Development of Novel Bimetallic Chiral Complexes & Formation of Cyclic Aminals under Friedländer Conditions

by

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A Thesis submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Master of Science

Graduate Program in Chemistry

written under the direction of

Dr. Daniel Seidel

and approved by

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New Brunswick, New Jersey

[May, 2010]

ABSTRACT OF THE THESIS

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The design of new chiral binuclear ligands was undertaken to address the challenge of catalyzing nucleophilic additions to simple α,β- unsaturated carbonyl compounds. The designs were based on natural bimetallic enzymes as well as on synthetic achiral bimetallic complexes. Ligands with different electronic and structural properties were synthesized and a variety of transition metal complexes prepared. Their catalytic activities were tested in 1,4-additions of indole to α,β-unsaturated carbonyl compounds. Single X-ray crystallography was used to gain an insight into the nature of these newly developed chiral bimetallic complexes. Efforts were made to synthesize chiral bimetallic complexes derived from amino indanol.

A new reaction methodology was investigated to form cyclic aminals from aminobenzaldehydes and secondary amines. The methodology was shown to be successful for broad range of substrates. L-proline could be used in place of secondary amines in a decarboxylative variant of the reaction. The use of microwave irradiation was explored as a means to extend the scope of this methodology.

Acknowledgement

My earnest thanks to Professor Daniel Seidel for giving me the opportunity to pursue my Master's research in his laboratory. He has consistently encouraged me to endeavor harder, think deeper, and grow as a chemist and a person while working in his group. Thanks are due, as well, to the members of my Masters committee, Professor Spencer Knapp and Professor Kai Hultzsch, who have been generous with their time and resources during my stay at Rutgers. I would also like to thank Professor Lawrence Williams for being kind with his time and advice all through the last 3 years.

I also thank Dr. Thomas Emge for all his guidance and help with crystallography. The members of the Seidel group, both past and present, are owed a great debt of gratitude for providing such a pleasurable environment; Indu, Madhu, Le, Chen, Eric, Deepankar, Matt, Nisha, Marlena, and especially, Chandra & Sandip. You've all had a huge hand in making this happen, and I will definitely miss working with you.

Table of Contents

List of Figures

Chapter 1

Chapter 2

List of Schemes

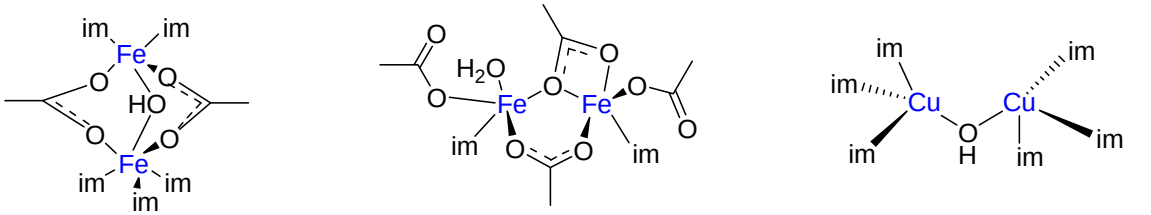
Chapter 1

Lists of tables

Chapter 1

Introduction

Chiral moieties are often essential fragments of biologically active drug molecules. This enhances the necessity of methods and processes, which provides controlling absolute stereochemistry in the synthesis of these compounds. Asymmetric catalysis is perhaps the most efficient way of obtaining these chiral targets. Catalytic asymmetric methods are potentially more economical and environmentally benign than methods using stoichiometric amounts of reagents. Lewis acidic metal containing chiral metal complexes allow us to achieve more general and flexible processes for asymmetric synthesis. The design of the ligand plays a major role in metal assisted asymmetric catalysis as binding activity as well as selectivity of the metal is tuned by the design of the chiral ligand. A delicate equilibrium between the electronic and steric properties of the catalyst determines the reaction efficiency. Most chiral catalysts nowadays are mononuclear metal complexes. These mononuclear metal complexes are extensively used in various asymmetric transformations.[1]



Hemerythrin active site (deoxy form)

Methane monooxygenase active site (reduced form)

Catechol Oxidase active site

Figure 1.1

Typically, these complexes require chelating substrates to be selective. We propose synthesizing bimetallic catalysts that would provide enantiomerically enriched products without any such restriction. Interestingly, chiral bimetallic complexes had received little

attention though numerous examples of bimetallic enzymes[2] can be found in nature. Hemerythrin (Fe-Fe)[3], methane oxygenase (Fe-Fe)[4], urease (Ni-Ni)[5,6], catechol oxidase (Cu-Cu)[7], and arginase (Mn-Mn)[8] are some of the bimetallic enzymes discovered in

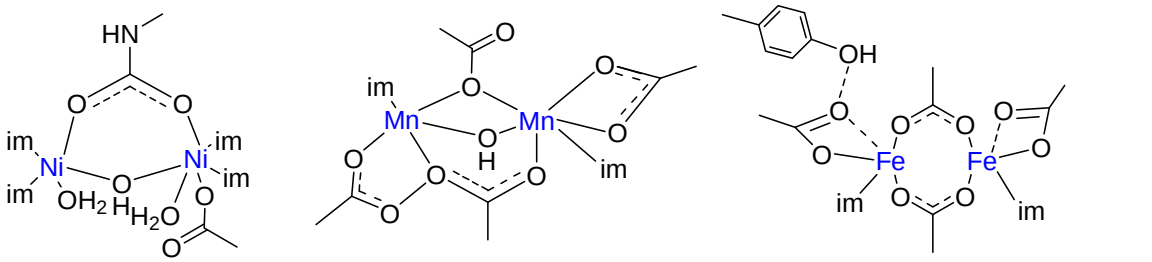


Figure 1.2

nature (Figure 1.1 & 1.2). One of the bimetallic enzymes that is extensively studied and modeled is urease. Urease consists of a bis nickel active site for the hydrolysis of urea to carbamate and ammonia. The identification of bimetallic complexes in nature inspired the inorganic as well as supramolecular communities to synthesize and study several achiral bimetallic complexes.[9-15] The Lippard group synthesized ligand **2 (**Figure 1.3a) which forms a bimetallic complex with nickel to hydrolyze amide or urea substrates similar to urease.[10,11] A bis (pyridine-armed) acylic Schiff base ligand (**1**) was synthesized by the Brooker group.[14,15] This achiral ligand having six nitrogen donor sites (Figure 1.3) provided bimetallic complexes with metals like copper, cobalt etc. The X-ray crystal structure shows a hydroxyl group bridged between the two metals and additional anions or coordinating solvent molecules fill up the remaining coordination sphere in these achiral bimetallic complexes.

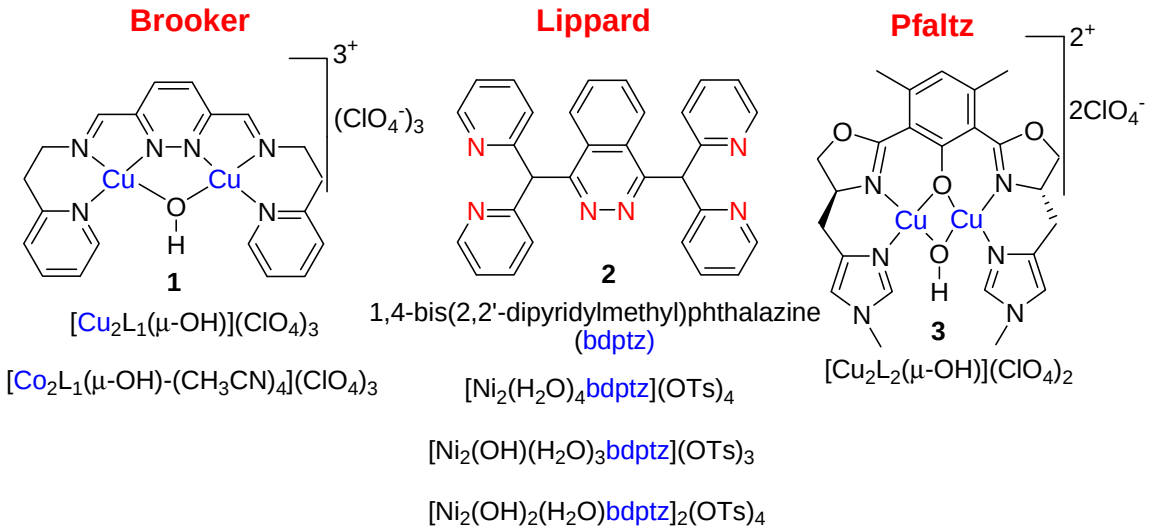


Figure 1.3a

The Pfaltz group[16] extensively studied structures and properties of transition metal complexes derived from phenoxide bridged C_2 symmetric binucleating ligands (Figure 1.3a). Recently, syntheses of dinuclear complexes derived from phenoxy (**4**) and pyridazine bridge (**5**) containing achiral ligands (Figure 1.3b) were reported.[17] These achiral dinuclear ligands were shown to coordinate with two palladium metals.

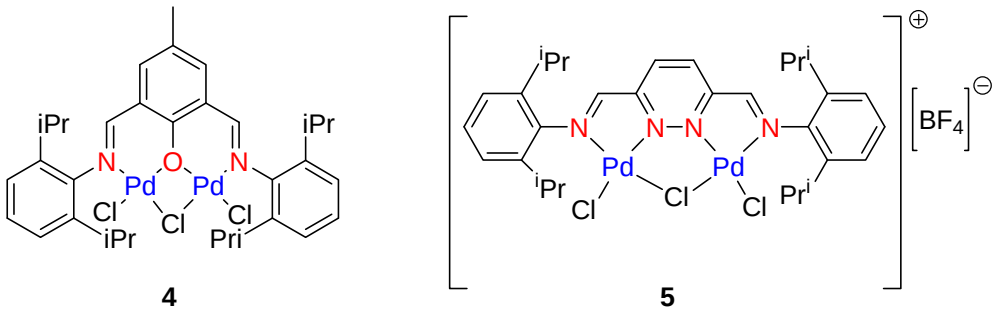
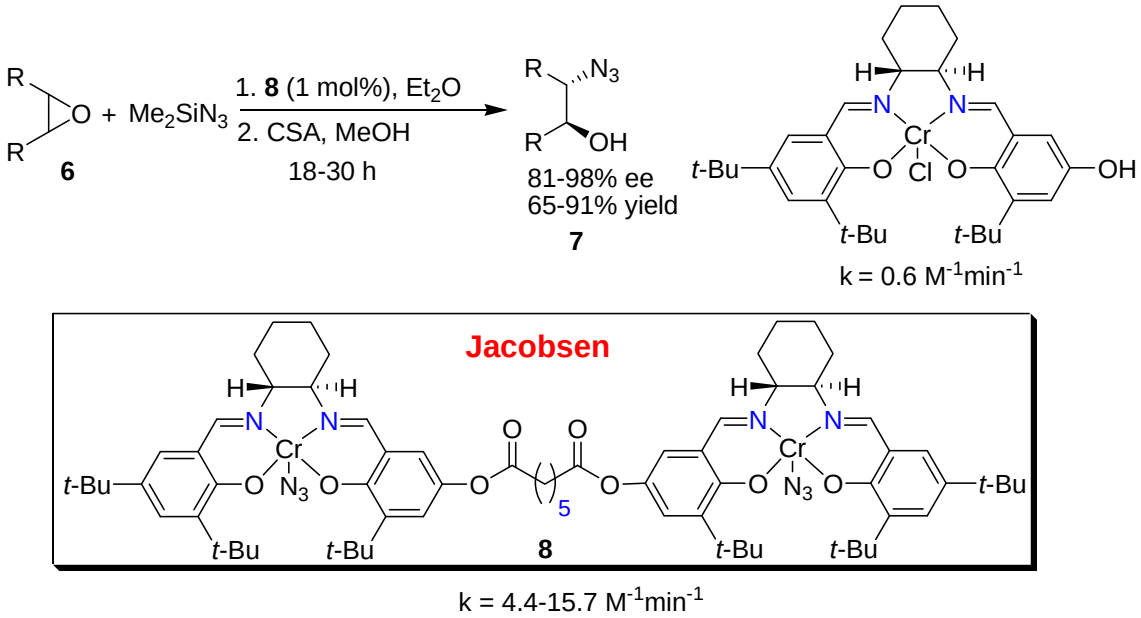


Figure 1.3b

X-ray crystal structures of these bispalladium complexes showed two point binding for each metal and a chloride bridged between the two metals. In addition to these bimetallic complexes, several chiral bimetallic[18-21] as well multimetallic[22-24] complexes were prepared and studied which facilitated useful asymmetric transformations. Most of these

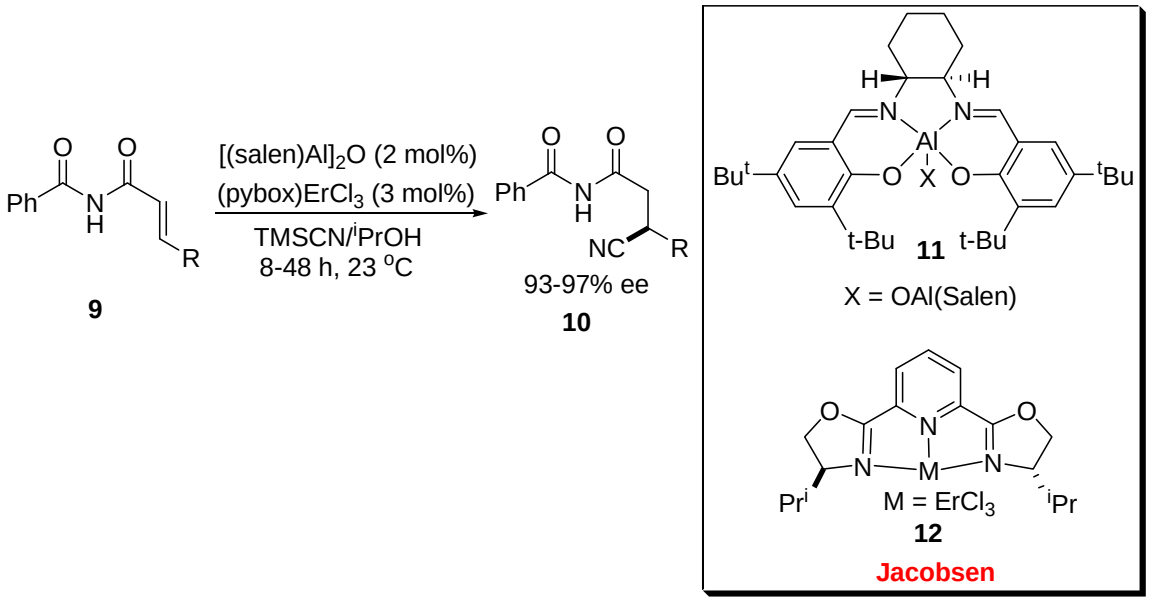
chiral catalysts were used in reactions that required two different reaction partners to be activated. The Jacobsen[18] group showed the advantage of chiral bimetallic complexes as they demonstrated successful asymmetric ring opening with the dimeric salen complex **8**.



Scheme 1.1

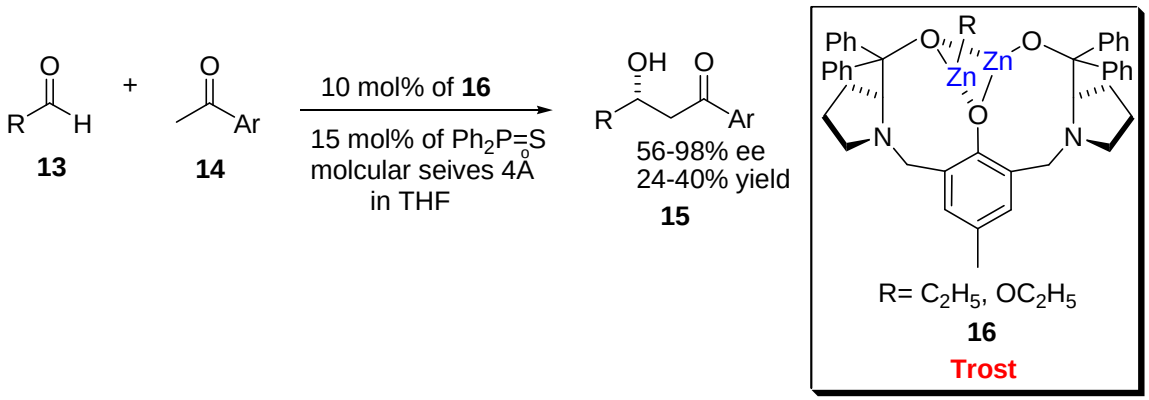
This bimetallic complex **8** (Scheme 1.1) enhanced the rate of asymmetric ring opening compared to the corresponding monometallic salen complex without any loss of enantiopurity. These dimeric analogues of salen complex were designed to incorporate cooperative mechanism maintaining similar enantiodiscriminating transition states as compared to the mononuclear salen complex. The Jacobsen group used cooperative heterobimetallic catalysis as a tool to achieve a highly efficient system[25] for the enantioselective conjugate addition of cyanide to α,β-unsaturated imides (**9**) (Scheme 1.2). Mechanistic studies of this conjugate addition reaction suggested a cooperative bimetallic mechanism involving activation of the imide by the aluminium complex and activation of cyanide by the erbium complex. Hence, the Jacobsen group showed the

utility of bimetallic chiral catalysts in performing cooperative reactivity towards various challenging asymmetric transformations.



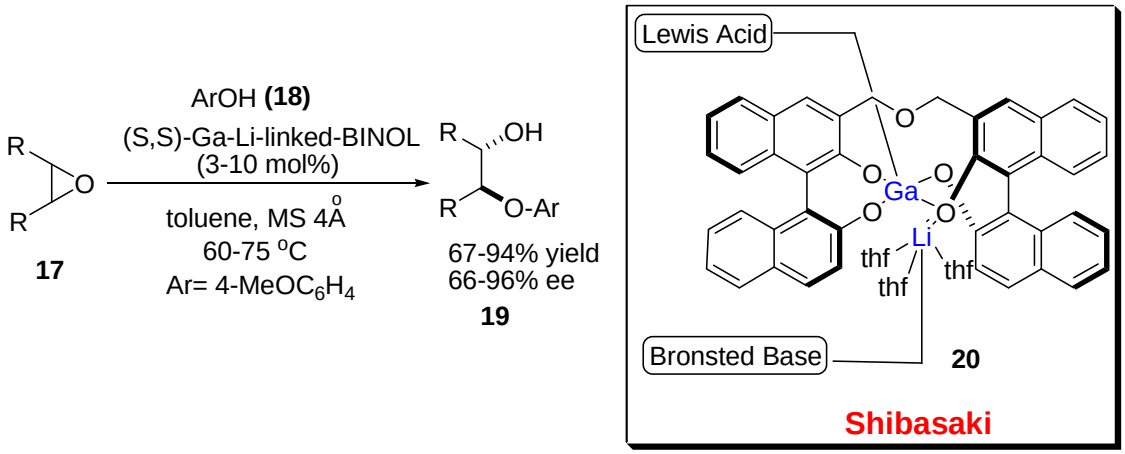
Scheme 1.2

The Trost group reported a chiral bimetallic zinc complex (**16)** (Scheme 1.3) possessing phenoxide linker.[20] The bimetallic zinc complex was prepared by treating a stoichiometric amount of the phenoxide ligand with dialkyl zinc. Successful asymmetric Aldol reactions with high levels of enantioselectivity were achieved using this bimetallic chiral catalyst.



Scheme 1.3

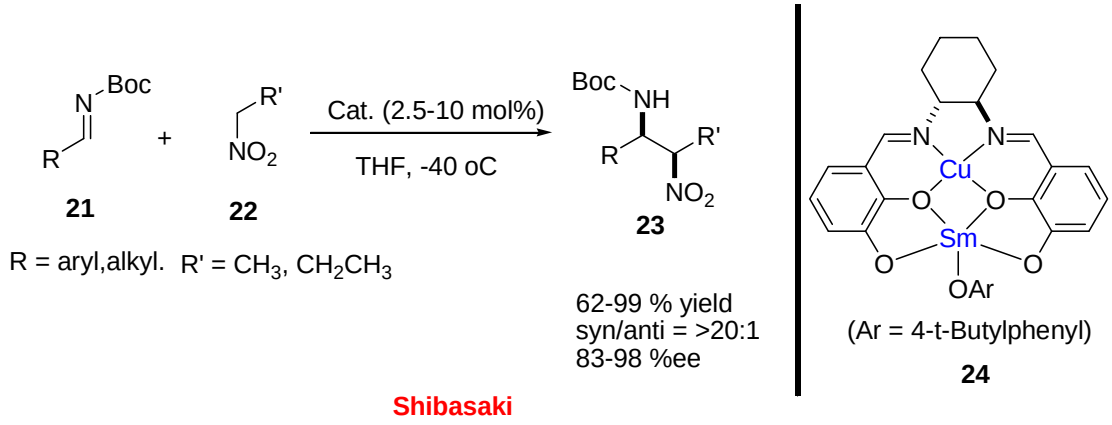
Various classes of bimetallic catalysts were reported by the Shibasaki group from the University of Tokyo. His group showed bimetallic complexes (**20**) derived from chiral BINOL derivatives to be highly efficient for various enantioselective transformations.[23]



Scheme 1.4

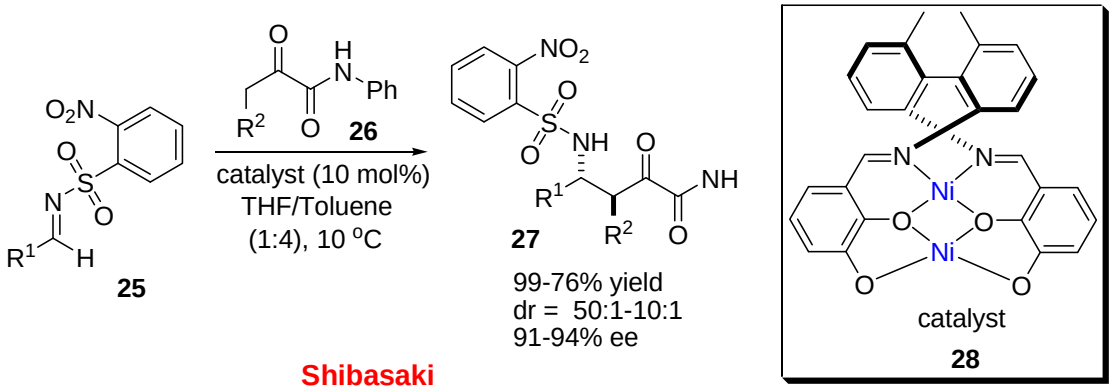
This class of chiral complexes promoted asymmetric transformations via dual activation of both the reaction partners (Scheme 1.4). The basic moiety of the catalyst (**20**) activated the nucleophile (**18**) by deprotonation. On the other hand, the Lewis acidic moiety of the complex activated the epoxide (**17**) which was the electrophilic reaction partner in this reaction. Since both these activations were performed in an asymmetric environment, the attack of the nucleophile was from a selective phase resulting in high enantioselectivity. The Shibasaki group not only explored heterobimetallic chiral catalysts resulting from BINOL derivatives but also reported a class of binucleating Schiff base ligands that can incorporate two metals (Scheme 1.5). These catalysts are presumed to have a transition metal in an inner N_2O_2 core and a lanthanide metal in the outer O_2O_2 core (**24**).Various nitro-Mannich reactions with high levels of enantioselectivity were achieved using these bimetallic chiral complexes.[26] As shown in Scheme 1.5, Cu/Sm bimetallic complexes

were effective for providing highly enantioselective nitro-Mannich reactions of nitroalkanes (**21**) and N-Boc imines (**22**).



