



TAMPEREEN TEKNILLINEN YLIOPISTO  
TAMPERE UNIVERSITY OF TECHNOLOGY

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**Chiral Indole Ligands: Preparation and Application in  
Catalytic Asymmetric Allylic Substitutions**



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## **Chiral Indole Ligands: Preparation and Application in Catalytic Asymmetric Allylic Substitutions**

Thesis for the degree of Doctor of Philosophy to be presented with due permission for public examination and criticism in Sähköotalo Building, Auditorium S1, at Tampere University of Technology, on the 1<sup>st</sup> of June 2012, at 12 noon.

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# Abstract

Indoles have high structural flexibility, and the functionalization of the indole skeleton has extensively been investigated. Therefore various possibilities are offered for the design of catalytic ligands with an indole core. The theory part of this thesis is divided into three parts: the first part is an introduction on the use of chiral catalytic ligands with focus on oxazoline-containing ligands; the second part introduces the modification of the indole ring system at the *N1*-, *C2*- and *C3*-position; the third part gives an overall introduction on catalytic asymmetric allylic substitution with hetero-nucleophiles. In the results part of the thesis, the design and preparation of novel indole-phosphine-oxazoline (IndPHOX) ligands from readily available starting materials are presented. These modular ligands include an indole skeleton with either a phosphine moiety at the 2- or 3-position or an oxazoline ring at the 1-, 2- or 3-position, respectively.

The IndPHOX ligands were first evaluated in palladium-catalyzed allylic alkylation with dimethyl malonate, generating the product in good yield and high *ee*. The ligands with a diphenylphosphine group and an oxazoline moiety at the 2 or 3-position, respectively, demonstrated high catalytic efficiency in palladium-catalyzed allylic amination with various *N*-nucleophiles, even with aromatic aniline having low nucleophilicity. *N*-functionalized IndPHOX ligands bearing various groups were also synthesized. The effects of *N1*-substituents to the reaction rate, yield and asymmetric induction in palladium-catalyzed asymmetric allylic amination have been discussed. In addition, the enhancement of enantioselectivity due to the presence of an oxygen atom in ligands with a *N*-MOM or a *N*-THP group has been presented in the thesis.

Moreover, an IndPHOX ligand was utilized to afford 2-aryl substituted chromans with stereocontrol at *C-2* *via* asymmetric allylic etherification using a novel synthetic route.

# Acknowledgements

The research work reported in this thesis has been carried out in Department of Chemistry and Bioengineering in Tampere University of Technology during the years 2008-2012. The National Technology Agency of Finland (TEKES), Orion, Fermion, KemFine (CABB), Hormos, PCAS Finland, and Pharmatory are gratefully acknowledged for funding the project.

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Dr. Jan Tois is a great mentor for his guidance and support as a lecturer when he was in this research group. My special thanks also go to Dr. Matti Vaismaa. I appreciate your support for the experimental work and writing publications which means a lot to me. I am grateful to my colleagues Noora Kuuloja and Annukka for kind help inside and outside the lab, and making my life in Finland enjoyable and colorful. My other workmates, Tuula, Antti, Ulla and Noora Katila, I have enjoyed working with you. I am really lucky to obtain this opportunity to work with all of you. I also would like to thank all the people in our department for the pleasant work atmosphere throughout the PhD years.

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Tampere, May 2012

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# Symbols and Abbreviations

BAr <sub>F</sub>	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -butyloxycarbonyl protection group
Box	bis(oxazoline)
BSA	<i>N,O</i> -bis(trimethylsilyl)-acetamide
cod	cyclo-octadiene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAH	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAC	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dtbpy	4,4'-di- <i>tert</i> -butyl-bipyridine
EDG	electron donating group
eth	ethene
EWG	electron withdrawing group
MOM	methoxymethyl ether
MsCl	methanesulfonyl chloride
nbd	2,5-norbornadiene
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methyl-2-pyrrolidone
Nu	nucleophile
OTf	trifluoromethane sulfonate
PPA	polyphosphoric acid
Pybox	pyridine bis(oxazoline)
THP	tetrahydropyran
TMDEA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TsCl	<i>p</i> -toluenesulfonyl chloride
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid

# List of Publications

This thesis is based on the following publications. In the text, these publications are referred to by Roman numerals:

**I. Preparation of indole-phosphine oxazoline (IndPHOX) ligands and their application in allylic alkylation**

Y. Wang, A. Hämäläinen, J. Tois, R. Franzén, *Tetrahedron: Asymmetry*, **2010**, *21*, 2376-2384.

**II. Utilization of IndPHOX-ligands in palladium-catalysed asymmetric allylic aminations**

Y. Wang, M. Vaismaa, A. Hämäläinen, J. Tois, R. Franzén, *Tetrahedron: Asymmetry*, **2011**, *22*, 524-529.

**III. N<sup>1</sup>-Functionalized Indole-Phosphane Oxazoline (IndPHOX) ligands in asymmetric allylic substitution reactions**

Y. Wang, M. J. P. Vaismaa, K. Rissanen, R. Franzén, *Eur. J. Org. Chem.* **2012**, *2012*, 1569-1576.

**IV. Synthesis of 2-aryl-substituted chromans by intramolecular C-O bond formation**

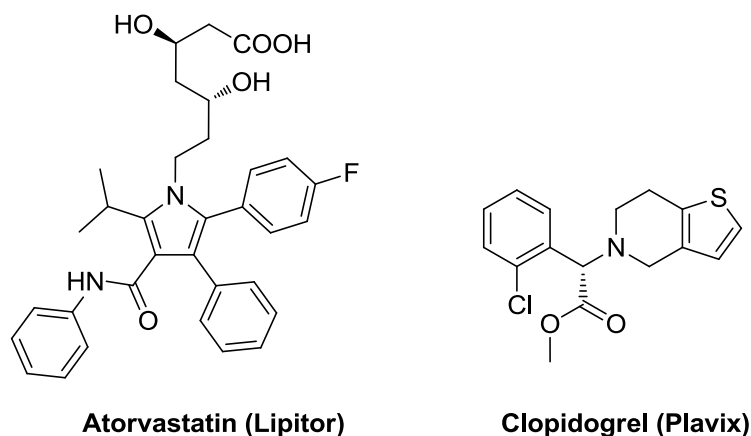
Y. Wang, R. Franzén, *Synlett.* **2012**, *23*, 925-929.

The author of this thesis contributed to the publications as follows. Yu Wang designed the synthesis plan, carried out the experimental work and measured the achieved data. The manuscripts were written in collaboration with the co-authors.



# 1. Introduction

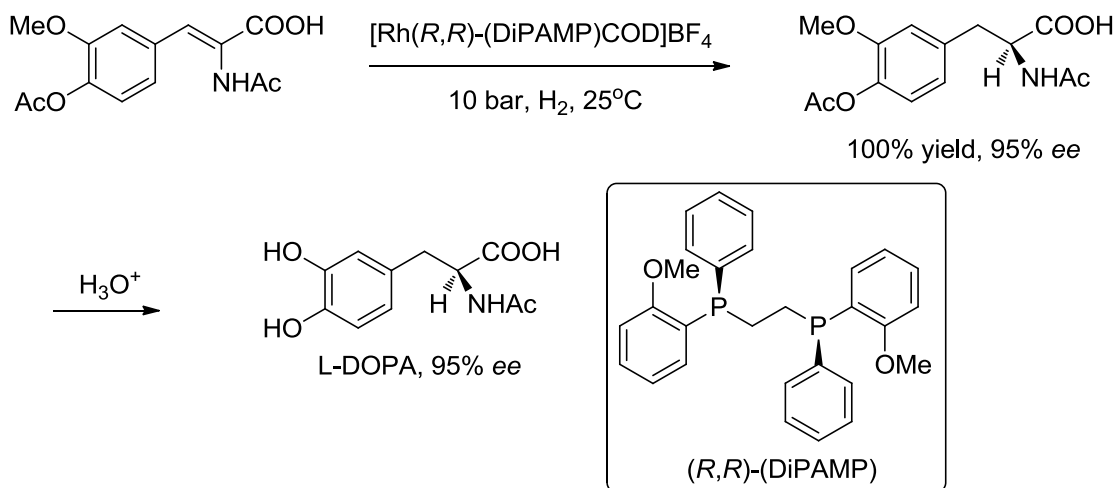
Enantiomerically pure compounds are important in pharmaceutical industry. Most isomers exhibit different biological activities, such as pharmacology, toxicology, pharmacokinetics and metabolism. Atorvastatin (Lipitor),<sup>1</sup> used for lowering blood cholesterol, and Clopidogrel (Plavix),<sup>2</sup> used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease, are representative chiral drugs (Figure 1).



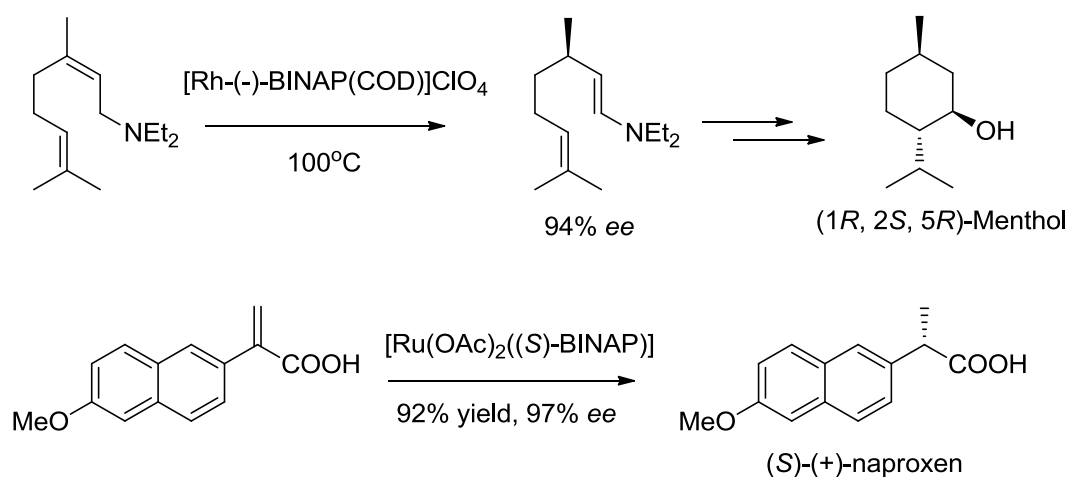
**Figure 1.** Active pharmaceutical ingredients of Lipitor and Plavix

Asymmetric synthesis *via* metal catalysts and chiral ligands is one of the most elegant and effective methods for preparation of chiral compounds. Chemists have developed numerous asymmetric catalytic transformations that convert prochiral substrates into chiral products with high enantioselectivities. These developments have had a significant impact in academia and chemical industry. The 2001 Nobel Prize in Chemistry was awarded to William Knowles,<sup>3</sup> Ryori Noyori<sup>4</sup> and Barry Sharpless<sup>5</sup> for their development in this vital and challenging area. Knowles and colleagues synthesized the rare amino acid, L-DOPA with  $[\text{Rh}((R,R)\text{-DiPAMP})\text{COD}]\text{BF}_4$  in 100% yield with 95% *ee*. This process was commercialised in 1974, which is recognized as the first industrial process using catalytic asymmetric synthesis (Scheme 1). Noyori is most famous for asymmetric hydrogenation using complexes of rhodium or ruthenium with a BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) ligand (Scheme 2) as catalysts. Each year 3000 tons of menthol are produced using Noyori's method by Takasago International Corporation.<sup>6</sup> The anti-inflammatory drug (*S*)-(+)-naproxen is synthesized in high *ee* and yield using  $[\text{Ru}(\text{OAc})_2((S)\text{-BINAP})]$  (Scheme 2). The Sharpless epoxidation reaction with chiral tartrate diester has been widely utilized for the enantiomeric synthesis of 2,3-epoxyalcohols from primary and secondary allylic alcohols. Using this

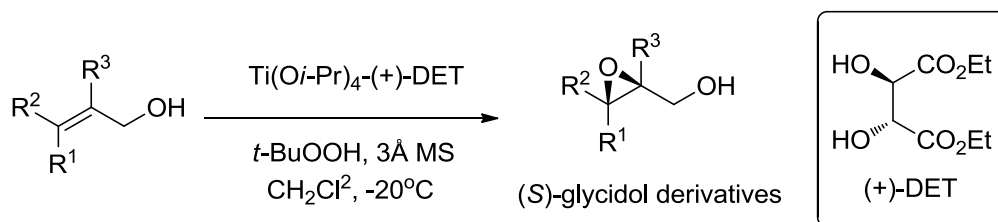
practical and reproducible catalytic variant, an industrial process for ton-scale productions of (*S*)- and (*R*)-glycidol has been developed (Scheme 3). These epoxy alcohols are versatile building blocks for numerous chiral molecules. In the pharmaceutical industry, glycidol is used to produce  $\beta$ -blocker drugs.



**Scheme 1** Industrial production of L-DOPA developed by Knowles

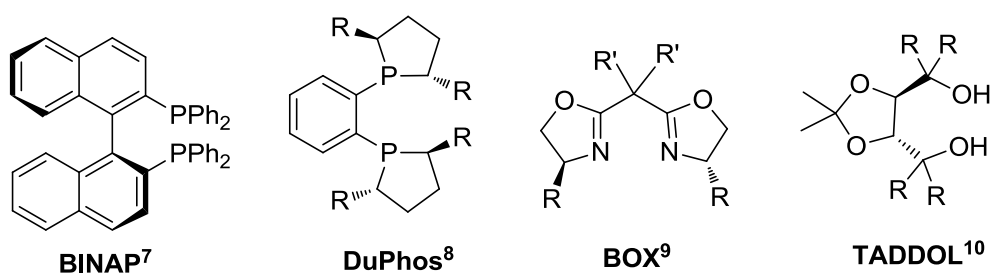


**Scheme 2** Commercial production of (*1R*, *2S*, *5R*)-Menthol and (*S*)-(+)-naproxen developed by Noyori



**Scheme 3** Industrial production of glycidol using Sharpless epoxidation

Chiral ligands play a crucial role in asymmetric catalytic transformations. A number of structural classes are enantioselective over a wide range of various reactions (Figure 2).<sup>7-11</sup> Despite remarkable progress in asymmetric catalysis, the design and preparation of suitable chiral ligands remain a challenging task.



**Figure 2.** Chiral ligand structures used in various asymmetric reactions

## 1.1 Chiral Oxazoline ligands

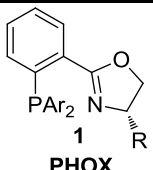
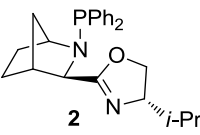
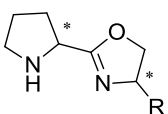
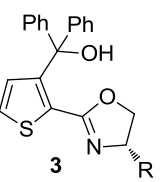
Among the diverse chiral ligands reported to date, chiral oxazoline-containing ligands (e.g. BOX<sup>9</sup>) are one of the most successful, versatile and commonly used types of ligands for asymmetric catalysis due to their ready accessibility, modular nature and applicability in metal-catalyzed transformations.<sup>12,13</sup> Since the first chiral oxazoline ligand was reported by Brunner in 1986,<sup>14</sup> a diverse range of ligands with one, two or more oxazoline rings have been synthesized and utilized with success in a wide range of asymmetric reactions (Table 1).<sup>15-22</sup> The oxazoline moiety can incorporate various heteroatoms, additional chiral elements and specific structural features. The stereogenic carbon atom in oxazoline ring is located next to the nitrogen atom coordinating with metals, thus having a direct influence on asymmetric induction.

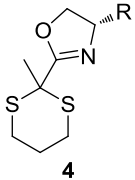
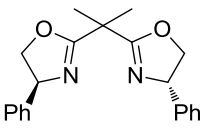
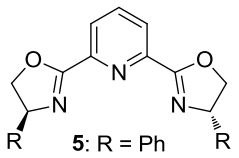
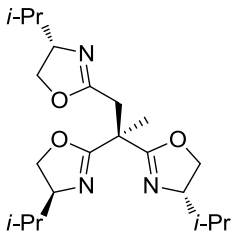
Phosphino-oxazoline (PHOX) ligand **1** containing a mono-oxazoline moiety, pioneered by Pfaltz,<sup>23</sup> Helmchen<sup>24</sup> and Williams<sup>25</sup> in 1993, are outstanding and tunable type of chiral P,N-ligands, and demonstrate excellent activities in organometallic transformations.<sup>15</sup> This type of ligands will later be presented in detail in chapter 1.2.

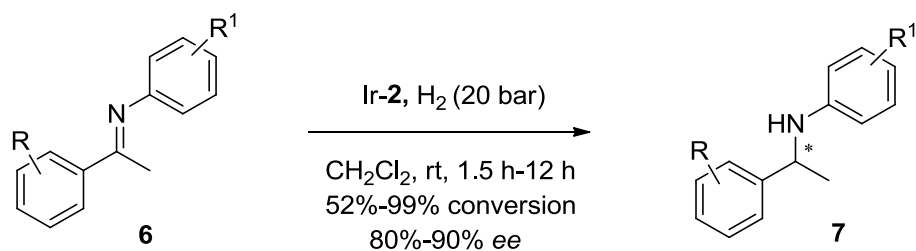
Mono-oxazoline phosphine ligand **2** has been utilized efficiently in iridium-catalyzed asymmetric hydrogenation of acyclic aromatic *N*-arylamines **6** (Scheme 4).<sup>16</sup> Having *ortho*-methyl substituent or bearing EWG (electron withdrawing group) or EDG (electron donating group) at the *para*-position on either aromatic ring resulted in lower enantiomeric excesses and reaction rates.

Pybox (pyridine bisoxazoline) ligands demonstrate high efficiency in various asymmetric reactions.<sup>26</sup> Shibasaki *et al.* described the application of Pybox ligand **5** in the enantioselective Diels-Alder reaction between alkene **8** and diene **9** (Scheme 5).<sup>21</sup> In that study, Ag<sup>+</sup> salts were examined as additive in order to improve the enantioselectivities and yields. Using FeBr<sub>3</sub> and AgSbF<sub>6</sub> in a 1:2 ratio as catalyst, product **10** was obtained in 75% yield with 92% *ee* at -50 °C. The phenyl group in the ligand was crucial for activity and enantioselectivity.

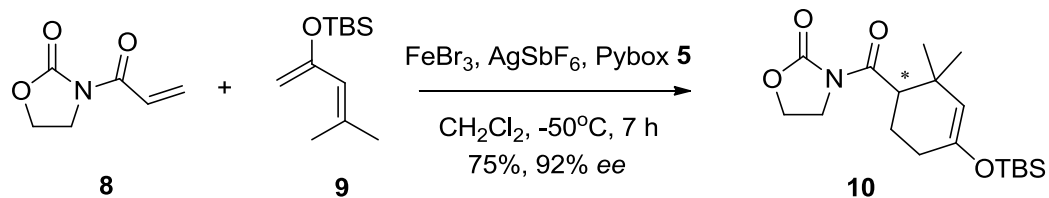
**Table 1** Examples of oxazoline containing chiral ligands

Ligand	Category	Application	Ref.
 <p><b>1</b> PHOX</p>	Mono-oxazoline Phosphine ligand	Pd-catalyzed enantioselective allylic substitutions, Heck reaction; Ir-catalyzed hydrogenation	15
 <p><b>2</b></p>	Mono-oxazoline Phosphine ligand	Ir-catalyzed enantioselective imine hydrogenation	16
	Mono-oxazoline <i>N,N</i> -ligand	Ir or Ru-catalyzed asymmetric transfer hydrogenation	17
 <p><b>3</b></p>	Mono-oxazoline <i>N,O</i> -ligand	Asymmetric phenyl transfer reaction to aldehydes with Ph(BO) <sub>3</sub> -Et <sub>2</sub> Zn	18

	Mono-oxazoline <i>N,S</i> -ligand	Pd-catalyzed asymmetric allylic substitution and copper-catalyzed 1,4-conjugate addition of Et <sub>2</sub> Zn to enones	19
	Bisoxazoline ligand	Copper or zinc-catalyzed enantioselective Diels-Alder reaction	20
	Bisoxazoline ligand 5: R = Ph	Fe and Ag-cocatalyzed enantioselective Diels-Alder reaction	21
	Trisoxazoline ligand	Copper-catalyzed enantioselective alkylation of indole	22

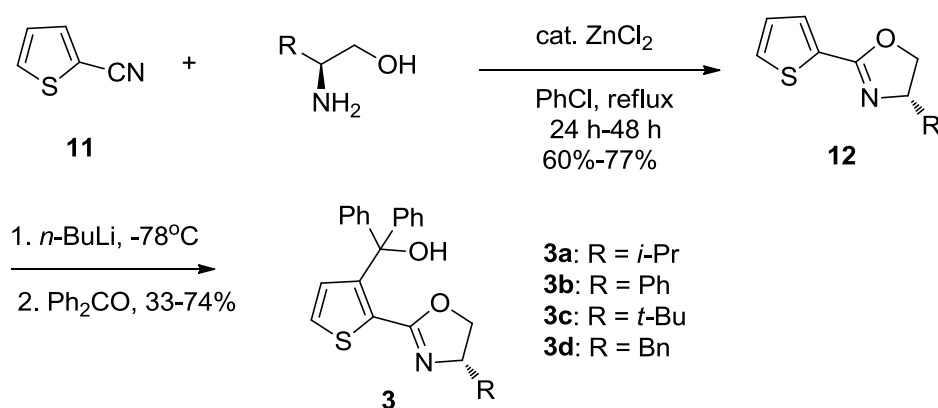


**Scheme 4** Iridium-catalyzed asymmetric hydrogenation with ligand **2**.



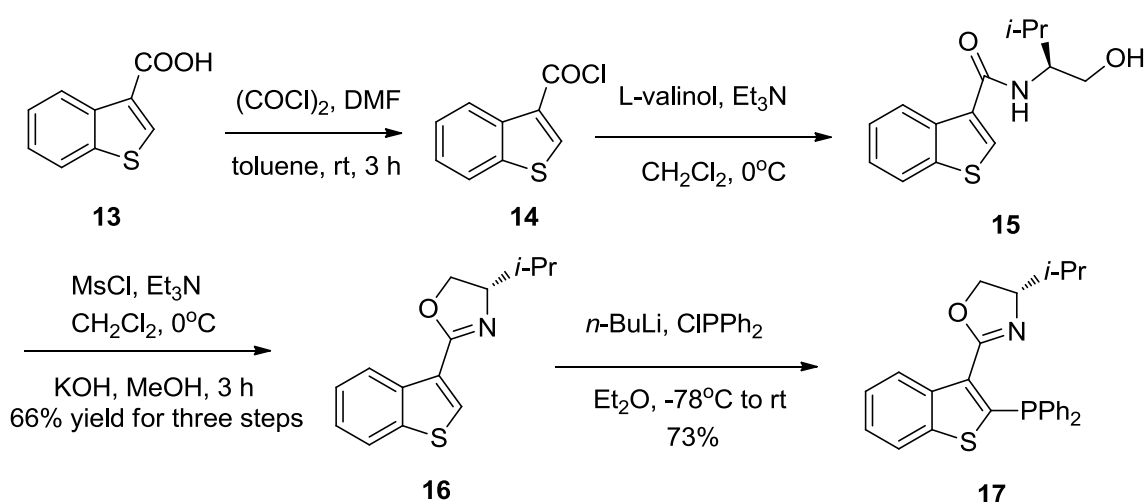
**Scheme 5** Enantioselective Diels-Alder reaction using pybox ligand **5**

The large majority of chiral oxazoline ligands are synthesized from readily available chiral amino alcohols. The Lewis acids catalyzed procedure with nitriles is one of the most commonly used preparation methods for oxazoline ligands. 2-cyanothiophene (**11**) was reacted with various chiral amino alcohols using  $\text{ZnCl}_2$  as catalyst in refluxing chlorobenzene to afford ligand scaffold **12** in moderate to good yields. Subsequent functionalization *via* lithiation yielded ligands **3a-d** (Scheme 6).<sup>18</sup> This approach gives a simple access to oxazolines, while the major drawback is the need for high temperature and long reaction time.



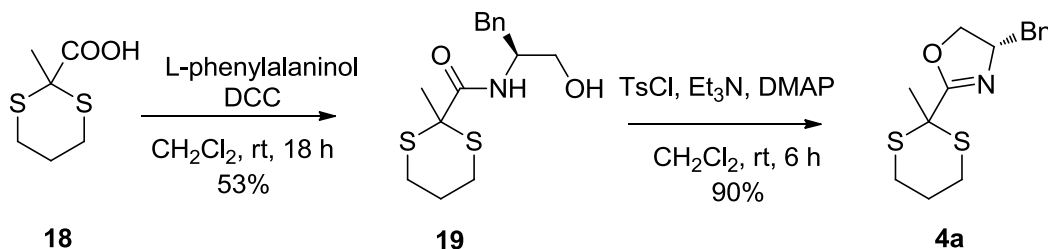
**Scheme 6**  $\text{ZnCl}_2$ -catalyzed synthesis of ligand **3**

Carboxylic acids are good starting materials for oxazolines because they are readily available, and the reaction conditions are mild, under which various functional groups are tolerated. The synthetic strategy from carboxylic acids lies on routine formation of a carboxamide from the acid and amino alcohol, followed by cyclization to form oxazoline. During synthesis of benzothiophene oxazoline ligand **17**,<sup>27</sup> benzo[*b*]thiophene-3-carboxylic acid (**13**) was transformed into the acid chloride which was then treated with L-valinol. The final ring closure was accomplished by mesylation and base induced cyclization with KOH in methanol (Scheme 7).



