ 7.69 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.52-7.37 (m, 4H), 7.18-7.16 (m, 1H), 7.07-7.01 (m, 3H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.66-6.64 (m, 1H), 3.77 (s, 3H), 2.43 (s, 3H); ^{13}C NMR δ 159.9, 140.7, 137.0, 133.3, 133.0, 131.9, 128.8, 127.2, 127.1, 126.8, 122.0, 121.3, 120.6, 115.1, 113.9, 111.2, 102.7, 94.8, 85.2, 55.4, 21.9 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{19}NNaO$ ($[M+Na]^+$) 360.1358, found 360.1359.

6-Fluoro-1-(2-((4-methoxyphenyl)ethynyl)phenyl)-1*H*-indole (1h): it was isolated by PTLC (hexane/ethylacetate = 95/5). The title compound was obtained as yellow viscous oil (81.0 mg, 80%). ^{1}H NMR δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.62-7.58 (m, 1H), 7.46-7.40 (m, 4H), 7.01 (d, *J* = 9.2 Hz, 3H), 6.95-6.90 (m, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 2.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR δ 161.3 (d, *J* = 237.5 Hz), 159.9, 140.2, 136.8 (d, *J* = 12.2 Hz), 133.3, 133.0, 128.9 (d, *J* = 3.8 Hz), 127.7, 126.9, 125.3, 121.6 (d, *J* = 10.0 Hz), 121.4, 114.8, 114.0, 109.1 (d, *J* = 24.4 Hz), 108.8, 102.9, 97.9 (d, *J* = 26.8 Hz), 95.1, 84.8, 55.3; ^{19}F NMR δ -120.8; HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{17}FNO$ ($[M+H]^+$) 342.1285, found 342.1289.

1-(2-(Hept-1-yn-1-yl)phenyl)-1*H*-indole (1i): it was isolated by PTLC (hexane/dichloromethane = 8/2). The title compound was obtained as a colourless viscous oil (93.7 mg, 44%); ^{1}H NMR δ 7.70 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.45-7.32 (m, 5H), 7.22-7.15 (m, 2H), 6.67 (d, *J* = 1.4 Hz, 1H), 2.18 (t, *J* = 6.9 Hz, 2H), 1.32-1.12 (m, 6H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 140.5, 136.3, 133.4, 128.9, 128.6, 128.1, 127.2, 126.9, 121.6, 121.5, 120.6, 119.8, 110.9, 102.5, 95.9, 77.3, 30.9, 26.7, 22.0, 19.4, 13.6; HRMS (ESI, positive): *m/z* calcd. for $C_{21}H_{22}N$ ($[M+H]^+$) 288.1747, found 288.1747.

(*Z*)-10-Benzylidene-10*H*-indolo[1,2-*a*]indole (2b): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as a yellow solid

(20.8 mg, 71%); mp 100-102 °C; ^{1}H NMR δ 8.62 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.75-7.71 (m, 2H), 7.69-7.67 (m, 1H), 7.64-7.60 (m, 1H), 7.55-7.30 (m, 6H), 7.12 (s, 1H), 6.87 (s, 1H); ^{13}C NMR δ 138.9, 136.7, 136.3, 133.6, 133.1, 129.1, 128.8, 128.6, 128.5, 128.4, 124.8, 123.1, 123.0, 122.1, 122.0, 121.5, 120.8, 115.5, 114.5, 97.9 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{16}N$ ($[M+H]^+$) 294.1280, found 294.1277.

(*Z*)-10-(4-Methoxybenzylidene)-10*H*-indolo[1,2-*a*]indole (2c): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as a yellow solid (24.5 mg, 76%); mp 120-122 °C; ^{1}H NMR δ 8.61 (d, *J* = 8.7 Hz, 1H), 8.51 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 6.9 Hz, 1H), 7.68-7.66 (m, 3H), 7.62-7.58 (m, 1H), 7.45-7.31 (m, 3H), 7.08 -7.04 (m, 3H), 6.87 (s, 1H), 3.90 (s, 3H); ^{13}C NMR δ 159.8, 136.9, 136.1, 133.5, 132.7, 131.3, 130.3, 129.7, 128.9, 128.3, 124.8, 123.0, 122.5, 121.9, 115.3, 114.4, 114.1, 97.8, 55.5 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{17}NNaO$ ($[M+Na]^+$) 346.1203, found 346.1202.