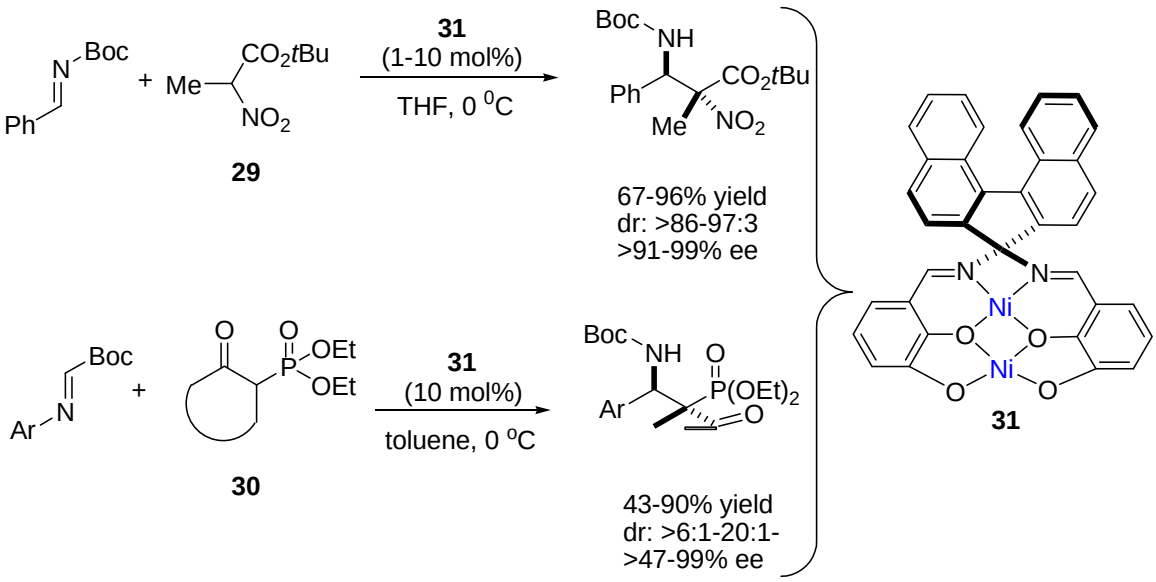
Scheme 1.5

High levels of diastereoselectivity (>20:1) were obtained for this Mannich reaction with the syn-isomer being the major product. Homobimetallic complexes of binucleating Schiff base ligands were also prepared (Scheme 1.6) by the Shibasaki group. A bis nickel complex with dimethyl biphenyl diamine as the chiral backbone (**28**) as shown in Scheme 1.6 produced highly enantioselective, anti-selective Mannich products of α-ketoanilide (**25**) and *o*-Ns imines (**26**).[27]



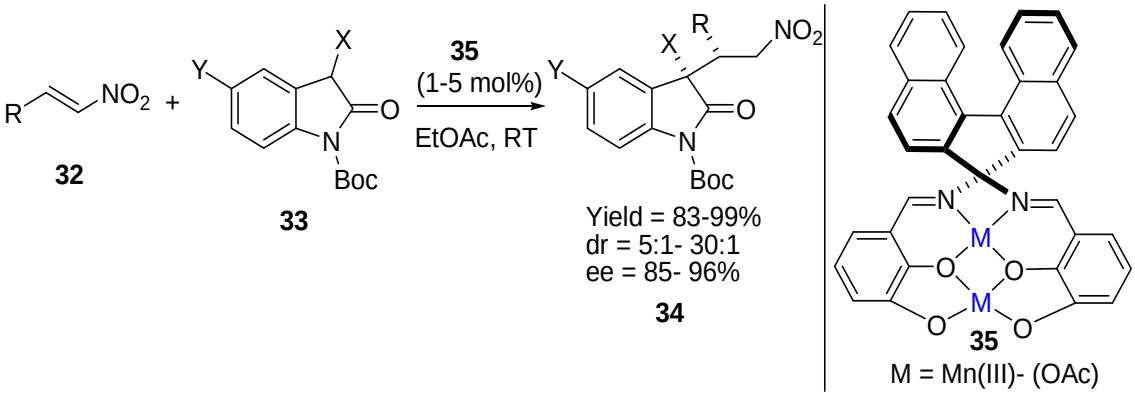
Scheme 1.6

Asymmetric Mannich-type reactions of ketophosphonates[28] (**30**) as well as nitroesters[29] (**29**) with N-Boc imines (Scheme 1.7) were also demonstrated with high levels of enantioselectivity using a dinuclear Ni/Schiff base complex (**31**) derived from chiral napthyl diamine.



Scheme 1.7

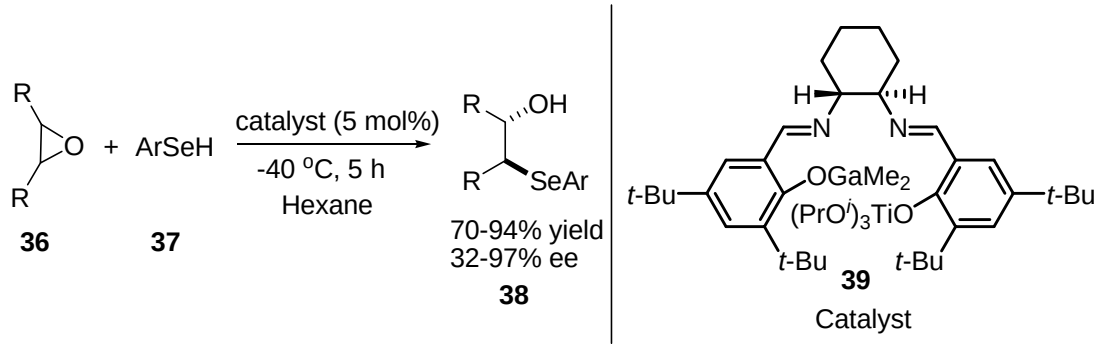
Recently the Shibasaki group reported catalytic asymmetric 1,4-additions of 3-substituted oxindoles (**33**) to β-aryl, β-heteroaryl, and β-alkenyl nitroalkenes[30] (**32**).



Scheme 1.8

A new homodinuclear $Mn_2(OAc)_2$-Schiff base complex (**35**) was required to achieve high levels of enantioselectivity in these 1,4-addition reactions. 1-5 mol % of **35**

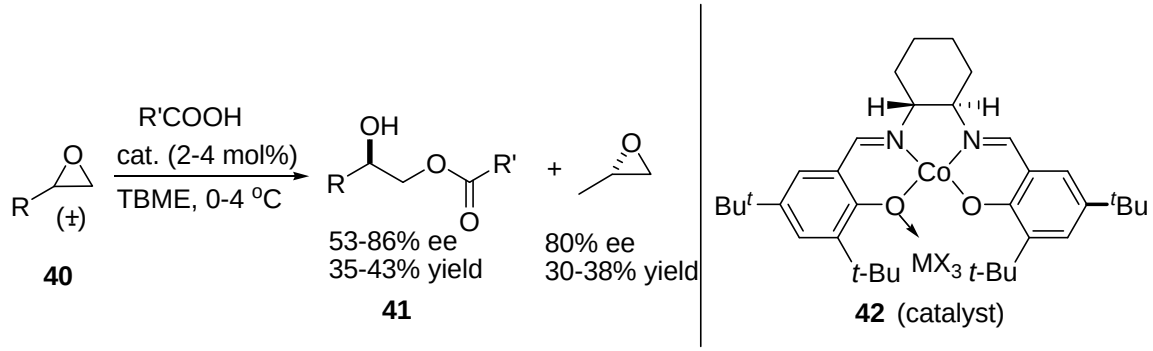
promoted these 1,4-additions at room temperature with 85-96 % ee and dr >5:1-30:1 thereby provided useful chiral building blocks for the synthesis of β-aminooxindoles. (Scheme 1.8).



36 **37** **38** **39** Catalyst

Scheme 1.9

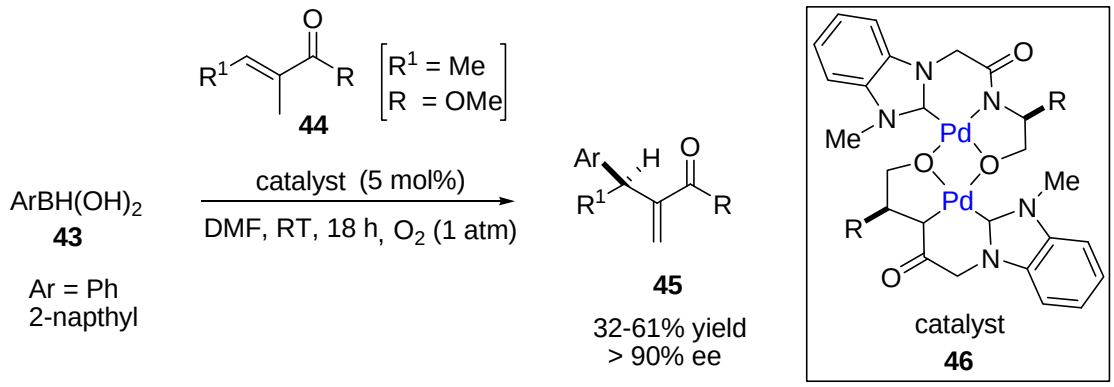
The first example of enantioselective ring-opening reactions of epoxides **(36)** by selenium nucleophiles[31] was demonstrated using a chiral Ti−Ga−Salen heterobimetallic catalyst **39** (Scheme 1.9). Aryl selenols (**37**) on reaction with epoxides in presence of 5 mol% of bimetallic catalyst **39** provided optically active β-arylseleno alcohols (**38**) with high enantioselectivity. The authors speculated that the epoxides chelate to the Titanium (hard Lewis acid) and gets activated while the selenophenol binds to the softer Lewis acid (Gallium) which probably directs the attack of selenophenol to the epoxides in an efficient and selective manner.



40 **41** **42** (catalyst)

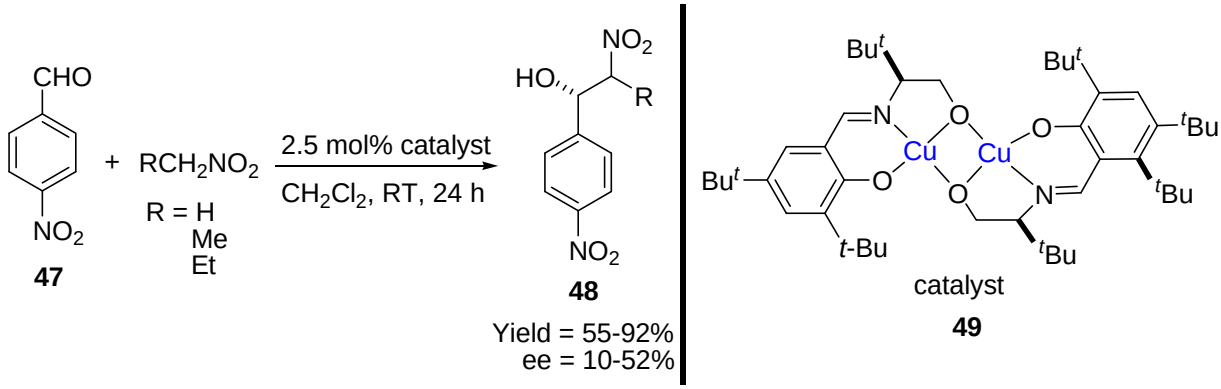
Scheme 1.10

Recently, enantioselective ring opening of terminal epoxides by carboxylic acids (Scheme 1.10) was reported using a heterobimetallic chiral salen complex (**42**). This methodology provided successful synthesis of optically active 2-hydroxy monoesters **(41)** via kinetic resolution of epoxides.



Scheme 1.11

Very recently, the Jung group reported[33] the synthesis of a chiral dimeric Pd complex **46** derived from a tridentate N-heterocyclic carbine amidate alkoxide ligand. This catalyst promoted successful asymmetric Heck reactions offering high levels of enantioselectivity (Scheme 1.11).



Scheme 1.12

Recently the Punniyamurthy group reported a bis copper containing Schiff base complex (**49)** that catalyzed nitroaldol reactions providing 50% ee under amiable conditions[34]

(Scheme 1.12). Hence, activation of substrates by two metals is not only found in nature but also a well established concept in asymmetric catalysis.

Based on bimetallic sites available in enzymes as well as synthetic chiral ligands chelating two metals, we designed ligands to address synthetic challenges towards various chiral building blocks. Mostly the chiral bimetallic complexes known till today are used as bifunctional catalysts. They activate both the electrophile as well as the nucleophile partner to facilitate the desired transformation. Again, monometallic chiral complexes are explored more extensively compared to bimetallic complexes (Figure 1.4).

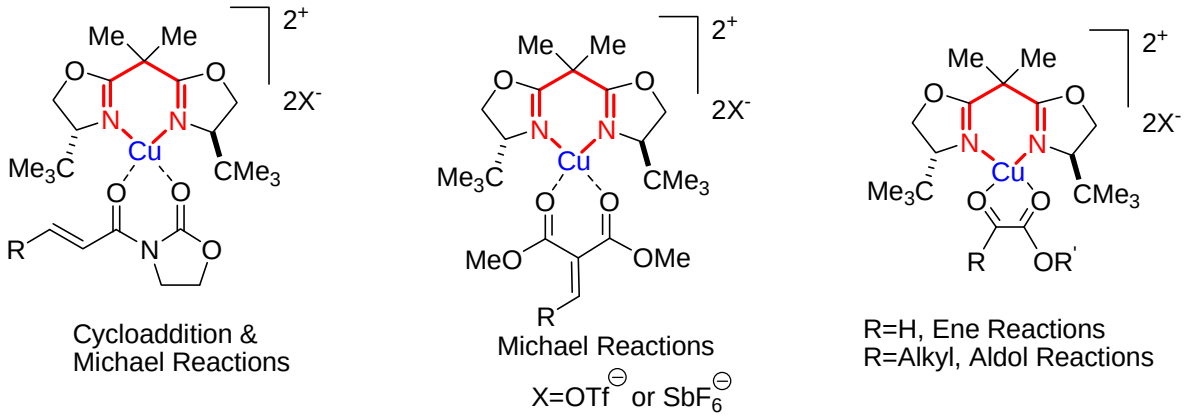


Figure 1.4

It is well known that bisoxazoline (box) ligands (Figure 1.4) are very successful in providing enantiomerically enriched products for a large number of asymmetric transformations. The transformations include aldol, Michael, ene to cycloaddition and amination.[35-37] The Lewis acidic metal binds to the chiral box ligand through two point chelation (Figure 1.4). The substrate gets activated by coordinating with the resulting chiral Lewis acid. Box ligands possess C_2 symmetry which means 180^o rotation of the substrate results in the identical complex. Bulky substituents on the oxazoline moieties of these C_2 symmetric box ligands essentially block the bottom face of the chelated α,β-unsaturated substrates. This leads to the attack of the nucleophile from the top face

resulting in high enantioselectivity. Substrates undergoing activation have to be capable of chelating to the chiral Lewis acidic complex. Chelation control and π-stacking interactions are the key elements to control the stereochemistry in these transformations. This results in influencing the absolute sterochemical course for family of reactions. As shown in Figure 1.4, several asymmetric transformations were performed with these mononuclear metal complexes. Owing to the efficacy of the box ligands towards variety of successful asymmetric transformations, these are referred to as privileged structures.[38] However; tailored substrates can only be activated by these monometallic chiral complexes. As shown in Figure 1.5, oxazolidinone is incorporated in the substrate to aid the chelation of substrate.

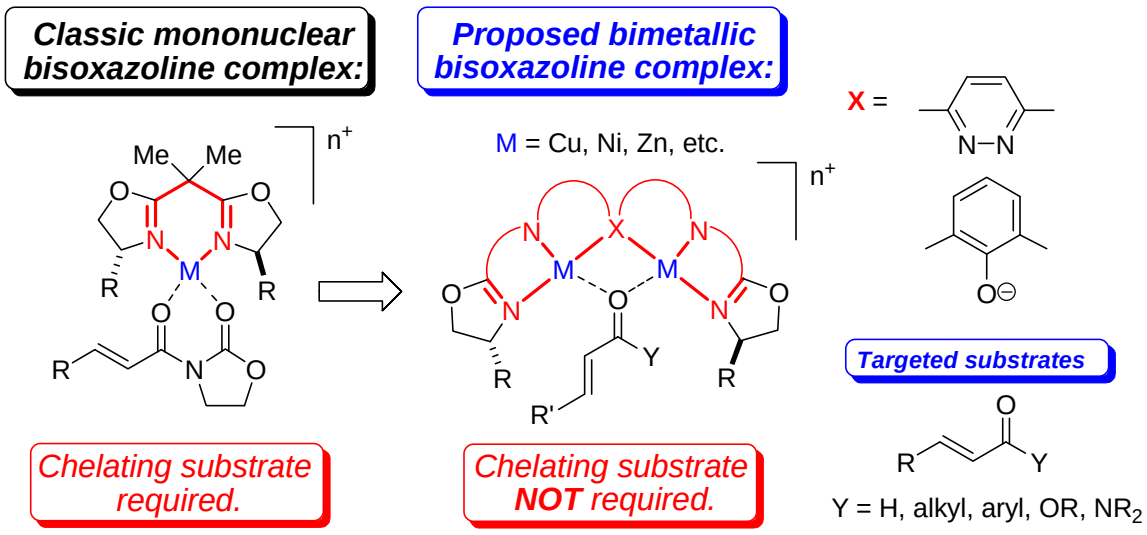


Figure 1.5

This often leads to extra steps in the synthetic sequence. To avoid these additional steps and enhance the substrate scope we designed novel chiral bimetallic complexes. We presume these bimetallic Lewis acidic metal complexes might bind to single a carbonyl (Figure 1.5) through the two lone pairs of oxygen. Besides facilitating a similar transition state as that of box ligands, activation of the simplest α,β-unsaturated carbonyl systems

can be plausible using these newly designed bimetallic complexes. Compared to previous chiral bimetallic complexes, these ligands are designed to doubly activate electrophilic partner instead of acting as bifunctional catalyst to stimulate both the electrophile and nucleophile. Instead of one metal of high acidity in monometallic catalysts, two metals of lower acidity can be used in these newly designed bimetallic complexes. The requirement of weakly bound anions for highly Lewis acidic metal can also be avoided for these bimetallic complexes, which should reduce the overall cost of the catalyst.

Bisoxazoline containing chiral complexes (Figure 1.6) are not new to the scientific community.[39-41] Pfaltz group reported bisoxazoline containing bimetallic chiral ligands having napthyridine, pyridazine and phenoxide linkers.

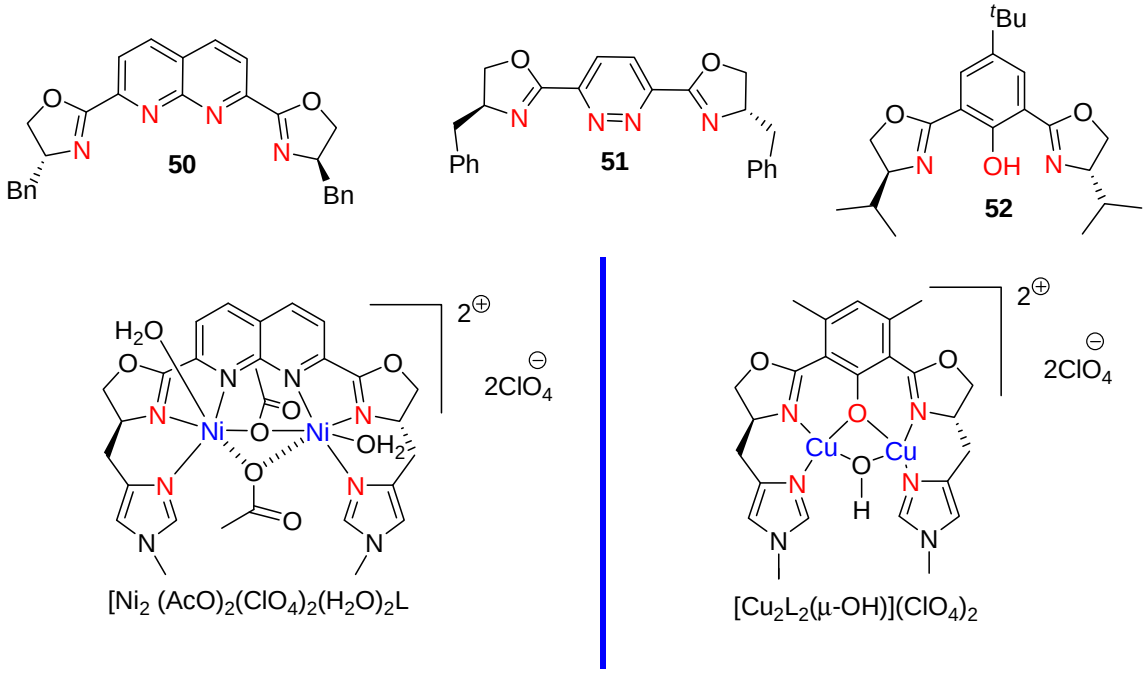


Figure 1.6

Successful bimetallic complex formation with these ligands was shown with nickel and copper (Figure 1.6). Some of these ligands (Figure 1.6) have two points of interaction per metal. Perhaps due to lack of rigidity in these bimetallic complexes, it was difficult to

achieve enatiomerically enriched products while using these as chiral catalysts. Fahrni reported (Figure 1.7) catalytic activity of phenoxide bridged bimetallic chiral complexes for asymmetric allylic oxidations of cyclohexenone.[41]

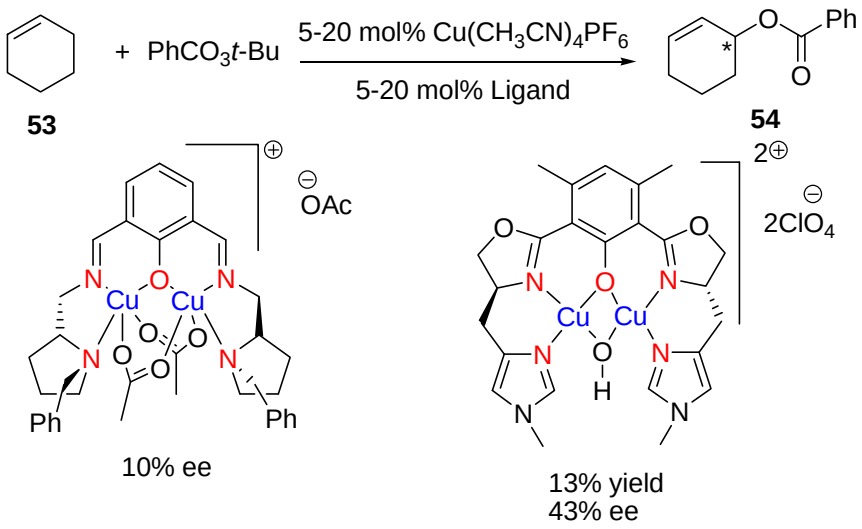


Figure 1.7

Unfortunately, very low levels of enantioselectivity were obtained using copper complexes derived from these binuclear chiral ligands (Figure 1.7). As shown in Figure 1.8, proposed ligands include bisoxazoline moiety as the source of chirality but other sources of chirality can also be used as the chiral backbone to synthesize similar binuclear ligands. Our proposed ligands can not only have 3 points of attachment per metal center but might also provide a rigid framework. By changing the linkers we can vary the distance between two metal centers which can be an important parameter to be explored.[42] This might be useful in tuning the size of the binding pockets for the substrate. Our designed bimetallic ligands not only can overcome the restriction of mononuclear metal complexes but also can provide different combinations of five- and six-membered chelation rings[9] to synthesize different classes of bimetallic catalysts which might be useful to address challenging asymmetric transformations.