**Scheme 7.** Synthesis of benzothiophene oxazoline ligand **17**

Carboxylic acids can also be activated *in situ* with different coupling reagents. Acid **18** was coupled to L-phenylalaninol with DCC in  $\text{CH}_2\text{Cl}_2$ , followed by cyclization using TsCl,  $\text{Et}_3\text{N}$  and DMAP as catalyst, affording chiral oxazoline ligand **4a** (Scheme 8).<sup>19</sup>



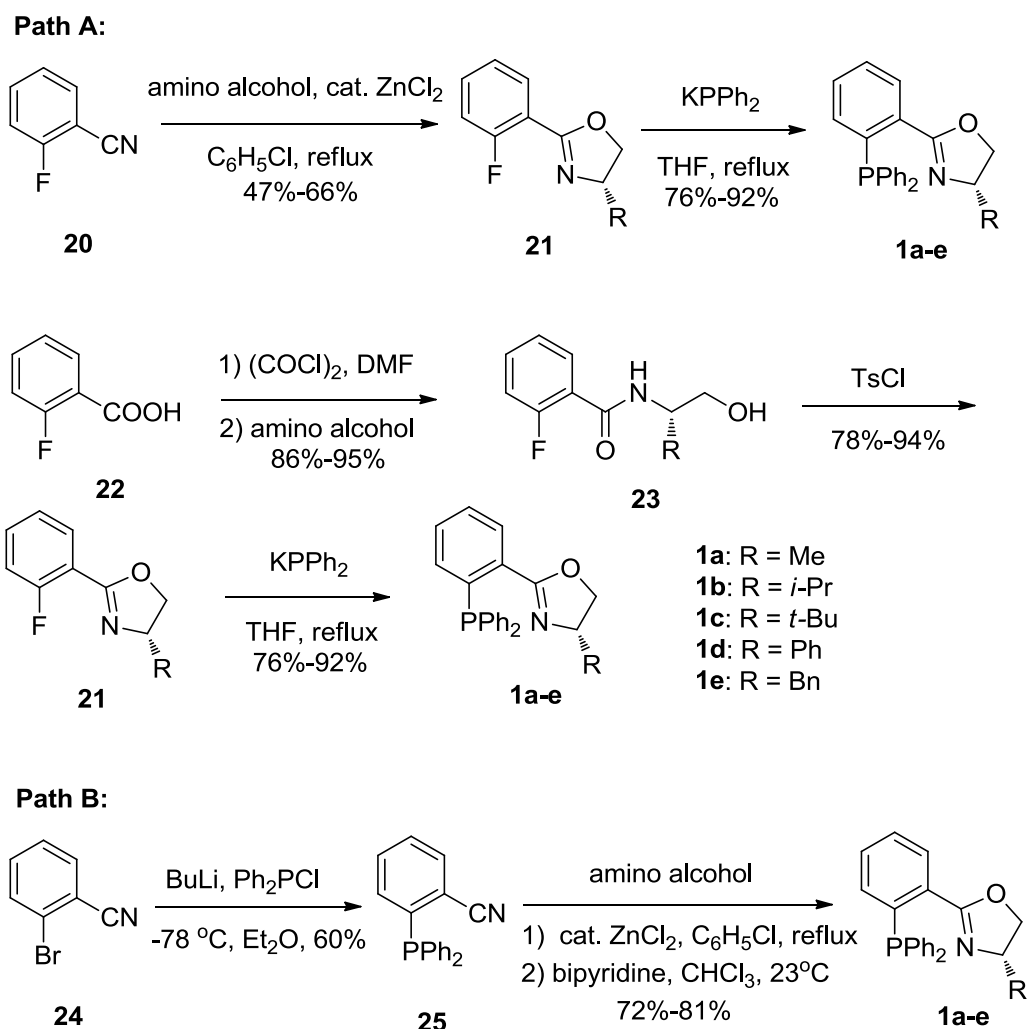
**Scheme 8.** Synthesis of chiral oxazoline ligand **4a**

## 1.2 Phosphino-oxazoline (PHOX) ligands

### 1.2.1 Synthesis and applications of PHOX ligands

There are several synthetically simple, straightforward routes for the synthesis of PHOX ligands from commercially available starting materials.<sup>24,25,28-30</sup> The oxazoline ring is usually prepared from 2-halobenzonitriles or 2-halobenzoic acids with the approaches mentioned

earlier (Schemes 6-8). The phosphine moiety can be introduced either before or after the oxazoline ring formation. Most commonly, the P-C bond is formed by  $S_NAr$ -reaction (addition-elimination reaction) with phosphine anion (Scheme 9, Path A) or with organometallic nucleophile and phosphine electrophile (Scheme 9, Path B).

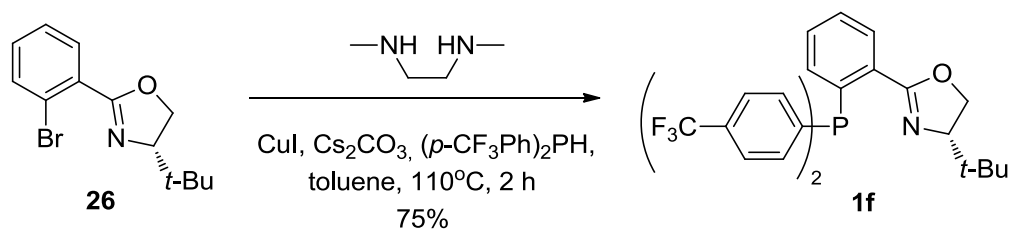


**Scheme 9** P-C bond formation of PHOX ligands

The  $S_NAr$  route with aryl fluoride does not tolerate EWG on the phosphine anion, while the organometallic route is often difficult to provide sterically hindered PHOX ligands. Recently Tani *et al.* reported an Ullman type coupling method to overcome these drawbacks.<sup>30</sup> The reaction was performed in toluene using CuI/DMEDA catalytic system in the presence of  $\text{Cs}_2\text{CO}_3$  as base. The reaction tolerated a range of functional groups including alkyl ethers, silyl ethers and heterocycles. An example of the electronically and sterically modified PHOX



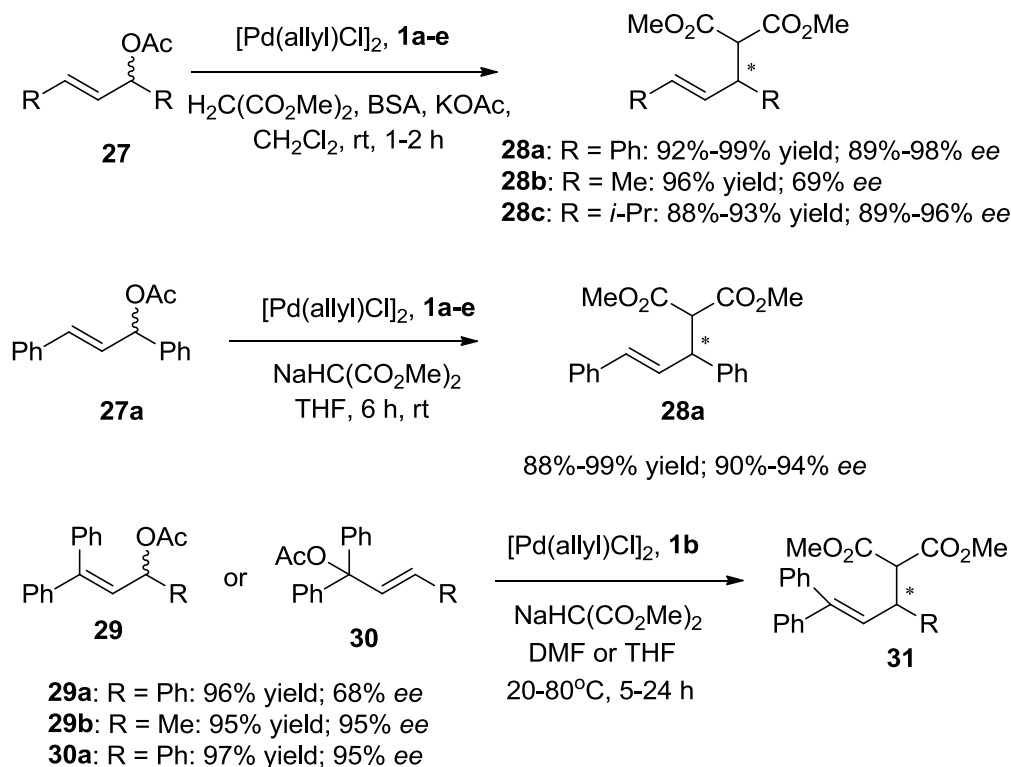
ligand **1f** was prepared from compound **26** and bis(4-(trifluoromethyl)phenyl)phosphine at 110°C in two hours with 75% yield (Scheme 10).



**Scheme 10** Synthesis of PHOX ligands using an Ullman type reaction

### Application in allylic substitutions

The initial application of PHOX ligands was in the field of palladium-catalyzed allylic substitution with dimethyl malonate nucleophiles.<sup>23-25</sup> The reaction with **27** as a substrate proceeded efficiently to provide high yields and enantioselectivities, employing ligand **1a-e** (Scheme 11). The Pd-PHOX complexes remarkably enhanced the reaction rate and increased the enantioselectivity compared to other catalysts.



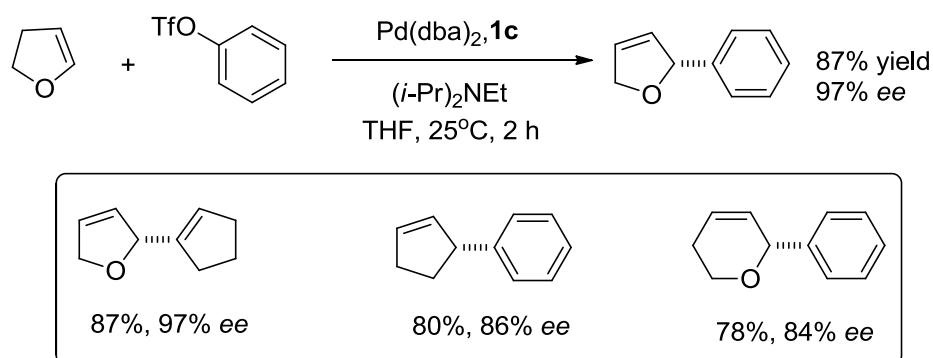
**Scheme 11** Pd-catalyzed allylic alkylation using PHOX ligands

Williams and coworkers continued to report an efficient allylic substitution reaction to afford diphenylallyl malonates **31** (Scheme 11).<sup>31,32</sup> Both regioisomers **29** and **30** can be converted into **31** in excellent yield and good enantioselectivity. Owing to the steric bulk of the geminal phenyl groups on one side of the allyl group, the substitution occurs exclusively on the less hindered side to yield the chiral product.

Allylic amination with PHOX ligands has also been explored successfully, which will be described in detail in chapter 1.4.2.

### Application in Heck reactions

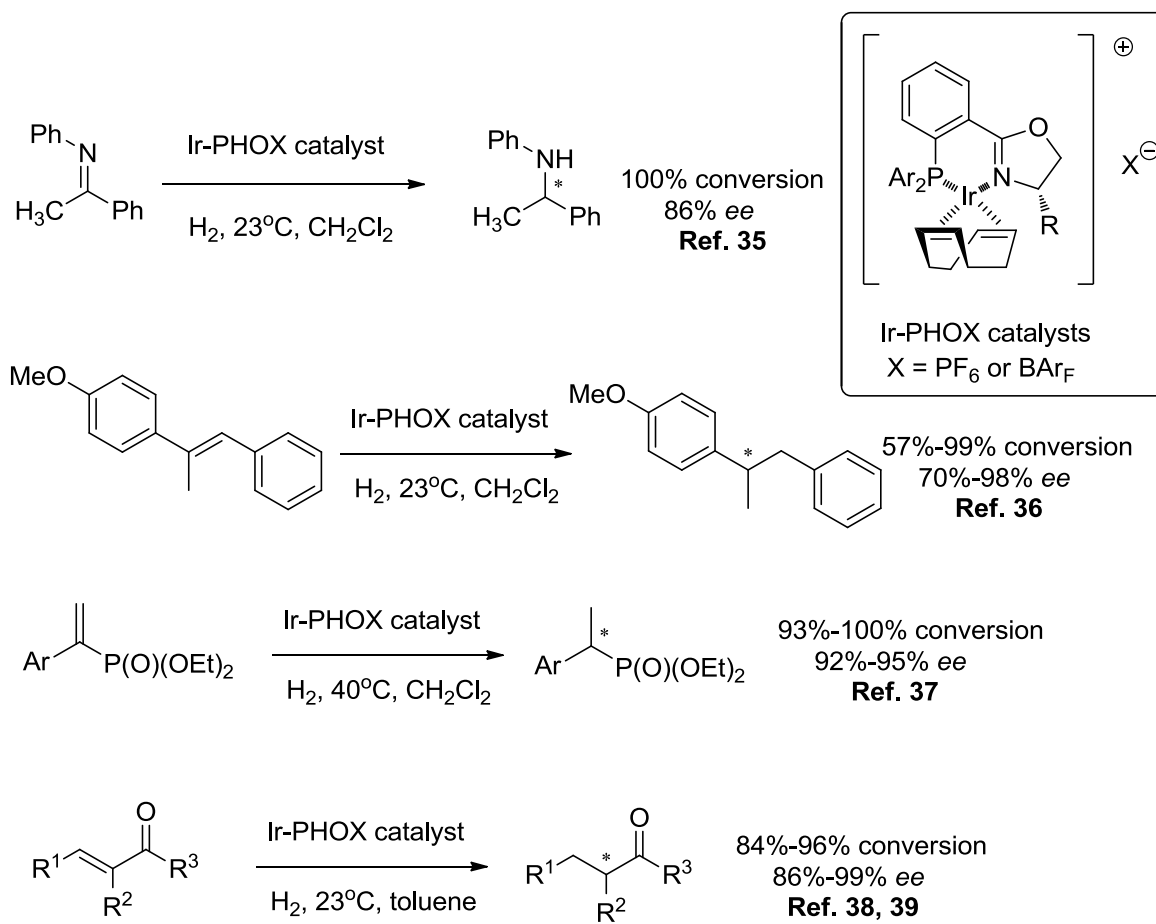
PHOX ligands have been applied in the enantioselective Heck reactions between dihydrofuran and various aryl or vinyl triflates.<sup>33</sup> This method also worked well for cyclopentene and dihydropyran as substrates,<sup>34</sup> and high region- and enantioselectivities were achieved (Scheme 12).



**Scheme 12** Asymmetric Heck reactions with PHOX ligands

### Application in hydrogenations

Iridium-catalyzed hydrogenation is one of the most recognized applications of PHOX ligands. An Ir (I)-PHOX-complex can be obtained by mixing  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and the PHOX ligand, and the subsequent anion exchange with more desirable  $\text{PF}_6$  or  $\text{BAr}_\text{F}$  anions. The Ir-PHOX catalysts have been successfully applied for the asymmetric hydrogenation of various substrates, such as imines,<sup>35</sup> trisubstituted olefins,<sup>36</sup> vinyl phosphonates<sup>37</sup> and  $\alpha,\beta$ -unsaturated ketones<sup>38,39</sup> (Scheme 13). The hydrogenation<sup>40</sup> and transfer hydrogenation<sup>41</sup> of ketones using PHOX ligands and  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  have also been reported.

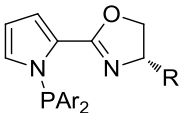
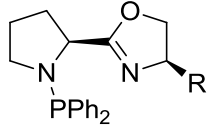
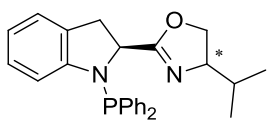
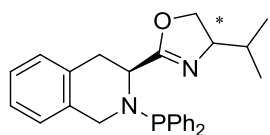
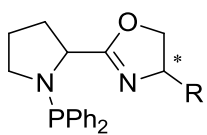
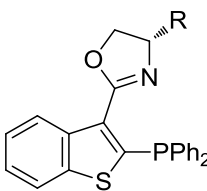
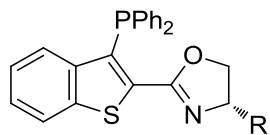
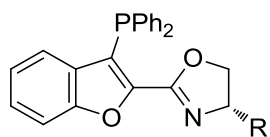
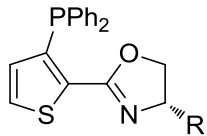


**Scheme 13** Hydrogenations catalyzed by Iridium-PHOX complexes

### 1.2.2 Hetero-PHOX ligands

Due to the success of PHOX ligands, a variety of derivatives have been prepared and used extensively in catalytic applications.<sup>42</sup> A successful strategy has been the replacement of the phenyl ring of the structural skeleton with a heterocycle. Several highly effective hetero-PHOX ligands have been prepared and utilized in asymmetric allylic substitutions,<sup>27,43</sup> Heck reactions,<sup>44</sup> hydrogenations,<sup>45</sup> hydrosilylations<sup>46</sup> and Kinugasa reactions<sup>47</sup> (Table. 2).

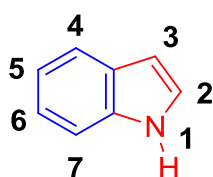
**Table 2** Reported Hetero-PHOX ligands

Ligand	Application	Ref.
	Pd-catalyzed enantioselective allylic alkylation, Ir-catalyzed hydrogenation of olefins	43a
	Pd-catalyzed enantioselective allylic alkylation and amination	43d
	Ir-catalyzed asymmetric hydrogenation of arylimines	45a
	Pd-catalyzed asymmetric allylic alkylation, Ir-catalyzed hydrogenation of arylimines	43b, 45a
	Pd-catalyzed asymmetric allylic alkylation, Ir-catalyzed hydrogenation of arylimines	43b, 45a
	Pd-catalyzed enantioselective allylic alkylation and Heck reaction, Ru or Ir-catalyzed hydrogenation	27, 43c, 44c, 44d, 45b
	Pd-catalyzed enantioselective allylic alkylation	27
	Pd-catalyzed enantioselective allylic alkylation	27
	Pd-catalyzed enantioselective allylic alkylation and Heck reaction, Ru-catalyzed hydrogenation, Rh-catalyzed hydrosilylation, copper-catalyzed Kinugasa reaction	27, 43c, 44, 45b, 46, 47

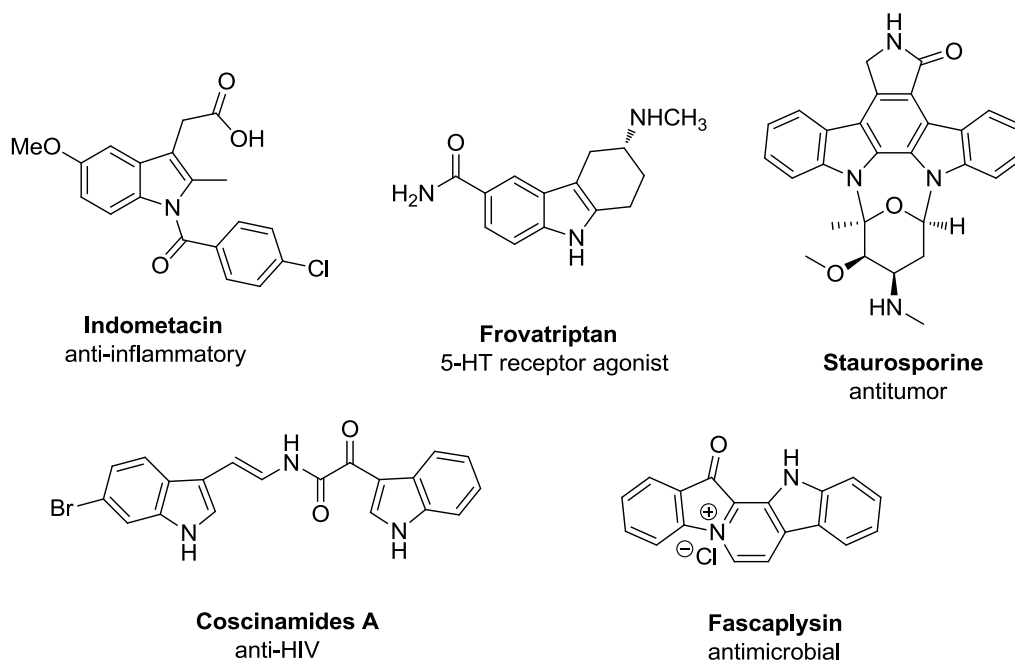
## 1.3 Indole as a ligand scaffold

### 1.3.1 Definition, property and reactivity of indole

Indole is a benzopyrrole in which the benzene and pyrrole rings are fused through the 2,3-positions of the pyrrole (Figure 3). This core structure can be found in numerous biologically active natural products and pharmaceuticals.<sup>48</sup> Indole derivatives demonstrate various biological activities, and examples are presented in Figure 4.

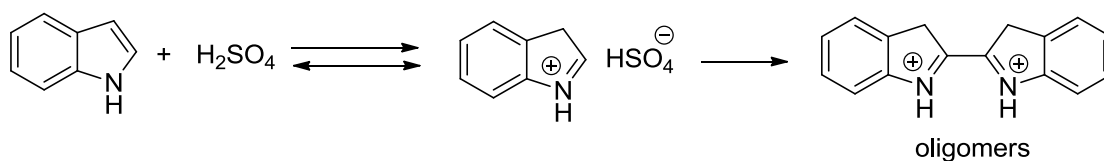


**Figure 3.** The basic structure and numbering system of indole compounds.



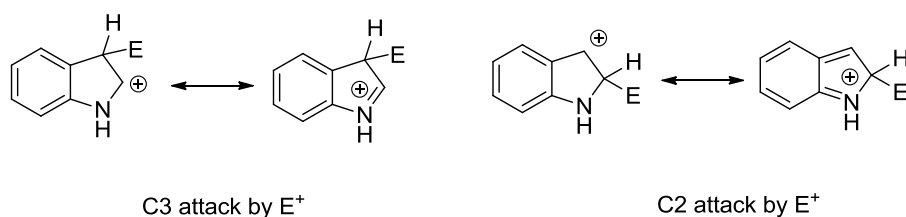
**Figure 4** Biologically active indole compounds

Indole is a weak base, and its protonated form has a  $pK_a$  value of  $-3.60 \pm 0.10$ . Protonation occurs mainly at the C-3 position with formation of the 3H-indolium ion which reacts further to give oligomers (Figure 5).<sup>49</sup>



**Figure 5** Protonation of indole

The indole NH is weakly acidic with  $pK_a$  value of 16.7 and 20.9 determined in water<sup>50</sup> and DMSO,<sup>51</sup> respectively. The neutral indole is of low nucleophilicity at nitrogen, whereas the anion is a good nucleophile for substitution reactions. Indole undergoes electrophilic substitution preferentially at C3-position. The cationic intermediate formed by C3-attack is more stable than that formed by C2-attack (Figure 6). On the other hand, the lithiation of indole is selective for C2 position because of the influence of the nitrogen atom. Compared to the pyrrole ring, the reactions on benzenoid ring are not under strong regiochemical control, and the site of substitution is usually case specific. The most common approach towards benzenoid part functionalization is metallation.<sup>52</sup>



**Figure 6** Intermediates formed by C3 and C2-attack

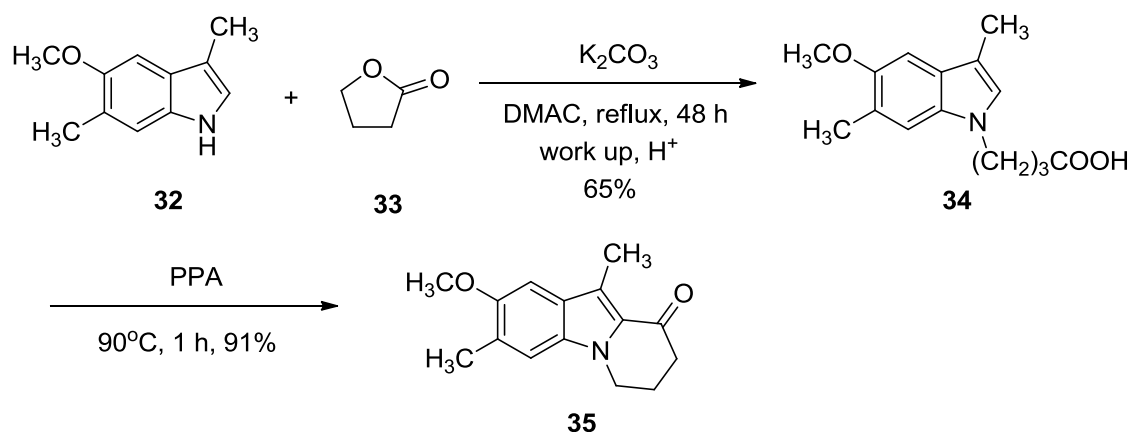
### 1.3.2 Modification of Indole

Indoles have been investigated over a century, and efforts have been devoted to the development of the functionalization of indole ring system.<sup>53</sup> This chapter focuses on the modifications at the 1, 2, and 3-position of indole, respectively.