(*Z*)-10-(4-Fluorobenzylidene)-10*H*-indolo[1,2-*a*]indole (2d): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as yellow solid (17.0 mg, 55%); mp 106-108 °C; ^{1}H NMR δ 8.61 (d, *J* = 8.7 Hz, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.71-7.68 (m, 3H), 7.64-7.60 (m, 1H), 7.46-7.32 (m, 3H), 7.23-7.17 (m, 2H), 7.07 (s, 1H), 6.81 (s, 1H); ^{13}C NMR δ 164.1 (d, *J* = 247.3 Hz), 136.6, 136.3, 134.9, 134.8, 133.5, 132.0, 130.7, 130.4 (d, *J* = 8.4 Hz), 128.7, 125.6, 123.1, 123.0, 122.2 (d, *J* = 8.9 Hz), 121.4, 120.9, 115.8, 115.6 (d, *J* = 21.8 Hz), 114.4, 97.8; ^{19}F NMR δ -113.4; HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{14}FN$ ($[M]^+$) 311.1105, found 311.1105.

(*Z*)-10-(4-(Trifluoromethyl)benzylidene)-10*H*-indolo[1,2-*a*]indole (2e): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as a yellow solid (18.1 mg, 50%); mp 125-127 °C; ^{1}H NMR δ 8.63 (d, *J* = 8.7 Hz, 1H), 8.52 (d, *J* = 8.7 Hz, 1H), 7.87-7.78 (m, 5H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.67-7.63 (m, 1H), 7.48-7.34 (m, 3H), 7.14 (s, 1H), 6.82 (s, 1H); ^{13}C NMR δ 136.4, 133.5, 131.7, 130.8, 129.3, 129.1, 129.0, 125.8 (q, *J* = 4.1 Hz), 125.1, 124.4, 123.6, 123.2, 122.2, 121.4, 121.2, 121.0, 115.5, 114.5, 111.2, 103.2, 97.7; ^{19}F NMR δ -62.4; HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{15}F_3N$ ($[M+H]^+$) 362.1149, found 362.1151.

(*Z*)-3-methoxy-10-(4-methoxybenzylidene)-10*H*-indolo[1,2-*a*]indole (2f): it was isolated by PTLC (hexane/dichloromethane = 7/3). The title compound was obtained as a yellow solid (23.7 mg, 67%); mp 162-164 °C; ^{1}H NMR δ 8.53 (d, *J* = 8.7 Hz, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 7.69-7.65 (m, 3H), 7.61-7.56 (m, 1H), 7.33-7.29 (m, 1H), 7.25-7.20 (m, 1H), 7.08-7.03 (m, 4H), 6.79 (s, 1H), 3.91 (s, 6H); ^{13}C NMR δ 159.7, 155.3, 137.2, 135.9, 132.4, 131.3, 129.7, 128.9, 128.7, 128.3, 124.6, 122.8, 122.3, 115.3, 114.9, 114.1, 112.2, 101.9, 97.4, 55.7, 55.5 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{20}NO_2$ ($[M+H]^+$) 354.1490, found 354.1489.

(*Z*)-10-(4-Methoxybenzylidene)-2-methyl-10*H*-indolo[1,2-*a*]indole (2g): it was isolated by PTLC (hexane/dichloromethane = 7/3). The title compound was obtained as a yellow solid (20.6 mg, 61%); mp 182-184 °C; ^{1}H NMR δ 8.59 (d, *J* = 8.2 Hz, 1H), 8.30 (s, 1H), 7.71-7.65 (m, 4H), 7.61-7.75 (m, 1H), 7.33-7.30 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.06-7.03 (m, 3H), 6.81 (s, 1H), 3.90 (s, 3H), 2.66 (s, 3H); ^{13}C NMR δ 159.7, 136.5, 136.2, 133.9, 132.8, 131.9, 131.4, 129.7, 128.8, 128.1, 124.9, 123.8, 122.9, 121.9, 120.9, 115.4, 114.4, 114.1, 97.7, 55.5, 22.6 (a pair of peaks 96at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{20}NO$ ($[M+H]^+$) 338.1541, found 338.1539.