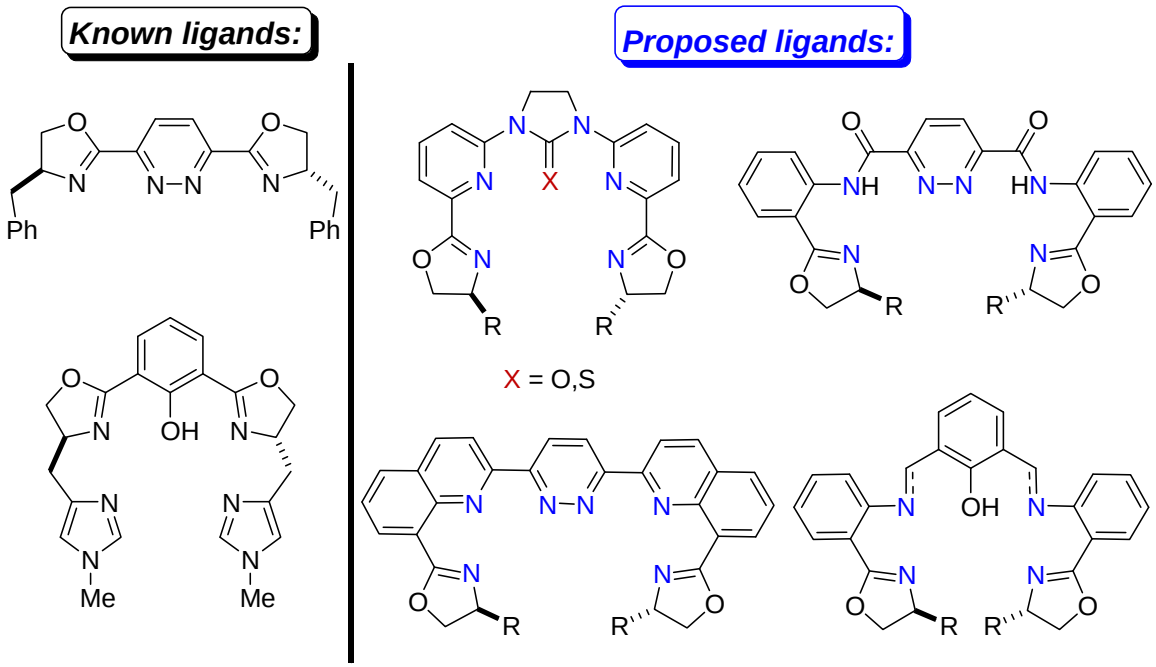


Figure 1.8

Similar to previously discussed achiral bimetallic complexes, these newly designed ligands consist of urea, pyridazine as well as phenolic fragments. These novel ligands should enhance the number of donor sites to facilitate chelation of the metals to the chiral ligand. Three points of attachment per metal center also play a key role in these designs which might lead to a rigid structure of the bimetallic complexes compared to previously known flexible ones. Changing the spacer or varying the size of chelation rings were other variables to explore which might give rise to catalysts of different geometries. The ligands designed were closely related to the known achiral ones (Figure 1.9) capable of binding to two metals.[8] The ligands were also designed to mimic the naturally available bimetallic sites to keep the two metals in similar proximity as seen in enzymes.

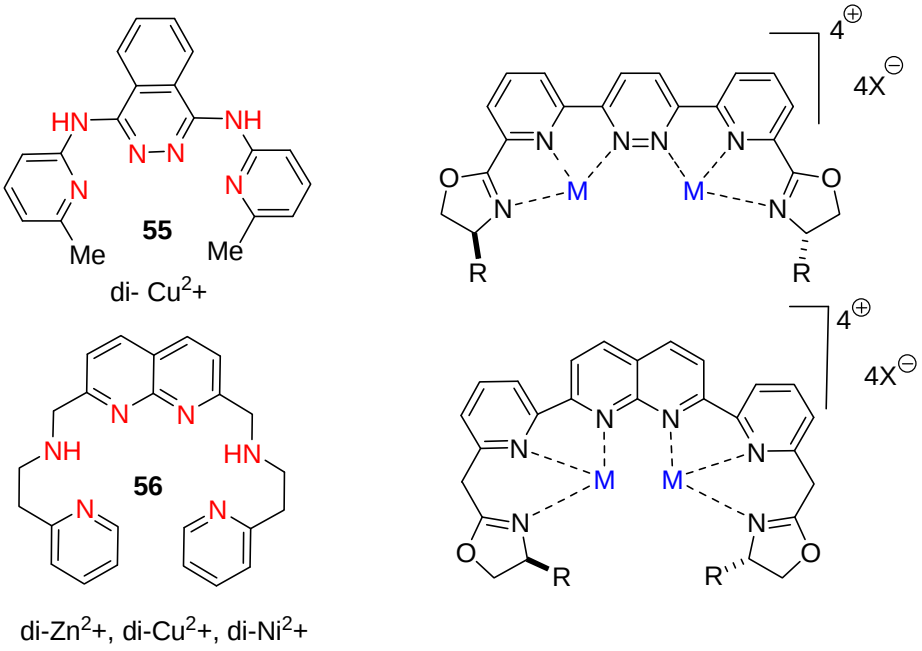


Figure 1.9

Complex formation with these ligands should readily occur as our newly designed chiral ligands constitute all the characteristics of natural bimetallic sites as well as the already known synthetic bimetallic complexes.[12, 42] For complexation to readily be achieved, the choice of metal is a critical factor for obtaining catalytically active complexes. However, copper may not be the best choice for bimetallic systems as it has been established that two copper centers in close proximity readily form hydroxide bridges. This could deactivate the catalyst and might prevent substrate binding and activation.[8] An X-ray crystal structure of a model urease complex containing a phenol bridge has recently been reported.[12] In this bis-nickel complex (Figure 1.10) the oxygen atom of an incorporated urea molecule was bound to both nickel centers, as would be desired for optimal substrate activation.

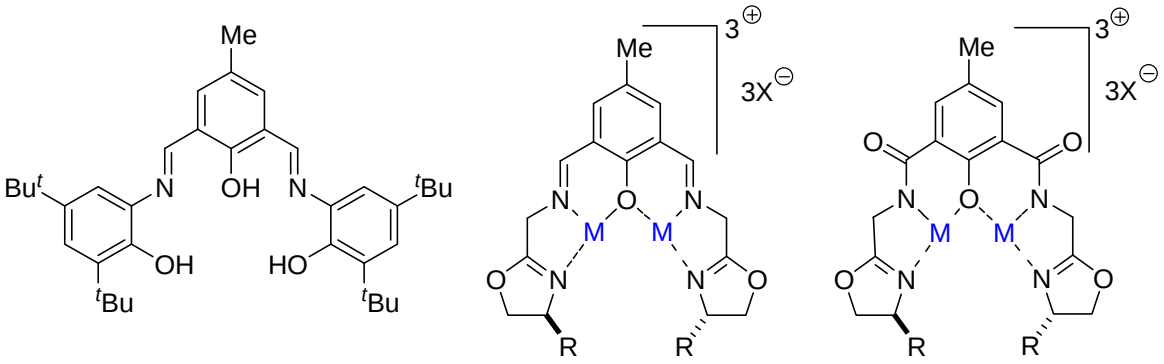


Figure 1.10

For our systems, we would evaluate a range of different metals not limited to nickel and not excluding copper. In addition to the first row transition metals, we would prepare and evaluate bimetallic complexes of lanthanides, palladium and silver for enantioselective reactions.[43] Our purpose was to get high levels of enantioselectivity for reactions which were reported only with chelating substrates. Often α,β-unsaturated aldehydes, ketones and esters were activated with mononuclear metal complexes but products were obtained with low selectivity. Mononuclear box ligands were effective to perform asymmetric catalysis for different families of reactions. In general, the substrate getting activated should have a chelating fragment to help binding to the Lewis acidic complex. Naturally, this limited the scope of the substrate. The designed bimetallic complexes might need no such restriction of substrate.

Mechanistic consideration of catalyst substrate complex is shown in Figure 1.11. We anticipated that the transition state with a s-trans system should be favorable over s-cis system for addition of nucleophile or cycloaddition partner. As shown in Scheme 1.11, we presumed that steric hindrance might limit only s-trans systems to be catalyzed by these bimetallic complexes. The nucleophile should attack the electrophile from one face (Scheme 1.11) resulting in successful asymmetric nucleophilic addition of simple

α,β-unsaturated carbonyl compounds similar to C_2 symmetric monometallic BOX ligands.

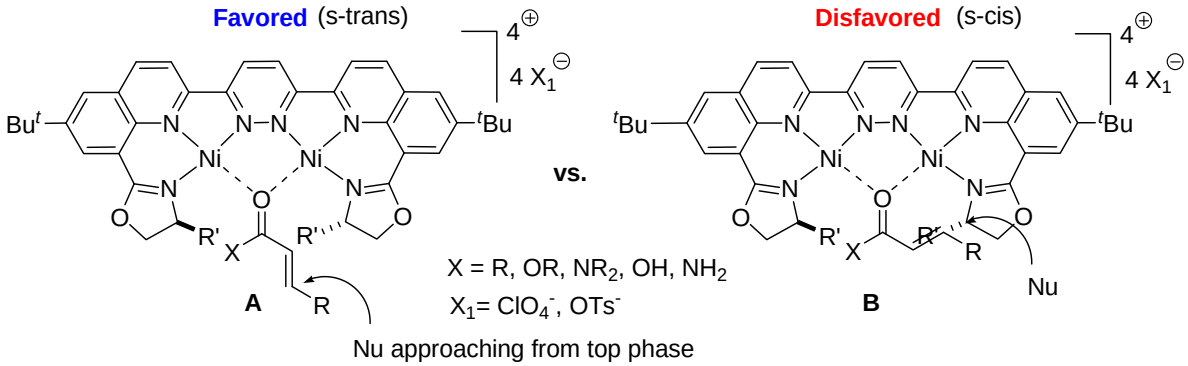
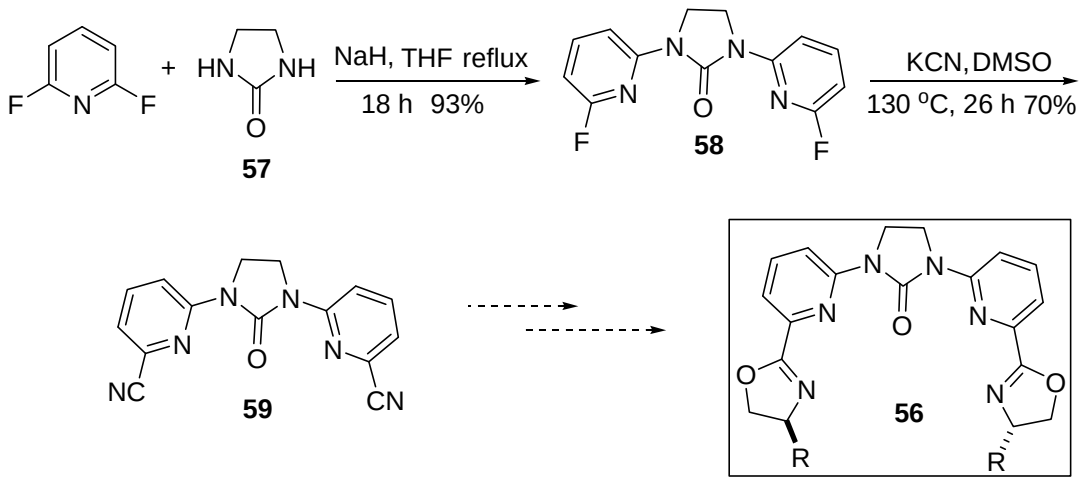


Figure 1.11

Our goal was to synthesize these novel chiral ligands through convenient synthetic routes and evaluate their catalytic activities towards a variety of challenging asymmetric transformations.

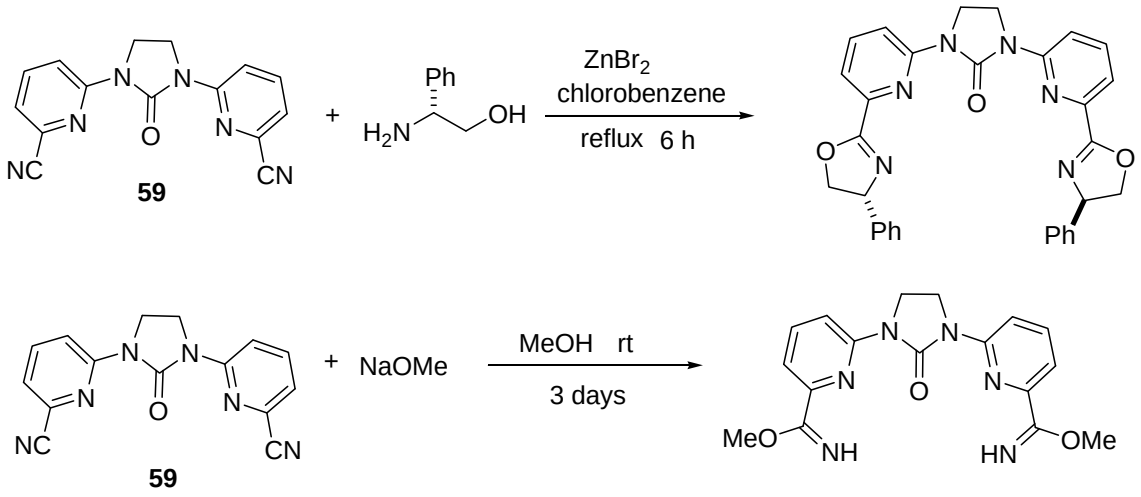
Results

Initially, we attempted preparing ligands with cyclic urea as the linker. The synthetic route was designed in a way that ligands can be easily accessible from commercially available materials via known methods.



Scheme 1.13

To synthesize the imidazolidinone bridged ligand **56**, the first step included a reaction of 2,6-difluropyridine with compound **57** to get the bisfluoroproduct **58** (Scheme 1.13). The bisfluoroproduct (**58**) was treated with KCN to obtain the dicyano compound **59** (Scheme 1.13). The cyano compound was extremely insoluble in most common organic solvents.

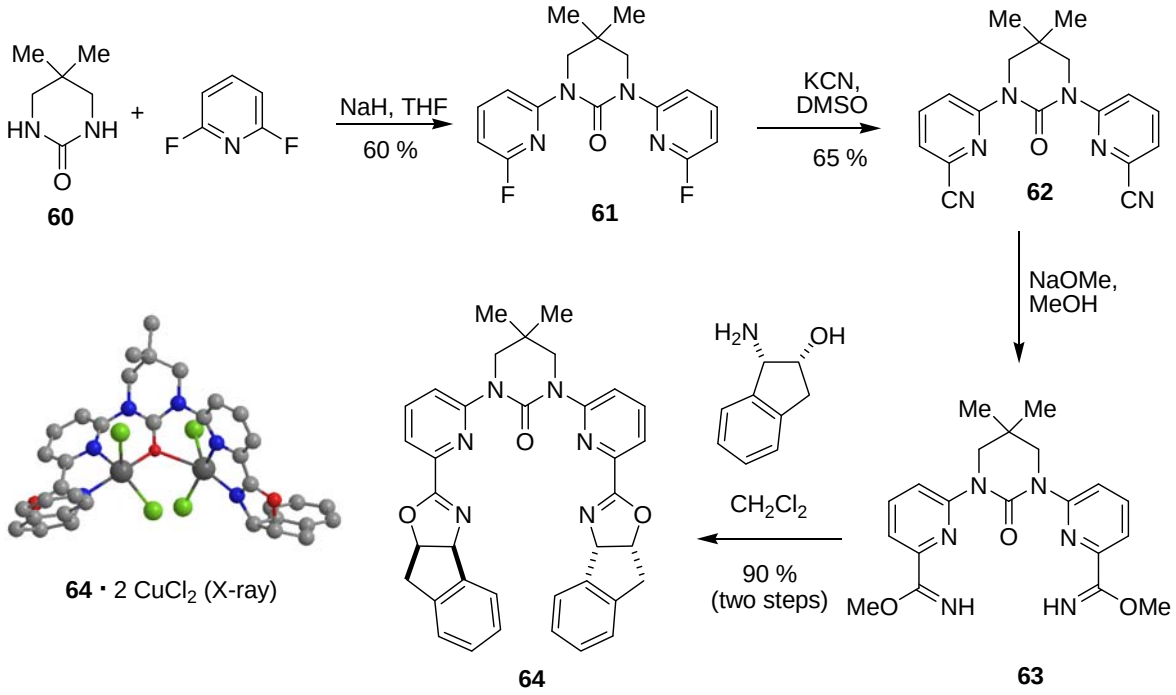


Scheme 1.14

We took this insoluble material and treated with enantiopure amino alcohol in the presence of zinc bromide for 6 h (Scheme 1.14). Though no starting material dinitrile compound was visible in TLC, pure final ligand was never isolated. As the direct inclusion of bisoxazoline did not work, we attempted a two step procedure via bisimidate intermediate (Scheme 1.14). The compound **59** was insoluble even in refluxing methanol resulting in a heterogeneous mixture over 3 days.

Owing to poor solubility of the crude material, we were unable to isolate the desired ligand. To obtain more soluble precursors we planned to synthesize a ligand derived from the cyclic urea **60**. Commercially available 2,6-difluoropyridine was treated with readily available urea **60**[44] in presence of NaH to obtain compound **61**.[45] The

dinitrile compound **62** was prepared by nucleophilic substitution of the bisdifluroro urea compound **61** with KCN.

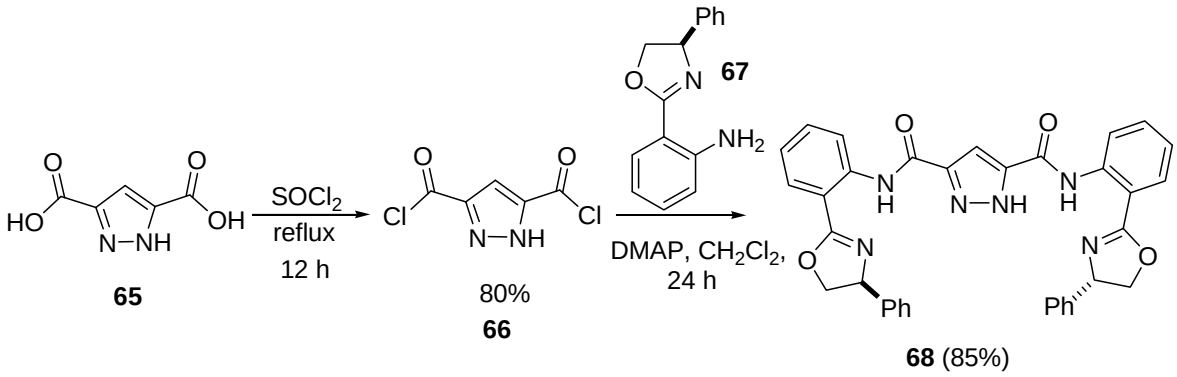


Scheme 1.15

Bisimidation of compound **62** using NaOMe[46] provided compound **63** (Scheme 1.15). Treatment of the bisimidate **63** with two equivalents of aminoindanol provided the desired bisoxazoline compound **64** with 90% yield over two steps. Complex formation of this novel chiral ligand was performed with various copper (II) salts. The X-ray crystal structure of the binuclear copper complex derived from the ligand and copper (II) chloride showed two copper metals are bound to the ligand with three donor sites per metal in a non-rigid framework (Scheme 1.15). Binuclear catalysts derived from the urea based bisoxazoline ligand **64** are under investigation to check their catalytic activity in asymmetric transformations.

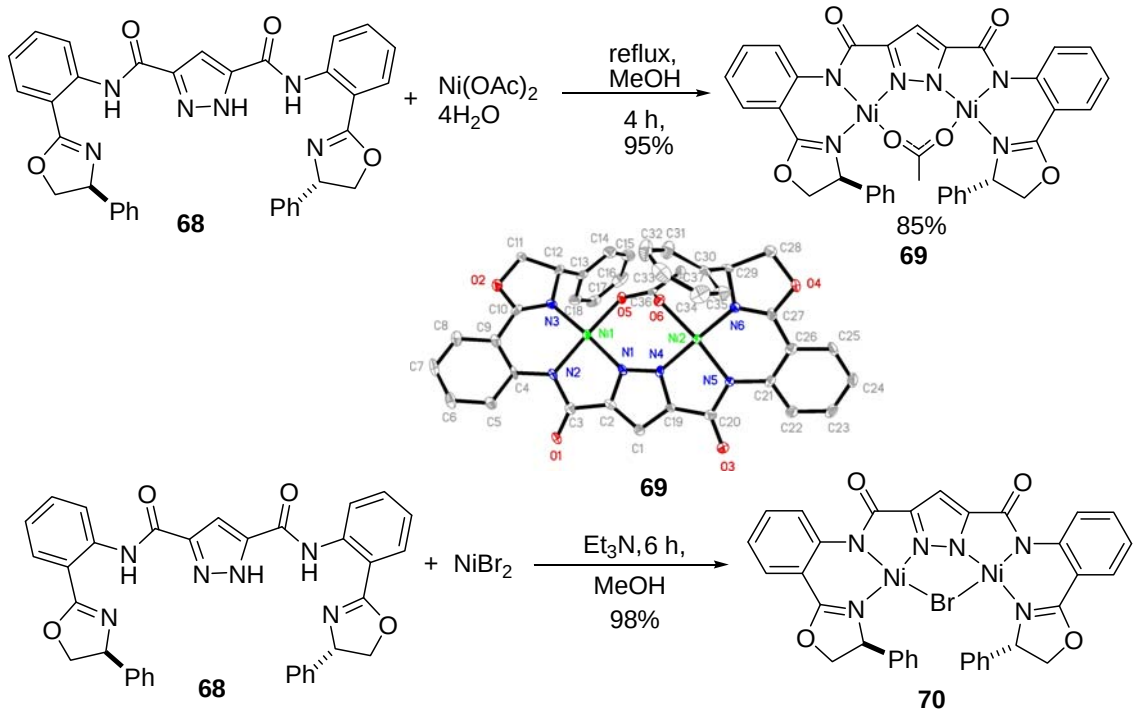
In addition to this urea containing neutral ligand we were also interested to prepare ligands possessing pyrazole as linker which would behave as trianionic ligand

providing a three point binding per metal center. As shown in Scheme 1.16, pyrazol-3,5-dicarboxylic monohydrate **(65)** was treated with thionyl chloride to obtain pyrazole-3,5-dicarbonyl chloride **66** in 80% yield.[47]



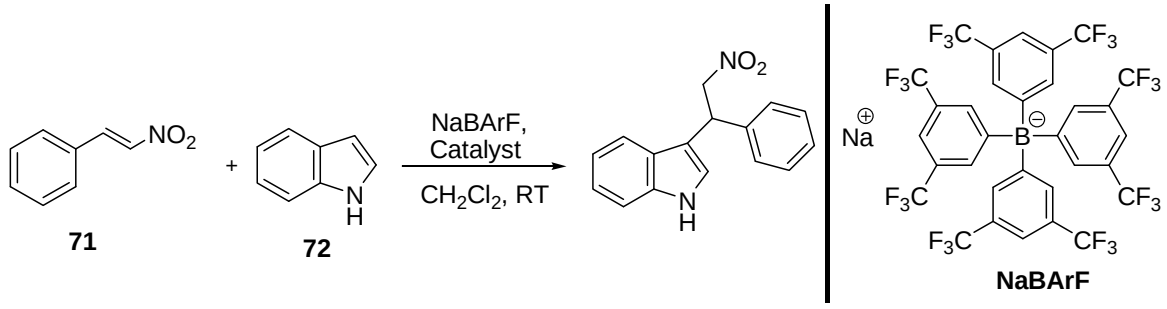
Scheme 1.16

The second step was condensation of readily available amine **67**[48] and the pyrazole diacid chloride **66** in presence of catalytic amounts of DMAP to afford the desired bisamide ligand **68**.