#### Modification of the *N1* position

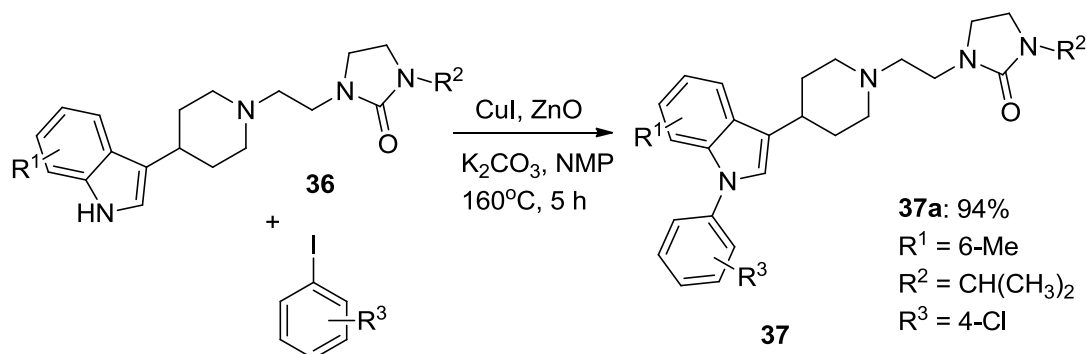
Procedures for *N1* functionalization normally involve a base promoted nucleophilic substitution or conjugate addition (usually the anion needs to be generated first), such as *N*-

alkylation,<sup>54</sup> acylation<sup>55</sup> and sulfonylation.<sup>56</sup> Moreover 1-substitution is important for introduction of directing groups. During the preparation towards pyrido[1,2-*a*]indole **35**, precursor **32** was *N*-alkylated by gamma-butyrolactone **33** (Scheme 14).<sup>57</sup> The reaction was performed in refluxing DMAC using K<sub>2</sub>CO<sub>3</sub> as base. Probably due to the thermodynamic instability of the *N*-acylindole intermediate, formed by attack at the carbonyl group, the alkylation procedure generated the thermodynamically favourable product **34**.<sup>58</sup>



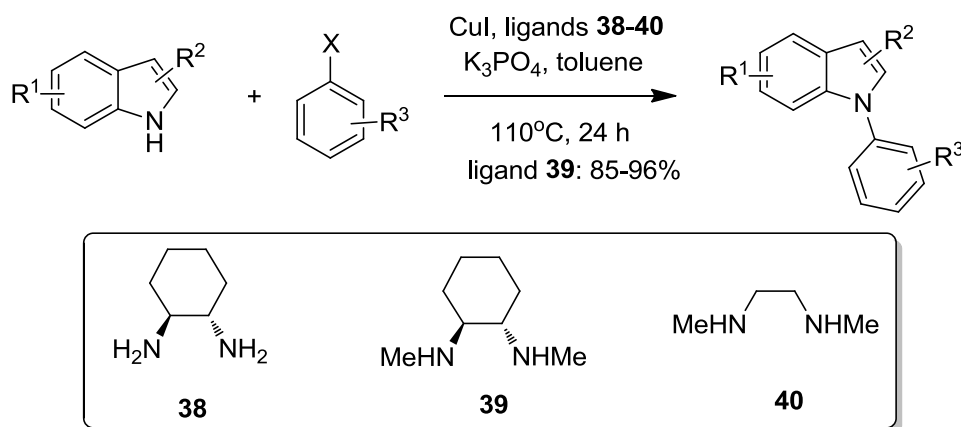
**Scheme 14** *N*-alkylation of indole with lactone

Copper and palladium-catalyzed cross-coupling reactions for *N*-arylation have been utilized widely.<sup>53c</sup> One of the first catalytic procedures, based on the Ullmann reaction, was reported in 1987.<sup>59</sup> The use of either copper oxide or a mixture of copper bromide and copper oxide as catalyst promoted the arylation of 2-carboxy-5-methoxy-1H-indole methyl ester in refluxing DMF without a ligand. This method was further adapted for the synthesis of 5-HT<sub>2</sub> antagonists.<sup>60</sup> The reaction was performed in NMP using copper iodide as catalyst, ZnO as co-catalyst, and K<sub>2</sub>CO<sub>3</sub> as base. Various substituted indoles **36** were *N*-arylated using aryl iodide derivatives to afford 5-HT<sub>2</sub> antagonists **37** (Scheme 15).



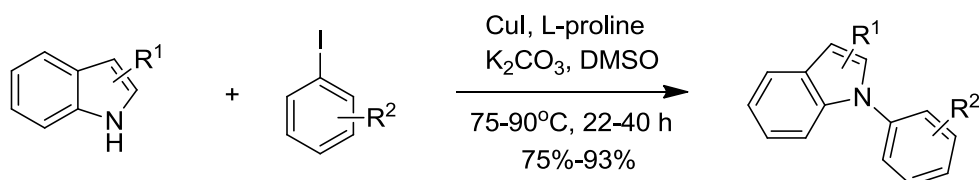
**Scheme 15** Synthesis of 5-HT<sub>2</sub> antagonists **37** by copper-catalysed *N*-arylation

Buchwald *et al.* reported a procedure for the arylation of various indoles using CuI as catalyst and diamines **38-40** as ligand in the presence of  $K_3PO_4$  in toluene.<sup>61</sup> Reaction conditions were mild, and various functional groups were tolerated, including amine, amide, cyano-, nitro-, ester, allyl and hydroxyl groups (Scheme 16).



**Scheme 16** Copper-catalyzed *N*-arylation of indoles in presence of diamine ligands

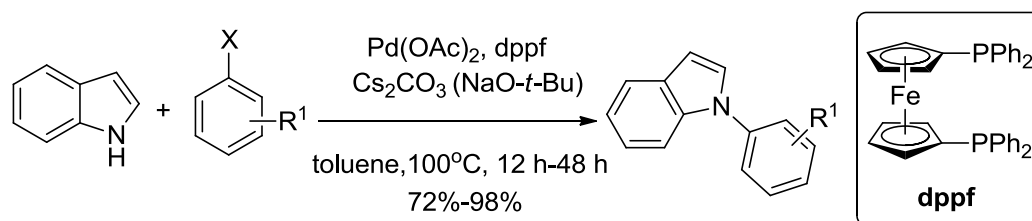
Also the amino acid, L-proline, has been utilized as ligand for *N*-arylation of various indoles with copper iodide as catalyst and  $K_2CO_3$  as base under mild reaction conditions in DMSO (Scheme 17).<sup>62</sup> Noteworthy is that the ligand can be easily removed from crude products by aqueous work up.



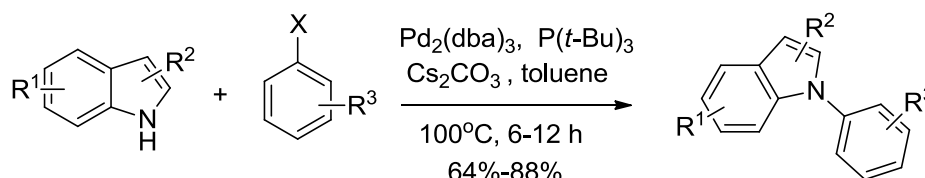
**Scheme 17** Copper-catalysed *N*-arylation of indoles using L-proline as ligand

Palladium-catalyzed procedures were initially reported by Hartwig *et al.*<sup>63</sup> Generally the reactions were run in toluene using  $Pd(OAc)_2$  as catalyst and dppf as ligand in the presence of  $Cs_2CO_3$  or  $NaO-t-Bu$  with electron-rich, electron-neutral or electron-poor aryl halides (Scheme 18). Complete reaction of electron-rich aryl halides required higher temperatures and longer times. Also a procedure with  $Pd_2(dba)_3/P(t-Bu)_3$  system has been reported.<sup>64</sup> The reaction between indoles and unhindered aryl halides, either activated or unactivated, occurred at  $100^\circ\text{C}$ . The use of  $Cs_2CO_3$  as base, rather than  $NaO-t-Bu$ , was crucial to the success of this reaction (Scheme 19).



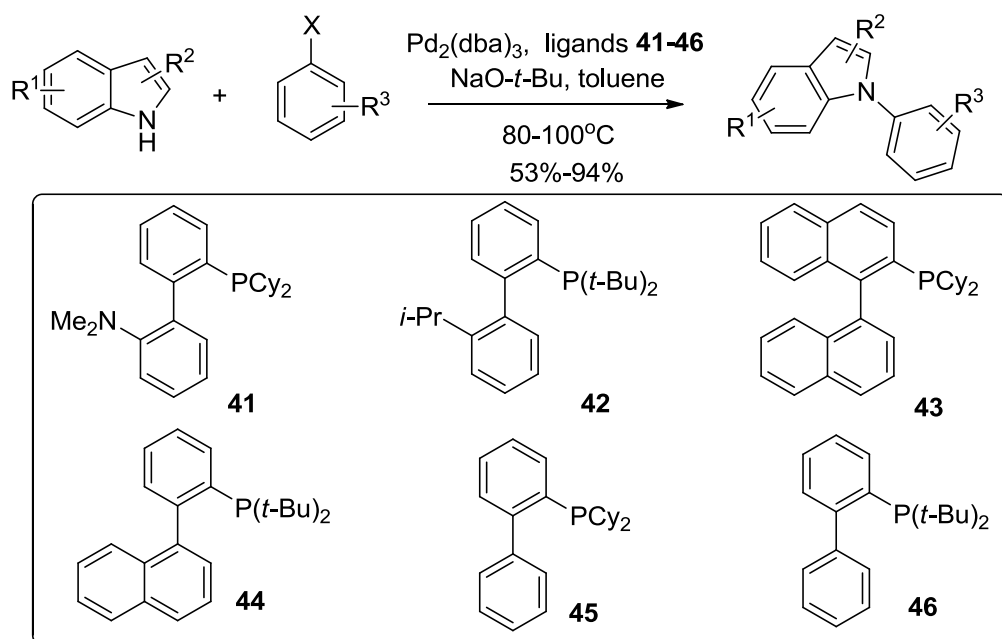


**Scheme 18** *N*-arylation of indole catalysed by the  $\text{Pd}(\text{OAc})_2/\text{dppf}$  catalytic system



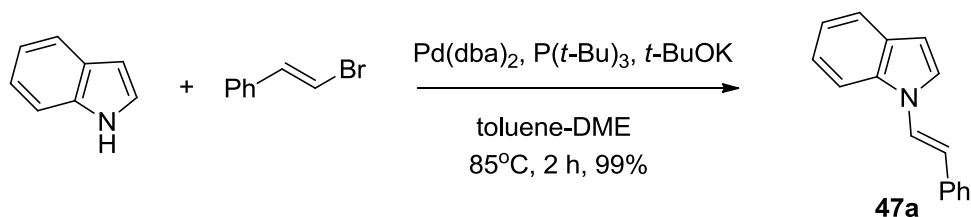
**Scheme 19** *N*-arylation of indoles catalysed by the  $\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3$  catalytic system

Buchwald *et al.* developed the Pd-catalyzed *N*-arylation of indoles.<sup>65</sup> Moderate to high yields have been obtained by utilizing bulky, electron-rich phosphine ligands in combination with  $\text{Pd}_2(\text{dba})_3$ . The efficient coupling of indole and a variety of substituted indoles with aryl iodides, bromides, chlorides and triflates can be achieved (Scheme 20).  $\text{NaOt-Bu}$  was the most effective base, while the use of other bases such as  $\text{NaH}$ ,  $\text{Et}_3\text{N}$  and  $\text{Cs}_2\text{CO}_3$  was less successful. In the reactions where the starting materials were incompatible with  $\text{NaOt-Bu}$  (including triflates),  $\text{K}_3\text{PO}_4$  can be a useful alternative.

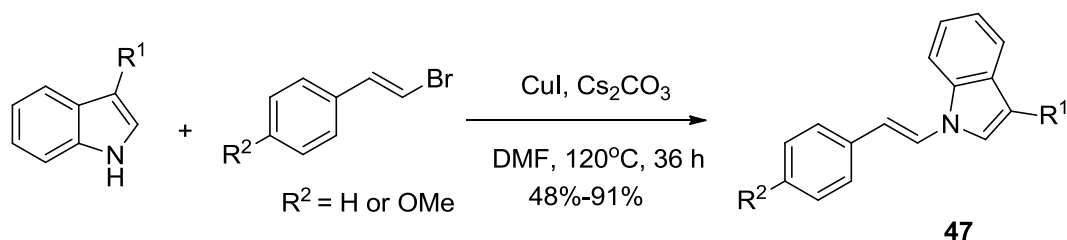


**Scheme 20** Palladium-catalyzed *N*-arylation of indoles with bulky and electron-rich ligands

Also *N*-vinylation can be performed with the aid of palladium or copper-catalyst. The reaction of indole and *trans*- $\beta$ -bromostyrene proceeded smoothly using the Pd<sub>2</sub>(dba)<sub>3</sub>/P(*t*-Bu)<sub>3</sub> system in the presence of *t*-BuOK in toluene/DME, affording *trans*-product **47a** in quantitative yield (Scheme 21).<sup>66</sup> The ligand-free copper-catalyzed vinylation of indoles with (*E*)-vinyl bromides has been reported recently (Scheme 22).<sup>67</sup> The products **47** were isolated with *E* configuration in moderate to good yields.



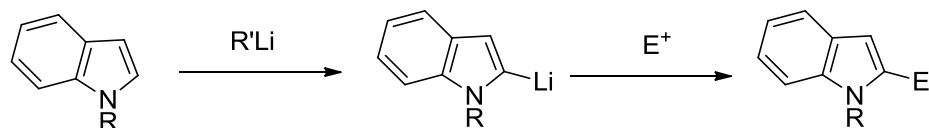
**Scheme 21** Palladium-catalyzed *N*-vinylation



**Scheme 22** Copper-catalyzed *N*-vinylation

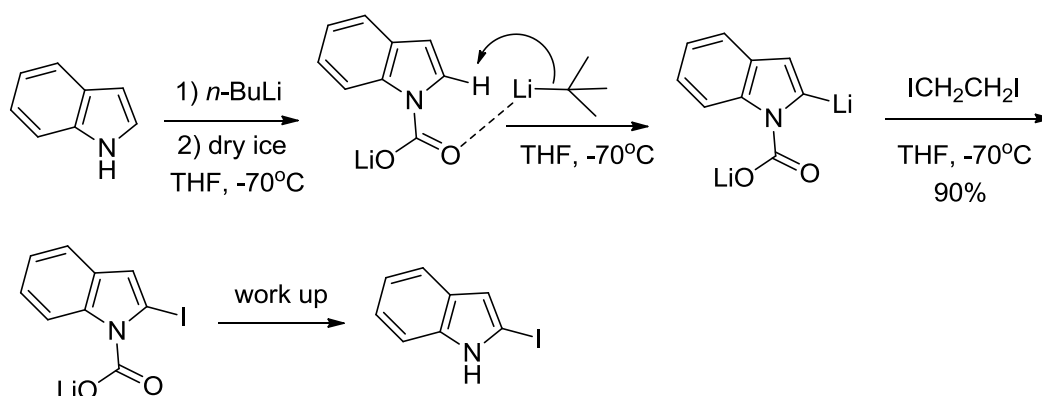
### Modification of the C2 position

Due to the lower reactivity of the C2-position toward electrophiles compared to the C3-position, the most reliable method for selective C2-position functionalization is based on lithiation. 2-Lithioindoles have been used to introduce a variety of substituents by the reaction with appropriate electrophiles (Scheme 23).<sup>68</sup>



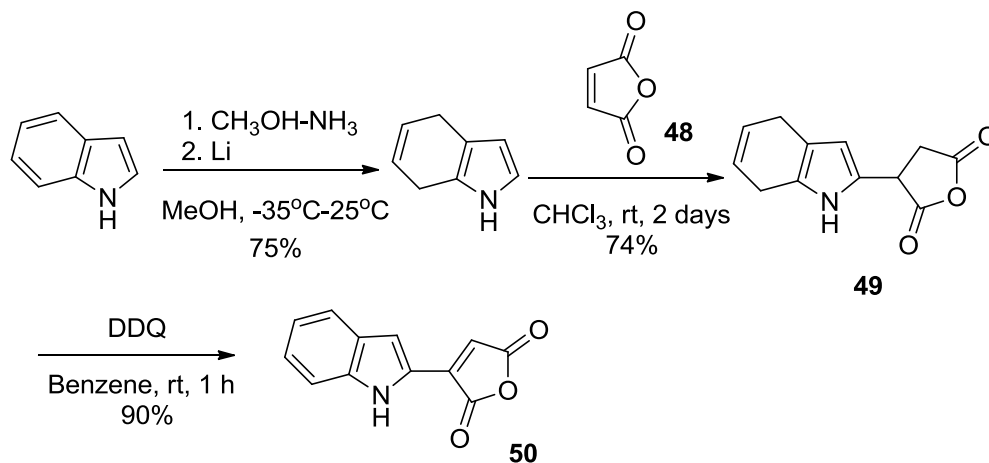
**Scheme 23** Selective C2-position functionalization based on lithiation

The directed *ortho*-lithiation is a powerful method for the preparation of aryllithium intermediates.<sup>69</sup> For C2-lithiation of indole, a directing group at the *N1* position, such as carboxylic acid, sulfonyl, amide, ether or carbamate, is usually utilized to direct the organolithium to attack the adjacent proton at the C2 position.<sup>70</sup> In the example below (Scheme 24), carbon dioxide was introduced to indole as an *N*-protecting and directing group. The lithiation occurred selectively at the 2-position, and after electrophilic quench, 2-iodoindole was obtained in high yields.<sup>71</sup>



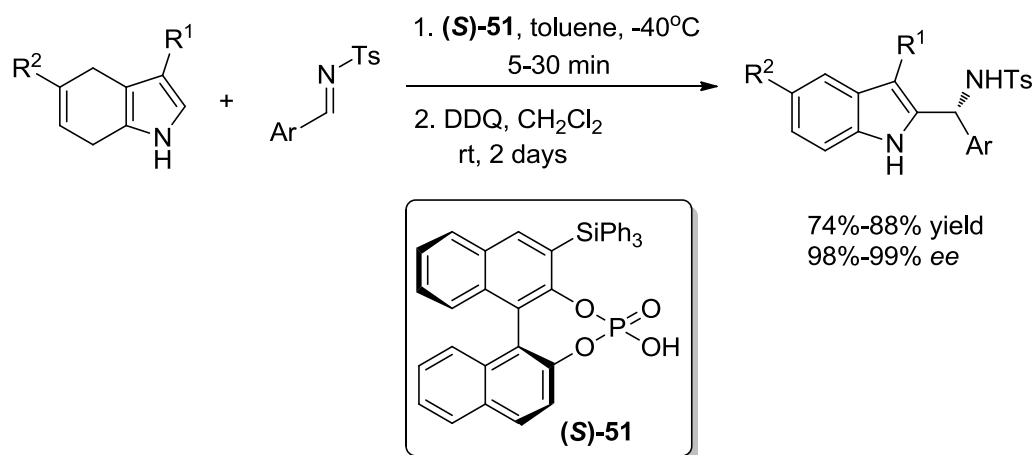
**Scheme 24** *Ortho*-lithiation of indoles

A useful strategy for alkylation reactions at the C2-position is reduction/oxidation. This method takes advantage of 4,7-dihydroindoles in which the 2-position is more reactive than the 3-position.<sup>72</sup> 4,7-Dihydroindoles can be prepared *via* Birch reduction reaction, which reduces the benzene ring but not the pyrrole ring. After the reaction with **48** and the oxidation with 2 equiv. of DDQ, the indole derivative **50** was obtained in good yield (Scheme25).



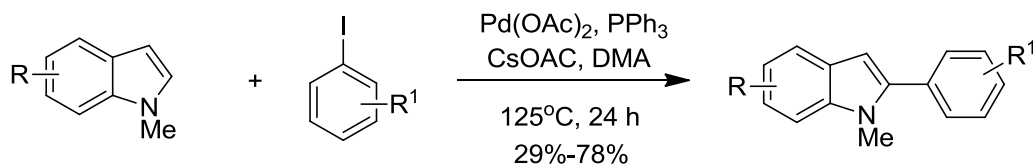
**Scheme 25** Alkylation at the C2-position of indole based on 4,7-dihydroindole

Furthermore this methodology has been extended to the asymmetric synthesis of 2-substituted indoles.<sup>73</sup> Using chiral phosphoric acid (*S*)-**51**, a one-pot procedure that incorporates the alkylation reaction of 4,7-dihydroindoles with imines and subsequent oxidation with DDQ has been developed. Substituted 4,7-dihydroindoles, containing either EDG or EWG were tested, and in all cases the corresponding final indole products were obtained smoothly in good overall yields with excellent enantioselectivities (Scheme 26).



**Scheme 26** Asymmetric alkylation of 4,7-dihydroindoles with imines.

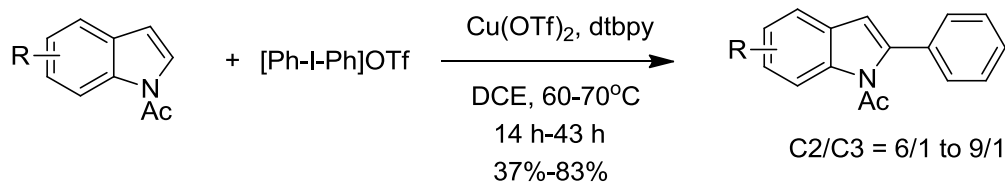
Recently a new methodology for the direct C2-arylation of indole was reported by Sames *et al.*<sup>74</sup> Substituted *N*-methyl indoles were selectively arylated in the C2-position with aryl iodides using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3$  and  $\text{CsOAc}$  as base in DMA (Scheme 27). The reaction was performed with low catalyst loading (0.5 mol%), and demonstrated a high degree of functional group tolerance. C2-arylation was generally preferred unless the aryl iodides contained a substituent in the *ortho*-position. Under these circumstances, a mixture of C2- and C3-arylation product was obtained.



**Scheme 27** Palladium-catalyzed regioselective C2-arylation of indoles.

Gaunt *et al.* reported the site-selective C2-arylation of *N*-acetylindoles with  $\text{Cu}(\text{OTf})_2$  catalyst and  $[\text{Ph-I-Ph}]\text{OTf}$  salt under mild reaction conditions (Scheme 28).<sup>75</sup> This procedure was

tolerant toward various substituted indoles, bearing either EDG or EGW. Good selectivities (up to 9/1 C2/C3) and moderate to good yields of the target C2-aryloindoles were achieved. In addition indole substrates with Br-substituent were not affected by this method.

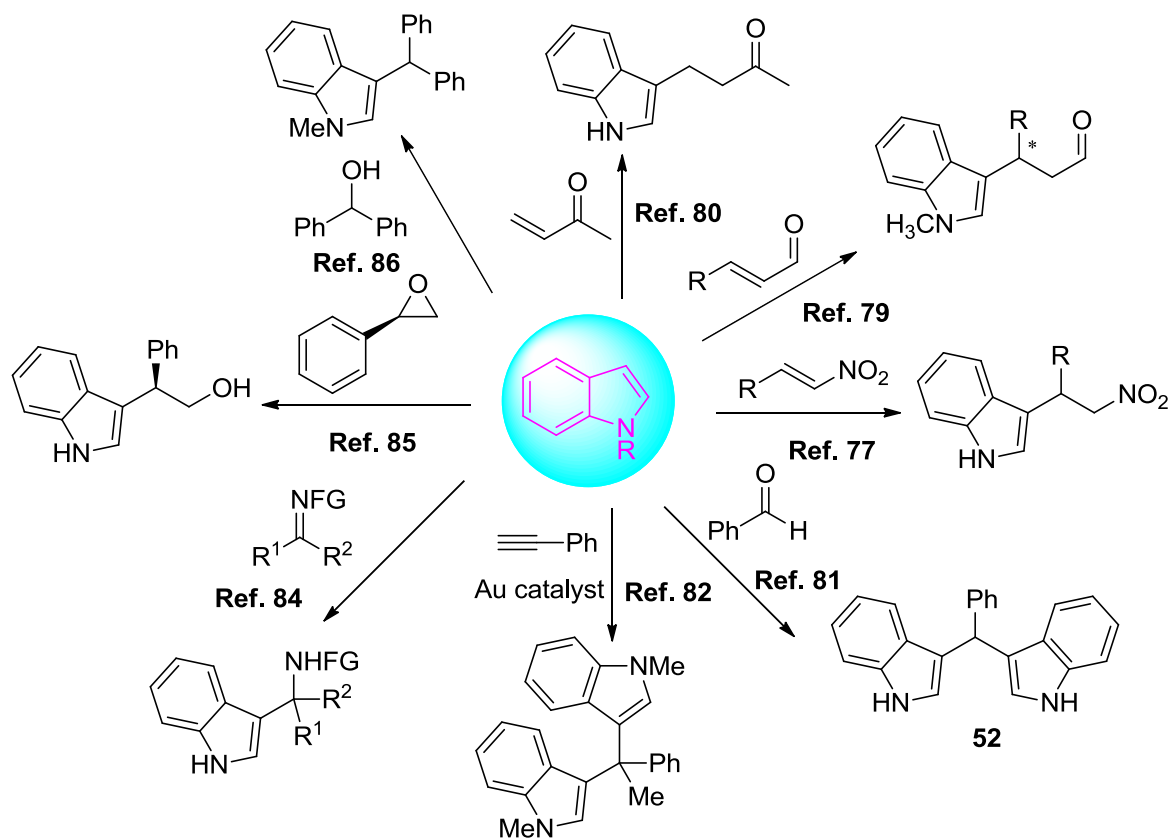


**Scheme 28** Copper-catalyzed C2-arylation of indoles

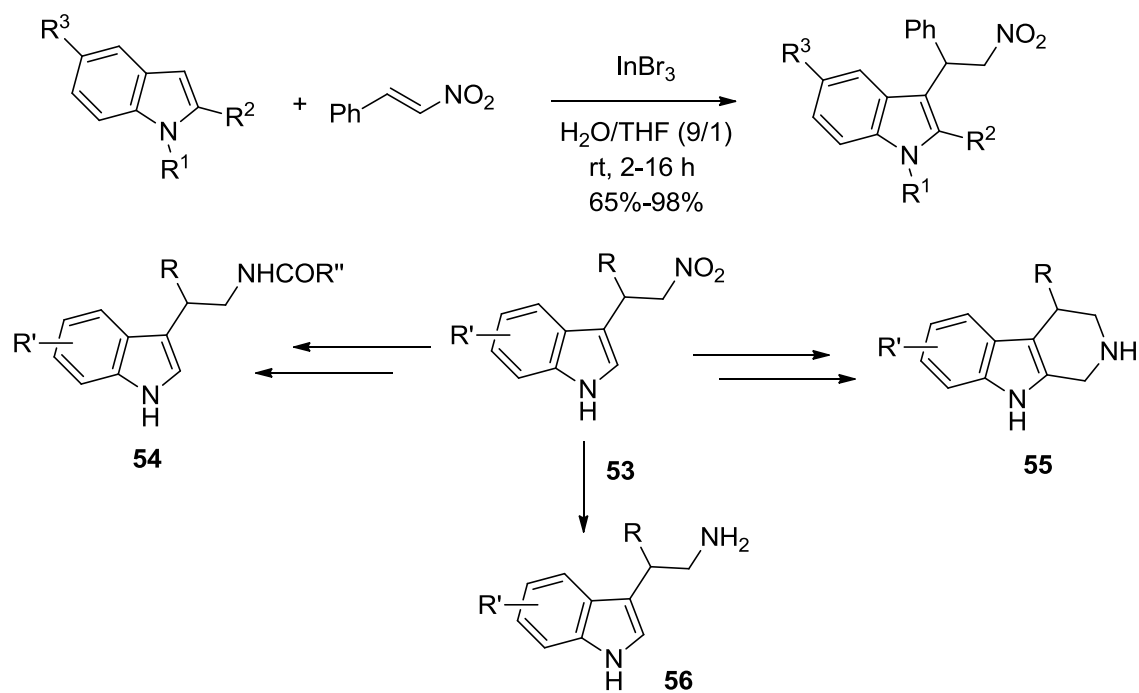
### Modification of the C3 position

There are a wide variety of methods for introducing substituents at the C3 since this is the preferred site for electrophilic substitution. Direct alkylations can be accomplished effectively with numerous electrophiles (Figure 7).<sup>53</sup> Michael-type alkylation is probably the most investigated approach for indole functionalization in recent years.<sup>76-81</sup> While the reaction with aldehydes<sup>81</sup> in the presence of Lewis or Bronsted acids generally affords a biindole compound (e.g. compound **52**). Metal-catalyzed hydroarylations of alkynes<sup>82</sup> and alkenes<sup>83</sup> have been achieved for the construction of benzylic stereocenters. Other electrophiles, such as imines,<sup>84</sup> epoxides<sup>85</sup> and alcohols,<sup>86</sup> have also been utilized for direct C3 alkylation of indole.