(*Z*)-2-Fluoro-10-(4-methoxybenzylidene)-10*H*-indolo[1,2-*a*]indole (2h): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as a yellow solid (20.5 mg, 60%); mp 157-159 °C; ^{1}H NMR δ 8.42 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 7.74-7.71 (m, 1H), 7.68-7.57 (m, 4H), 7.35-7.32 (m, 1H), 7.18-7.13 (m, 1H), 7.06-7.04 (m, 3H), 6.82 (s, 1H), 3.90 (s, 3H); ^{13}C NMR δ 161.0, 160.6 (d, *J* = 237.9 Hz), 159.8, 137.4 (d, *J* = 3.6 Hz), 135.8, 132.9 (d, *J* = 15.3 Hz), 131.1, 129.7, 128.9, 128.3, 126.8, 124.9, 123.4, 122.2, 121.9 (d, *J* = 10.1 Hz), 114.9, 114.2, 110.9 (d, *J* = 24.7 Hz), 101.3 (d, *J* = 28.3 Hz), 97.7, 55.5; ^{19}F NMR δ -119.1; HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{17}FNO$ ($[M+H]^+$) 342.1292, found 342.1289.

6-Pentylindolo[1,2-*a*]quinolone (3i): it was isolated by PTLC (hexane/dichloromethane = 9/1). The title compound was obtained as a green viscous oil (15.6 mg, 54%); ^{1}H NMR δ 8.57 (d, *J* = 8.5 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 7.87 (dd, *J* = 6.2, 1.7 Hz, 1H), 7.63 (dd, *J* = 6.2, 1.7 Hz, 1H), 7.57-7.54 (m, 1H), 7.42-7.36 (m, 2H), 7.32-7.29 (m, 1H), 6.98 (s, 1H), 6.85 (s, 1H), 2.83 (t, *J* = 7.9 Hz, 2H), 1.87-1.81 (m, 2H), 1.49-1.37 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 3H) ; ^{13}C NMR δ 137.5, 136.0, 133.4, 132.3, 130.3, 128.3, 127.7, 124.7, 122.8, 121.9, 121.7, 121.3,

121.2, 115.2, 114.5, 95.3, 32.6, 32.0, 28.3, 22.7, 14.2; HRMS (ESI, positive): *m/z* calcd. for $C_{21}H_{22}N$ ($[M+H]^+$) 288.1747, found 288.1747.

- **References**

1.(a) Michelet, V. " Nobel metal-catalysed enyne cycloisomerizations and related reactions" in *Comprehensive Organic Synthesis* (*2nd edition*), ed. By Knochel, P.; and Molander, G. A. **2014**, *5*, 1483-1536; (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal*. **2006**, *348*, 2271-2296; (c) Michelet, V.; Toullec, P. Y.; Genet, J. P. *Angew. Chem. Int. Ed*. **2008**, *47*, 4268-4315.

2. (a) Ito, M.; Inoue, D.; Kawasaki, R.; Kanyiva, K. S.; Shibata, T. *Heterocycles* **2017**, *94*, 2229-2246; (b) Ito, M; Inoue, D; Takaki, A; Kanyiva, K. S; Shibata, T. *Eur. J. Org. Chem.* **2018**, 4740-4747.

3. Verma, A. K; Jha, R. R; Chaudhary, R; Tiwari, R. K; Reddy, K. S. K; Danodia, A. *J. Org. Chem.* **2012**, *77*, 10382-10392.

4. Dorel, R; Echavarren, A. M. *Chem. Rev*. **2015**, *115*, 9028-9072.

Chapter 6

Conclusion

The author synthesized planar chiral paracyclophanes with a hydroxyl or amino group through enantioselective *ortho*-lithiation and converted them to paracyclophanyl phosphites and phosphoramidites by reacting with 2,2'-biarylene phosphorochloridites. A ligand library was constructed by variation of substituents at the paracyclophane moiety or biarylene moiety derived from BINOL and biphenol as backbone. Most of these ligands were stable under air. The obtained phosphites were used as chiral ligands in the Pd-catalyzed allylic alkylation and Rh-catalyzed 1,4-addition. Moderate enantioselectivity was achieved in both reactions and enantioinduction was governed by the planar chirality of paracyclophane. In case of phosphoramidites, their efficiency was examined in Pd-catalyzed allylic alkylation and Cu-catalyzed conjugate addition and moderate to good enantioselectivity was achieved. The cooperative effect of both planar and axial chiralities was examined in Cu-catalyzed conjugate addition.