Scheme 1.17

The bisoxazoline ligand (**68**) was treated with 2 equivalents of nickel acetate tetrahydrate in methanol to give almost a quantitative yield of the desired binuclear chiral metal complex **69** (Scheme 1.17). We were able to characterize the metal complex not only by ^{1}H-NMR, but also by X-ray crystallography. We also prepared the bimetallic complex of this pyrazole ligand with nickel (II) bromide (Scheme 1.17). Once the structure of the binuclear metal complex was confirmed by X-ray, we tested the catalytic activity of the complex for our targeted 1,4-additon reactions. To test the catalytic activity of the homobimetallic nickel complexes, 1,4- addition of indole **72** to trans-nitrostyrene **71** was attempted (Scheme 1.18). Unfortunately, racemic products were obtained even after replacing the bromide (in compound **70**) with weakly coordinating anions such as $BArF^{-}$.



yield	[a]55%	[b]45%	[c]85%
ee	racemic	[b]23%	[c]8%
time	24 h	24 h	3 h

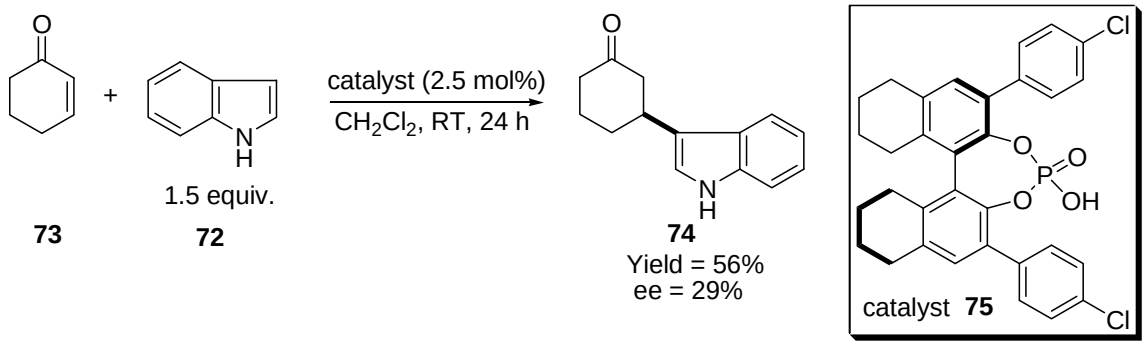
yield	[b]60%	[c]70%
ee	[b]13%	[c]8%
time	24 h	24 h

[a]Catalyst only
[b]NaBARF & Catalyst mixed in RT.
[c]NaBArF & Catalyst refluxed for 10 min, cool to RT & substrates added.

Scheme 1.18

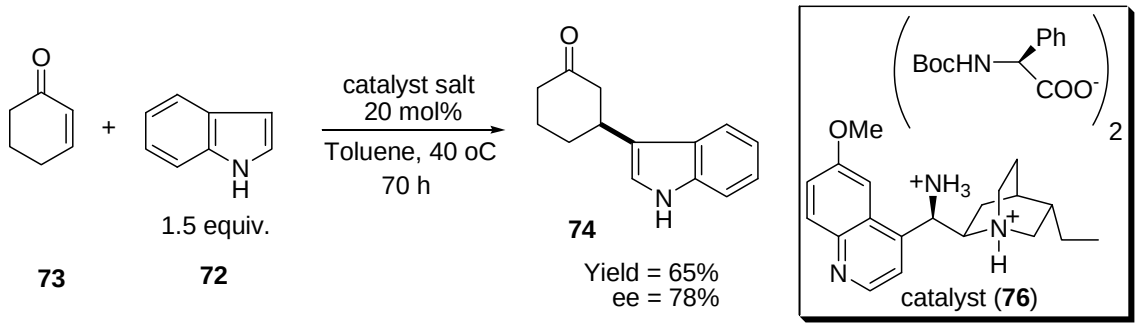
Unfortunately, there was no significant change either in yield or in enantioselectivity in any of the cases. To favor a square planar geometry for the two metals coordinated to the

ligand, we prepared a bispalladium complex. Palladium dibromide and the ligand (**68**) were heated in methanol for 6 hours to obtain a dark green precipitate. Attempts to obtain an X-ray crystal structure for the bispalladium complex are still underway. One of our primary goals was to tune these catalysts to activate non chelating carbonyl compounds towards nucleophilic addition or Diels-Alder reactions. We designed these binuclear ligands to successfully catalyze nucleophilic additions to both cyclic and acylic α,β-unsaturated ketones.



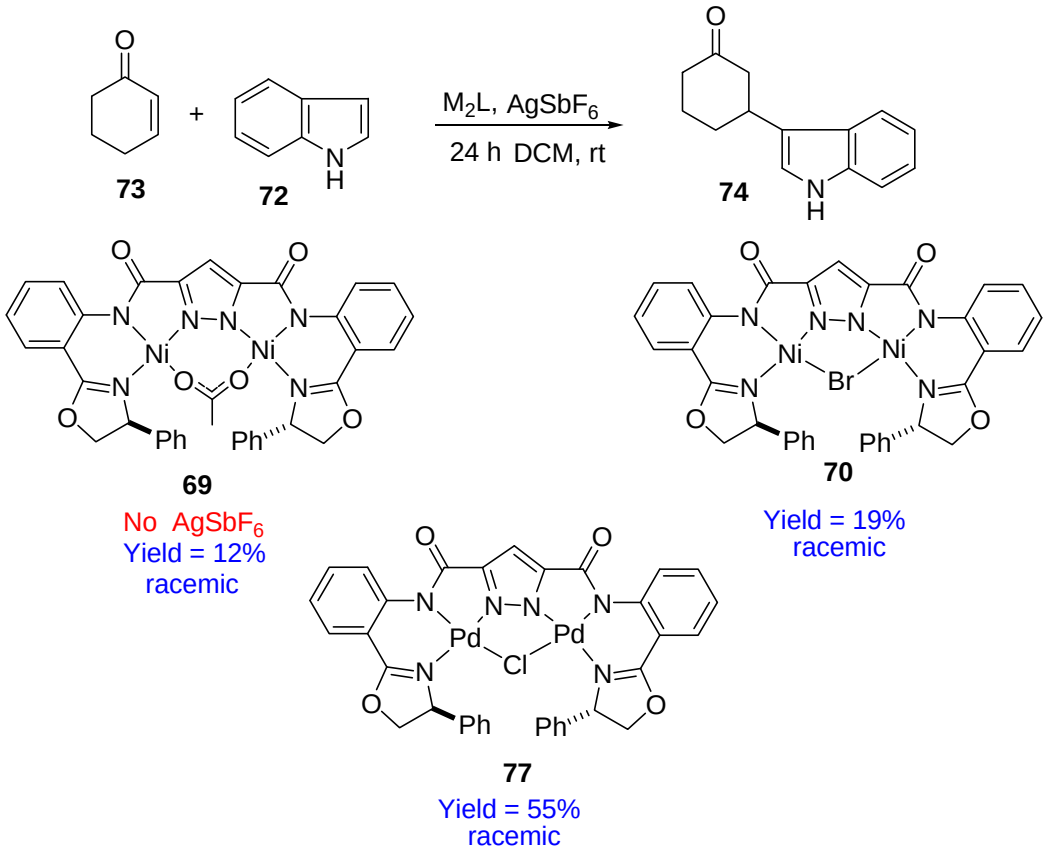
Scheme 1.19

To our knowledge enantioselective 1,4-addition of indole to 1,3-cyclohexenone is known with organocatalysts having ee obtained up to 75%. Recently, Zhou et al demonstrated successful enantioselective 1,4-addition of indole[49] (**72**) to 1,3-cyclohexenone (**73**) with 29% ee and 56% yield (Scheme 1.19) using a chiral phosphoric acid derived catalyst (**75**). The Melchiorre group showed[50] moderately selective 1,4-indole addition to 1,3-cyclohexenone with ee up to 78% using a cinchonine derivative based chiral catalyst **76** as shown in Scheme 1.20. We tested 1,4-Michael addition of indole to 1,3-cyclohexenone to test if our bimetallic catalysts can activate non chelating substrates to undergo nucleophilic addition (Scheme 1.21).



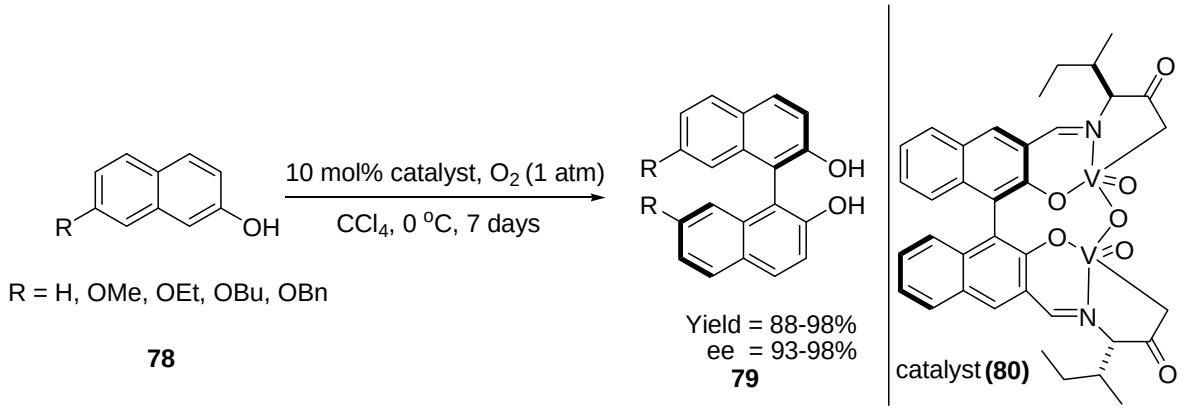
Scheme 1.20

Both the nickel complexes (**69** & **70)** as well as palladium complex **77** were tested. All the reactions were run at room temperature for 24 h. Less than 20% yield was obtained for the bisnickel complexes. Interestingly, the yield in case of the palladium complex was considerably higher compared to that with the nickel complexes (Scheme 1.21). But, unfortunately in all the three cases racemic products were obtained.



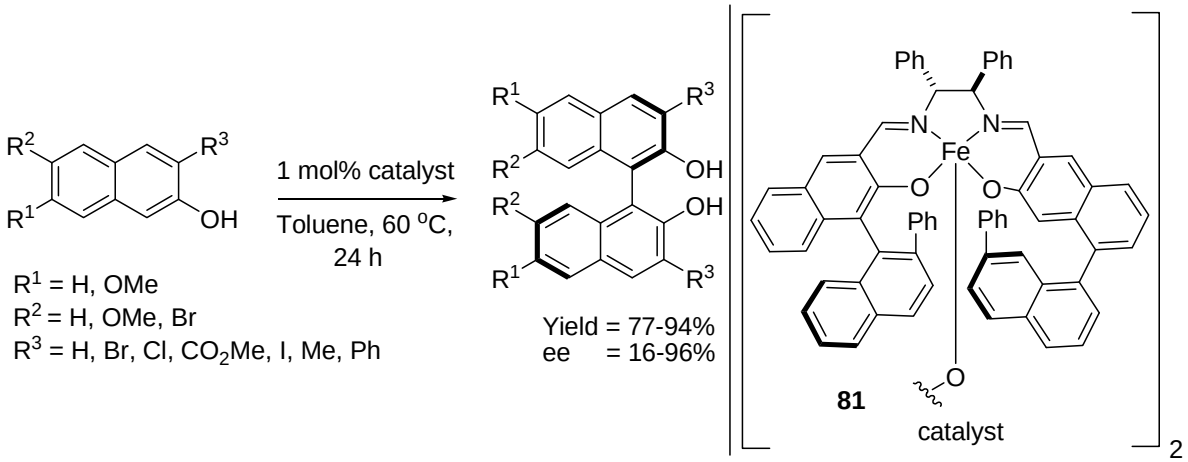
Scheme 1.21

Enantioselective oxidative coupling of 2-napthols is a challenging problem in asymmetric catalysis. In recent years, this reaction was performed with high levels of enantioselectivity by several groups. The Kozlowski group from University of Pennsylvania has reported some pioneering work regarding enantioselective oxidative coupling of 2-napthol and its derivatives.[51] Highly enantioselective oxidative coupling of 2-Napthol (**78**) to obtain chiral BINOL **79** was shown by Gong group[52] using a chiral bimetallic oxovanadium complex **80** mediated either by oxygen or air as the oxidant in CCl_4 as solvent (Scheme 1.22). They were able to achieve more than 90% ee for different 2-napthol derivatives with high levels of yield using 10 mol% of the oxovanadium catalyst (Scheme 1.22).



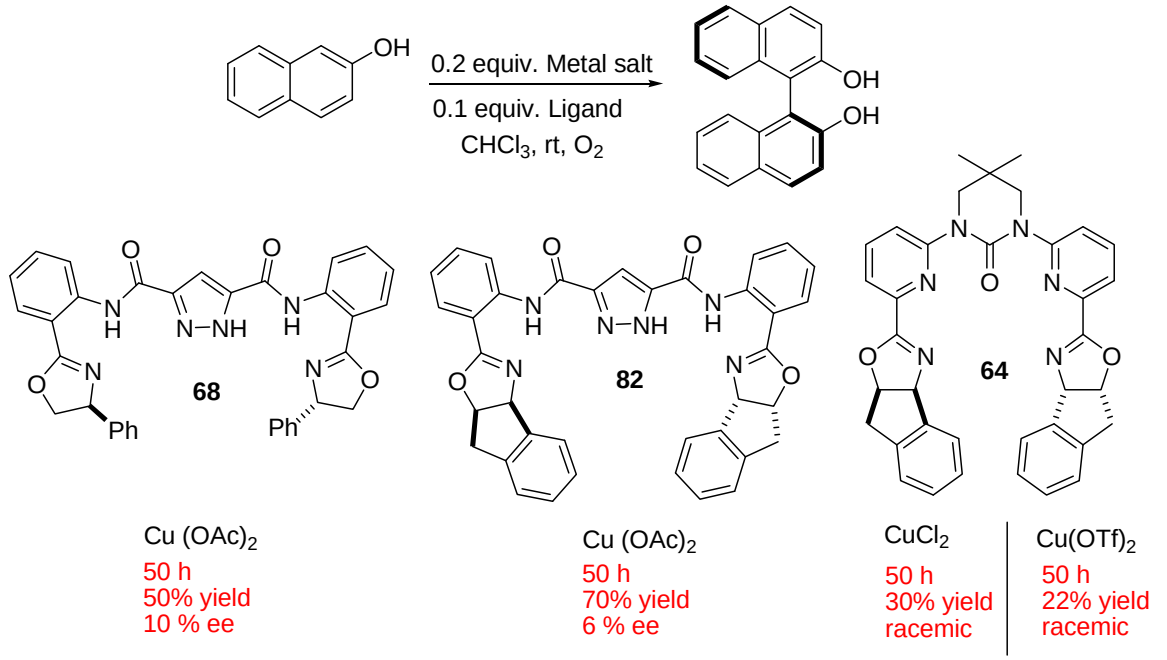
Scheme 1.22

The Katsuki group from Japan very recently reported[53] an iron catalyzed aerobic oxidation of 2-napthols using a salen type chiral complex **81**. High levels of enantioselectivity were achieved but the reaction had to be performed at high temperature (60 ^oC) (Scheme 1.23). Since the previous reports were mostly successful with derivatives of 2-napthol and involved long reaction time, we thought of testing our bimetallic chiral catalysts towards this challenging oxidative coupling reaction.



Scheme 1.23

We were able to obtain the desired product but without any levels of enantioselectivity. The bimetallic complex of copper acetate and the trianionic pyrazole ligand **68** provided 50% yield and 10 % ee after 50 h (Scheme 1.24). The trianionic ligand possessing an aminoindanyl moiety (**82**) provided 6% ee with 70% yield after the same time under oxygen. The urea based ligand **64** after complexation with copper salts were introduced to the oxidative coupling of 2-napthol under oxygen only to provide racemic products.



Scheme 1.24

After investigating the catalytic activities of the homobimetallic complexes having urea and pyrazole as the linkers, we decided to synthesize a pyridazine based chiral ligand which should provide a neutral environment. We presumed that this new ligand could give rise to electronically and geometrically different catalyst which might provide more promising selectivity. The synthetic route to this neutral pyridazine chiral ligand **83** included as the key step a Friedländer condensation (Figure 1.13) of compound **85** and aminocarbonyl systems (**86**).

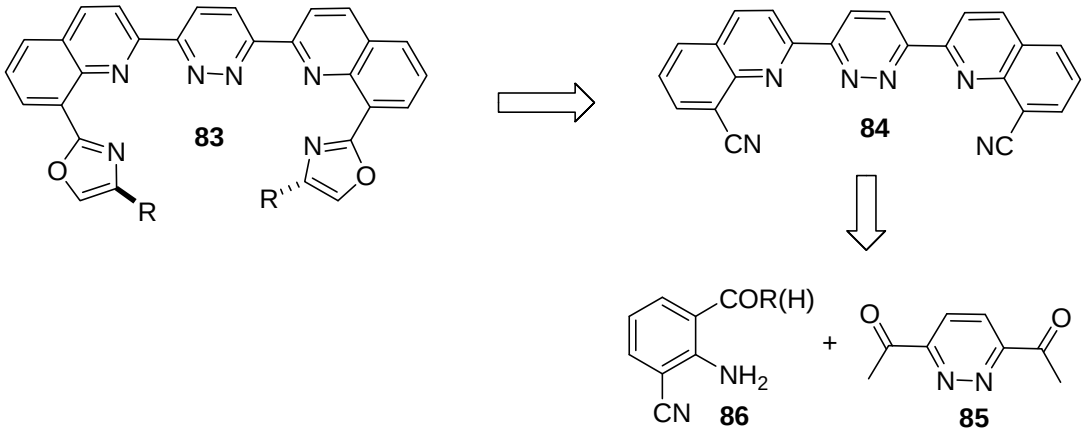
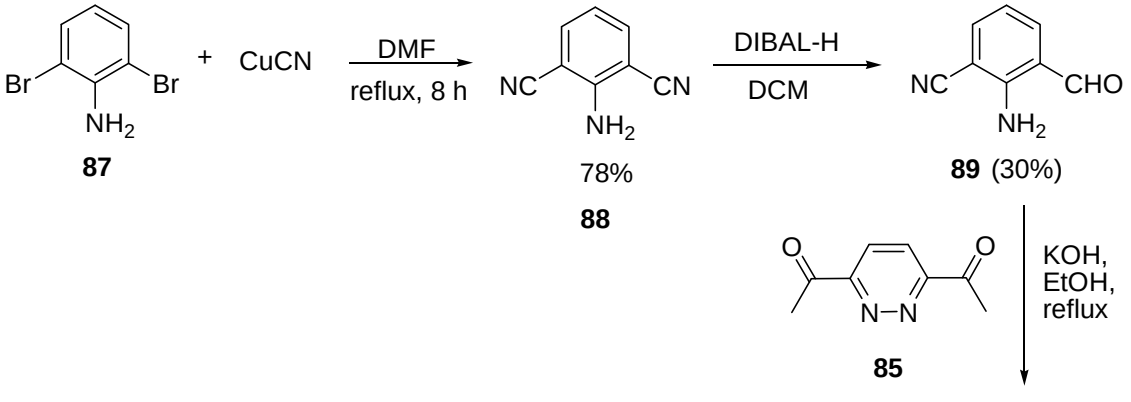


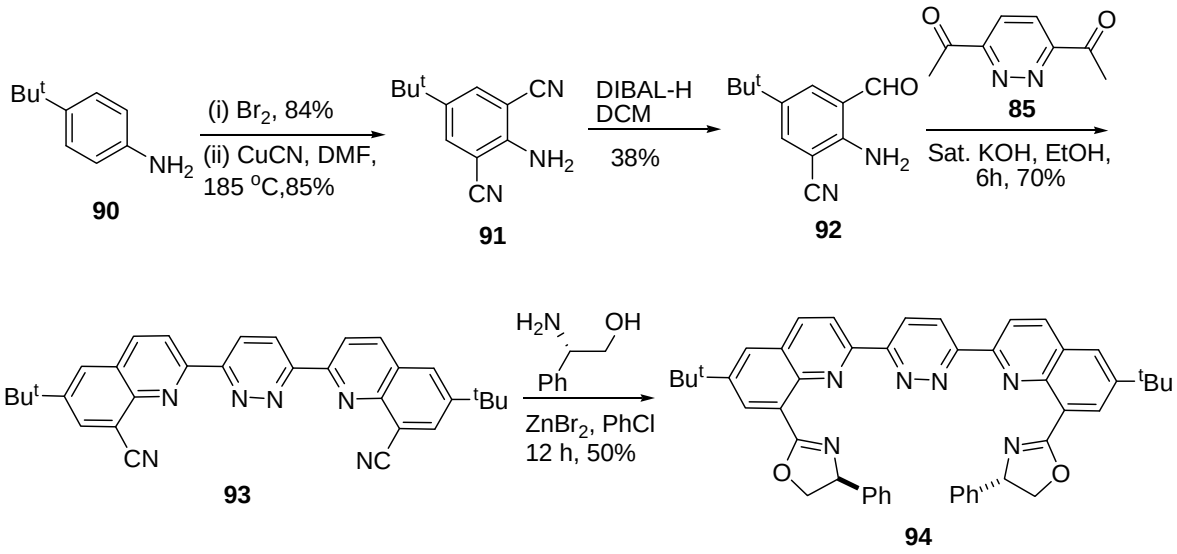
Figure 1.13

The first step included 2, 6-dibromoaniline (**87)** being treated with CuCN to provide dicyanoaniline (**88)** in good yield.