A general and mild  $\text{InBr}_3$ -catalyzed protocol for the conjugate addition between indoles and nitroalkenes has been reported.<sup>77</sup> The process was performed in aqueous media at room temperature, providing the functionalized indoles in excellent yields. The catalyst was reused several times without loss of activity. 2-Indolyl-1-nitroalkanes **53** are highly versatile intermediates for the preparation of several biologically active compounds such as melatonin analogs **54**, 1,2,3,4-tetrahydro- $\beta$ -carbolines **55** and triptans **56** (Scheme 29).

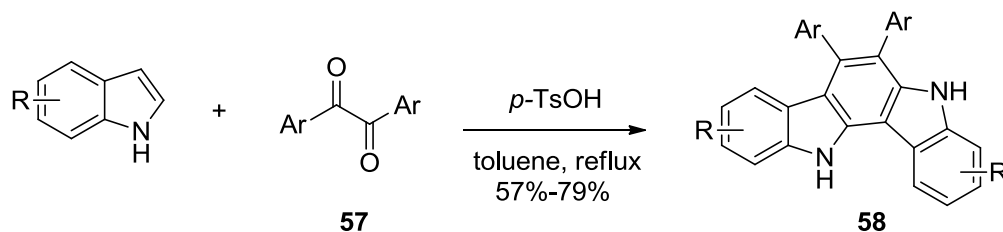


**Figure 7** C3-alkylation of indoles with various electrophiles



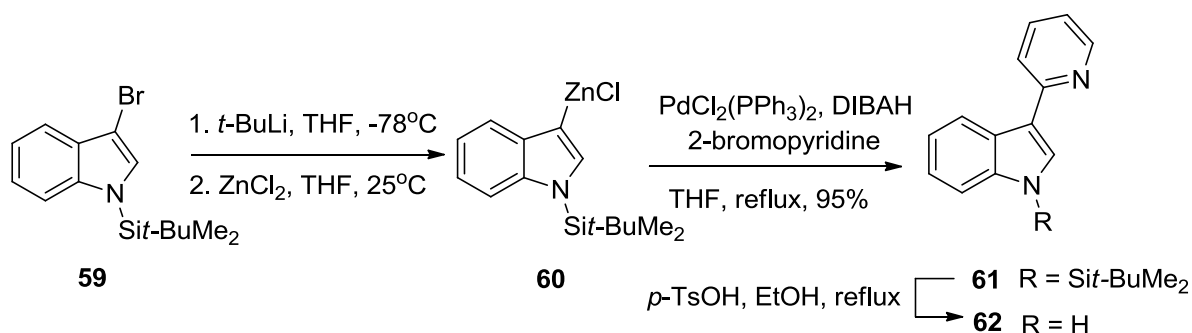
**Scheme 29** C3 alkylation of indole with nitroalkenes

The Bronsted acid catalyzed synthesis of polycyclic compound **58** with diverse biological activities has been presented recently.<sup>78</sup> The protocol is very convenient and involves a sequence of condensations between indoles and benzil derivatives **57** in the presence of *p*-TsOH (Scheme 30).



**Scheme 30** Synthesis of **58** by catalytic condensation of indoles with benzils.

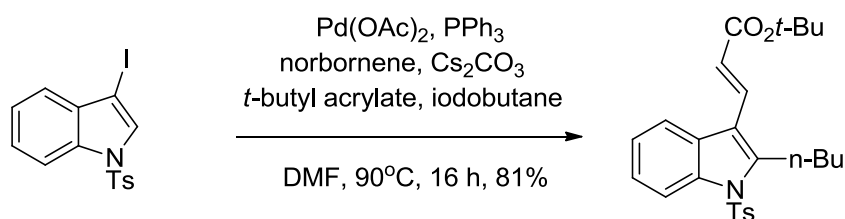
Access to 3-lithioindoles is usually achieved by halogen-lithium exchange. The zinc derivative **60** was prepared from **59** by halogen-metal exchange with *t*-butyllithium, followed by transmetalation of the resulting 3-lithioindole with  $\text{ZnCl}_2$ .<sup>87</sup> *t*-Butyldimethylsilyl group provided lateral protection of the indole 2-position without coordinating effect.<sup>88</sup> In addition, the corresponding 3-lithio-1-silylindole was stable specie, which did not rearrange to the 2-lithio isomer.<sup>89</sup> After Negishi coupling and further deprotection, **62** was obtained in high yield (Scheme 31).



**Scheme 31** The preparation of **62** via halogen-lithium exchange procedure

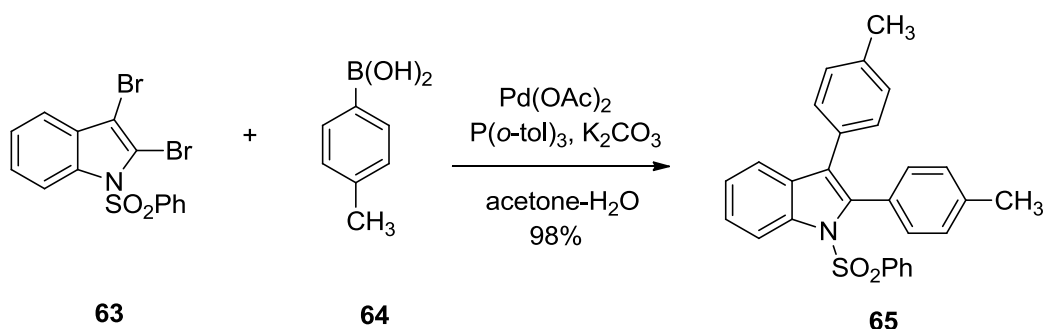
Indolyl halides and triflates have been used in the synthesis of a large number of indole derivatives mainly by metal-catalyzed coupling reactions.<sup>53a</sup> Recently Lautens *et.al*<sup>90</sup> described 2,3-coupling of *N*-tosyl-3-iodoindole with alken and alkylhalide by a one-pot palladium-catalyzed *ortho*-alkylation sequence terminated by either Heck or C-H coupling (Scheme 32). The nature of the nitrogen protecting group was found to be crucial to the

efficiency of the reaction. The use of a methyl protecting group yielded only the Heck product.



**Scheme 32** 2,3-Coupling of 3-Iodoindole and alkene

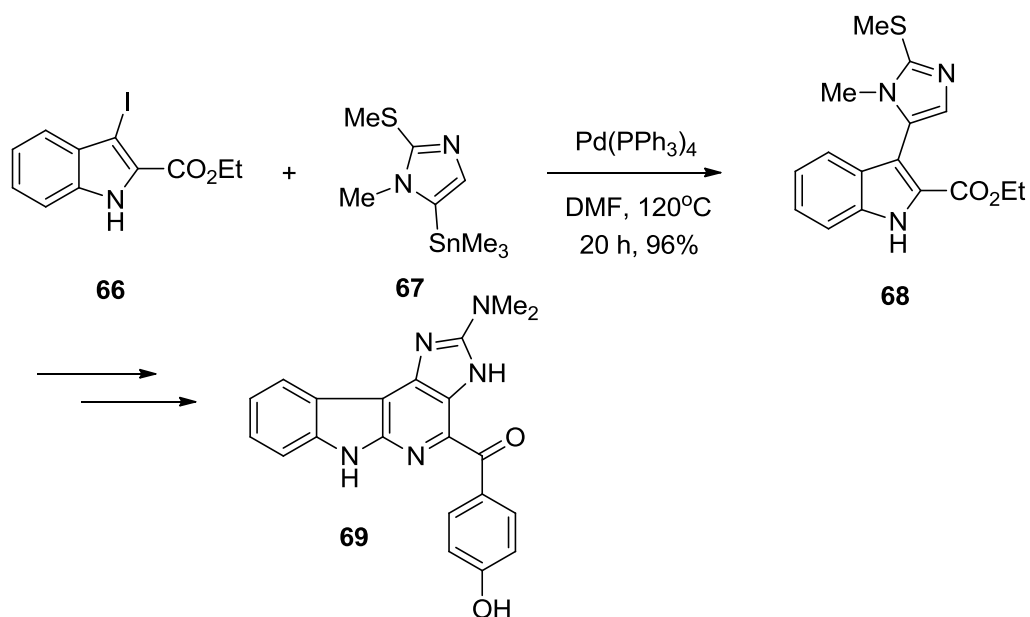
A bis-Suzuki cross-coupling reaction between 2,3-dihalo-1-(phenylsulfonyl)indoles and arylboronic acids has been utilized for the synthesis of 2,3-diarylindoles.<sup>91</sup> **63** was reacted with two equiv. of boronic acid **64** under typical Suzuki conditions to generate indole derivative **65** in excellent yield (Scheme 33).



**Scheme 33** Bis-Suzuki cross-coupling reaction between **63** and boronic acid

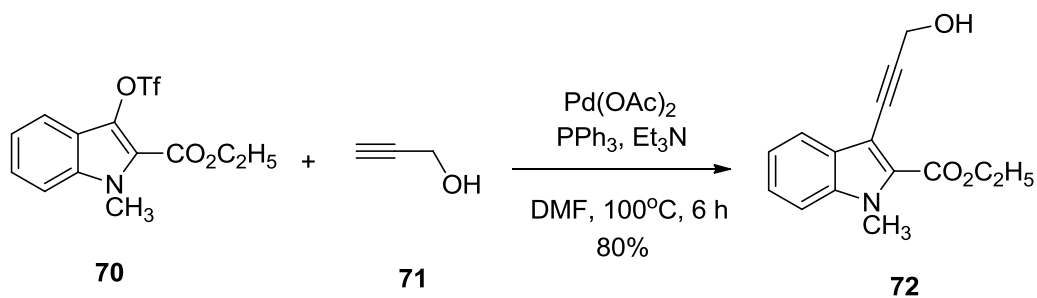
The Stille reaction of 3-iodoindole **66** was employed as a key step for the synthesis of grossularines-2 (**69**) possessing antitumor properties.<sup>92</sup> Stannylimidazole **67** was subjected to the cross-coupling reaction with **66** in the presence of  $\text{Pd(PPh}_3)_4$  in DMF to yield the important intermediate **68** in excellent yield (Scheme 34).





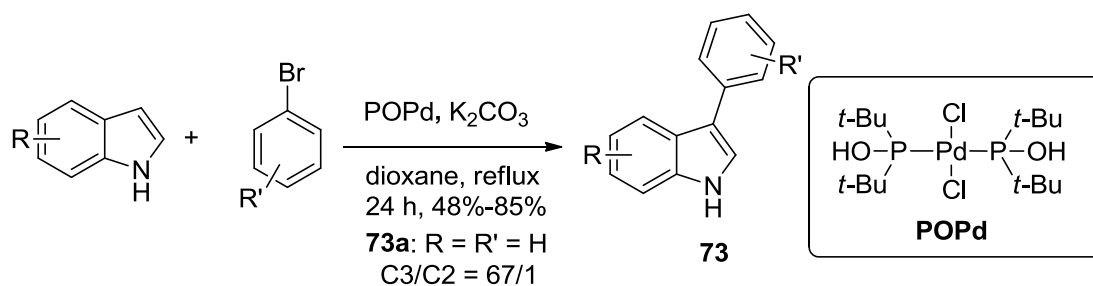
**Scheme 34** The Stille synthesis of grossularine-2 (**69**)

The Sonogashira reaction of indole triflate **70** with propargylic alcohol (**75**)<sup>93</sup> was carried out using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> system and Et<sub>3</sub>N as base in DMF to provide compound **72** in good yield (Scheme 35). Surprisingly, 3-iodo substituted indoles failed to give any detectable product on reaction with **71**.



**Scheme 35** The Sonogashira reaction of indole triflate

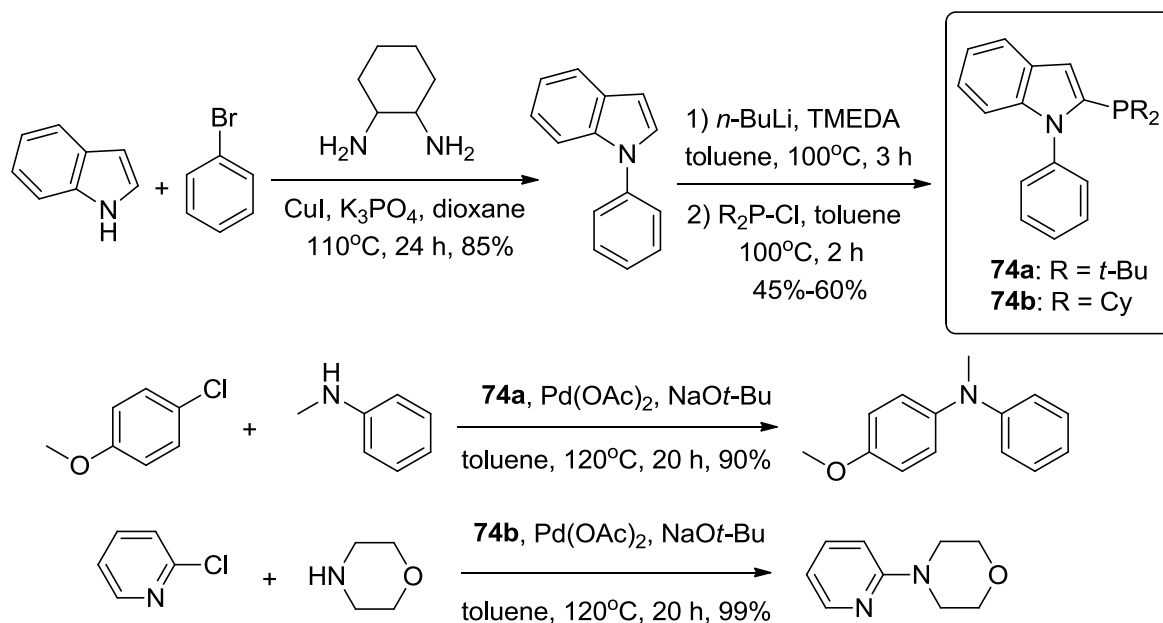
Metal-catalyzed direct arylation is also an effective approach for C3 modification of indole. Zhang *et.al* reported the direct palladium-catalyzed C3-arylation of free (NH)-indoles with aryl bromides.<sup>94</sup> C3-arylindoles **73** were obtained by using the air-stable POPd catalyst and K<sub>2</sub>CO<sub>3</sub> in refluxing dioxane in moderate to good isolated yields with high C3/C2 selectivities (Scheme 36). However, indoles bearing EWG were quite unreactive under these conditions.



**Scheme 36** Pd-catalyzed direct C3 arylation of indoles

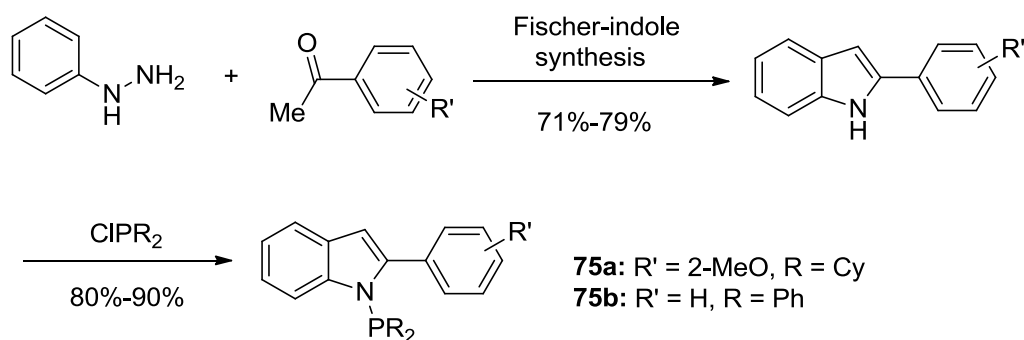
### 1.3.3 Achiral Indole ligands

The indole core has gained attention as a ligand in metal-catalyzed transformations only recently. The first palladium-catalyzed aminations of both activated and deactivated aryl chlorides with various amines have been performed in the presence of indole ligands **74a** and **74b**,<sup>95</sup> and high yields were achieved, even under mild conditions (60°C) in some cases. These ligands can readily be synthesized from indole in two steps (Scheme 37).

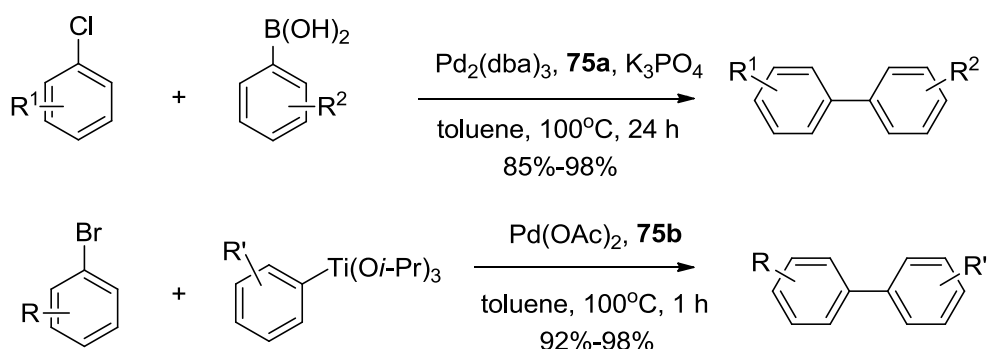


**Scheme 37** Aminations of aryl and heteroaryl chlorides with indole ligands **74a** and **74b**

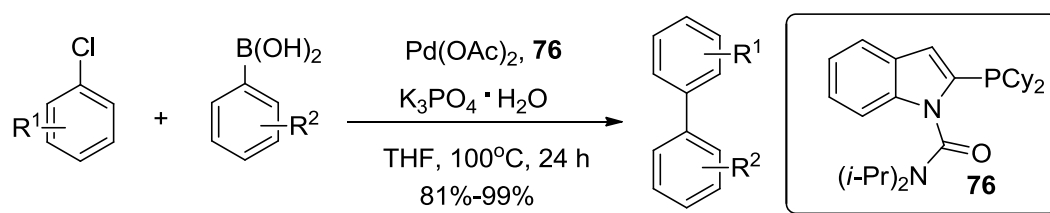
In 2007 Kwong *et al.* described a type of easily accessible indolyl phosphine ligands **75a** and **75b**, prepared *via* an efficient protocol involving Fischer indolization from readily available phenylhydrazine and substituted acetophenones (Scheme 38).<sup>96</sup> The Suzuki-Miyaura coupling of unactivated aryl chlorides with boron compounds using Pd<sub>2</sub>(dba)<sub>3</sub> and ligand **75a** was performed in toluene with K<sub>3</sub>PO<sub>4</sub> as base with excellent yields. Furthermore, palladium-mediated cross-couplings of organotitaniums and aryl bromides were promoted by ligand **75b**.<sup>97</sup> Titanium nucleophiles bearing either EDG or EWG have been utilized to achieve excellent yields with high reaction rates (Scheme 39). It is noteworthy that additional solid inorganic bases are not required. Also ligand **76**, synthesized by the same group,<sup>98</sup> has been utilized successfully in the Suzuki coupling of functionalized aryl chlorides and heteroaryl chlorides (Scheme 40).



**Scheme 38** Synthesis of Indolyl Phosphine ligands **75a-b**



**Scheme 39** Suzuki-Miyaura coupling reactions using Indolyl Phosphine ligands.

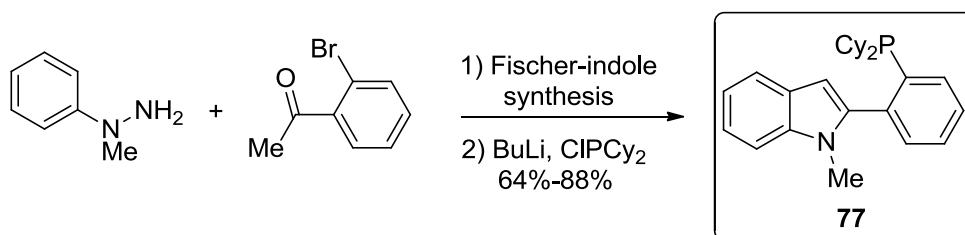


**Scheme 40** Suzuki-Miyaura coupling reactions using Indolyl Phosphine ligand **76**

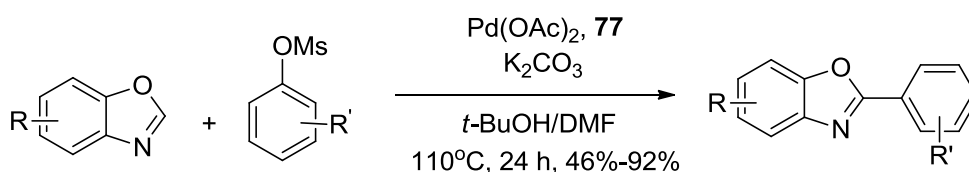
The next generation of indole-ligand **77** has demonstrated excellent reactivities in a series of palladium-catalyzed coupling reactions of aryl mesylates which are attractive substrates due to the direct access from readily available phenols (Scheme 41).<sup>99-102</sup> The first general palladium-catalyzed direct arylation of benzoxazoles with aryl mesylates was performed using ligand **77** with  $K_2CO_3$  as base.<sup>100</sup> The corresponding products were obtained in good to excellent yields without the use of common additives for the C-H activation reaction, such as copper salts and organic acids.

The  $Pd(OAc)_2/77$  catalytic system was active for Suzuki coupling reactions of functionalized aryl mesylates with various arylboronic acids, aryltrifluoroborate salts and boronate esters.<sup>99,101</sup> In addition, the system was also highly effective in Hiyama cross-coupling of various aryl mesylates using organosilicon as the coupling partner.<sup>102</sup> The use of acetic acid additive efficiently suppressed the mesylate decomposition and generally promoted the coupling product yields.

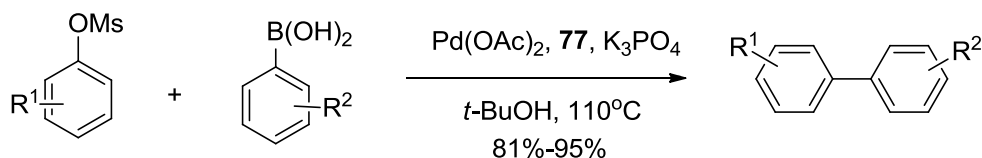
The Sonogashira coupling reactions with aryl mesylates and tosylates were performed successfully using  $Pd(OAc)_2/77$  system and  $K_3PO_4$  as base in *t*-BuOH (Scheme 42).<sup>103</sup> Good yields were obtained with aryl alkynes and conjugated alkynes as the coupling partners. The procedure enables the use of challenging phenolic derivatives as the electrophilic partners. This method offers different substitution patterns with respect to aryl halides for aromatic alkyne synthesis.