The author has developed a facile protocol for the synthesis of indoloindole derivatives by Au-catalyzed cycloisomerization of *N*-(2-alkynylphenyl)indoles. While 5-*exo*-*dig* products were selectively provided from aryl group-substituted alkyne, 6-*endo*-*dig* product was obtained from alkyl-substituted substrate. The author has also measured photophysical properties, such as UV-VIS absorption, and fluorescence spectroscopies, and fluorescence quantum yield. There was little effect of the substituents on the UV-VIS spectra. Fluorescence was observed at the visible region of 400-600 nm. Moderate quantum yield was achieved except phenyl-substituted compound.

Acknowledgements

My appreciation goes to Prof. SHIBATA Takanori for providing me an opportunity to work under his laboratory. My heartiest thanks to him for providing me with constant encouragement and support and useful advice through discussion.

My sincere thanks to reviewers Prof Nobuhiro Kanomata, Prof. Masahisa Nakada and Associate Prof. Kana Yamamoto for their helpful discussion.

I would like to thank Mr. Kyalo Stephen Kanyiva for his useful advice.

My deepest thanks to Ms. Fukai and Mr. Sekine for their helpful contribution in my Phd thesis. I also thank all the members of Shibata laboratory for helpful advice and discussion.

At last but not least, I would like to thank my father Mr. Supriya Hazra and mother Mrs. Kakali Hazra for their constant encouragement.

Madhurima Hazra

早稲田大学　博士（理学）　学位申請　研究業績書

種類別 (By Type)	題名、　発表・発行掲載誌名、　発表・発行年月、　連名者（申請者含む）(theme, journal name, date & year of publication, name of authors inc. yourself)
論　文	○ "Synthesis of Indolo[1,2-*a*]indole Derivatives by Cationic Au(I)-Catalyzed *Exo*-Selective Cycloisomerization and Their Photophysical Properties" *Heterocycles,* DOI : 10.3987/COM-18-S(F)88. Madhurima Hazra, Daisuke Inoue, Mamoru Ito, Kyalo Stephen Kanyiva, Takanori Shibata ○"Enantioselective synthesis of planar-chiral 1,11-dioxa-[11]paracyclophane-derived phosphoramidites and their use as chiral ligands" *Tetrahedron: Asymmetry*, **2016**, *27*, 1081-1087. Madhurima Hazra, Kyalo Stephen Kanyiva, Takanori Shibata ○ "Enantioselective Synthesis of Planar-Chiral 1,*n*-Dioxa[*n*]paracyclophane-Based Phosphites and Their Application as Chiral Ligands" *Synthesis*, **2016**, *48*, 2664-2670. Takanori Shibata, Miku Fukai, Ryosuke Sekine, Madhurima Hazra, Kyalo Stephen Kanyiva
講　演	"Synthesis of Indolo[1,2-*a*]indole Derivatives and Evaluation of Their Photophysical Properties" Frontiers in Chemical Sciences, IIT Guwahati, India, December 2018. Madhurima Hazra, Daisuke Inoue, Mamoru Ito, Kyalo Stephen Kanyiva, Takanori Shibata. "Asymmetric Synthesis of Phosphite and Phosphoramidite ligands possessing a planar-chiral [*n*]paracyclophane and their application as chiral ligands." 110th Symposium on Organic Synthesis, Waseda University, Japan, November 2016. Madhurima Hazra, Ryosuke Sekine, Miku Fukai, Kyalo Stephen Kanyiva, Takanori Shibata "Synthesis and Evaluation of Phosphite and Phosphoramidite ligands possessing a planar-chiral [*n*]paracyclophane skeleton" 63rd Symposium on Organometallic Chemistry, Waseda University, Japan, September 2016. Madhurima Hazra, Ryosuke Sekine, Miku Fukai, Kyalo Stephen Kanyiva, Takanori Shibata

	「面不斉パラシクロファン骨格を有する新規不斉ホスファイト配 位子の合成および評価」 日本化学会第 96 春季年会, 同志社大学（京都）, 2016 年 3 月, 4H1- 10 深井　実紅，関根良輔, ハズ ラ マデュリマ, カニヴァ ステイヴィン キャロ, 柴田高範