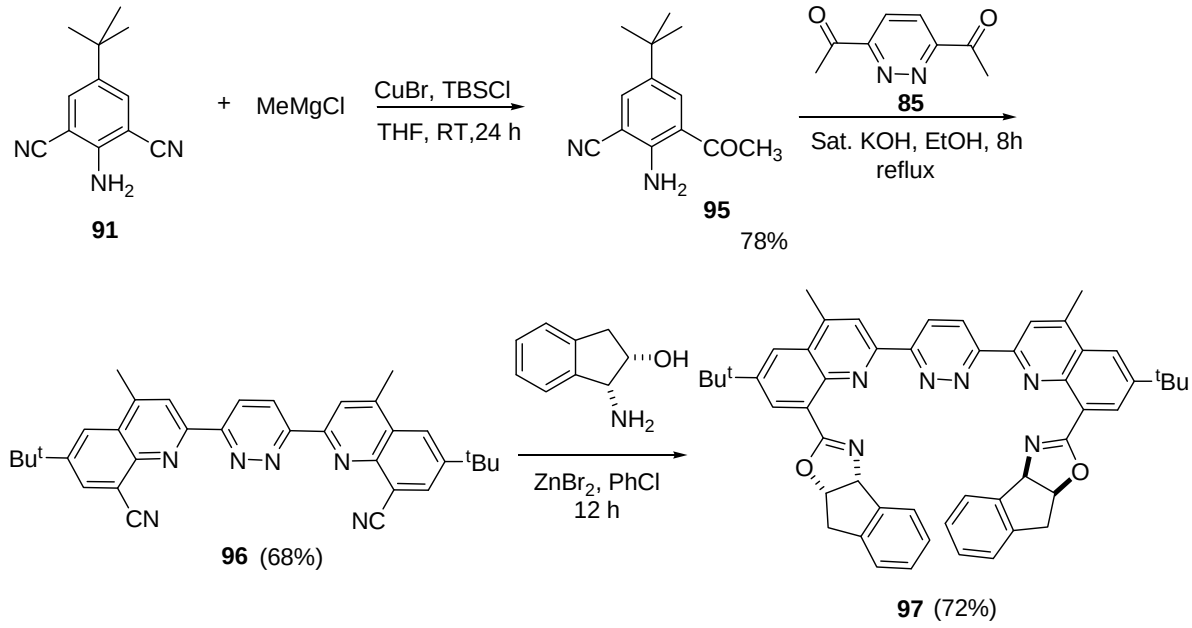
Scheme 1.25

The dicyano compound, on controlled treatment with DIBAL-H afforded 30% of the cyanoaminobenzaldehyde **89** along with recovered starting material and the dialdehyde product. Unfortunately the Friedländer condensation of the cyanoaminobenzaldehyde (**89**) with 3,6-diacetyl pyridazine (**85**)[54] provided a precipitate (Scheme 1.25). This precipitate remained insoluble in all regular organic solvents and we were unable to analyze it. To obtain a more soluble Friedländer product, we designed a route to a pyridazine bridged ligand starting from 4-*t*-butylaniline (**90**). Presumably, this should provide a more soluble Friedländer product, and we might proceed further to incorporate bisoxazoline moieties. When 4-*t*-butylaniline was treated with bromine at room temperature, 2, 6-dibromo-4-*t*-butylaniline was obtained[55] in 84% yield. The dibromo compound was transformed to the corresponding bisnitrile compound **91** using CuCN providing 85% yield. Similarly as before, treating the dicyano compound with 1.2 equivalents of DIBAL-H resulted in the corresponding cyanoaminobenzaldehyde **92** with 38% yield.



Scheme 1.26

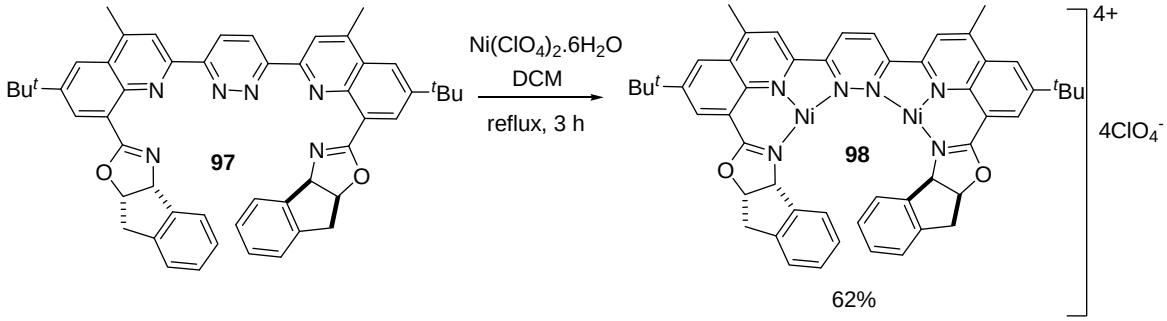
Almost equal amounts of the starting material as well as cyanodialdehyde were also isolated and we failed to increase the yield of the desired product (**92**) in spite of controlling parameters such as temperature or amount of DIBAL-H. We were delighted to observe that the Friedländer product **93** obtained[56] from this cyanoaminobenzaldehyde (**92**) and 3,6-diacetylpyridine was readily soluble in regular organic solvents like DCM, $CHCl_3$, and EtOAc. The Friedländer product (**93**) was then treated with enantiopure phenyl glycinol in presence of zinc bromide in chlorobenzene.[48] Although we were able to get the desired ligand (**94)** we failed to purify it either by coloumn chromatography or recrystallization. 95% purity was obtained by chromatography using triethyl amine neutralized silica gel.



Scheme 1.27

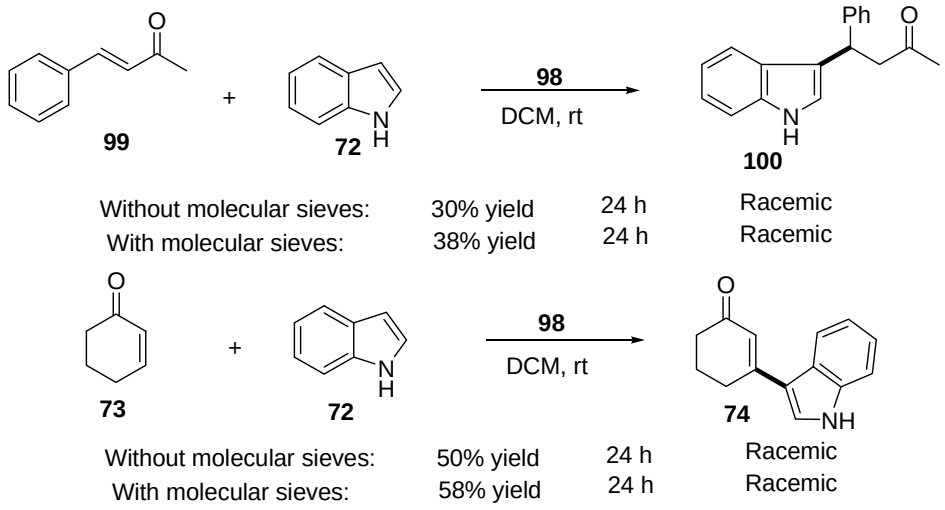
We anticipated that using an aminoketone instead of the aminobenzaldehyde might result in a dimethyl substituted Friedländer product (**96**). Interestingly, when compound **91** was treated with CH_3MgBr in presence of CuBr and TBDMS, we were able to obtain 78% of the desired monoketone **95**. The monoketone was treated with 3,6-

diacetylpyridazine **85** under Friedländer conditions using KOH as the base to provide the desired bisnitrile compound **96**. The dimethyl bisnitrile compound (**96)** was then treated with (1S, 2R)-aminoindanol in presence of $ZnBr_2$ in chlorobenzene reflux for 24 h. To our delight, the desired ligand **97** was obtained with a moderate yield of 72%.



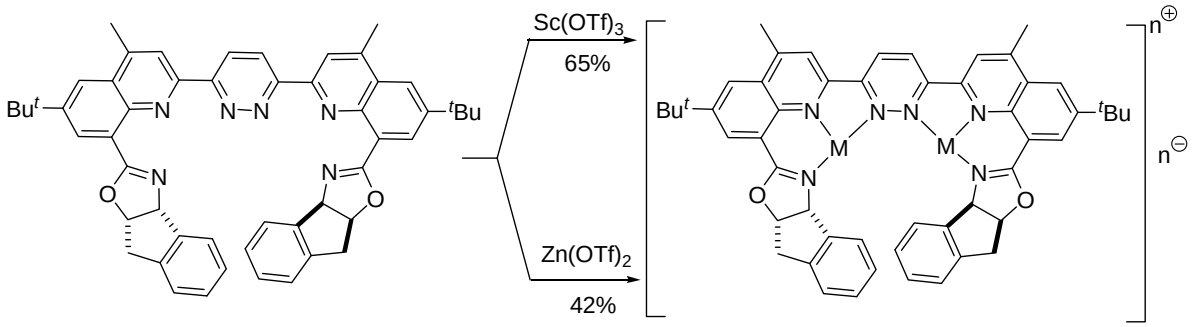
Scheme 1.28

Once the ligand was obtained, we attempted preparing bimetallic complexes with various transition metals (Scheme 1.28 & Scheme 1.29). A yellow solid was obtained on complexation of ligand **97** with nickel perchlorate (Scheme 1.28). The catalytic activity of this new metal complex was tested for 1,4-addition of indole to non-chelating α, β-unsaturated ketones.



Scheme 1.29

1,4-indole addition to acyclic α, β-unsaturated ketone **99** in presence of 20 mol% catalyst (**98**) provided the desired product with moderate yield but was racemic (Scheme 1.29). There was no improvement of selectivity in presence of molecular sieves. When the reaction was attempted with 1,3-cyclohexenone (**73**), racemic products were obtained both in absence and presence of molecular sieves (Scheme 1.29). Complex formation of the neutral pyridazine ligand (**97**) was attempted with other transition metals such as Sc and Zn. When the ligand was treated with $Sc(OTf)_3$ as well as $Zn(OTf)_2$, homogenous solutions were observed in both cases (Scheme 1.30). The solutions were filtered and powdery solid was obtained in either case on removal of solvent from the filtrate.



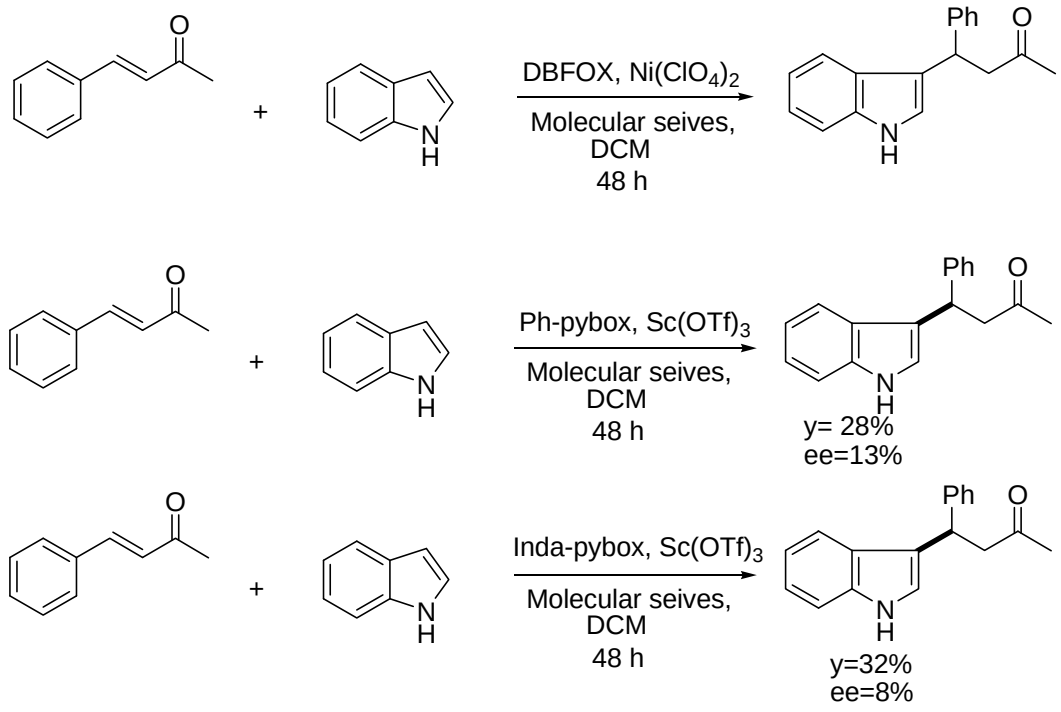
Scheme 1.30

The catalytic activity of both the complexes was studied for indole addition to α,β-unsaturated ketones. However, racemic products were obtained with yields less than 25% using these new bimetallic complexes (Scheme 1.31).

Catalyst	Solvent	Time (h)	Yield (%)	ee (%)
Sc-complex	CH_2Cl_2	24	22	racemic
Zn-complex	CH_2Cl_2	24	15	racemic

Scheme 1.31

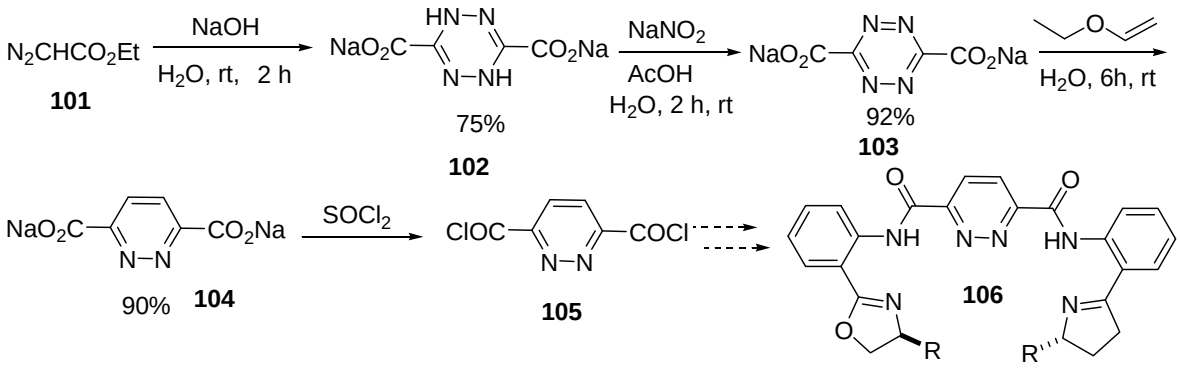
Since only racemic products were obtained, we could not confirm single carbonyl activation by two metals in the catalytic cycle. To get an insight and compare with already known monometallic box complexes, we performed the same reaction with monometallic chiral complexes as shown in Scheme 1.32. Interestingly, DBFOX-$Ni(ClO_4)_2$ system showed no reaction. But when Ph-pybox-$Sc(OTf)_3$ and Inda-pybox-$Sc(OTf)_3$ systems were used as catalysts, desired products were obtained in both cases even providing some levels of enantioselectivity.



Scheme 1.32

Currently, we are trying to get single X-ray crystal structures for these catalysts to get an insight into the geometry of these complexes which might facilitate us to design new bimetallic chiral ligands to attain our goal of successful asymmetric transformations for simple α,β-unsaturated carbonyl compounds. After testing the catalytic activity of neutral pyridazine ligand, we opted to synthesize a dianionic pyridazine ligand (**106**) as shown in Scheme 1.33. Owing to the fact that 3, 6-pyridazinedicarboxylic acid[57] is highly unstable,

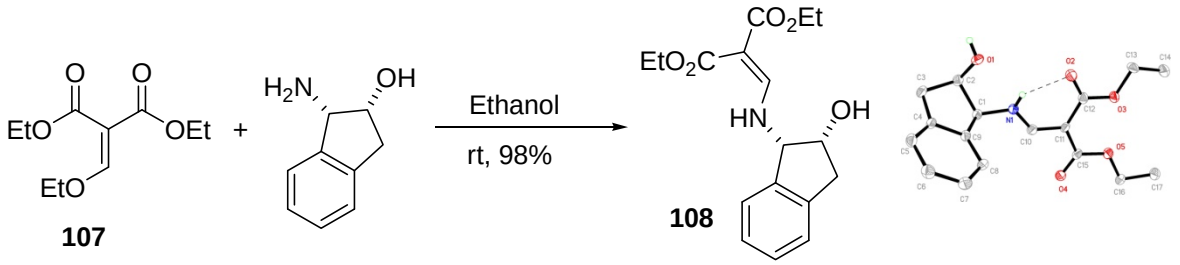
3,6-pyridazine diacid chloride (**105**) was chosen to be the precursor for the desired ligand (Scheme 1.33) . Following a known synthetic route[57], we were able to obtain a reduced tetrazine (**102)** by treating ethyl diazoacatate (**101)** with NaOH. Compound **102** was oxidized with sodium nitrite in presence of acetic acid to get the sodium salt of tetrazine diacid[57] (**103)**.



Scheme 1.33

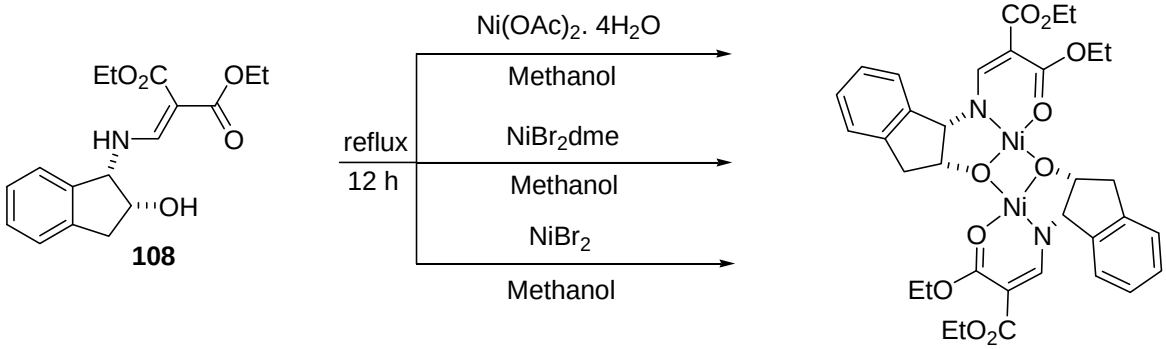
Upon reaction with ethyl vinyl ether, the tetrazine sodium salt (**103**) provided the pyridazine sodium salt **104**. Unfortunately, this salt was insoluble in common organic solvents and we were unable to obtain the desired ligand **106** following this synthetic route.

We were able to synthesize a chiral binuclear ligand starting from compound **107** and an enantiopure amino indanol (Scheme 1.34).



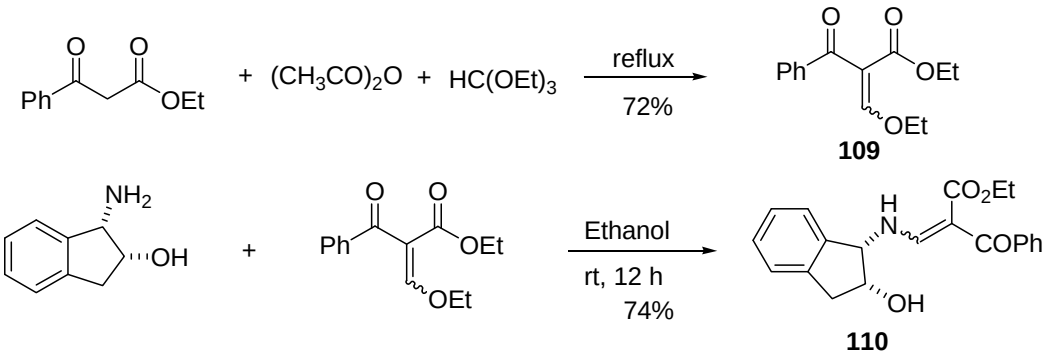
Scheme 1.34

The aminoindanol was reacted with the vinylethoxy compound (**107)** in ethanol to obtain the hydroxylamine type ligand **108** with almost quantitative yield. A single X-ray crystal structure of this new ligand was obtained (Scheme 1.34). Unfortunately, complex formation of this new ligand (**108**) with various transition metals was not successful (Scheme 1.35). ^{1}HNMR always showed the presence of the ligand only.



Scheme 1.35

A similar ligand was also synthesized starting from the ethoxy vinyl compound **109**. Compound **109** was treated with chiral aminoindanol to obtain the corresponding enamine ligand **110** as an E/Z mixture (Scheme 1.36). Several transition metal salts under various conditions were treated with this ligand only to recover unreacted compound **110**.



Scheme 1.36

Conclusion

Development of novel chiral bimetallic complexes has been demonstrated in this chapter. Ligands with different electronic and geometric properties were prepared. These binucleating chiral ligands were synthesized in a few steps from easily accessible precursors. Various transition metal complexes were prepared and tested in 1,4-additions of indole to α,β-unsaturated carbonyl compounds. X-ray crystal structures of these novel chiral complexes show that these catalysts can be capable of activating simple to α,β-unsaturated carbonyl systems and might catalyze 1,4-Michael additions, or Diels-Alder reactions of these systems including ketones, esters or amides.

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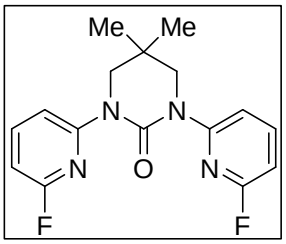
Experimental

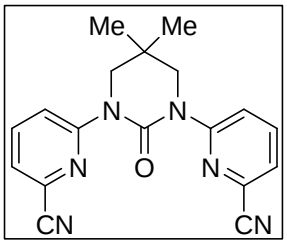
General information: Starting materials, reagents and solvents were purchased from commercial sources and were used as received. Methanol was distilled over magnesium methoxide prior to use. Tetrahydrofuran was distilled over sodium/benzophenone prior to use. Chlorobenzene and anhydrous DMSO were purchased from commercial sources and were used without further purification. Reactions were run under an atmosphere of dry nitrogen unless mentioned otherwise. Purification of the reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, iodine stain or permanganate stain followed by heating. Melting points were recorded on an open end Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.26 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, app = apparent), coupling constant(s) in Hz and integration. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Optical rotation was recorded on a Perkin-Elmer 343 polarimeter at 589 nm and 293 K.

Preparation of 1,3-difluoro-5,5-dimethyltetrahydropyrimidin-2(1H)-one (61). To a



slurry of NaH (11.02 mmol, 0.441g, 60 weight % in mineral oil) in 8 mL of THF was added 5,5-dimethyltetrahydropyrimidin-2(1H)-one[1] (**60**) (5.01 mmol, 0.642 g). The reaction mixture was subsequently heated under reflux for 30 min. To the resulting thick slurry was added 2,6-difluoropyridine (11.02 mmol, 1 mL) in 3 mL of THF and heating under reflux was continued for 24 h. After completion the reaction mixture was allowed to cool to room temperature and the volatiles were removed under reduced pressure. Ethyl acetate (100 mL) was added to the residue and the resulting solution was washed with saturated $NaHCO_3$ (100 mL) followed by brine, then dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (4:1 v/v Hexanes/ EtOAc) to provide the title compound (61%) as a white crystalline solid; R_f = 0.35 (4:1 Hexanes/EtOAc); mp: 120 °C; IR (KBr) 3080, 2967, 2895, 1668, 1579, 1305, 1246, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.79 (m, 2H), 7.76-7.69 (m, 2H), 6.66-6.62 (m, 2H), 3.77 (s, 4H), 1.20 (s, 6H) ^{13}C NMR (126 MHz, $CDCl_3$) 161.91 (d_{C-F}, J = 238.6 Hz), 153.68, 153.33 (d_{C-F}, J = 13.2 Hz), 141.74 (d_{C-F}, J = 7.4 Hz), 116.45 (d_{C-F}, J = 4.6 Hz), 104.08 (d_{C-F}, J = 35.9 Hz), 56.8, 29.7, 24.5; *m/z* (ESIMS) 319.5 $[M + H]^+$.