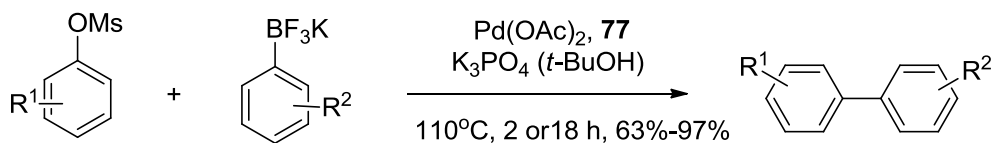
**Direct Arylation of Heteroarenes with Aryl Mesylates (Ref. 100)**



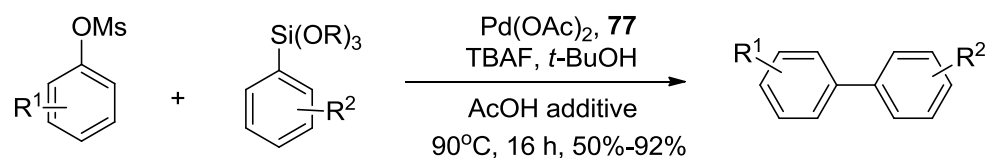
**Suzuki-Miyaura Coupling Using boron reagents (Ref. 99)**



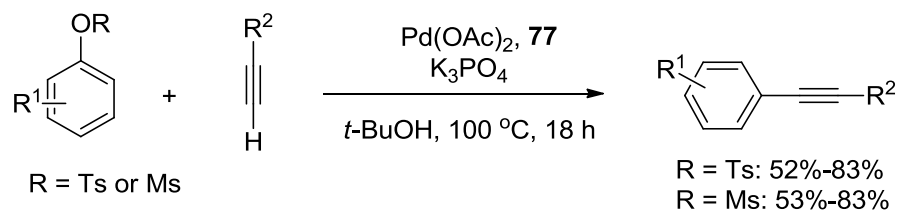
**Suzuki-Miyaura Coupling with Potassium Aryltrifluoroborates (Ref. 101)**



**Hiyama Cross-Coupling of Aryl Mesylates (Ref. 102)**

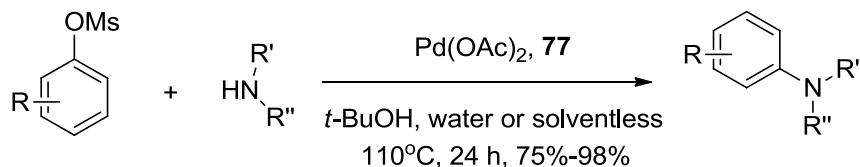


**Scheme 41** Coupling reactions using Pd(OAc)<sub>2</sub>/**77** system



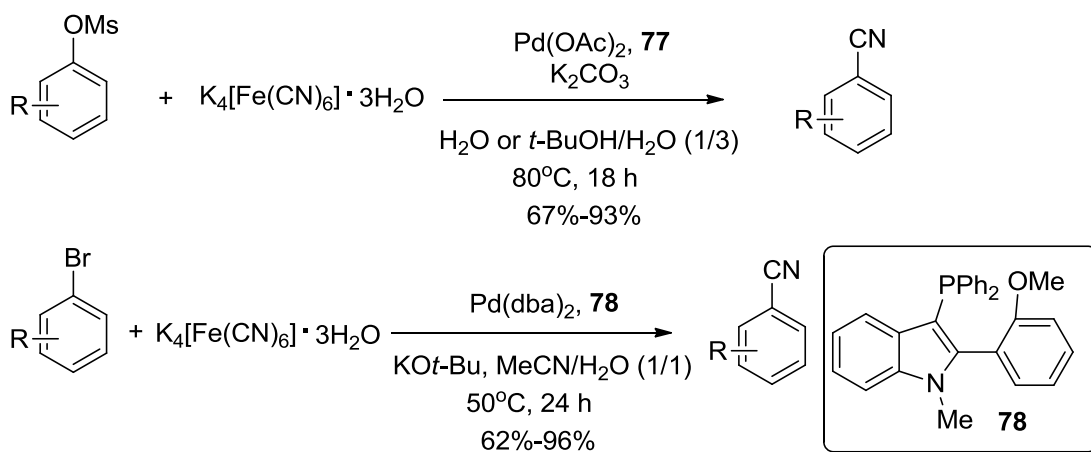
**Scheme 42** Sonogashira coupling reactions using Pd(OAc)<sub>2</sub>/**77** system

The same system has also been reported to facilitate the reaction between aryl mesylates and amines.<sup>104</sup> Various amines have been utilized as nucleophiles, including anilines, aliphatic amines, indole, pyrrole and carbazole, resulting in good to excellent yields (Scheme 43).



**Scheme 43** Pd-catalyzed amination of aryl mesylates

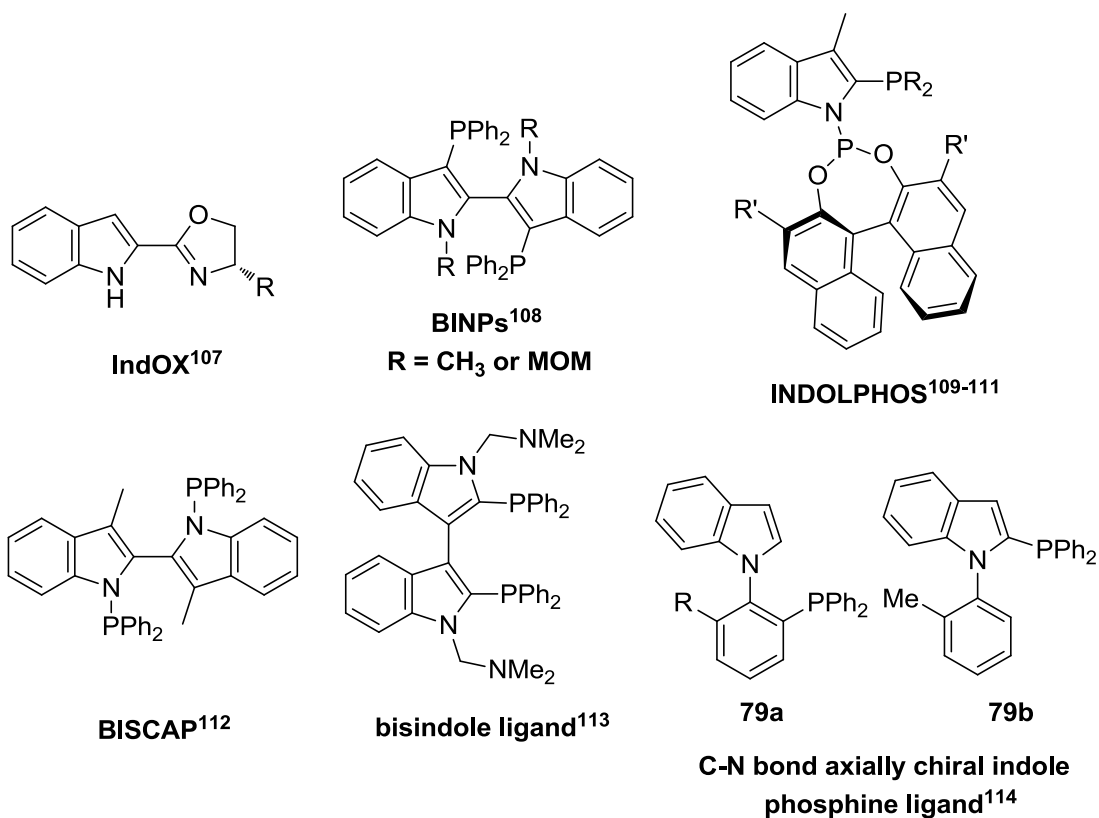
Very recently cyanations of aryl mesylates<sup>105</sup> and aryl bromides<sup>106</sup> have been developed using Pd(OAc)<sub>2</sub>/**77** and Pd(dba)<sub>2</sub>/**78**, respectively. The reaction took place under aqueous conditions, and K<sub>4</sub>[Fe(CN)<sub>6</sub>] was utilized as cyanide source (Scheme 44). The catalyst systems exhibited excellent functional-group tolerance: nitrile, ester, keto, aldehyde, free amine and heterocyclic groups remained intact during the reaction. The reactions were conducted under mild conditions (at 80°C and 50°C, respectively), and the desired aryl nitriles were afforded in good to excellent yields.



**Scheme 44** Palladium-catalyzed cyanation using ligands **77** and **78**

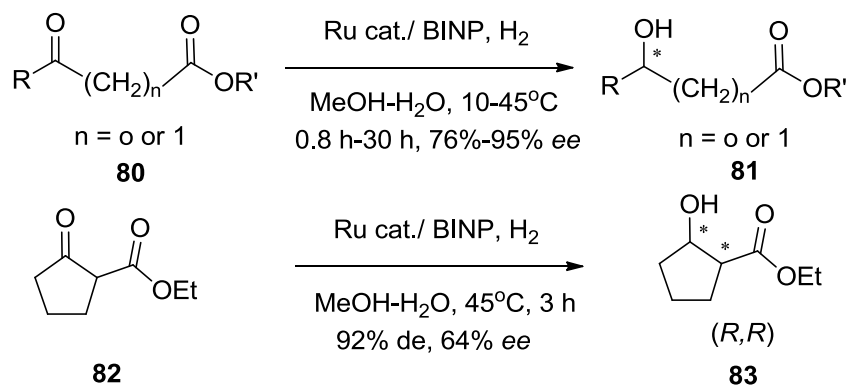
### 1.3.4 Chiral indole ligands

The applications of chiral indole ligands in asymmetric reactions are much less reported until now (Figure 8).<sup>107-114</sup>



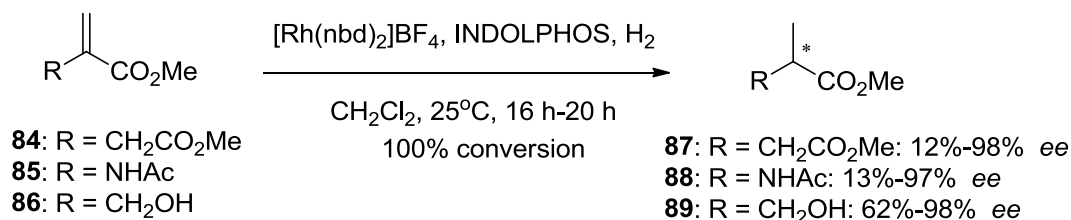
**Figure 8** Indole based ligands with chirality

BINPs (3,3'-bis(diphenylphosphino)-2,2'-biindole)<sup>108</sup> have been utilized in ruthenium-catalyzed hydrogenation reactions of  $\alpha$ - and  $\beta$ -ketoesters. High enantioselectivities were achieved with linear substrates **80**; but in the case of cyclic substrate **82**, only moderate *ee* was obtained with good diastereoselectivity (Scheme 45).

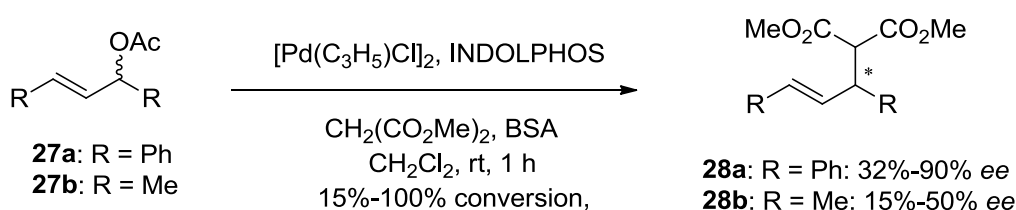


**Scheme 45** Ruthenium-catalyzed hydrogenation with BINP

INDOLPHOS (phosphine-phosphoramidite) ligands have displayed efficiency in rhodium-catalyzed hydrogenations of dimethyl itaconate (**84**) and methyl 2-acetamidoacrylate (**85**).<sup>109</sup> A series of INDOLPHOS ligands were screened and quantitative conversions were achieved. The enantioselectivities varied from low to excellent values (Scheme 46). Their coordination mode to rhodium was controlled by the steric properties of the ligand, which played a major role in the reactions. When Roche ester **86** was subjected to the optimized conditions, high yields and enantioselectivities were obtained (Scheme 46).<sup>110</sup> Furthermore, INDOLPHOS ligands were evaluated in the Pd-catalyzed asymmetric allylic substitution.<sup>111</sup> The allylic alkylation with substrates **27a** and **27b** proceeded well to generate the products in moderate to good enantioselectivities (Scheme 47). However, the reactions using nitrogen nucleophiles such as benzylamine and aniline did not yield the desired products.



**Scheme 46** Rh- catalyzed hydrogenation with INDOLPHOS

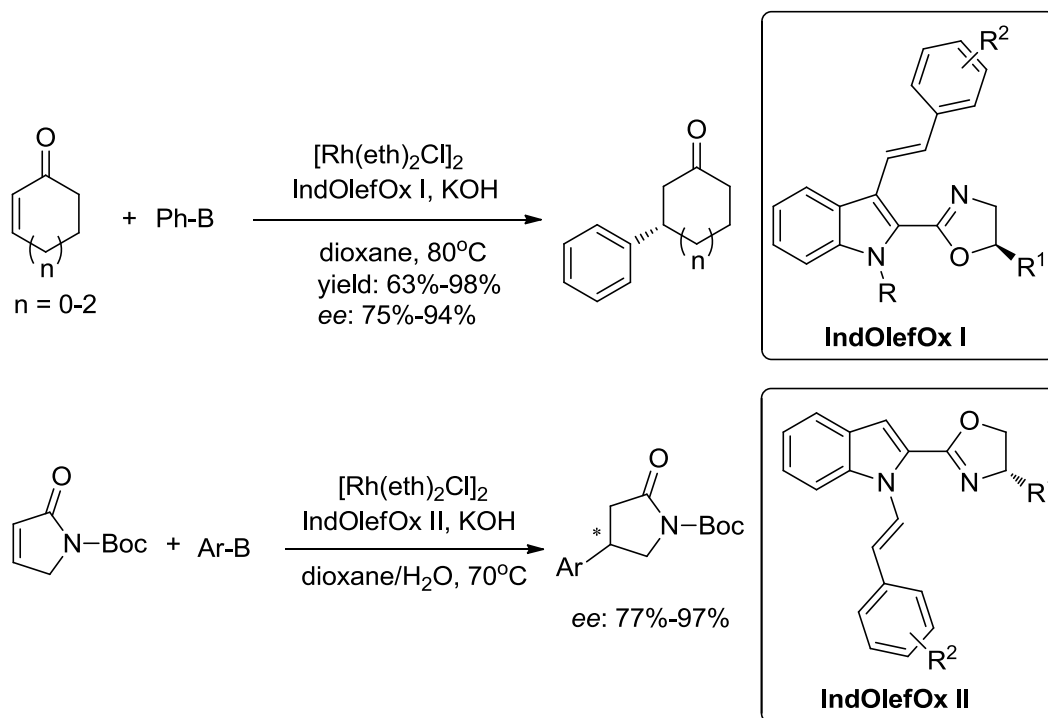


**Scheme 47** Pd- catalyzed allylic alkylation with INDOLPHOS

C–N bond axially chiral indole phosphines ligands **79a** and **79b** were reported recently.<sup>114</sup> The enantiomers were resolved by HPLC over a chiral stationary phase column. Ligand **79a** demonstrated high reactivity in allylic alkylation of **27a** with dimethyl malonate, producing the product **28a** with excellent yield and enantioselectivity. Whereas the use of ligand **79b** decreased the yield and enantioselectivity remarkably.



Very recently novel IndOlefOx (indole-olefin-oxazoline) ligands have been introduced.<sup>115</sup> IndOlefOx I<sup>115a</sup> demonstrated high efficiency in rhodium-catalyzed asymmetric 1,4-addition reaction with organoboron reagents. Whereas IndOlefOx II<sup>115b</sup> was evaluated in the Rh-catalyzed reactions between organoboronics and a lactam or a lactone substrate (Scheme 48).



**Scheme 48** Rh-catalyzed conjugate addition with IndOlefOx ligands

## 1.4 Catalytic asymmetric allylic substitutions with hetero-nucleophiles

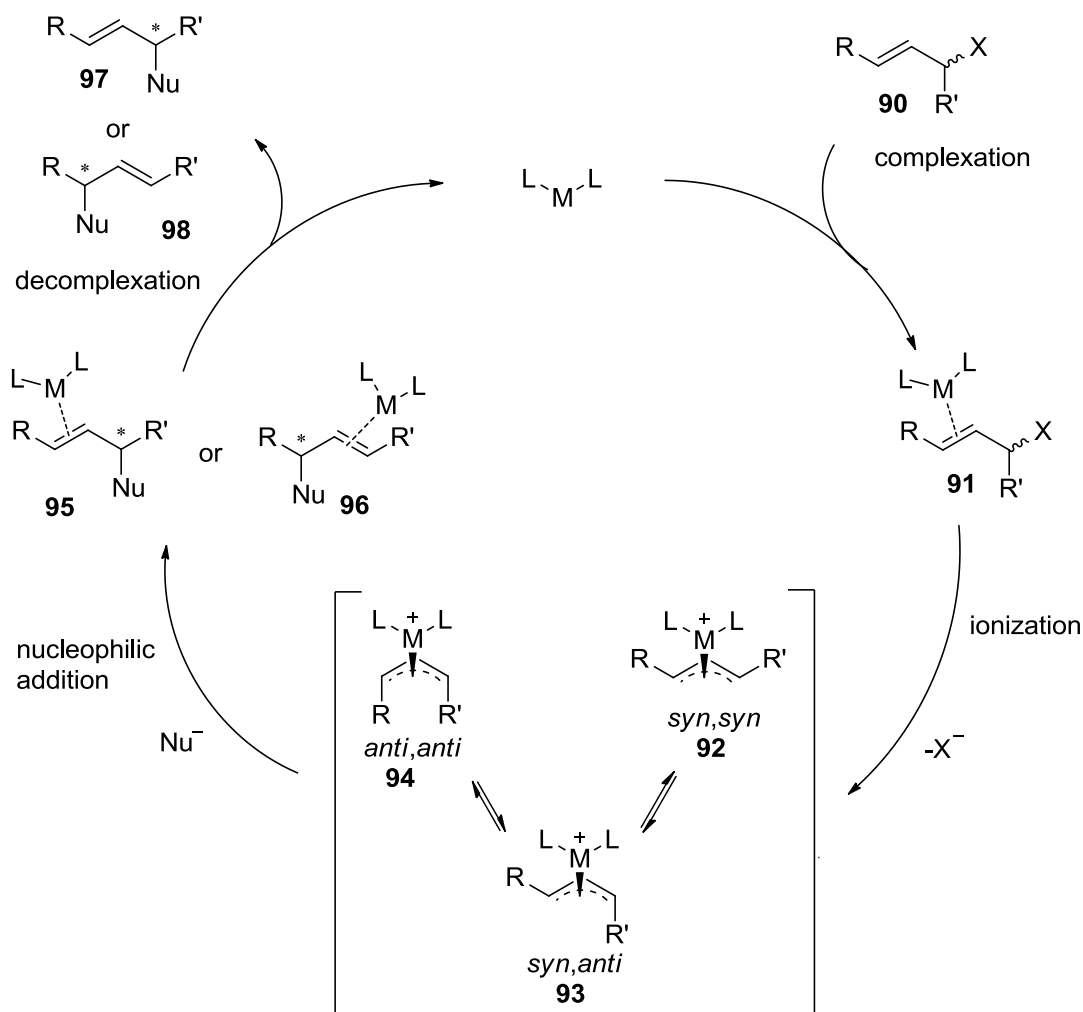
### 1.4.1 Mechanism of asymmetric allylic substitution

Metal-catalyzed asymmetric allylic substitution is one of the most powerful approaches for the enantioselective formation of a variety of chemical bonds, including C-C, C-O, C-N, C-S and C-P.<sup>116</sup> This reaction has been extensively studied with a great variety of substrates and nucleophiles under different reaction conditions.

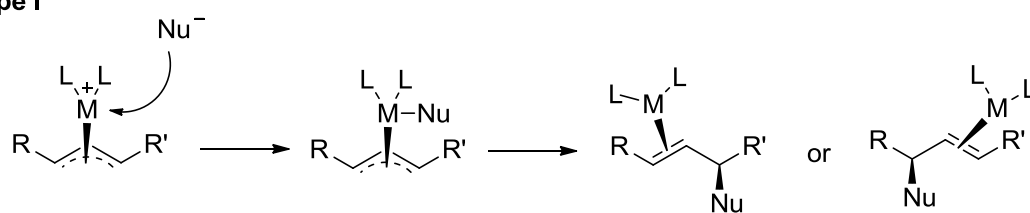
The general catalytic cycle of asymmetric allylic substitution involves coordination of the olefin of the substrate to a low-valent metal centre, followed by ionization of the allylic leaving group. The generated intermediate  $\pi$ -allyl metal complexes **92** or **93** may equilibrate through  $\pi$ - $\sigma$ - $\pi$  isomerization before nucleophilic addition (Scheme 49). The configuration of the  $\pi$ -allyl complex may be *syn-syn* (**92**), *syn-anti* (**93**) or *anti-anti* (**94**). The complexes resulting from an *E*-olefin electrophile typically prefers the *syn-syn* configuration, while the cyclic substrate is necessarily locked into the *anti-anti* geometry. Finally, trapping of these metal  $\pi$ -allyl complexes by the nucleophile enables the product to be released from the catalyst.

Depending on the nature of the metal and nucleophile, there are two distinct mechanistic pathways for the nucleophilic substitution step in the allylic substitution catalytic cycle. The nucleophile may first attack the metal center followed by subsequent reductive elimination to form the new bond (Type I), or the nucleophile may attack the allylic carbon center directly from the opposite face where the metal resides (Type II). The reaction *via* a Type I procedure results in retention<sup>117</sup> of stereochemistry from the metal-allyl complex. While the nucleophilic attack *via* a Type II process results in inversion<sup>118</sup> of stereochemistry from the metal-allyl complex. Generally, “hard” nucleophiles typically proceed through a Type I process, while “soft” nucleophiles proceed through the Type 2 process.

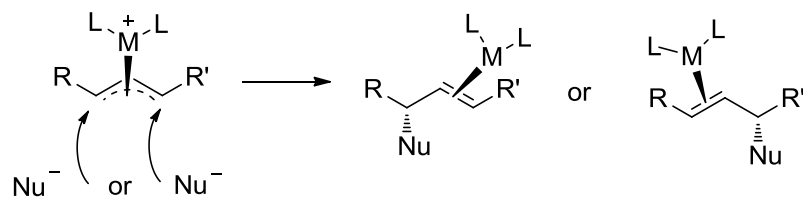
Except for decomplexation of the olefin from the metal-ligand system, each of the allylic substitution catalytic cycle steps provides an opportunity for enantioselection. The mechanism includes discrimination of prochiral olefin faces, enantiotopic ionization of leaving groups, enantiofacial exchange of the  $\eta^3$ -allyl complex, enantiotopic allyl termini differentiation and stereospecific allylic alkylation.<sup>116</sup>



**Type I**



**Type II**

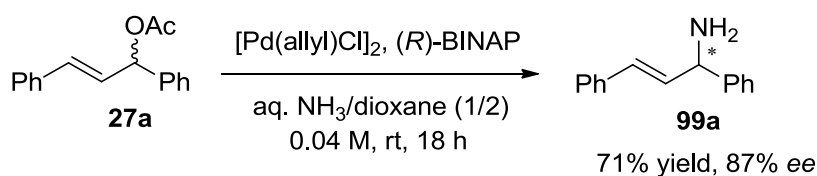


**Scheme 49** The reported allylic substitution reaction mechanism

## 1.4.2 Asymmetric Allylic Amination

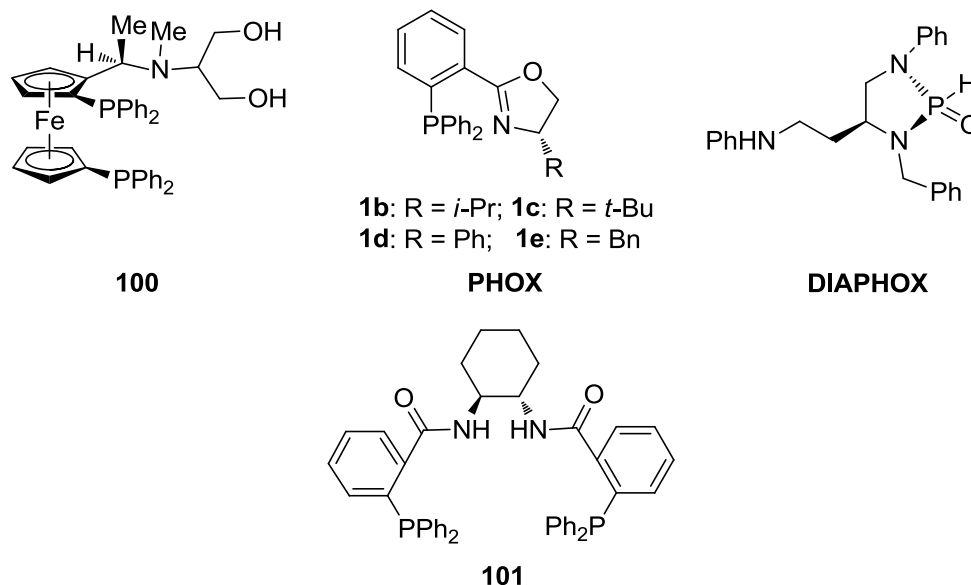
Catalytic asymmetric allylic amination is an important reaction to synthesize the allylamine moiety, which is encountered in natural products, and often converted into compounds possessing biological activities, such as amino acids,<sup>119</sup> carbohydrate derivatives<sup>120</sup> and various alkaloids.<sup>121</sup>

Direct allylic amination employing ammonia for chiral primary allylic amine is rarely reported. The first palladium-catalyzed asymmetric allylic amination with aqueous ammonia was reported recently, using (*R*)-BINAP as the ligand (Scheme 50).<sup>122</sup> The monoalkylated product **99a** was obtained in 71% yield and 87% *ee*. The effective chiral induction suggested that ammonia did not replace the ligand to coordinate to the metal catalyst.

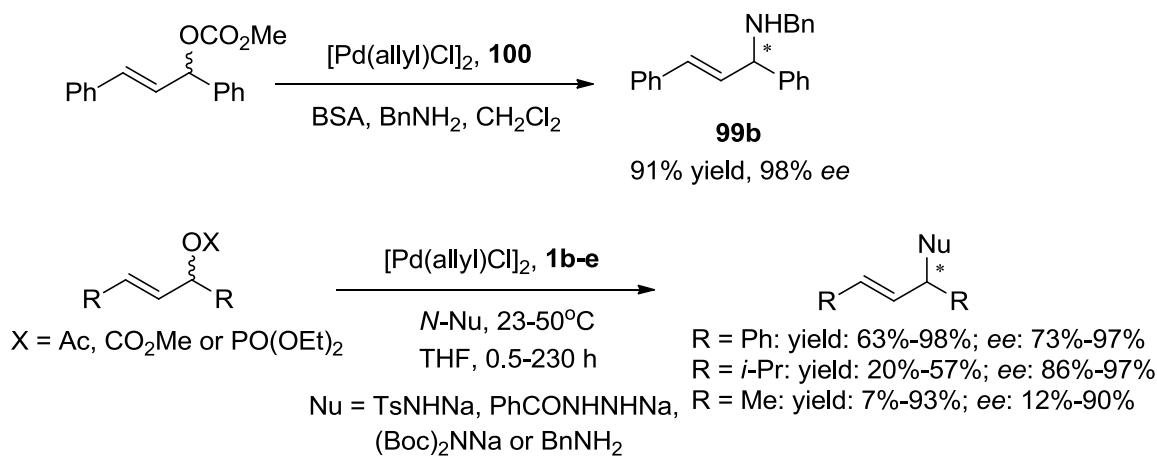


**Scheme 50** Allylic amination with aqueous ammonia

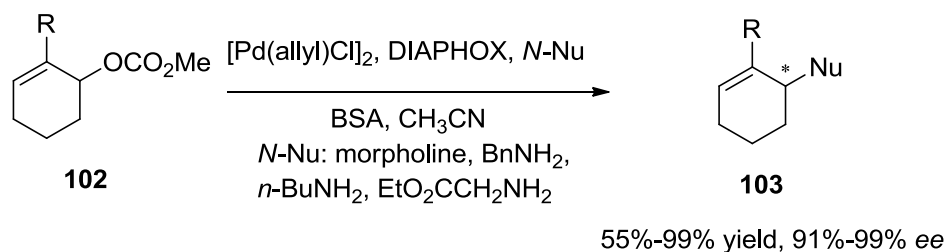
Enantioselective allylic aminations applying reactive alkyl amines as nucleophiles have been achieved using various chiral ligands (Figure 9).<sup>123-126</sup> The first example was reported using carbonates and ligand **100** with benzylamine as nucleophile (Scheme 51).<sup>123</sup> The attached hydroxy chain on the ligand was required for high enantioselectivity, which likely directed the nucleophile to attack a particular side of the allyl terminus. PHOX ligands are highly effective in the same type of reactions.<sup>124</sup> Benzylamine or the sodium salts of *p*-toluenesulfonamide, benzoylhydrazine and (Boc)<sub>2</sub>NH were utilized as nucleophiles in the reactions with 1,3-diphenyl- and 1,3-dialkyl-2-propenyl acetates, carbonates or phosphates. Moderate to high enantioselectivities of up to 97% have been obtained (Scheme 51).



**Figure 9** Chiral ligands utilized in allylic amination with alkyl amines



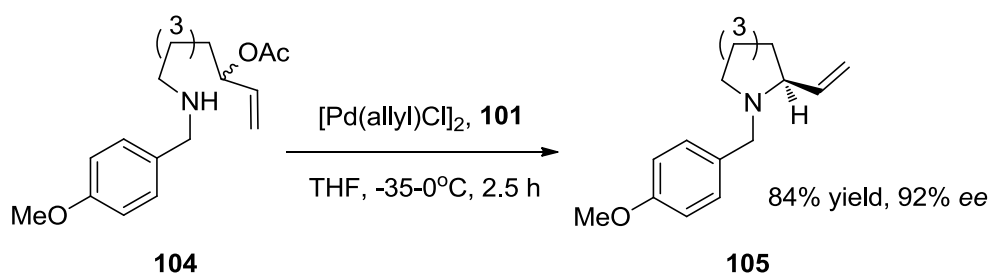
**Scheme 51** Pd-catalyzed allylic amination using chiral ligands.



**Scheme 52** Pd-catalyzed allylic amination of cyclic substrates using DIAPHOX ligand

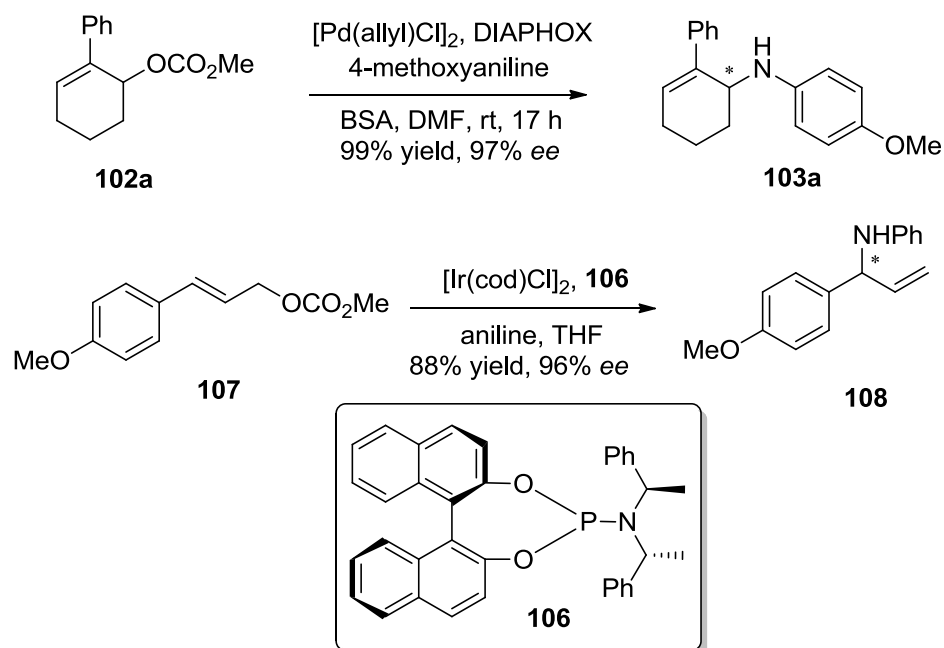
DIAPHOX (diaminophosphin oxide) ligand<sup>125</sup> has been successfully utilized in asymmetric allylic amination of cyclic substrates **102** using primary and secondary amines as nucleophiles (Scheme 52). DIAPHOX as preligand was activated *in situ* by BSA induced P(V) to P(III) transformation to afford trivalent phosphorus ligand. The reactions proceeded at room temperature to provide the corresponding products in good yields with high enantioselectivities.

The palladium-catalyzed asymmetric intramolecular allylic amination has been performed with Trost ligand **101**.<sup>126</sup> The reaction went to completion with 1% catalyst between -35 and 0 °C in 2.5 h to give both high yield and *ee* of the monocyclic amine **105** (Scheme 53).



**Scheme 53** Pd-catalyzed asymmetric intramolecular allylic amination

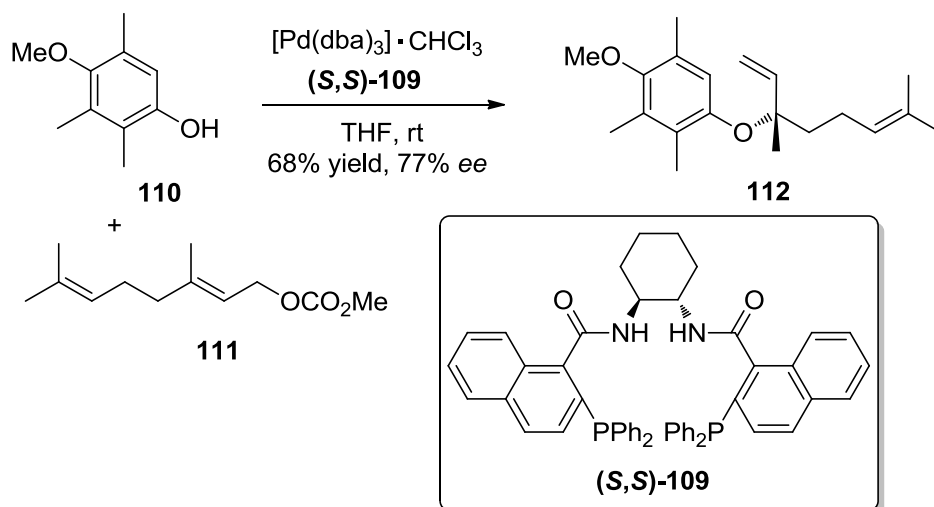
There are few reports concerning the use of aromatic amines as nucleophiles, presumably due to their low nucleophilicity. Pd–DIAPHOX catalyst systems have been successfully utilized in enantioselective allylic amination with aromatic amine nucleophiles.<sup>127</sup> The reaction was performed in DMF with 4-methoxyaniline as nucleophile to afford the product **103a** in 99% yield with 97% *ee* (Scheme 54). Iridium-catalyzed asymmetric allylic amination developed by Hartwig group is also applicable to aromatic amines.<sup>128</sup> The branched product **108** was obtained with good yield and excellent regio- and enantioselectivities using ligand **106** and aniline as nucleophile in THF (Scheme 54).



**Scheme 54** Asymmetric allylic amination using aromatic amines as nucleophiles

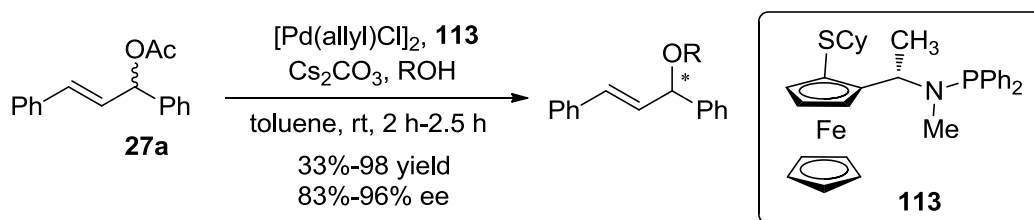
### 1.4.3 Asymmetric Allylic Etherification

Enantioselective allylic etherification reactions provide efficient methods for the synthesis of enantiomerically enriched building blocks presenting in many natural products and useful organic molecules. Phenols represent one of the best types of oxygen nucleophiles in allylic etherification, and they have been successfully utilized in a variety of allylic systems. The reaction of substituted phenol **110** with 2,6-dienyl carbonate **111** in the presence of (*S,S*)-**109** led to the formation of the branched allyl aryl ether **112** in high regioselectivity and good *ee* (Scheme 55).<sup>129</sup>



**Scheme 55** Allylic etherification with phenols using ligand **109**

Aliphatic alcohols are challenging nucleophiles because these are of poor nucleophilicity for allylic substitution, and the high basicity of alkoxides can induce elimination processes and catalyst deactivation. Recently Lam *et.al* described a new ferrocenyl ligand **113**.<sup>130</sup> The ligand has been utilized effectively in the palladium-catalyzed asymmetric allylic etherification of **27a** with a wide array of aliphatic alcohols with good to excellent enantioselectivities (Scheme 56). This scaffold of ligand has several beneficial features, including ease of accessibility, and the possibility of fine-tuning the steric and electronic properties of the donor atoms.

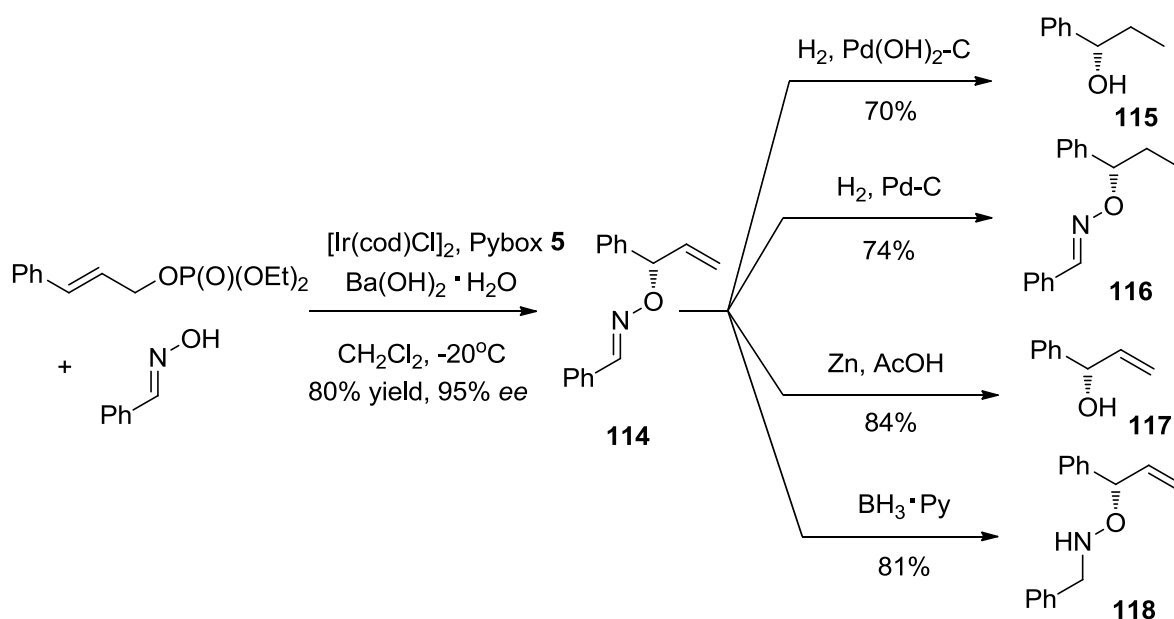


**Scheme 56** Allylic etherification with aliphatic alcohols using ligand **113**

Recently oximes have attracted interest as nucleophiles in asymmetric allylic etherification. Takemoto *et.al*<sup>131</sup> reported the asymmetric iridium-catalyzed allylic substitutions using Pybox ligand **5** with oximes. The branched chiral oxime ether **114** was obtained with good yield and high region- and enantioselectivities when barium hydroxide monohydrate was employed at -

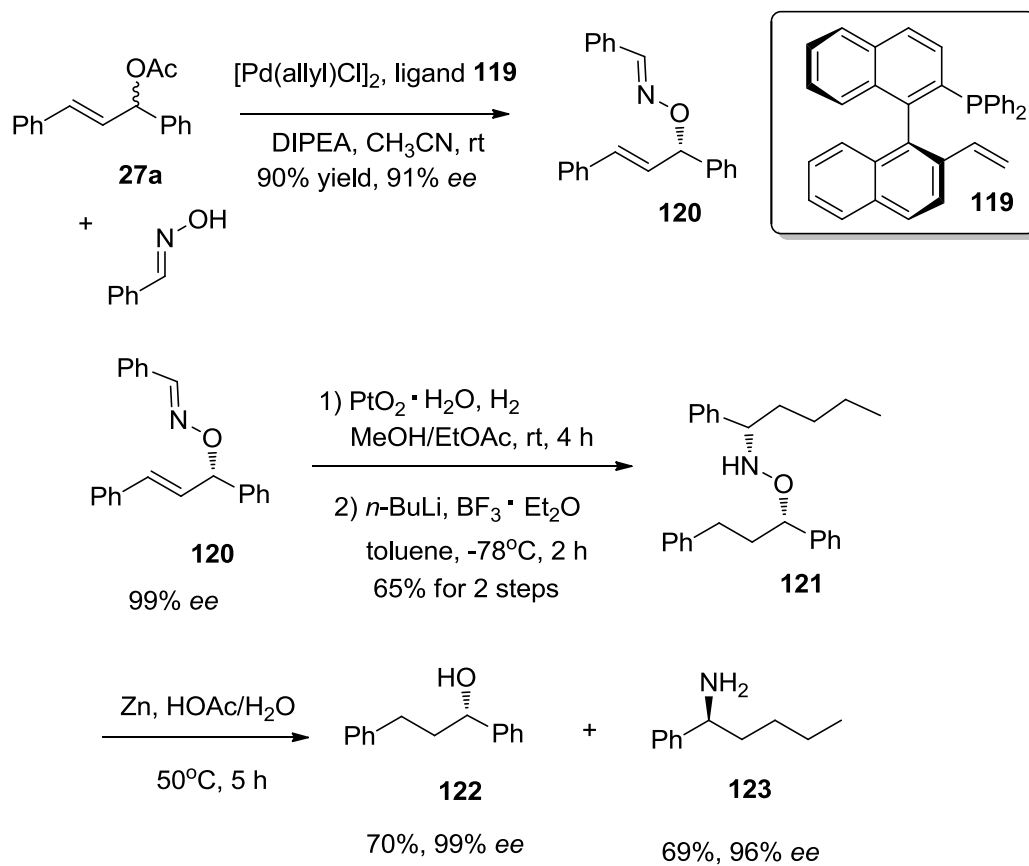


20 °C.<sup>131a</sup> The product **114** could be further converted into **115-118** via the selective reduction of C=C, C=N or N-O bond (Scheme 57).



**Scheme 57** Iridium-catalyzed allylic etherification with oximes using Pybox ligand **5**

Ligand **119** has demonstrated high efficiency in palladium-catalyzed asymmetric allylic etherifications with a variety of oximes as nucleophiles.<sup>132</sup> The reaction was performed in  $\text{CH}_3\text{CN}$  using DIPEA as base, and oxime ether **120** was obtained in high yield with excellent enantioselectivity. In addition, the resulting oxime ether can easily be converted to compound **121** with excellent diastereoselectivity after hydrogenation with  $\text{H}_2$  and addition with *n*-butyllithium. The N-O bond was then cleaved efficiently by treating with  $\text{Zn}/\text{HOAc}$  to afford both optically active alcohol **122** and amine **123** (Scheme 58).



**Scheme 58** Palladium-catalyzed allylic etherification with oximes using ligand **119**

## 2 Aim of the study

Indoles have been investigated widely since these are found in numerous biologically active natural products and pharmaceuticals. Various functionalization approaches of indole core structure have been extensively reported. However, the utilization of indole derivatives as chiral ligands in asymmetric transformations is much less reported. In this thesis, the goal was to synthesize chiral indole-phosphine oxazoline (IndPHOX) ligands, which would be based upon an indole scaffold combined with an oxazoline moiety.

The diversity of IndPHOX ligands can easily be accessed, and provides a high level of steric and electronic fine-tuning. The strategy of this study was to synthesize structurally different IndPHOX ligands from commercially available starting materials. The modification of the oxazoline moiety and the *NI*-position of the ligand structure could readily be accomplished. IndPHOX ligands were utilized in allylic substitutions for the enantioselective formation of C-C, C-N and C-O bond, respectively.

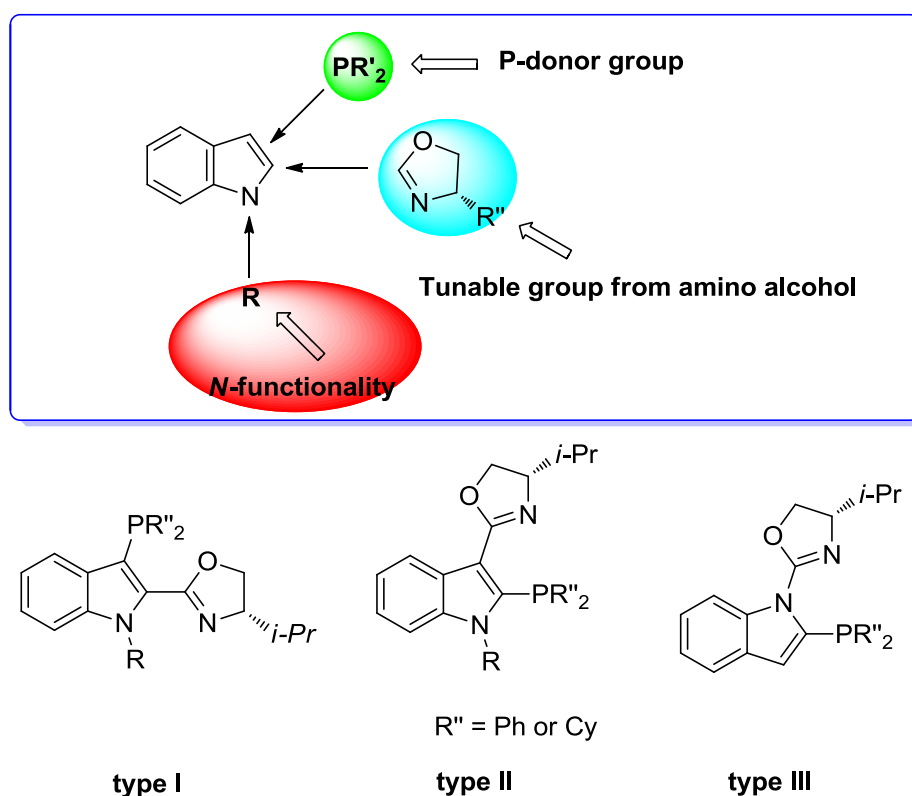
The aims of the work described here are outlined as follows:

1. Preparation of IndPHOX ligands [I - III]
2. Application in allylic substitution [I - III]
3. Synthesis of 2-aryl-substituted chroman [IV]

### 3 Results and Discussion

#### 3.1 Preparation of IndPHOX ligands

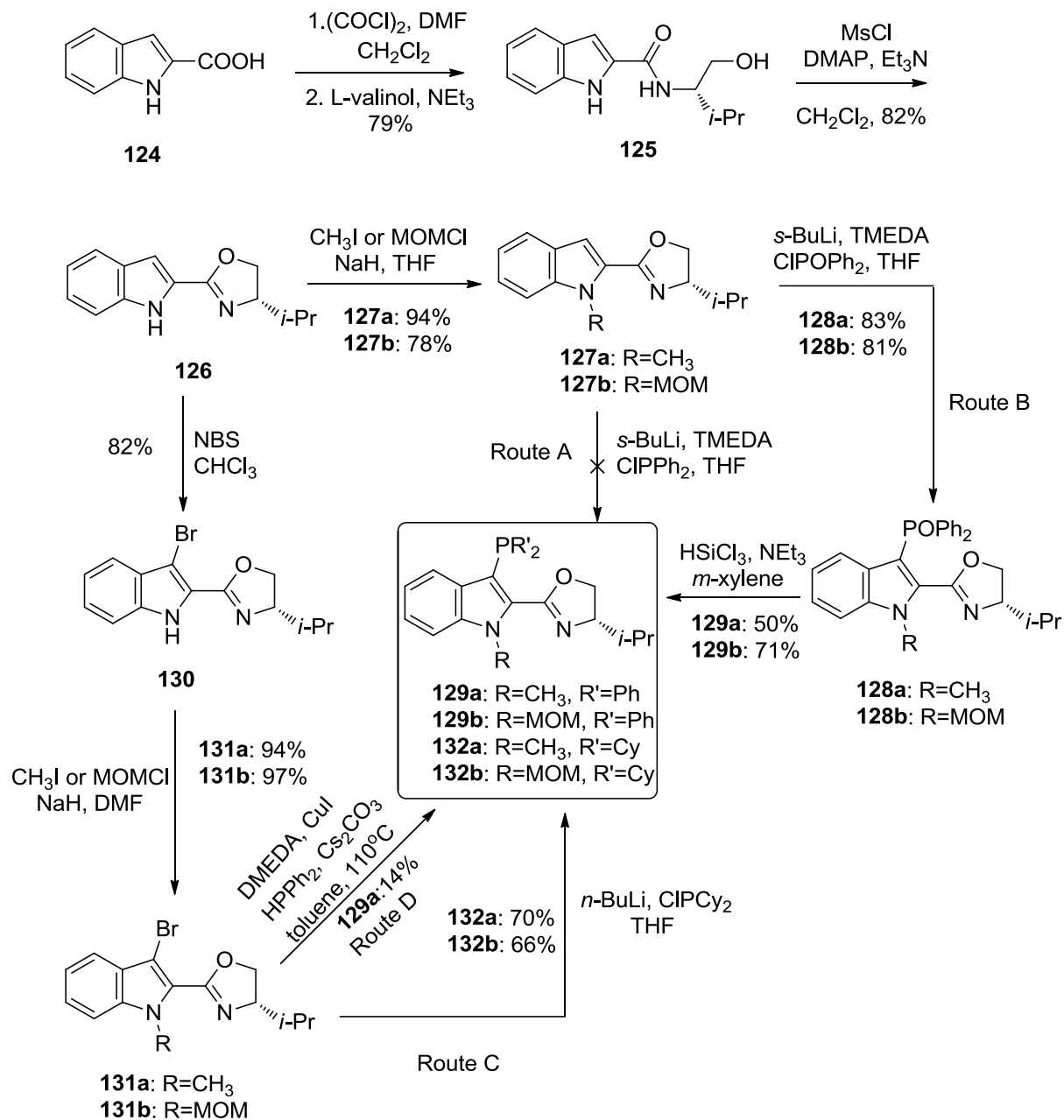
The accessible diversity and tunability of indole structure offer various possibilities for the design of IndPHOX ligands. During this study, structurally different IndPHOX ligands having an oxazoline moiety at the 1, 2, or 3-position, and a phosphine group at the 2 or 3-position, were designed and synthesized (Figure 10) [I - III].