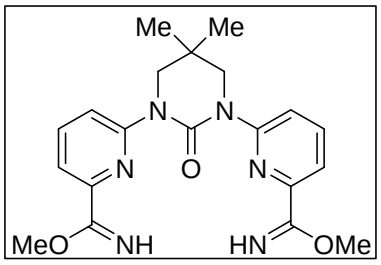
Preparation of 1,3-dicyano-5, 5-dimethyltetrahydropyrimidin-2(1H)-one (62). To a



mixture of compound **61** (2.80 mmol, 0.890 g) and KCN (8.77 mmol, 0.571 g) was added 30 mL of anhydrous DMSO. The resulting mixture was heated at 130 °C for 40 h. The reaction mixture was allowed to cool to room temperature and water

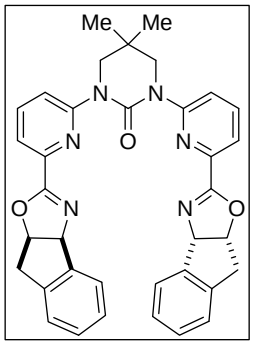
(200 mL) was added. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude material was purified by silica gel column chromatography (1:1 v/v Hexanes/ EtOAc) to give the title compound (66%) as white crystalline solid with R_f = 0.40 (1:1 Hexanes/ EtOAc); mp: 208-210 °C; IR (KBr) 3131, 2976, 2235, 1672, 1582 cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.6, 0.7 Hz, 2H), 7.76 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.45 (dd, *J* = 7.4, 0.8 Hz, 2H), 3.85 (s, 4H), 1.24 (s, 6H) ^{13}C NMR (125 MHz, $CDCl_3$) 155.5, 153.6, 137.5, 131.0, 124.3, 123.4, 117.0, 56.7, 29.5, 24. 4 ; *m/z* (ESIMS) 333.3 $[M+H]^+$.

Preparation of Dimethyl 6,6'-(5,5-dimethyl-2-oxodihydropyrimidine-1,3(2H,4H)-diyl) dipicolinimidate (63). Compound **62** (1.77 mmol, 0.589 g) was suspended in methanol (10 mL). Freshly prepared 1.1 (M) NaOMe (0.354 mmol, 0.322 mL) was added to the reaction mixture. After 36 h of stirring at room temperature, a clear solution was obtained. Acetic acid (0.372 mmol, 0.021 mL) was added and the solvent was removed under reduced pressure to give the title compound which was used directly in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 2H), 7.92 (app d, *J* = 8.3 Hz, 2H), 7.70-7.63 (m, 2H), 7.51 (app d, *J* = 7.5 Hz, 2H), 3.93 (s, 6H), 3.82 (s, 4H), 1.18 (s, 6H) ^{13}C NMR (125 MHz, $CDCl_3$) 166.6, 154.1, 153.6, 144.9, 137.8, 121.6, 116.6, 56.6, 53.6, 29.4, 24.4.



Preparation of 1,3-bis(6-((3aS,8aR)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-pyridin-2-yl)-5,5-dimethyltetrahydropyrimidin-2(1H)-one (64). Compound **63** (0.926 mmol, 0.367 g) was mixed with (1S, 2R)-1-amino-2,3-dihydro-1H-inden-2-ol (2.03 mmol 0.304 g) in 5 mL of anhydrous dichloromethane. The resulting mixture was heated

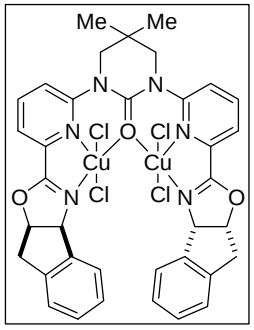
at 70 °C in a sealed tube for 48 h. The crude material was purified by silica gel column



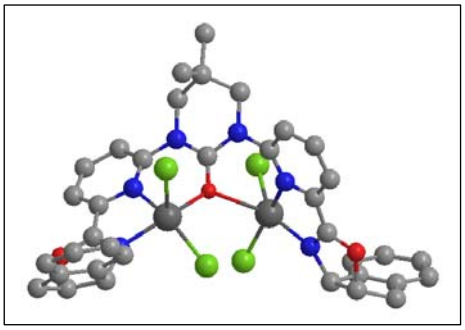
chromatography which provided the title compound as a pale yellow solid in 84% yield. (R_f = 0.25, EtOAc). mp = 125–130 °C; $[\alpha]_D^{20}$ – 74.8 (C 1, EtOH); IR (KBr) 3069 , 2959, 1666, 1576, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (app d, *J* = 7.89 Hz, 2H), 7.75-7.71 (m, 2H), 7.69 – 7.62 (m, 2H), 7.61-7.56 (m, 2H), 7.29 – 7.26 (comp, 6H), 5.81 (d, *J* = 8.0 Hz, 2H), 5.58 – 5.53 (m, 2H), 3.89-3.80 (comp, 4H), 3.52 (dd, *J* = 11.3, 6.8 Hz, 2H), 3.47-3.40 (m, 2H), 1.20 (s, 6H) ^{13}C NMR (125 MHz, $CDCl_3$) 163.3, 155.1, 154.2, 145.0, 141.9, 140.0, 137.3, 128.8, 127.8. 126.0, 125.5, 122.4, 120.47, 83.9, 77.5, 57.0, 40.0, 30.0, 24.9; *m/z* (ESIMS) 597.4 $[M + H]^+$, 619.5 $[M + Na]^+$.

Alternative route for 1,3-bis(6-((3aS,8aR)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)pyridin-2-yl)-5, 5-dimethyltetrahydropyrimidin-2(1H)-one (64). Compound **62** (0.602 mmol, 0.2 g), (1S, 2R)-1-amino-2, 3-dihydro-1H-inden-2-ol (1.324 mmol, 0.198 g), $ZnBr_2$ (1.324 mmol, 0.298 g) were mixed in 2 mL of chlorobenzene. The resulting mixture was heated under reflux for 12 h. Once cooled to room temperature, EtOAc (50 mL), water (20 mL), saturated NH_4Cl (10 mL) and 2 mL of aqueous ammonia were added. The resulting biphasic mixture was stirred rapidly for 15 min. The organic layer was separated and then washed with water (50 mL) followed by brine. It was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude material was purified by silica gel column chromatography (R_f = 0.25, EtOAc), to provide the title compound with 80% yield. The desired compound can also be purified by recrystallization (Hexanes/EtOAc) with 72% yield.

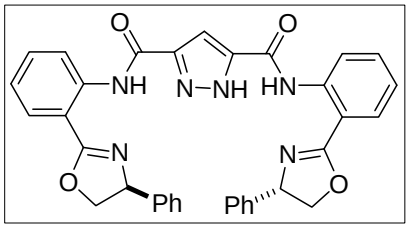
Preparation of 64•2CuCl$_2$. Compound **64** (0.05 mmol, 0.03 g) was dissolved in 2 mL of



anhydrous dichloromethane. Anhydrous $CuCl_2$ (0.106 mol, 0.014 g) was added and the resulting mixture was stirred for 3 h at room temperature. The resulting green solution was filtered and subsequently layered with hexanes. Crystals suitable for single X-ray crystallographic analysis were obtained after several days.



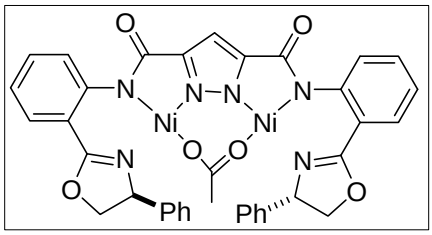
Preparation of N3,N5-bis(2-((S)-4-phenyl-4,5-dihydrooxazol-2yl)phenyl) 1Hpyrazole-3, 5-dicarboxamide (68). 9 mL anhydrous dichloromethane was added to



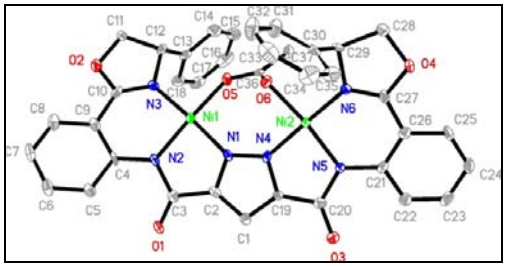
pyrazole diacidchloride (0.166 g, 0.858 mmol) followed by DMAP (0.262 g, 2.146 mmol) and stirred for 15 minutes. Compound **67** (0.450 g, 1.88 mmol) was added to the mixture and stirred for 24 h at room temperature. The solvent was removed under reduced pressure. The crude material was purified by silica gel coloumn chromatography (7:3 Hexanes/EtOAc, R_f = 0.45) to obtain the desired product as white solid with 85% yield. Mp: 126 ^{o}C; IR (KBr) 3434, 3175, 3027, 2966, 1679, 1633, 1586, 1534, 1448, 1299 cm^{-1}; ^{1}H NMR (500 MHz, cdcl$_3$) δ 13.30 (s, 2H), 12.25 (s, 1H), 8.91 (s, 2H), 7.93 (app dd, *J* = 7.8, 1.3 Hz, 2H), 7.54 (app dd, *J* = 11.4, 4.3 Hz, 2H), 7.38 – 7.23 (comp, 8H), 7.14 (comp, 4H), 5.54-5.50 (m, 2H), 4.71 (dd, *J* = 25.1,

15.6 Hz, 2H), 4.24 (d, J = 68.6 Hz, 2H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.08, 164.04, 141.20, 139.57, 132.61, 129.29, 128.66, 127.58, 126.29, 122.61, 120.02, 113.54, 105.87, 72.81, 69.61, 60.32, 20.96, 14.12. *m/z* (ESIMS) 597.2 $[M]^+$, 619 $[M+Na]^+$.

Preparation of 68•2Ni(OAc)$_2$. To a suspension of compound **68** (0.125 g, 0.21 mmol))

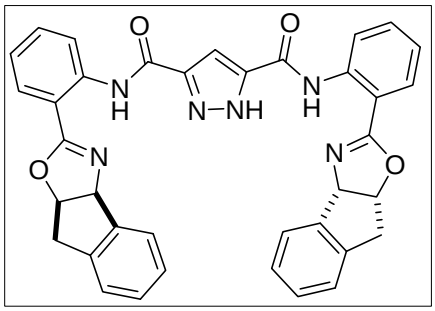


in (8 mL) anhydrous methanol, $Ni(OAc)_2$•$4H_2O$ (0.13 g, 0.524 mmol) was added and was refluxed in methanol. After 2 h the mixture was a clear solution. A precipitate formation took place after 2.5 h. After 6 h, the mixture was cooled down to room temperature and the precipitate was filtered and washed with cold 10 mL methanol. The green precipitate was taken up in 10 mL dichloromethane and solvent was removed to dryness to provide green solid with 95% yield. Subsequently, it was layered with DCM/ Hexanes. Crystals suitable for single X-ray crystallographic analysis were obtained after several days.



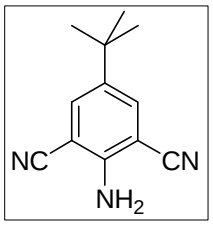
Preparation of N3,N5-bis(2-((3aS,8aR)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)phenyl)-1H-pyrazole-3,5-dicarboxamide (82). DMAP (0.166 g, 1.362 mmol) was added to a suspension of pyrazole diacidchloride (0.105 g, 0.545 mmol) in 5 mL anhydrous dichloromethane and stirred for 10 min at room temperature. Compound **67** was added (0.3 g, 1.19 mmol) to the mixture and was stirred for 24 h. The solvent was removed under reduced pressure and the desired product (white solid) was isolated (R_f =

0.4) by silica gel coloumn chromatography (7:3 Hexanes/EtOAc) with 85% yield. ^{1}H



NMR (300 MHz, $CDCl_3$) δ 13.53 (s, 2H), 12.49 (s, 1H), 8.96 (app d, *J* = 8.4 Hz, 2H), 7.87 (app d, *J* = 7.9 Hz, 2H), 7.83 – 7.68 (comp, 3H), 7.49-7.53 (m, 2H), 7.14-7.24 (comp, 3H), 7.11 (comp, 5H), 5.81 (d, *J* = 17.5 Hz, 2H), 5.43 (m, 2H), 3.51 (dd, *J* = 18.0, 6.6 Hz, 2H), 3.36 (d, *J* = 18.0 Hz, 2H).

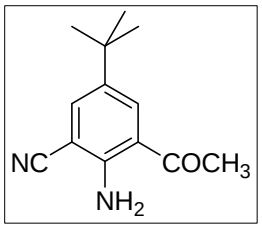
Preparation of 2,6-dicyano-4-*t*-butylaniline (91). To a solution of 2, 6-dibromoaniline



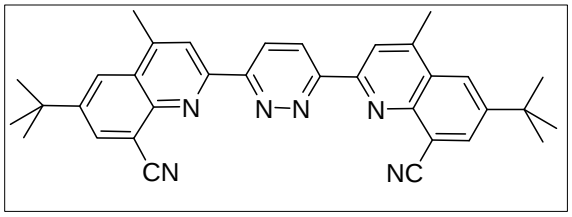
(10 g, 32.6 mmol) in 250 mL anhydrous DMF, 12 g (131 mmol) CuCN was added and the resultant mixture was refluxed for 12 h. As TLC shows complete consumption of starting material, the reaction mixture was cooled to room temperature and a solution of $FeCl_3$ (6.5 x 12) in 24 mL conc. HCl and 80 mL of water was added to the mixture. It was heated at 75 ^{o}C for 1 h, cooled to room temperature and extracted with ethyl acetate (5 x 400 mL). The collected organic layer was washed with saturated NaCl solution (2 x 300 mL) and dried over anhydrous Na_2SO_4 followed by removal of solvent under reduced pressure. The crude product was purified by silica gel chromatography using 7:3 Hexanes/Et_2O (R_f = 0.35) to provide the labeled compound with 70% yield as white solid. Mp: 100 ^{o}C; IR (KBr) 3473, 3250, 2869, 1655, 1639, 1365 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 2H), 5.03 (s, 2H), 1.23 (s, 9H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.07, 141.17, 134.41, 116.13, 97.26, 34.09, 30.86; *m/z* (ESIMS) 198.2 $[M-H]^{+}$.

Preparation of 2-acetyl-6-cyano-4-*t*-butylaniline (95). To a solution of MeMgCl (4 mmol, 1.5 mL, 3 M) in 4 mL anhydrous THF, CuBr (0.078 mmol, 0.011 g) was added at

–78°C. The reaction mixture was then warmed to room temperature and stirred for 10 min. A solution of compound **91** (2.5 mmol, 0.498 g) and TBSCl (2.76 mmol, 0.414 g)) in THF (4 mL) was added to the mixture at -78°C. Subsequently, the reaction mixture was warmed to room temperature and stirred for 3 h. As TLC shows completion of the starting material, the mixture was cooled down to 0°C. 10 mL distilled water was added to the mixture and was extracted with diethyl ether (2 x 15 mL). The combined organic layer was dried over anhydrous $MgSO_4$ followed by solvent removal under reduced pressure. The crude material was purified by silica gel chromatography using 1: 4 Diethyl ether/Hexanes to provide the labeled compound as yellow solid (R_f = 0.4) with 75% yield. Mp: 106 °C; IR (KBr) 2964, 2218, 1655, 1624, 1564, 1359 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.59 (s, 1H), 6.90 (s, 2H), 2.60 (s, 3H), 1.29 (s, 9H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.02, 149.54, 138.20, 135.23, 133.64, 118.49, 98.04, 33.87, 31.06, 27.75, 25.60; *m/z* (ESIMS) 240.3 $[M+Na]^+$.

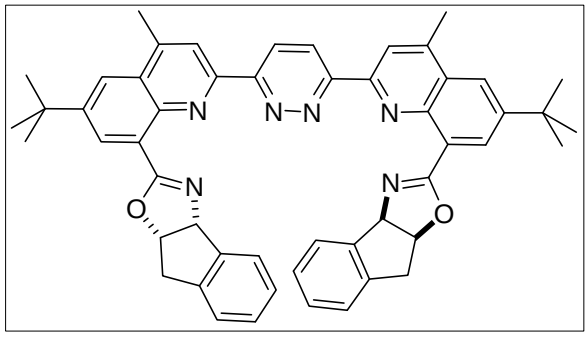


Preparation of 2,2'-(pyridazine-3, 6-diyl)bis(6-tert-butyl-4-methylquinoline-8-carbonitrile) (96). To a suspension of 3,6-diacetyl pyridazine (104 mg, 0.634 mmol) and compound **95** (1.33 mmol, 0.288 g) in absolute ethanol (13.48 mL), saturated ethanolic KOH (0.6 mL) was added and refluxed for 12 h. After completion of starting material (checked by TLC), solvent was removed under reduced pressure until ~3 mL solvent remained. 3 mL distilled water was added to obtain a solid precipitate. The precipitate was filtered and washed with ethanol to obtain a yellow solid with 85% yield. Mp: >250 °C; IR (KBr) 1597, 1463, 2339, 1487,



1397, 2963 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 2H), 8.89 (s, 2H), 8.26 (m, 2H), 8.20 (m, 2H), 2.88 (s, 6H), 1.48 (s, 18H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.86, 153.61, 149.59, 145.86, 145.32, 134.47, 128.18, 126.14, 123.87, 120.83, 117.46, 113.53, 35.27, 31.24, 31.16, 30.99, 18.96; *m/z* (ESIMS) 526.0 $[M+H]^+$.

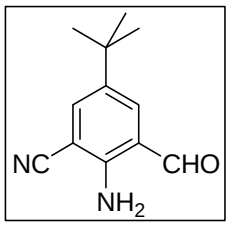
Preparation of 3,6-bis(6-tert-butyl-8-((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-4-methylquinolin-2-yl)pyridazine (97). To a mixture of compound **96**



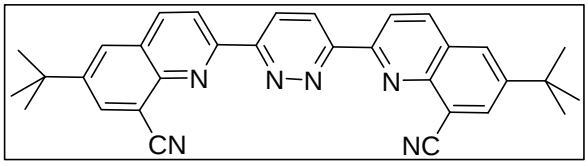
(0.191 mmol, 0.1 g), (1S, 2R)-1-amino-2, 3-dihydro-1H-inden-2-ol (0.42 mmol, 0.063 g) in 4 mL chlorobenzene, $ZnBr_2$ (0.419 mmol, 0.094 g) was added and refluxed for 24 h. As the starting material was consumed (checked by TLC) the reaction mixture was cooled to room temperature. 0.1 mL ammonia, followed by 0.6 mL sat. NH_4Cl and EtOAc (2 mL) was added and stirred for 30 min resulting in a biphasic mixture. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The crude material was subjected to silica gel chromatography (EtOAc) to obtain the desired product (R_f = 0.1) with 60% yield. Mp: 150°C; IR (KBr) 2957, 2868, 1655, 1597, 1478, 1459, 1363 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 2H), 8.46 (s, 2H), 8.16 – 8.02 (m, 4H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.53 – 7.35 comp, 7H), 6.03 (d, *J* = 8.0 Hz, 2H), 5.82-5.76 (m, *J* = 6.6 Hz, 2H), 3.67 (dd, *J* = 17.9, 6.4 Hz, 2H), 3.60 (d, *J* = 17.7 Hz, 2H), 2.83 (s, 6H), 1.46 (s, 18H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.91, 158.42, 152.74, 149.21, 145.14, 144.18, 142.45, 140.03, 129.91, 128.51, 128.49, 128.42, 127.60, 126.00, 125.82,

125.22, 121.60, 120.08, 83.51, 77.54, 40.18, 35.30, 31.22, 19.31; *m/z* (ESIMS) 789.4 $[M]^+$.

Preparation of 2-amino-5-(tert-butyl)-3-formylbenzonitrile (92). Compound **91** (0.38 g, 1.907 mmol) was dissolved in 5 mL of anhydrous dichloromethane followed by slow addition of diisobutyl aluminium hydride (2.28 mL, 1 molar) at 0°C. After 3 h stirring at room temperature, 5 mL ether was added and cooled to 0°C. 3 mL water was added slowly followed by addition of 3 mL 15% aqueous sodium hydroxide. 9 mL water was added and the mixture was warmed to room temperature to stir for 15 minutes. Anhydrous $MgSO_4$ was added and stirred for 15 minutes. The salts were filtered and solvent was removed under reduced pressure. The desired product was isolated as yellow solid by silica gel coloumn chromatography (4:1 Hexanes/Ether, R_f = 0.35) with 32% yield. Mp: 108°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.68 (app d, *J* = 2.3 Hz, 1H), 7.61 (app d, *J* = 2.3 Hz, 1H), 6.69 (s, 2H), 1.28 (s, 9H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.29, 149.08, 139.28, 137.58, 135.81, 118.92, 116.59, 97.42, 33.90, 30.99.

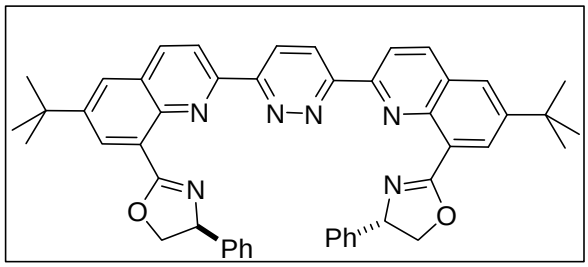


Preparation of 2,2'-(pyridazine-3,6-diyl)bis(6-(tert-butyl)quinoline-8-carbonitrile) (94). To a suspension of 3,6-diacetyl pyridazine (**93**) (100 mg, 0.609 mmol) and compound **92** (0.308 g, 1.52 mmol) in absolute ethanol (12 mL), saturated ethanolic KOH (0.6 mL) was added and refluxed for 12 h. After completion of starting material (checked by TLC), solvent was removed under reduced pressure until 3 mL solvent remained. 3 mL distilled water was added to obtain a solid precipitate. The precipitate was filtered and washed with ethanol



to obtain a brown solid with 76% yield. IR (KBr) 3051, 2957, 2904, 2868, 2226, 1594, 1561, 1488, 1440.1, 1242.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99-8.89 (m, 4H), 8.34 (d, *J* = 8.6 Hz, 2H), 8.21 (app d, *J* = 2.0 Hz, 2H), 8.02 (app d, *J* = 2.0 Hz, 2H), 1.47 (s, 18H); *m/z* (ESIMS) 497.4 $[M]^+$, 535.3 $[M+K]^+$.

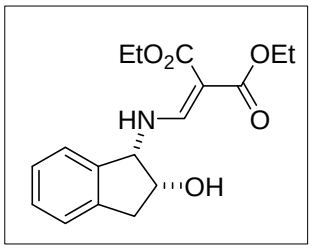
Preparation of 3,6-bis(6-(tert-butyl)-4-methyl-8-((S)-4-phenyl-4,5-dihydrooxazol-2-yl)quinolin-2-yl)pyridazine (95). To a mixture of compound **94** (0.201 mmol, 0.1 g),



(S)-2-phenylglycinol (0.443 mmol, 0.061 g) in chlorobenzene (4 mL), $ZnBr_2$ (0.443 mmol, 0.1 g) was added and refluxed for 24 h. As the starting material is consumed (checked by TLC) the reaction mixture was cooled. 0.1 mL ammonia, followed by 0.6 mL sat. NH_4Cl and EtOAc (2 mL) was added and stirred for 30 min to result in a biphasic mixture. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The crude material was purified by alumina coloumn chromatography using EtOAc as eluent to obtain the desired product (50%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.6 Hz, 1H), 8.81 (s, 1H), 8.49 – 8.19 (m, 3H), 8.0-7.8 (m, 2H), 7.50 (dd, *J* = 31.0, 5.4 Hz, 3H), 7.41 – 7.27 comp, 6H), 7.24 – 7.13 (comp, 4H), 5.78 – 5.37 (m, 2H), 4.97 (dd, *J* = 10.2, 8.5 Hz, 2H), 4.45 (dd, *J* = 27.5, 19.5 Hz, 2H), 1.55 (s, 18H); *m/z* (ESIMS) 737.4 $[M]^+$.

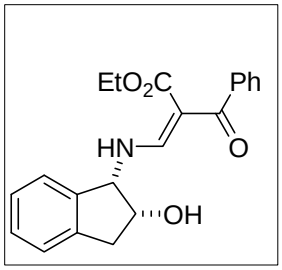
Preparation of Diethyl 2-((((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)methylene)malonate (108). (1S, 2R)-1-amino-2, 3-dihydro-1H-inden-2-ol (0.500 g, 3.35 mmol) was dissolved in absoulte ethanol (7 mL). After 5 minutes of vigourous stirring a clear solution was obtained. Diethyl 2-(ethoxymethylene)malonate

(0.797 g, 3.69 mmol) was added to the mixture. After stirring the mixture at room



temperature for 20 minutes, a solid white precipitate formed. After 2 h, the white solid was filtered and washed with cold ethanol. The precipitate provided the desired product with 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (dd, *J* = 14.1, 8.3 Hz, 1H), 8.13 (d, *J* = 14.4 Hz, 1H), 7.47 – 6.99 (comp, 4H), 4.88 – 4.48 (m, 2H), 4.35 – 4.02 (m, 4H), 3.95 – 3.52 (m, 1H), 3.22 – 2.79 (m, 2H), 1.51 – 1.03 (m, 6H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.48, 166.27, 159.00, 140.20, 139.09, 128.61, 126.97, 125.32, 124.37, 89.89, 73.24, 66.76, 59.60, 59.48, 39.05, 14.20, 14.10.

Preparation of Ethyl 2-benzoyl-4-(((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)amino)but-3-enoate (110). (1S, 2R)-1-amino-2, 3-dihydro-1H-inden-2-ol (0.100 g, 0.67 mmol) was dissolved in absoulte 3 mL ethanol. E/Z mixture of ethyl 3-ethoxy-2-

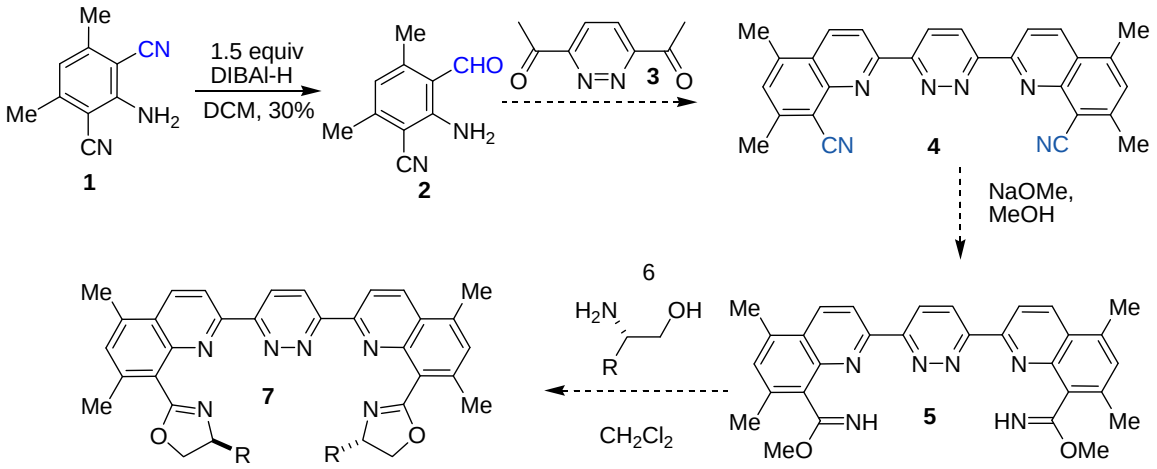


phenylacrylate (0.183 g, 0.737 mmol) was added to the mixture. After 2 h of stirring at room temperature, the solvent was removed under reduced pressure. The desired product was isolated by silica gel coloumn chromatography (7:3 Hexanes/EtOAc, R_f = 0.2) with 67% yield. ^{1}H NMR (300 MHz, cdcl$_3$) δ 10.77 (dd, *J* = 13.9, 8.2 Hz, 1H), 8.15 (d, *J* = 14.1 Hz, 1H), 7.57 (app d, *J* = 7.0 Hz, 1H), 7.38-7.36 (m, 4H), 7.26 – 7.17 (m, 4H), 4.78 – 4.59 (m, 2H), 4.01 – 3.95 (m, 2H), 3.70 – 3.41 (m, 1H), 3.15 – 2.96 (m, 2H), 0.93 (t, *J* = 7.1 Hz, 3H).

Chapter 2

Introduction

One of our first attempts towards the synthesis of binuclear chiral ligands included formation of quinoline containing systems (Scheme 2.1). We presumed that a Friedländer condensation of aminobenzaldehyde **2** with 3, 6-diacetyl-pyridazine **(3)** might lead to the dinitrile pyridazine compound **4**.[1]



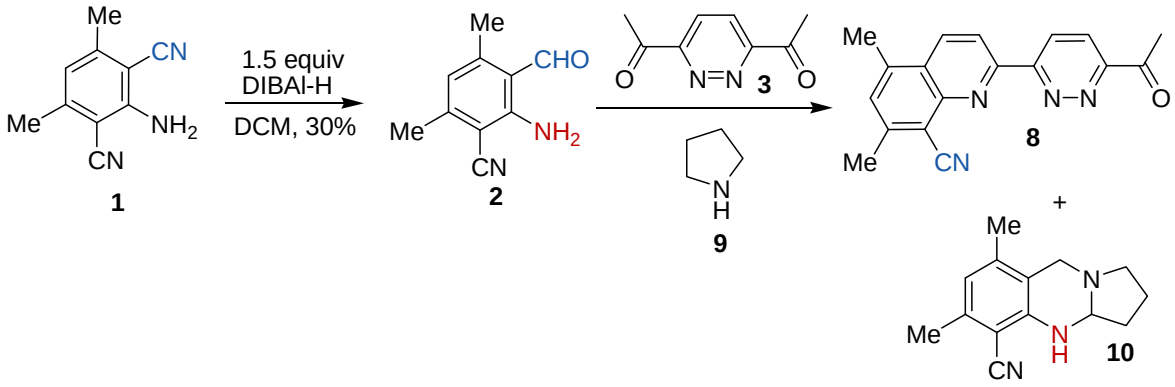
Scheme 2.1

We presumed that the dinitrile compound (**4**) should provide the bis-imidate[2] **5** on treatment with NaOMe. In the final step, incorporation of bisoxazoline[3] using a chiral amino alcohol (**6)** should provide the desired chiral binuclear ligand (**7)**.

Discovery

Based on the regular protocol, we tried a Friedländer condensation of cyanoaminobenzaldehyde **2** and 3, 6-diacetylpyridazine (**3**) in presence of pyrrolidine as the base to obtain the quinoline moiety of the targeted ligand (**7**). My colleague Mr. Chen Zhang discovered that the aminobenzaldehyde **2** can react with the pyrrolidine itself under Friedländer conditions resulting in a ring-fused aminal **10** (Scheme 2.2). The

formation of this new structural motif was confirmed by various analytical methods including single X-ray crystallography. A side product was isolated from the same reaction which was found to be the mono Friedländer condensation product **8.** A completely insoluble precipitate was isolated from the reaction which we anticipated to be the desired bis Friedländer product.

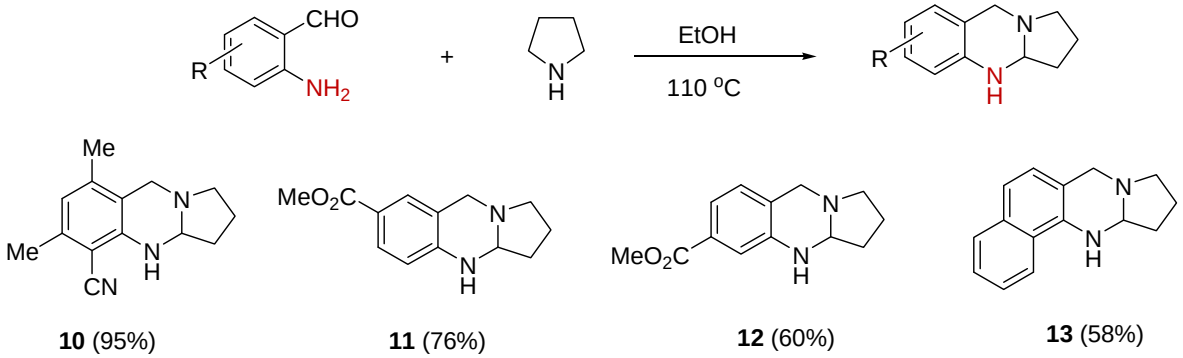


Scheme 2.2

To our knowledge, aminals have not previously been reported as side product of Friedländer reactions. We recently reported this new α-functionalization reaction of cyclic amines to form ring fused aminals without using any metal or additive.[4] This is an important finding as we can directly functionalize nitrogen containing heterocycles that are essential fragments of important drug targets.[4]

Scope of the reaction

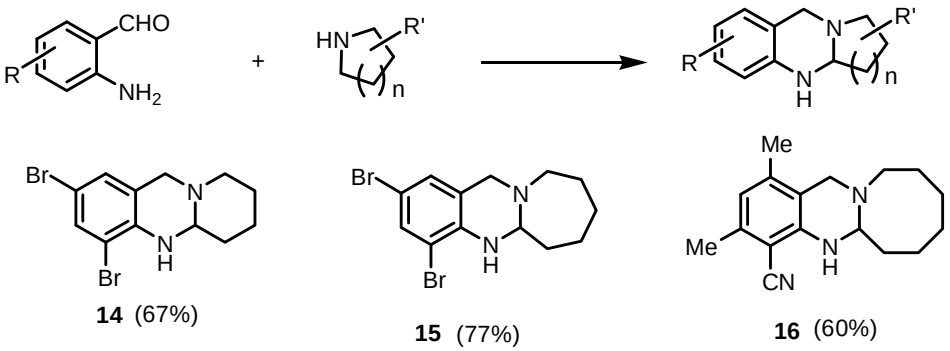
As the structure of the aminal was confirmed, we explored substrate scope of this novel reaction. Several aminobenzaldehydes were allowed to react with pyrrolidine (3 equiv.) in ethanol solution at reflux (Scheme 2.3). In general, we allowed the starting material aminobenzaldehydes to be consumed or performed the work up after 72 hours. Aminobenzaldehydes with different substituents patterns proved to be suitable substrates for this reaction providing the corresponding products in good yields Scheme 2.3).



10 (95%) **11** (76%) **12** (60%) **13** (58%)

Scheme 2.3

After successful reactions with variety of aminobenzaldehydes we investigated the scope of the base partner in this new methodology (Scheme 2.4). We observed almost no aminal when piperidine was used as a base partner. There was considerable improvement in yield once we attempted the reaction in sealed tube at 140 ^{o}C (Scheme 2.4). Interestingly, the seven membered azacycle provided the corresponding aminal (**15**) with improved yield (77%) under sealed tube condition. However, the eight membered analogue provided the desired aminal **16** but there was no improvement in yield from reflux to sealed tube (Scheme 2.4).



14 (67%) **15** (77%) **16** (60%)

Scheme 2.4

Mechanism & Application

A possible mechanism for this new methodology was hypothesized (Figure 2.1) that goes through a quinoidial intermediate **D**. We assume this intermediate (**D)** to be achieved

from iminium ion **C** by loss of proton. The quinoidial intermediate **D** might undergo a 1, 6-hydrogen shift to form the dipolar intermediate **E**. Finally **E** can form the ring fused aminal product.

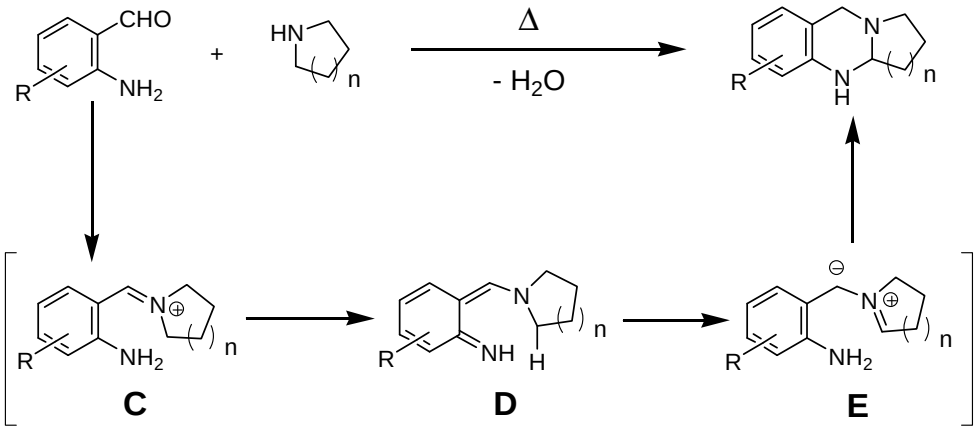
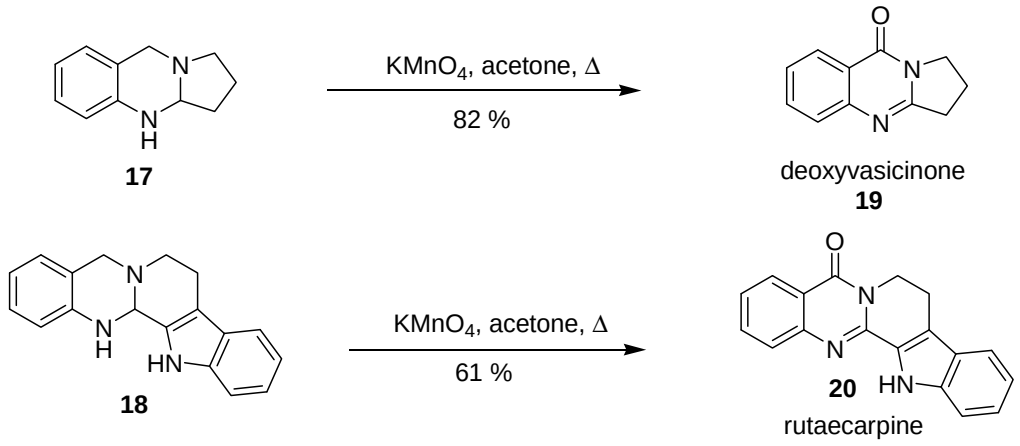


Figure 2.1

Interestingly, the reaction of aminobenzaldehyde with proline provided the same product as obtained in the corresponding reaction with pyrrolidine under identical conditions. Formation of 1, 3-dipolar intermediates in a decarboxylative manner on reaction of aldehydes with proline or other N-alkylated amino acids is well established in literature. Hence, our results with proline enriched the fact that the ring fused aminal formation is occurring through a 1, 3-dipolar intermediate supporting the mechanistic hypothesis we proposed for this newly developed methodology

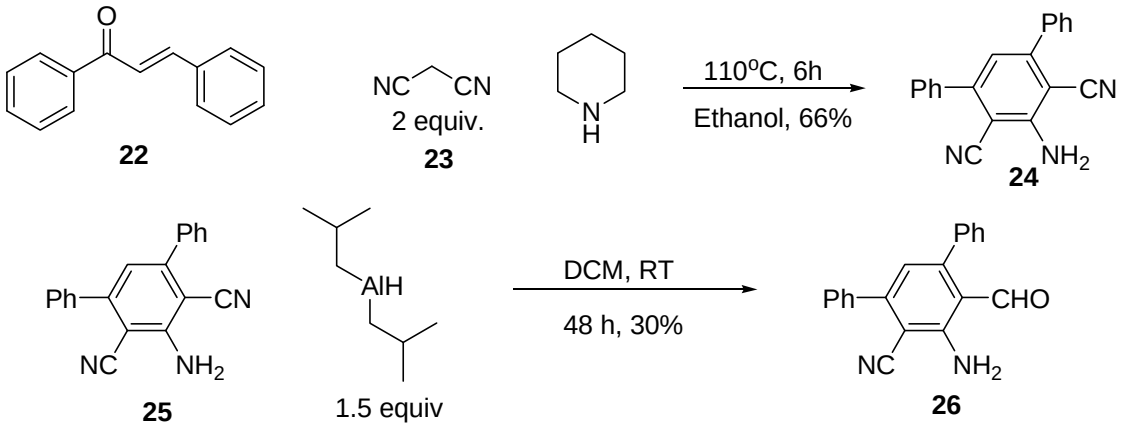
We were interested to explore the application of this newly discovered reaction in the synthesis of structural moieties that are of biological importance. To our delight we found that, in one step from aminal **17**, we achieved the natural product deoxyvasicinone **19** (Scheme 2.5) by selective oxidation with $KMnO_4$. The aminal **18** on treatment with $KMnO_4$, provided the natural product rutaecarpine **20**. This clearly shows that this newly

developed method not only takes place in mild conditions but can also provide natural products having diverse array of biological activities.[4]



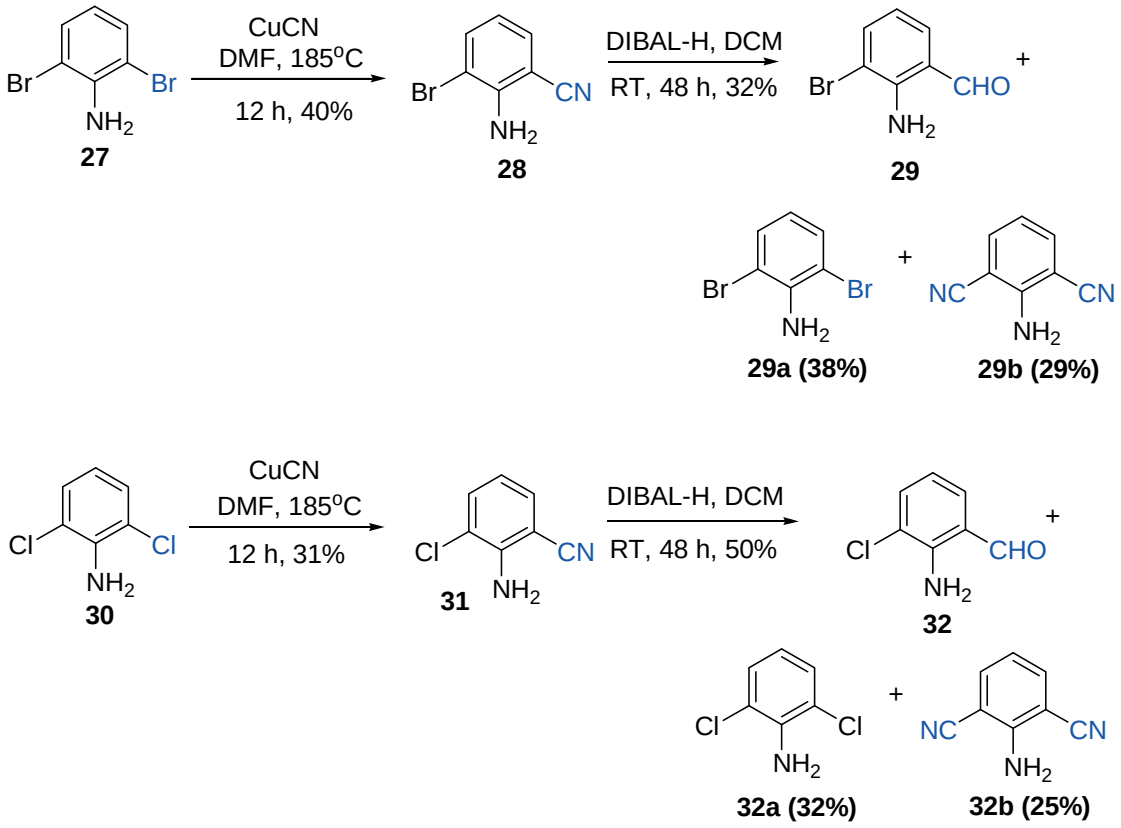
Scheme 2.5

All the aminobenzaldehydes were synthesized from commercially available compounds in either one or two steps. The aminobenzaldehydes were obtained by reduction of either aminonitriles or nitrobenzaldehydes following already known synthetic routes. The syntheses of the previously unknown aminobenzaldehydes were recently reported by our group.[4] The diphenyl aminobenzaldehyde **26** was synthesized from commercially available materials in two steps (Scheme 2.6).



Scheme 2.6

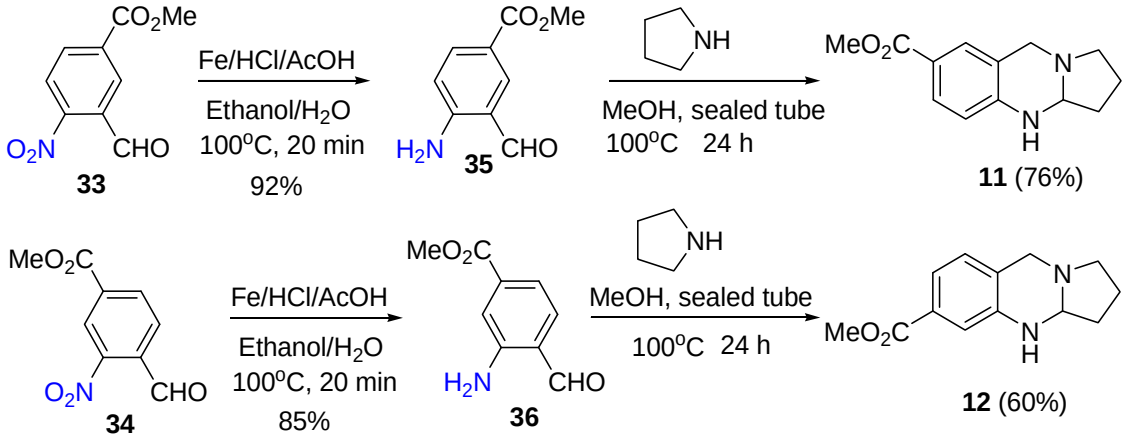
Chalcone (**22**) was treated with 2 equivalents of malonitrile **23** in presence of piperdine to provide the diphenyldicyanoaniline **24** in good yield (Scheme 2.6). The dicyano compound **24** was then reduced to the corresponding aminobenzaldehyde **26** using DIBAL-H. The aminobenzaldehyde **26** was isolated with only 30% yield. Attempts to increase the yield failed as considerable amounts of unconsumed starting material as well as bisaldehyde product were obtained. The halogentated aminobenzaldehydes (**29 & 32**) were synthesized from commercially available 2, 6-dihaloanilines in two steps (Scheme 2.7).