**Figure 10** Design of IndPHOX ligands

Indole-2-carboxylic acid was converted into the corresponding acid chloride using oxalyl chloride, and the subsequent amidation with L-valinol provided **125**. Oxazoline formation was accomplished by treatment of MsCl in the presence of DMAP under basic condition to yield **126**.<sup>107</sup> *N*-functionalized compound **127** was treated with *sec*-BuLi and TMEDA, followed by electrophilic quenching by ClPPh<sub>2</sub> or ClPCy<sub>2</sub>, but no desired ligands were

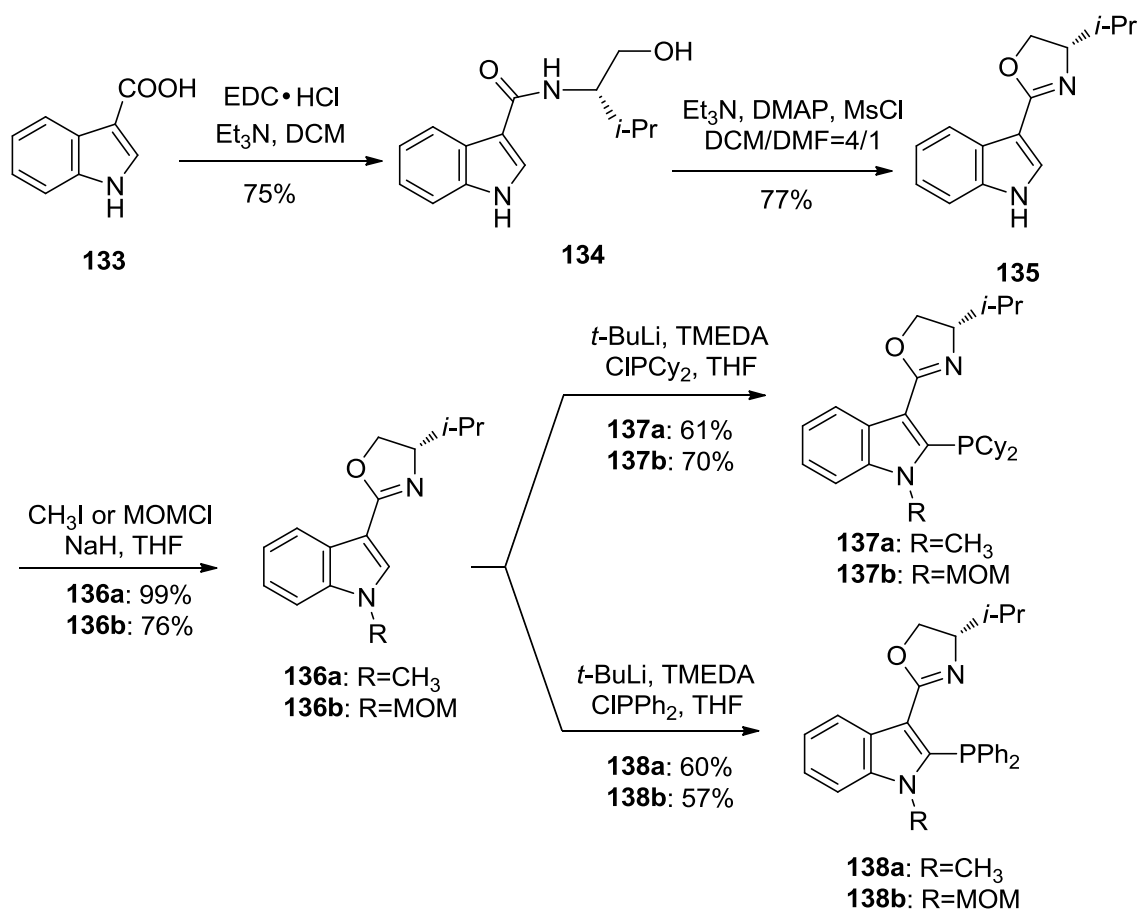
obtained (Route A, Scheme 59). Thus the lithiated **127a** and **127b** were treated with diphenylphosphinic chloride,<sup>133</sup> a more powerful P-electrophile, to afford **128a** and **128b** in good yields. Subsequent reduction by trichlorosilane in the presence of Et<sub>3</sub>N afforded ligands **129a** and **129b** in moderate yields (Route B).



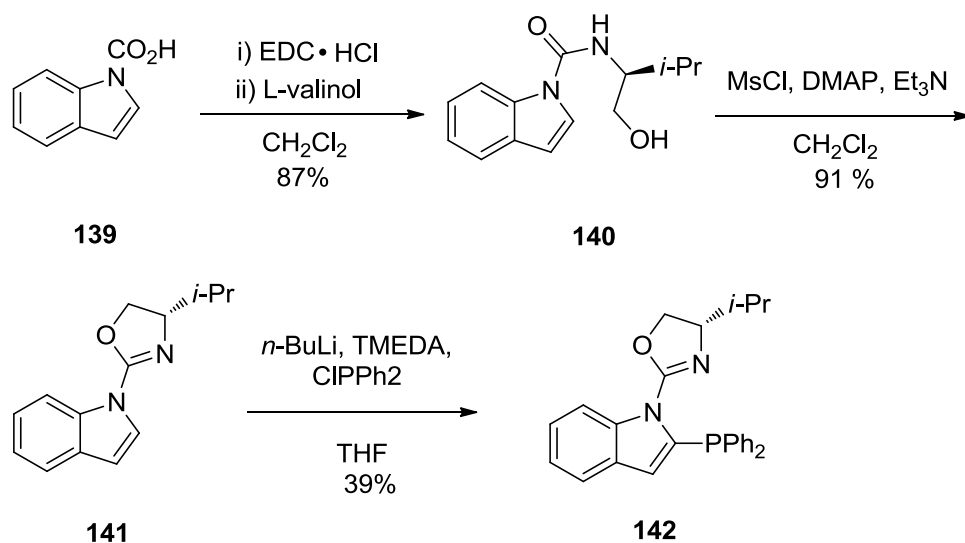
**Scheme 59** Synthesis of IndPHOX ligands of type I

In order to attempt the preparation of **132a** and **132b** by halogen–lithium exchange, compound **130** was brominated with NBS in  $\text{CHCl}_3$  in 82% yield. After the *N*-functionalization, the bromine–lithium exchange of **131** and treatment with  $\text{ClPCy}_2$ , ligands **132a** and **132b** were obtained (Route C). Moreover the Ullman type coupling approach<sup>30</sup> (Scheme 10) was investigated preliminarily to generate IndPHOX ligand **129a** in low yield (Route D).

A similar synthetic strategy was utilized for ligand type II and III starting from indole-3-carboxylic acid and indole-1-carboxylic acid, respectively (Schemes 60 and 61).



**Scheme 60** Synthesis of IndPHOX ligands of type II



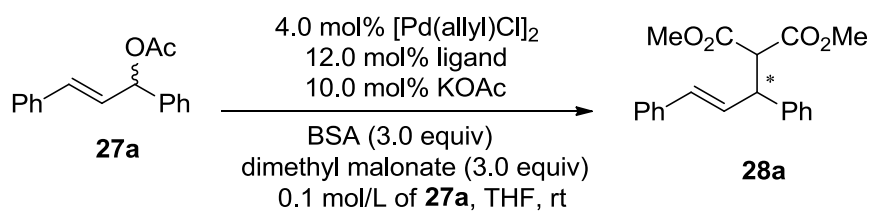
**Scheme 61** Synthesis of IndPHOX ligand of type III

## 3.2 Applications in allylic substitutions

### Application in allylic alkylation

IndPHOX ligands were first investigated in the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**27a**) with dimethyl malonate, a standard model reaction for evaluation of novel chiral ligands (Table 3) [I].

**Table 3** Asymmetric allylic alkylation with IndPHOX ligands



Entry	Ligand	Time (h)	Isolated Yield (%)	<i>ee</i> (%)	Configuration
1	<b>129a</b>	2	77	97	S
2	<b>129b</b>	2	79	97	S
3	<b>132a</b>	24	42	93	S
4	<b>132b</b>	24	63	90	S
5	<b>137a</b>	24	17	72	S
6	<b>137b</b>	24	17	86	S
7	<b>138a</b>	24	55	97	S
8	<b>138b</b>	0.5	95	98	S
9	<b>(R)-138b</b>	0.5	77	98	R
10 <sup>a</sup>	<b>142</b>	24	76	92	S

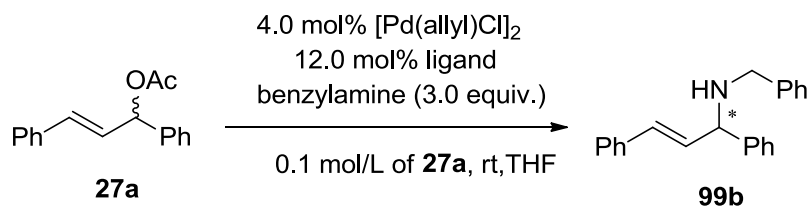
<sup>a</sup>) 3.0 mol% catalyst and 6.0 mol% ligand were used.

For ligands of type I, **129a** and **129b** with a diphenylphosphine group greatly increased the reaction rate compared to ligands **132a** and **132b** with dicyclohexylphosphine. All of the ligands provided excellent enantiomeric excess (entries 1-4). In contrast, the different phosphorus substituents of type II have a bigger influence on the results than type I. Although ligands **137a** and **137b** resulted in good *ee*, the yields were poor. While ligands **138a** and **138b** increased the yield, reaction rate and enantioselectivity (entries 5-8). The opposite configured ligand **(R)-138b** was synthesized utilizing the developed route from D-valinol. When **(R)-138b** was subjected to the alkylation reaction, **28a** was obtained with an (*R*)-configuration (entry 9). In addition good yield and enantioselectivity were also achieved using ligand **142** with lower amount of catalyst and ligand (entry 10).

## Application in Allylic Amination

We initiated the investigation for the asymmetric allylic amination of **27a** with benzylamine (Table 4, with 4.0 mol% catalyst, 12.0 mol% ligand and 0.1 mol/L of **27a**, not optimized reaction condition) [II]. Ligands **138a** and **138b** adorned with a 2-diphenylphosphine substituent demonstrated good catalytic activities, and achieved high yields (72% and 85%) and excellent *ee* values (both 94%) at room temperature (entry 7 and 9). When the reaction was performed at 40 °C, the yield was improved at the expense of enantioselectivity.



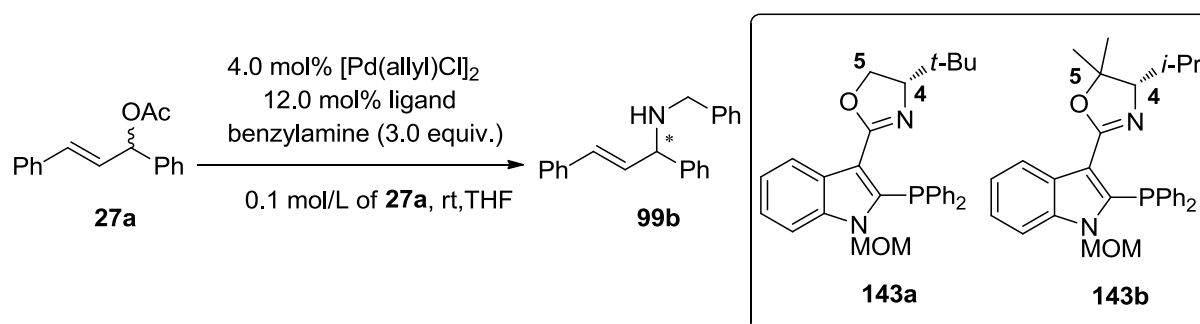
**Table 4** Asymmetric allylic amination with IndPHOX ligands

Entry	Ligand	Time (h)	Isolated yield (%)	<i>ee</i> (%)
1	<b>129a</b>	48	52	52
2	<b>129b</b>	48	21	89
3	<b>132a</b>	24	71	62
4	<b>132b</b>	24	84	65
5	<b>137a</b>	24	29	23
6	<b>137b</b>	48	21	39
7	<b>138a</b>	24	72	94
8 <sup>a</sup>	<b>138a</b>	2	98	66
9	<b>138b</b>	24	85	94
10 <sup>a</sup>	<b>138b</b>	2	87	88

<sup>a</sup>) The reaction was performed at 40°C.

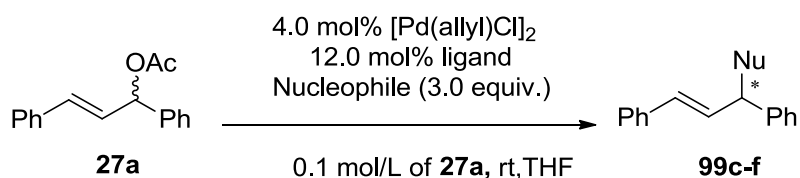
Generally, the use of PHOX-ligands with a *tert*-butyl group at C-4 in the oxazoline ring affords the highest enantioselectivities in various asymmetric catalysis.<sup>134</sup> It is reported that an effective substitute for *t*-Bu-PHOX-ligands can be obtained by modifying *i*-Pr-PHOX-ligands with two methyl substituents at C-5.<sup>135</sup> Therefore *tert*-butyl variant **143a** and ligand **143b** were synthesized based on the structure of ligand **138b**.

In asymmetric allylic amination of **27a** with benzylamine (Table 5), the *ee* values were further improved to 99% and 96% with **143a** and **143b**, respectively (entries 2 and 3). As a conclusion, ligands **138** and **143** resulted in better enantioselectivities than when using the *t*-Bu-PHOX ligand (entry 4) or any hetero-PHOX ligand reported previously.<sup>27</sup>

**Table 5** Asymmetric allylic amination with IndPHOX ligands

Entry	Ligand	Time (h)	Isolated yield (%)	ee (%)
1	<b>138b</b>	24	85	94
2	<b>143a</b>	24	78	99
3	<b>143b</b>	24	91	96
4	<b><i>t</i>-Bu-PHOX</b>	96	87	89

I continued the examination with various *N*-nucleophiles using ligand **143a** (Table 6). Excellent enantioselectivities were obtained when using 4-methoxybenzylamine and morpholine as nucleophiles (entries 1 and 2). Whereas the reactions with bulky potassium phthalimide and low nucleophilic aniline as nucleophiles did not proceed as expected (entries 3 and 4). These results might be rationalized in terms of steric hindrance of the catalytic centre caused by the *t*-butyl group in the oxazoline ring. Thus ligand **138b** was investigated in these two reactions, and the yields and enantioselectivities were both improved (entries 5-7).

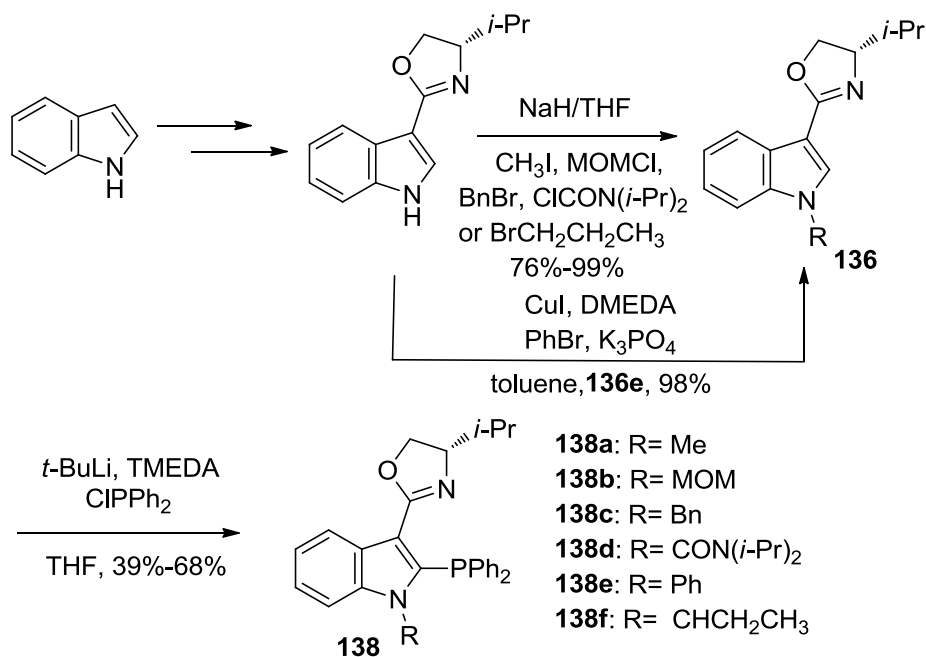
**Table 6** Asymmetric allylic amination with various *N*-nucleophiles

Entry	Ligand	Nucleophile	Time (h)	Product	Isolated yield (%)	<i>ee</i> (%)
1	<b>143a</b>	4-methoxy benzylamine	24	<b>99c</b>	91	98
2	<b>143a</b>	morpholine	24	<b>99d</b>	73	99
3	<b>143a</b>	potassium phthalimide	48	<b>99e</b>	21	84
4	<b>143a</b>	aniline	24	<b>99f</b>	24	42
5	<b>138b</b>	potassium phthalimide	48	<b>99e</b>	50	97
6 <sup>a</sup>	<b>138b</b>	potassium phthalimide	24	<b>99e</b>	73	97
7	<b>138b</b>	aniline	24	<b>99f</b>	51	89

<sup>a</sup>) 3.0 mol% catalyst and 6.0 mol% ligand were used with 0.2 mol/L of **27a**

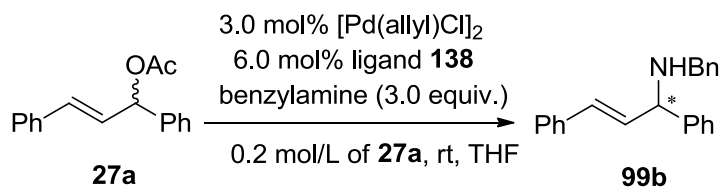
The *N1* modification can offer possibilities for tuning the electronic and steric properties of the indole-core. Recently *Kwong* has described the synthesis of indolyl-phosphine ligands with various groups at the *N1*-position, and the application of these in Suzuki-Miyaura coupling.<sup>97</sup>

A series of ligands **138** bearing various groups at the *N1* position were prepared for the further investigation due to the high efficiency of this ligand-type in allylic substitutions (Scheme 62) [III]. The ligands were investigated in the asymmetric allylic amination reaction between **27a** and benzylamine under further optimized reaction conditions (Table 7, with 3.0 mol% catalyst, 6.0 mol% **138** and 0.2 mol/L of **27a**). Good to excellent enantioselectivities and high yields were achieved. The introduction of a bulkier group at the *N1*-position gave better asymmetric induction at the cost of isolated yields.



**Scheme 62** Synthesis of IndPHOX ligand **138**

**Table 7** Asymmetric allylic amination with IndPHOX ligands



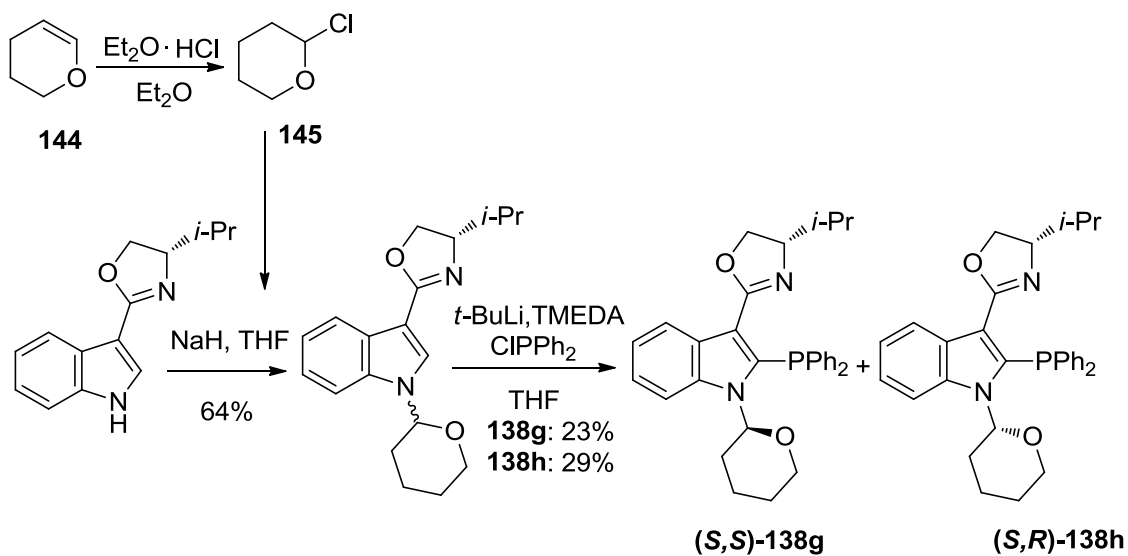
Entry	Ligand	Time (h)	Isolated Yield (%)	<i>ee</i> (%)
1	<b>138a</b>	18	97	77
2	<b>138b</b>	18	96	96
3	<b>138c</b>	24	93	98
4	<b>138d</b>	24	72	97
5	<b>138e</b>	24	84	97
6	<b>138f</b>	18	90	87
7	<b>138g</b> ( <i>S,S</i> )	24	81	97
8	<b>138h</b> ( <i>S,R</i> )	24	81	80

There is a significant difference in enantioselectivities obtained by ligands **138a** and **138b** having a -CH<sub>3</sub> and MOM-group at the *NI* position (entries 1 and 2). The two ligands have similar electronic and steric properties, and the positive effect of the oxygen atom in P,N,O-ligand structures as enhancement of the enantioselectivity has previously been reported.<sup>136</sup> Therefore I assume that besides the steric factor, the oxygen atom in the MOM group of ligand **143b** might contribute to the catalytic transition as well.

Ligand **138f** with a *N*-propyl substituent, which has similarity to *N*-MOM ligand **138b** in steric bulkiness, was synthesized and utilized in the asymmetric allylic amination to determine the existence of the oxygen effect. When compared to *N*-methyl ligand **138a**, the increased steric effect of **138f** led to an enhancement of the enantioselectivity at the expense of the yield (entries 1 and 6). On the other hand, *N*-MOM ligand **138b** bearing similar steric property as ligand **138f** still exhibited better enantiodiscriminating power (entries 2 and 6). A possible explanation would be that the oxygen atom in the MOM group stabilized the catalytic intermediate, and therefore increased conformational restriction, thus achieving high enantioselectivity.

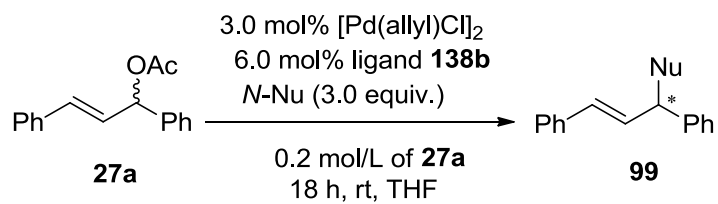
Two similar ligand diastereomers having a THP-group bound to the indole-nitrogen were further prepared (Scheme 63). Assuming the existence of the oxygen effect, the ligands could demonstrate altered enantiodiscriminating powers because of the different stabilizing abilities caused by dissimilar spatial positions of oxygen atom in the catalysis. The THP ligands **138g** and **138h** provided the product with the same yield (81%), but different enantioselectivities (97% and 80% *ee*%, respectively) in allylic amination of **27a** with benzylamine (Table 7, entries 7 and 8), which further indicated that the oxygen played a positive role in enantioselectivity.

The effect of electronic properties of *N*-nucleophiles on the reaction was surveyed using ligand **138b** (Table 8). Compared to benzylamine, the enantioselectivities maintained excellent (96%) when using either electron-donating 4-methoxybenzylamine or electron-withdrawing 4-chlorobenzylamine as nucleophiles with slightly decreased yields (89% and 91%, respectively, entries 2 and 3).



**Scheme 63** Synthesis of *N*-THP IndPHOX ligands

**Table 8** Asymmetric allylic amination with various *N*-nucleophiles

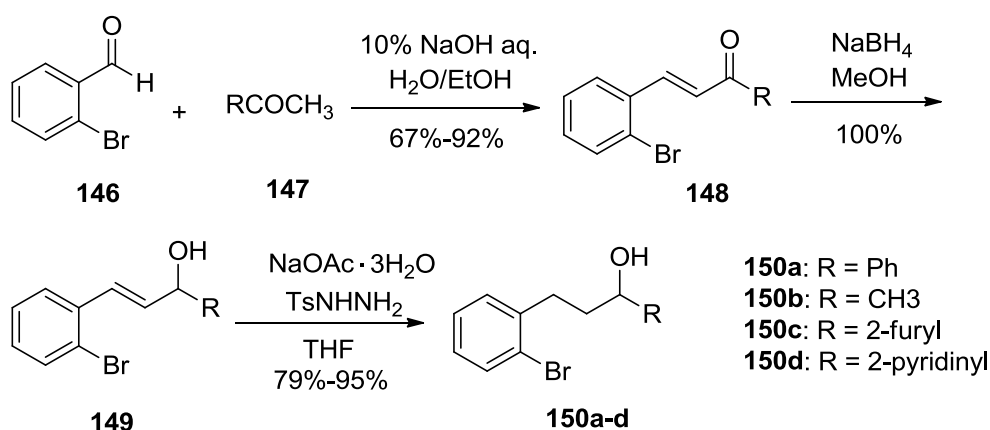


Entry	Nucleophiles	Product	Isolated Yield (%)	<i>ee</i> (%)
1	Benzylamine	<b>99b</b>	96	96
2	4-Methoxybenzylamine	<b>99g</b>	89	96
3	4-Chlorobenzylamine	<b>99h</b>	91	96

### 3.3 Synthesis of 2-aryl substituted Chromans

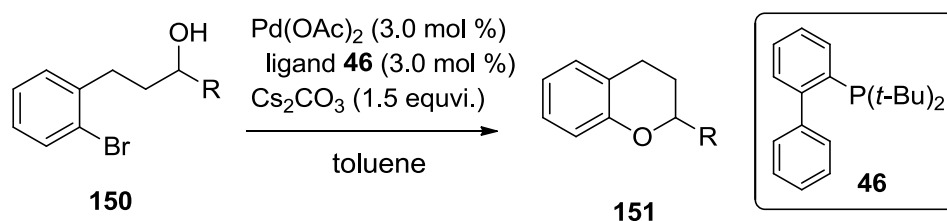
The synthetic approaches toward 2-substituted chromans (tetrahydrobenzopyran) have attracted considerable attention continuously because they constitute the core of numerous natural products exhibiting a wide spectrum of biological activities.<sup>137</sup> In this study I developed a new synthetic route mainly for 2-aryl substituted chromans with the intramolecular cyclization of aryl bromides as the key step [IV].

Chalcones **148**, prepared from commercially available 2-bromoaldehyde and ketones **147**, were readily converted to the corresponding alcohols **149** in quantitative yields using sodium borohydride (Scheme 64). The following reduction of allylic double bond with *para*-toluenesulfonyl hydrazide and sodium acetate trihydrate led to the desired *ortho*-bromophenylpropanols **150a-d** in high yields without notable cleavage of aryl-bromide bond.



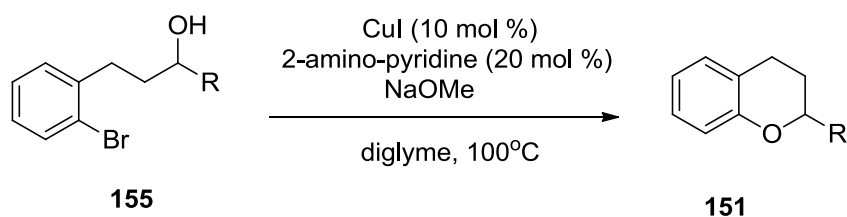
**Scheme 64** Synthesis of compounds **150a-d**

The subsequent intramolecular C-O bond formation was first studied with palladium-catalyzed cyclization employing biaryl ligand **46** (Table 9).<sup>138</sup> The phenyl and methyl substituted chromans **151a** and **151b** were obtained in good yields (71% and 79%, respectively, entry 1 and entry 2). Whereas the results for 2-furyl-chroman **151c** (entry 3) and 2-pyridyl-chroman **151d** (entry 4) were poor due to the formation of the  $\beta$ -hydride elimination byproduct<sup>138</sup> and palladium catalyst deactivation caused by the pyridinyl group, respectively.

**Table 9** Palladium-catalyzed intramolecular cyclization

Entry	Temp. (°C)	Time (h)	Product	Isolated Yield (%)
1	90	24	<b>151a</b>	71
2	65	24	<b>151b</b>	79
3	90	24	<b>151c</b>	43
4	90	96	<b>151d</b>	16

An intramolecular Ullmann alkoxylation approach was applied for the cyclization of **151** to overcome the limitation of the palladium-catalyzed method (Table 10). Despite of the low yield of 2-alkyl chroman **151b** (44%, entry 2), the method worked well to afford other 2-aryl chromans in high yields (78%, 74% and 88% respectively, entries 1, 3 and 4).

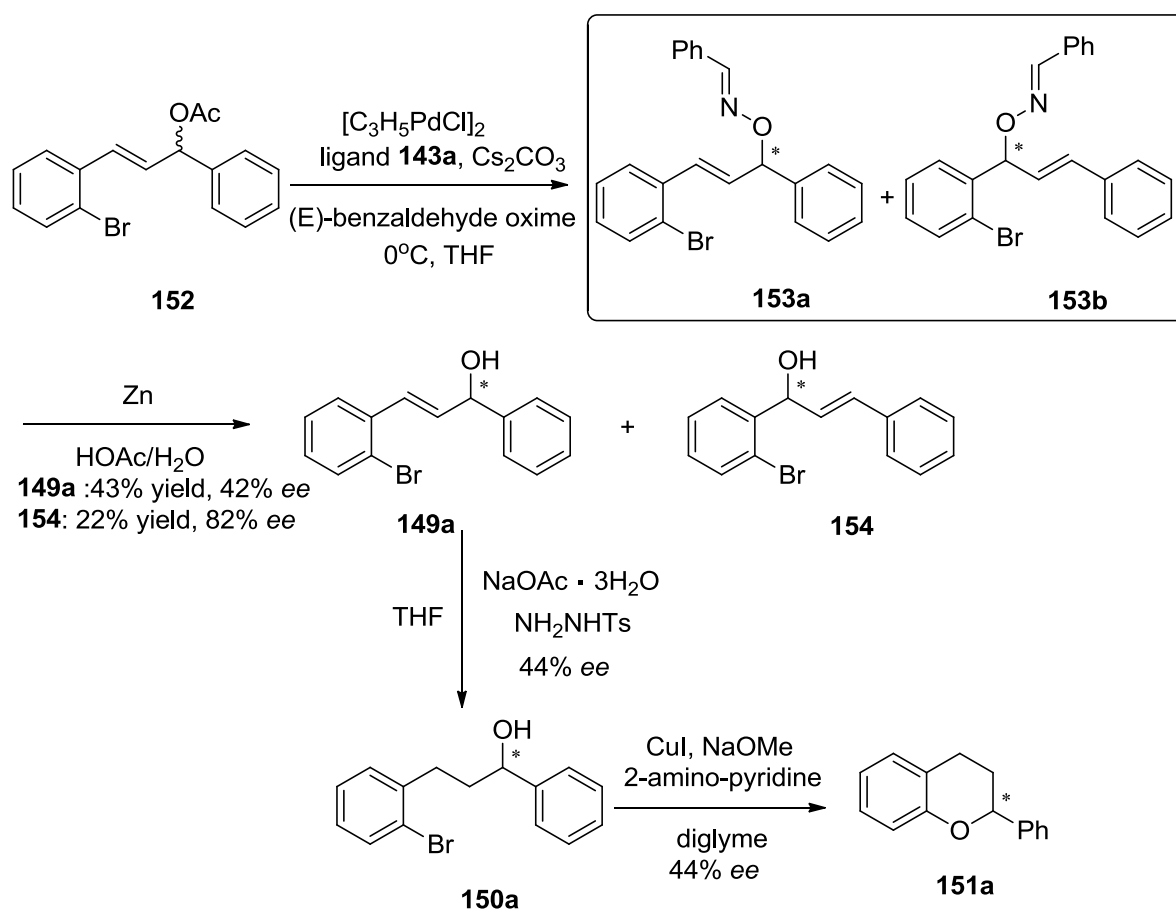
**Table 10** Copper-catalyzed intramolecular cyclization

Entry	$\text{NaOMe}$ (equiv.)	Time (h)	Product	Isolated Yield (%)
1	1.5	24	<b>151a</b>	78
2	2.1	24	<b>151b</b>	44
3	1.5	48	<b>151c</b>	74
4	1.5	24	<b>151d</b>	88



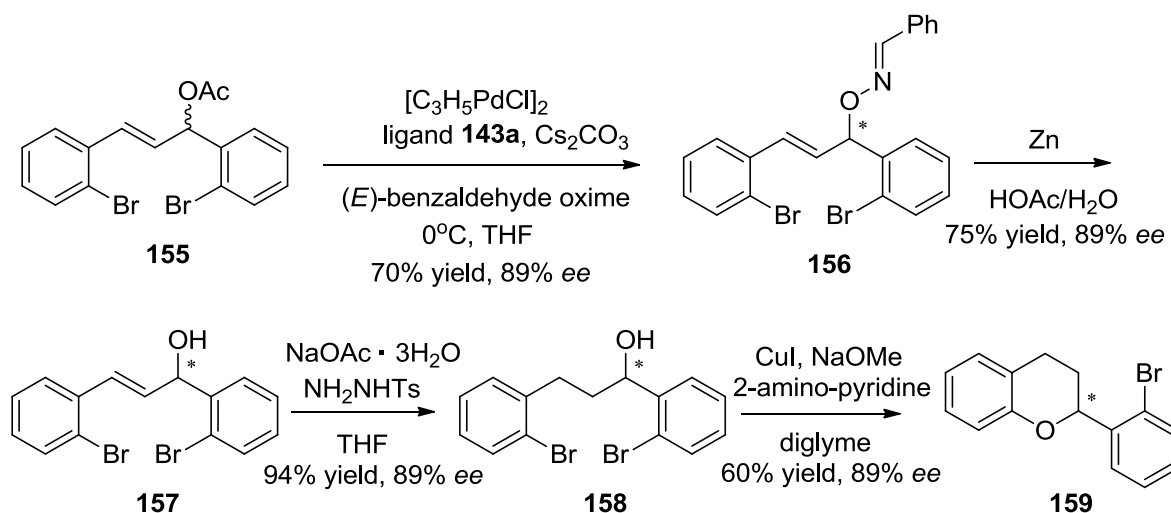
Based on the successful preparation of racemic 2-aryl substituted chromans, I further studied the synthesis of chromans with stereo-control at C-2 *via* the chiral alcohol **149**, which could be prepared by an asymmetric allylic etherification procedure using IndPHOX ligands.

Preliminary experiments were carried out for chiral 2-phenylchroman (Scheme 65). The catalytic reaction utilizing IndPHOX ligand **143a** with (*E*)-benzaldehyde oxime was performed, followed by the treatment of Zinc powder, to yield linear alcohol **149a** in moderate enantioselectivity (41%). After reduction of double bond, followed by the copper-catalyzed cyclization, chiral chroman **151a** was achieved in 44% enantioselectivity without loss of the original enantiometric purity.



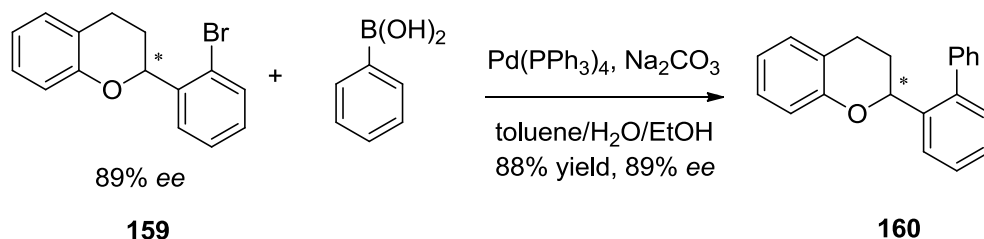
**Scheme 65** Synthesis of chiral chroman **151a**

It is noteworthy that the branched alcohol **154**, derived from the attack of the nucleophile to the more sterically hindered position by  $S_N2'$  mechanism, was obtained in good *ee* value (82%). This inspired me to continue the investigation with (*E*)-1,3-bis(2-bromophenyl)allyl acetate (**155**), which was chosen based on the following aspects: i) to suppress regioselectivity; ii) to enhance the enantioselectivity; and iii) to afford diversity to chroman derivatives. As expected, alcohol **157** was prepared in high enantioselectivity (89%), which was further converted to chroman **159** (Scheme 66).



**Scheme 66** Synthesis of chiral chroman **159**

The adjacent 2-bromophenyl group in the structure of **159** offers various possibilities for further applications *via* catalytic transformations. A Suzuki-coupling reaction was performed with chroman **159** and phenylboronic acid, and the reaction proceeded well to afford product **160** in high yield (88%) without loss of *ee* (Scheme 67).



**Scheme 67** Suzuki-coupling reaction with chroman **159** and phenylboronic acid

## 4 Conclusions

Novel chiral indole-phosphine oxazoline ligands have been designed and synthesized conveniently from indole carboxylic acids. IndPHOX ligands demonstrated high catalytic activity in Pd-catalyzed allylic alkylation. The ligands containing a diphenylphosphine-group resulted in higher enantioselectivities than the ligands containing a dicyclohexylphosphine moiety. The ligands with a diphenylphosphine group at the 2-position and an oxazoline moiety at the 3-position of the indole skeleton were highly efficient in Pd-catalyzed allylic amination. Good to excellent enantioselectivities of up to 99% were achieved using various nucleophiles, including highly nucleophilic morpholine, sterically bulky potassium phthalimide and low nucleophilic aniline. The effects of the *NI*-substituent to the reaction rate, yield and enantioselectivity were investigated in asymmetric allylic amination by utilizing a series of IndPHOX ligands with different substituents attached to the position. In addition it was found that by introducing an *N*-alkoxymethyl group in the ligand structure, the enantioselectivity in the catalytic reaction could be improved using ligands with a MOM-group or a (*S*)-THP group. An IndPHOX ligand was also utilized in a synthesis route to prepare enantiomerically pure 2-aryl-substituted chromans. Starting from readily available starting materials, the route was accomplished *via* intramolecular cyclization of aryl bromides as the key step. The chirality-control at C2-position was achieved *via* asymmetric allylic etherification.

## 5 References

1. Roth, B. D.; Mich, A. A. US5273995.
2. Savi, P.; Zacharyus, J. L.; Delesque-Touchard, N.; Labouret, C.; Herve, C.; Uzabiaga, M. F.; J. M.; Pereillo, Culouscou, J. M.; Bono, F.; Ferrara, P.; Herbert, J. M. *Proceedings of the National Academy of Sciences of the USA* **2006**, *103*, 11069-11074.
3. Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998-2007.
4. Noyori, R. *Chem. Commun.* **2005**, *14*, 1807-1811.
5. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
6. Japan: Takasago to Expand L-Menthol Production in Iwata Plant. *FlexNews*. **10/01/2008**
7. Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15-32.
8. Burk, M. J.; Gross, M. F.; Harper, G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37-44.
9. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.
10. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92-138.
11. Yoon, P. Y.; Jacobsen, E. N. *Science* **2003**, *299*, 1691-1693.
12. Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505-2550.
13. McManus, H. A.; Guity, P. J. *Chem. Rev.* **2004**, *104*, 4151-4202.
14. Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1-C3.
15. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345.
16. Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825-3827.
17. McManus, H. A.; Barry, S. M.; Andersson, P. G.; Guiry, P. J. *Tetrahedron* **2004**, *60*, 3405-3407.
18. Chai, Z.; Liu, Z.-Y.; Wu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2442-2447.
19. Capito, E.; Bernardi, L.; Comes-Franchini, M.; Fini, F.; Fochi, M.; Pollicino, S.; Ricci, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3232-3240.
20. Endeshaw, M. M.; Bayer, A.; Hansen, L. K.; Gautun, O. R. *Eur. J. Org. Chem.* **2006**, *23*, 5249-5259.
21. Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387-4390.
22. Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099-6102.
23. von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566-568.

24. Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1772.
25. Dawson, G. J.; Frost, C. G.; Coote, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.
26. Desimoni, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119-3154.
27. Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083-2085.
28. Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron*, **1996**, *52*, 7547-7583.
29. Sedinkin, S. L.; Rath, N. P.; Bauer, E. B. *J. Organomet. Chem.* **2008**, *693*, 3081-3091.
30. Tani, K.; Behenna, D.C.; McFadden, R. M.; Stoltz, B.M. *Org. Lett.* **2007**, *9*, 2529-2531.
31. Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535-2546.
32. Bower, J. F.; Williams, J. M. J. *Synlett* **1996**, 685-686.
33. Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 200-202.
34. Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338-1345.
35. Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F.M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887-892.
36. Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897-2899.
37. Goulioukina, N.S.; Dolgina, T.y.M.; Bondarenko, G.N.; Beletskaya, I.P.; Ilyin, M.M.; Davankov, V.A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397-1401.
38. Lu, S. M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920-8923.
39. Lu, W. J.; Chen, Y. W.; Hou, X. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133-10136.
40. Naud, F.C.; Malan, C.; Spindler, F.; Rugeberg, C.; Schmidt, A.T.; Blaser, H.U. *Adv. Synth. Catal.* **2006**, *348*, 47-50.
41. Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381-1384.
42. (a) Zhang, W.; Xie, F.; Yoshinaga, H.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett.* **2006**, 1185-1188; (b) Frolander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882-9891; (c) Smidt, S. S.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023-2026.
43. (a) Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450-454; (b) Blanc, C.; Hannedouche, J.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2003**, *44*, 6469-6473; (c) End, N.; Berens, U.; Di Pietro, P.; Cozzi, P.G. *Tetrahedron: Asymmetry* **2004**, *15*, 2235-2239; (d) Xu, G. P.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811-2814.
44. (a) Fitzpatrick, M. O.; Muller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, *12*, 1889-1895; (b) Fitzpatrick, M. O.; Coyne, A. G.; Guiry, P. *Synlett* **2006**, 3150-3154; (c) Kilroy, T.

- G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synlett* **2004**, *1*, 106-110; (d) Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synthesis* **2004**, 1879-1888.
45. (a) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159-2163; (b) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833-836.
46. Coyne, A. G.; Guiry, P. *Tetrahedron Lett.* **2007**, *48*, 747-750.
47. Coyne, A. G.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 199-207.
48. (a) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601-1614; (b) Aygun, A.; Pindur, U. *Curr. Med. Chem.* **2003**, *10*, 1113-1127; (c) Gupta, L.; Talwar, A.; Chauhan, M. S. *Curr. Med. Chem.* **2007**, *14*, 1789-1803; (d) Sharma, V.; Kumar, P.; Pathak, D. *Journal of Heterocyclic Chemistry* **2010**, *47*, 491-502; (e) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489-4497.
49. Orhan, S.; Sultan, U.; Muzaffer, C. *Colloid Polym. Sci.* **2011**, *289*, 903-909.
50. Balon, M.; Carmona, M. C.; Munoz, M. A.; Hildalgo, J. *Tetrahedron* **1989**, *45*, 7501-7504.
51. Bordwell, F. G.; Zhang, X.; Cheng, J. P. *J. Org. Chem.* **1991**, *56*, 3216-3219.
52. (a) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106-5110; (b) Yang, Y.; Martin, A. R.; Nelson, D. L.; Regan, J. *Heterocycles* **1992**, *34*, 1169-1175; (c) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815-817; (d) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899-1902.
53. (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920; (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608-9644; (c) Joucla, L.; Djakovitch, L.; *Adv. Synth. Catal.* **2009**, *351*, 673-714; (d) Zeng, M.; You, S. L. *Synlett* **2010**, 1289-1301.
54. (a) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, *5*, 499-500; (b) Kikugawa, Y.; Miyake, Y. *Synthesis* **1981**, 461-462.
55. (a) Kikugawa, Y. *Synthesis* **1981**, 460-461; (b) Dhanak, D.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1986**, *5*, 2181-2186.
56. Illi, V. O. *Synthesis* **1979**, 136.
57. Khdour, O.; Ouyang, A.; Skibo, E. B. *J. Org. Chem.* **2006**, *71*, 5855-5863.
58. Benson, S. C.; Li, J. H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285-5287.
59. Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J. *J. Heterocycl. Chem.* **1987**, *24*, 811-815.
60. Perregaard, J.; Andersen, K.; Hyttel, J.; Sanchez, C. *J. Med. Chem.* **1992**, *35*, 4813-4822.
61. Antilla, J.; Klapars, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684-11688.

62. (a) Ma, D.; Cai, Q. *Synlett* **2004**, 128-130; (b) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496-499; (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164-5173.
63. Mann, G.; Hartwig, J. F.; Driver, F. M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827-828.
64. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580.
65. Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403-1406.
66. Lebedev, A. Y.; Izmer, V. V.; Kazyulkin, D. N.; Beletskaya, I. P.; Voskoboinikov, A. Z. *Org. Lett.* **2002**, *4*, 623-626.
67. Mao, J.; Hua, Q.; Guo, J.; Shi, D.; Ji, S. *Synlett* **2008**, 2011-2016.
68. Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935-5938.
69. Sniecus, V. *Chem. Rev.* **1990**, *90*, 879-933.
70. Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155-302.
71. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495-2497.
72. Çavdar, H.; Saraçoğlu, N. *Tetrahedron* **2005**, *61*, 2401-2405.
73. Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem. Eur. J.* **2008**, *14*, 3539-3542.
74. Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897-2900.
75. Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174.
76. Saracoglu, N. *Top Heterocycl Chem.* **2007**, *11*, 1-61.
77. Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110-1114.
78. Nair, V.; Nandialath, V.; Abhilash, K. G.; Suresh, E. *Org. Biomol. Chem.* **2008**, *6*, 1738-1742.
79. Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438-15439.
80. Dujardin, G.; Poirer, J.-M. *Bull. Soc. Chim. Fr.* **1994**, *131*, 900-909.
81. Hong, C.; Firestone, G. L.; Bjeldanes, I. F. *Biochem. Pharmacol.* **2002**, *63*, 1085-1097.
82. (a) Li, Z.; Shi, Z.; He, C.; *J. Organomet. Chem.* **2005**, *690*, 5049-5054; (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358-1373; (c) Barluenga, J.; Fernandez, A.; Rodriguez, F.; Fananas, J.; *J. Organomet. Chem.* **2009**, *694*, 546-550.
83. Liu, C.; Han, X.; Wang, X.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700-3701.
84. Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541-2569.
85. Westermaier, M.; Mayr, H. *Chem. Eur. J.* **2008**, *14*, 1638-1647.
86. Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311-314.
87. Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158-3175.

88. (a) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324-3330; (b) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325-7334.
89. Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10-11.
90. Mitsudo, M.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939-3942.
91. Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717-8721.
92. Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899-5904.
93. Malapel-Andrieu, B.; Merour, J.-Y. *Tetrahedron* **1998**, *54*, 11079-11094.
94. Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415-2419.
95. Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983-2990.
96. So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 2795-2798.
97. Lee, H. W.; Lam, F. L.; So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7436-7439.
98. So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803-7806.
99. So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059-8063.
100. So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem. Eur. J.* **2011**, *17*, 761-765.
101. Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2010**, *75*, 5109-5112.
102. So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2009**, *11*, 317-320.
103. Choy, P. Y.; Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem. Eur. J.* **2010**, *16*, 9982-9985.
104. So, C. M.; Zhou, Z. Y.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402-6406.
105. Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918-8922.
106. Yeung, P. Y.; Tsang, C. P.; Kwong, F. Y. *Tetrahedron Lett.* **2011**, *52*, 7038-7041.
107. Oila, M. J.; Tois, J. E.; Koskinen, M. P. *Synth. Commun.* **2008**, *38*, 361-370.
108. Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolo, F. *J. Org. Chem.* **2000**, *65*, 8340-8347.
109. Wassenaar, J.; Reek, J. N. H. *Dalton Trans.* **2007**, *34*, 3750-3753.
110. Wassenaar, J.; Kuil, M.; Reek, J. N. H. *Adv. Synth. Catal.* **2008**, *350*, 1610-1614.



111. Wassenaar, J.; Zutphen, S.; van Mora, G.; Le Floch, P.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Organometallics* **2009**, *28*, 2724-2734.
112. Benincori, T.; Brenna, E.; Sannicolb, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T.; Zotti, G. *J. Organomet. Chem.* **1997**, *529*, 445-453.
113. Berens, U.; Brown, J. M.; Long, J.; Seike, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285-292.
114. Mino, T.; Komatsu, S.; Wakui, K.; Yamada, H.; Saotome, H.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2010**, *21*, 711-718.
115. (a) Kuuloja, N.; Tois, J.; Franz é n, R. *Tetrahedron: Asymmetry* **2011**, *22*, 468-475; (b) Kuuloja, N.; Vaismaa, M.; Franz é n, R. *Tetrahedron* **2012**, *68*, 2313-2318.
116. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422; (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258-297; (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2943; (d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427-440.
117. Trost, B. M.; Verhoeven, R. *J. Org. Chem.* **1976**, *41*, 3215-3216.
118. Matsushita, H.; Negishi, E.-I. *J. Chem. Soc., Chem. Commun.* **1982**, *3*, 160-161.
119. (a) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, *9*, 141-1420; (b) Jumnah, R.; Williams, J. M. J.; Williams, A. C. *Tetrahedron Lett.* **1993**, *34*, 6619-6622; (c) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758-4763; (d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301-6311.
120. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444-458.
121. (a) Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087-11110; (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173-1792.
122. Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200-4201.
123. (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301-6311; (b) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871.
124. von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1994**, *5*, 573-584.
125. Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447-4450.
126. Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297-6298.
127. Nemoto, T.; Tamura, S.; Sakamoto, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1751-1759.
128. Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797-4800.

129. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074-9075.
130. Lam, F. L.; Tin-Lok Au-Yeung, T.; Kwong, F. Y.; Zhou, Z. Y.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 1280-1283.
131. (a) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y.; *Org. Lett.* **2004**, *6*, 4631-4634; (b) Miyabe, H.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 2148-2153; (c) Miyabe, H.; Matsumura, A.; Yoshida, K.; Takemoto, Y. *Tetrahedron* **2009**, *65*, 4464-4470.
132. Cao, Z. P.; Liu, Z. Q.; Liu, Y. L.; Du, H. F. *J. Org. Chem.* **2011**, *76*, 6401-6406.
133. Gray, M.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **1996**, *35*, 1558-1560.
134. (a) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162-16163; (b) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873-6876.
135. Bédanger, é; Pouliot, M.-F.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 2201-2204.
136. Frölander, A.; Moberg, C. *Org. Lett.* **2007**, *9*, 1371-1374.
137. Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465-475.
138. Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202-12206.

## Paper I

### **Preparation of indole-phosphine oxazoline (IndPHOX) ligands and their application in allylic alkylation**

Yu Wang, Antti Hännänen, Jan Tois, Robert Franzén

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## Paper II

### **Utilization of IndPHOX-ligands in palladium-catalysed asymmetric allylic aminations**

Yu Wang, Matti J. P. Vaismaa, Antti M. Hänninen, Jan E. Tois, Robert Franzén

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## Paper III

### ***N*<sup>1</sup>-Functionalized Indole-Phosphane Oxazoline (IndPHOX) Ligands in Asymmetric Allylic Substitution Reactions**

Yu Wang, Matti J. P. Vaismaa, Kari Rissanen, Robert Franz 

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## Paper IV

### **Synthesis of 2-Aryl-Substituted Chromans by Intramolecular C–O Bond Formation**

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