Scheme 2.7

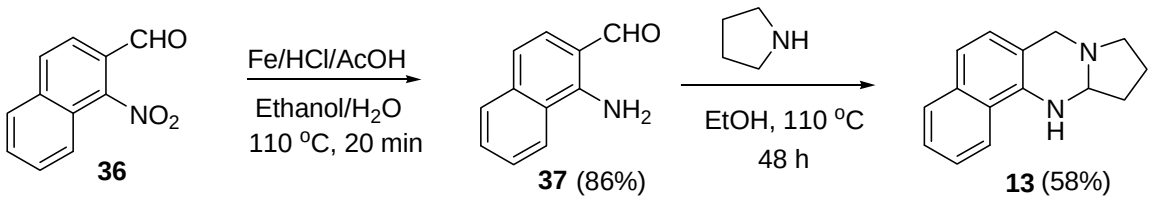
The first step included the nucleophilic displacement of halogens by copper cyanide (Scheme 2.7). 2, 6-dibromoaniline (**27**) provided better monocyanation compared to 2, 6-dichloroaniline (**30**) to obtain the corresponding mononitrile compounds (**28 & 31**).

These nitrile compounds were then reduced to the corresponding aminobenzaldehydes (**29** & **32**) by DIBAL-H. Due to formation of the dialdehyde as well as remaining starting material, yields were always less than 50%. Ester substituted aminobenzaldehydes were prepared from the commercially available nitrobenzaldehyde compounds (**33 & 34**) in two steps (Scheme 2.8). Reduction of the nitroesters (Scheme 2.8) with iron in presence of acid provided the corresponding aminobenzaldehydes in good yields. Aminal formation from compounds **33** & **34** in ethanol as solvent provided the corresponding transesterified products. To avoid transesterification, the reactions were performed in methanol as solvent in sealed tube. The aminobenzaldehydes provided the desired ring fused aminals with at least 60% yield when MeOH was used as the solvent (Scheme 2.8).



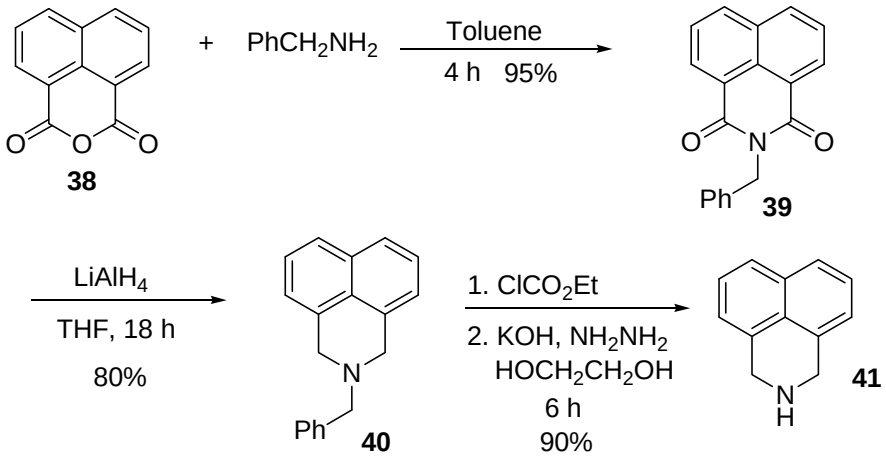
Scheme 2.8

The aminobenzaldehyde **37** was obtained (Scheme 2.9) from the corresponding nitro compound (**36**) by reduction using iron. Compound **37** provided the corresponding aminal (13) with 58% yield.



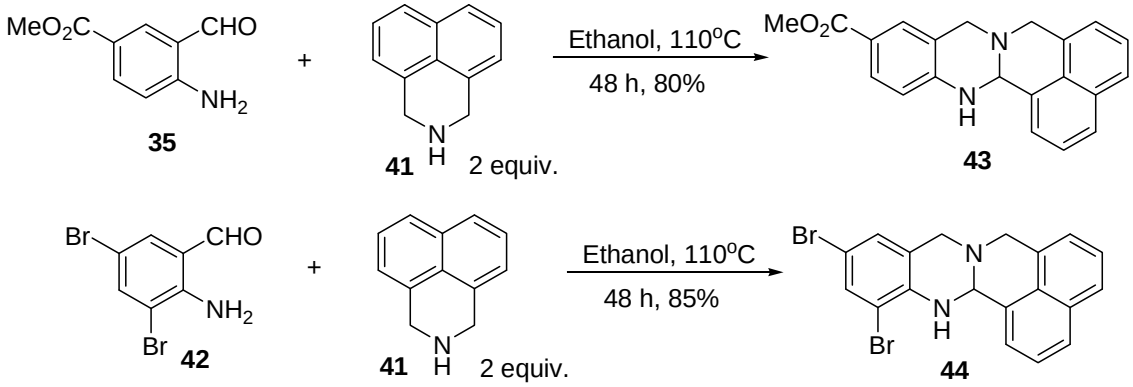
Scheme 2.9

Most of the bases used to explore the scope of the reaction were commercially available. A secondary amine (**41**) was synthesized in our laboratory following a known synthetic sequence. The first step included the treatment of napthalic anhydride (**38**) with benzyl amine (Scheme 2.9) to obtain compound **39** with almost quantitative yield. Compound **39** was then reduced to benzyl substituted amine **40** using $LiAlH_4$ as the reducing agent. In the final step, the benzyl group was cleaved (Scheme 2.10) to generate the free amine **41** using ethyl chloroformate, potassium hydroxide and hydrazine.



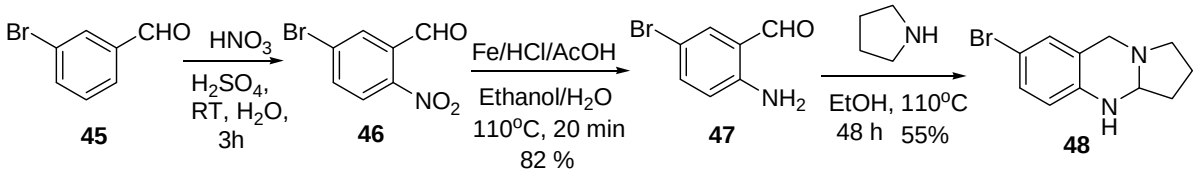
Scheme 2.10

Reaction of the dibromoaminobenzaldehyde **42** as well as the ester substituted aminobenzaldehyde **35** with the secondary amine **41** provided the corresponding ring fused aminals (**43** & **44**) with good yields (Scheme 2.11).



Scheme 2.11

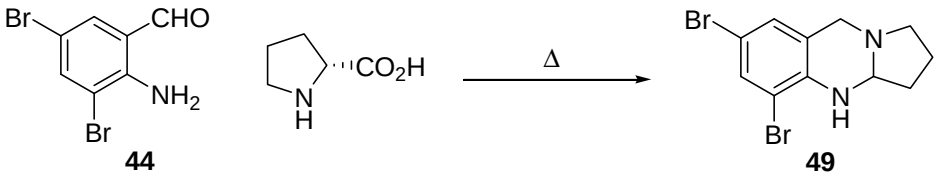
The bromoaminobenzaldehyde **47** was synthesized from commercially available 3-bromobenzaldehyde (**45**) via two steps.[5] 3-bromobenzaldehyde (**45)** was treated with nitric acid and sulphuric acid to provide 2-nitro-5-bromobenzaldehyde (**46**). Compound **46** was reduced with iron in presence of HCl to achieve the desired aminobenzaldehyde (**47**). The bromoaminobenzaldehyde (**47**) on reaction with pyrrolidine in refluxing ethanol resulted in the corresponding aminal **48** with 55% yield after 48 h.



Scheme 2.12

Attempts towards extension of the reaction

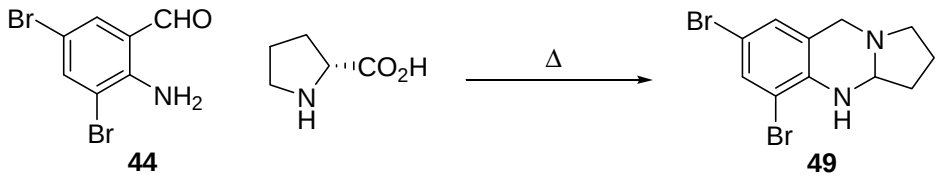
Not only to broaden scope of the reaction but also to get an insight into the mechanism of the reaction, we explored the aminal formation reaction with proline as the base partner (Table 1 & Table 2). Since only 50% desired product (**49**) was isolable under regular conditions, different parameters of this reaction were tried to improve the yield (Table 1a & 1b). The yield of the reaction showed no improvement in the presence of additives like HMDS or p-TsOH (Table 1a).



44	L-proline	solvent (0.2 M)	additive	time	**49** (yield)
1 equiv	1.2 equiv	Toluene	No	24 h	53%
1 equiv	1.2 equiv	Toluene	HMDS	24 h	50%
1 equiv	1.2 equiv	Toluene	p-TsOH	24 h	53%

Table 1a

There was insignificant change in yields when various solvents were tested (Table 1b). The best yield (66%) was obtained by using 2.5 equivalents of L-proline and n-Butanol as the solvent (Table 1b).

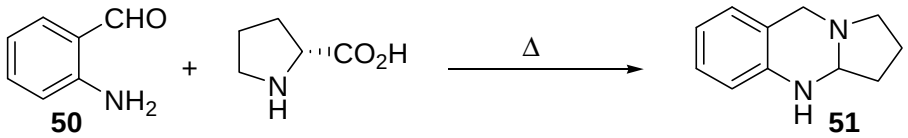


44 **49**

44	L-proline	solvent (0.2 M)	additive	time	**49**(yield)
1 equiv	1.2 equiv	Acetonitrile	No	24 h	44%
1 equiv	1.2 equiv	DMF	No	24 h	42%
1 equiv	2.5 equiv	Toluene	No	30 h	58%
1 equiv	2.5 equiv	n-Butanol	No	30 h	66%

Table 1b

We speculated that, under high temperature aminobenzaldehydes can give rise to self-polymerized side products which might be the reason for the moderate yield of the desired ring fused aminal.



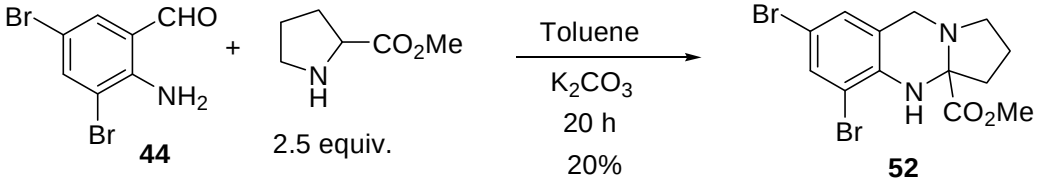
50 **51**

50	L-proline	solvent(0.2 M)	additive	time	**51** (yield)
1 equiv	1.2 equiv	Toluene	HMDS	30 h	20%
1 equiv	1.2 equiv	Toluene	No	24 h	34%
1 equiv	1.2 equiv	Acetonitrile	No	24 h	20%
1 equiv	2.5 equiv	Toluene	No	30 h	15%
1 equiv	2.5 equiv	n-Butanol	No	30 h	36%

Table 2

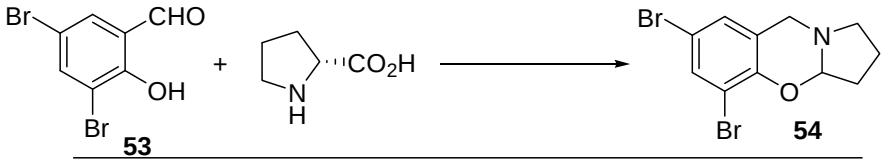
The yield of aminal formation achieved from the reaction of unsubstituted aminobenzaldehyde (**50)** and L-proline was always less than 40% (**44)** (Table 2). Even increasing the amount of L-proline neither did accelerate the reaction nor did increase the percentage yield of the desired aminal.

We also explored formation of aminals from proline derivatives. The methyl ester of L-proline on reaction with dibromoaminobenzaldehyde **44** provided 20% of one regioisomer (**52**) as confirmed by ^{1}H-NMR (Scheme 2.13).

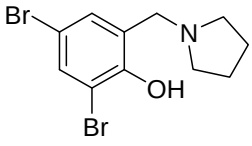


Scheme 2.13

We were also interested in obtaining similar ring-fused systems with heteroatoms other than nitrogen. A reaction of dibromosalicylaldehyde (**53**) and L-proline in toluene or n-butanol (Table 3) did not provide the desired product. However, when 2.5 equiv. of proline was used reduced product **55** was isolated (Table 3).



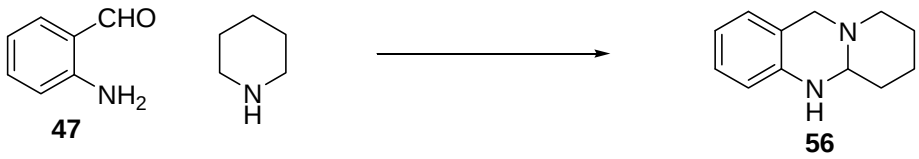
53	L-proline	Solvent	Time	Yield
1 equiv	1.2 equiv	Toluene	24 h	—
1 equiv	1.2 equiv	Toluene/HMDS	24 h	—
1 equiv	2.5 equiv	Toluene	12 h	40% of **55**
1 equiv	2.5 equiv.	n-Butanol	12 h	42% of **55**



55

Table 3

Once refluxing did not provide improved yields, we opted for more vigorous conditions of sealed tube heating and microwave irradiations. Both of these conditions improved the yields (Scheme 2.14 & 2.15) but the reactions were never clean.

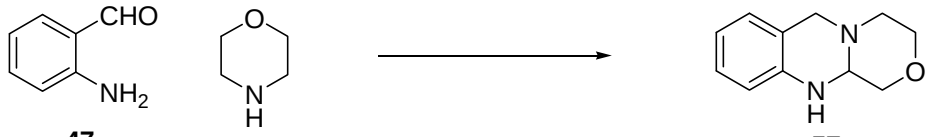


	Base	solvent(0.1 M)	Temp.	time	yield(%)
Sealed tube	3 equiv	n-Butanol	160 ^{o}C	24 h	12%
Microwave	3 equiv	n-Butanol	195 ^{o}C	2 h	67%

Scheme 2.14

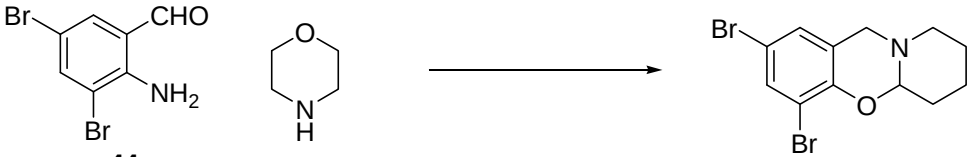
Unsubstituted aminobenzaldehyde (**47**) in presence of piperidine produced 67% of the corresponding aminal (**56**) using microwave irradiaitions which was a remarkable improvement from both reflux and sealed tube heating (Scheme 2.14). When a reaction of aminobenzaldehyde **47** with morpholine as the base promoter was performed in sealed tube no desired aminal was obtained. Using microwave irradiations, we were able isolate the corresponding aminal (**57**) with 18% yield (Scheme 2.15). When morpholine was used as base promoter to react with dibromoaminobenzaldehyde **44** in a sealed tube we got only 18% of the corresponding aminal (**58)**. More than 3 fold increase in the yield was observed once we performed the reaction in microwave (Scheme 2.15). The reactions in microwave were performed at 200 ^{o}C temperature and 220 psi pressure. Probably due to such strong conditions, self condensed products of the aminobenzaldehydes were formed which prevented from achieving higher yields of the

desired aminals. While we were exploring the scope of this novel methodology, a report was published showing aminal formation using microwave irradiations.[6]



47 **57**

	Base	solvent(0.1 M)	Temp.	time	yield(%)
Sealed tube	3 equiv	n-Butanol	160 °C	24 h	No desired product
Microwave	3 equiv	n-Butanol	195 °C	2 h	18%



44 **58**

	Base	solvent(0.1 M)	Temp.	time	yield(%)
Sealed tube	3 equiv	n-Butanol	160 °C	24 h	18%
Microwave	3 equiv	n-Butanol	195 °C	2 h	65%

Scheme 2.15

Conclusion

A new α-functionalization reaction of cyclic amines that proceeds without the involvement of transition metals or other additives was introduced. Mild conditions of this aminal formation reaction might make this methodology attractive in acquiring heterocycles of biological importance. In conclusion, we demonstrated a useful nitrogen heterocycle functionalization that led to easy formation of precursors for bioactive molecules.

References

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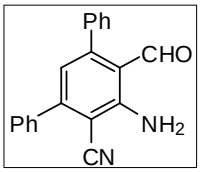
3. Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *J. Org. Chem.* **1997**, *62*, 7937–7941.
4. Hu, Y. Z.; Zhang, G.; Thummel, R. P. *Org. Lett.* **2003**, *5*, 2251-2253.
5. Polshettiwar, V.; Varma, R.S. Ring-Fused aminals: catalyst and solvent-free microwave-assisted a-amination of nitrogen heterocycles *Tet. Lett.* **2008,** *49*, 7165–7167.

Experimental

General Information: Starting materials, reagents and solvents were purchased from commercial sources and were used as received with the exception of pyrrolidine, piperidine, and hexamethyleneimine which were distilled prior to use. Reactions were run under an atmosphere of nitrogen unless mentioned otherwise. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light and permanganate stain, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. The starting materials 2-aminobenzaldehyde (**37**),[7] 1-amino-2-naphthaldehyde (**48**),[8] and 2,3-dihydro-1H-benzo[de]isoquinoline (**41**),[9] were prepared according to literature methods.

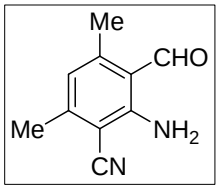
2-amino-3-cyano-4,6-diphenylbenzaldehyde (26): To a solution of 2,6-dicyano-3,5-diphenylaniline[8] (0.6 g, 2.03 mmol) in 5 mL of anhydrous dichloromethane at 0 °C, was slowly added 3.04 mL of DIBAL-H (3.04 mmol, 1 M solution in toluene). The reaction

mixture was allowed to warm up to room temperature and was stirred for an additional 24



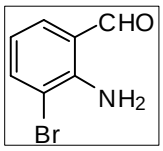
h. The reaction mixture was diluted with ether and cooled to 0°C. Water (0.12 mL) was added slowly, followed by careful addition of 15 % aqueous NaOH (0.12 mL). Subsequently, water (0.3 mL) was added slowly and the reaction mixture was stirred rapidly at room temperature for 15 minutes. Anhydrous magnesium sulfate was then added, it was stirred for 15 minutes and the salts were removed by filtration. The volatile components were removed under reduced pressure and the crude product was purified by column chromatography to give the title compound as a solid in 30% yield. (R_f = 0.17 in 40% DCM/Hex); mp: 220-222 °C; IR (KBr) 3474, 3316, 2923, 2877, 2209, 1650, 1593, 1570, 1499, 1400, 1296, 1226, 779, 763, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.86 (s, 1H), 7.63-7.59 (comp, 2H), 7.53-7.44 (comp, 6H), 7.42-7.37 (comp, 2H), 6.75 (s, 1H), 1.57 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 193.4, 153.3, 153.2, 151.5, 138.0, 137.6, 130.0, 129.8, 129.1, 129.0, 128.8, 128.7, 120.1, 116.6, 115.1, 96.1; *m/z* (ESIMS) 299.2 $[M + H]^+$.

2-amino-3-cyano-4,6-dimethylbenzaldehyde (2): Starting from 2,6-dicyano-3,5-



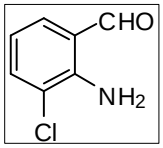
dimethylaniline, the reaction was carried out in analogy to the preparation of **26**. After purification by column chromatography, the title compound was obtained as a solid in 50% yield. (R_f = 0.33 in DCM); mp: 175-181 °C; IR (KBr) 3440, 3321, 2208, 1658, 1651, 1607, 1585, 1548, 1505, 1441, 1405, 1375, 1309, 1225, 868, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.29 (s, 1H), 7.11 (br s, 2H), 6.39 (s, 1H), 2.57 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 152.5, 150.2, 148.3, 120.8, 115.8, 114.5, 96.9, 21.3, 19.3; *m/z* (ESIMS) 175.2 $[M + H]^+$.

2-amino-3-bromobenzaldehyde (29): Starting from 2-amino-3-bromobenzonitrile, the



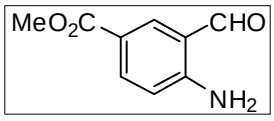
reaction was carried out in analogy to the preparation of **26**. After purification by column chromatography, the title compound was obtained as oil in 32% yield. (R_f = 0.19 in 20% DCM/Hex); IR (KBr) 3467, 3350, 2851, 2765, 1666, 1609, 1578, 1538, 1446, 1409, 1307, 1198, 1139, 1061, 882, 763, 726, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.80 (s, 1H), 7.59 (dd, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz), 7.45 (dd, 1H, *J* = 1.4 Hz, *J* = 7.7 Hz), 6.69 (br s, 2H), 6.64 (app t, 1H, *J* = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 193.1, 146.8, 137.9, 135.2, 119.5, 116.7, 110.0 ; *m/z* (ESIMS) 200.1 $[M]^+$.

2-amino-3-chlorobenzaldehyde (32): Starting from 2-amino-3-chlorobenzonitrile, the



reaction was carried out in analogy to the preparation of **26**. After purification by column chromatography, the title compound was obtained as a solid in 50% yield. (R_f = 0.34 in 30% DCM/Hex); mp: 30-31 °C; IR (KBr) 3480, 3359, 2860, 2774, 1681, 1612, 1581, 1546, 1465, 1450, 1408, 1327, 1196, 1146, 1075, 884, 765, 726, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.85 (s, 1H), 7.42 (ddd, 2H, *J* = 1.5 Hz, *J* = 5.6 Hz, *J* = 7.4 Hz), 6.70 (app t, 1H, *J* = 7.8 Hz), 6.62 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$)193.1, 146.8, 137.9, 135.2, 119.5, 116.8, 110.0; *m/z* (ESIMS) 156.6 $[M + H]^+$.

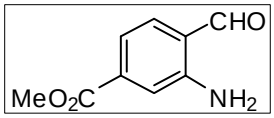
Methyl 4-amino-3-formyl benzoate (35): Methyl 3-formyl-4-nitro benzoate (0.5 g, 2.39



mmol), iron powder (1.02 g, 18.35 mmol), and conc. HCl (2 drops), were added to a mixture of EtOH, HOAc and H_2O (2:2:1, 25 mL). The resulting suspension was heated at reflux for 15 min and then stirred at 25 °C for 30 min. Subsequently, it was filtered, diluted with water (100 mL) and extracted

with EtOAc (3 x 100 mL). The organic layer was washed with saturated $NaHCO_3$ (2 x 100 mL) and H_2O (2 x 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound as a solid in 91% yield. (R_f = 0.41 in 20% EtOAc/Hex); mp: 122-124 °C; IR (KBr) 3451, 3334, 3200, 2961, 2803, 2728, 1683, 1613, 1549, 1485, 1444, 1391, 1368, 1275, 1164, 983, 901, 825, 767, 703, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.88 (s, 1H), 8.22 (d, 1H, *J* = 2.0 Hz), 7.93 (dd, 1H, *J* = 2.0 Hz, *J* = 8.7 Hz), 6.64 (d, 1H, *J* = 8.7 Hz), 6.56 (br s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 193.9, 166.4, 153.2, 138.9, 136.1, 118.4, 118.1, 116.0, 52.1; *m/z* (ESIMS) 180.4 $[M + H]^+$.

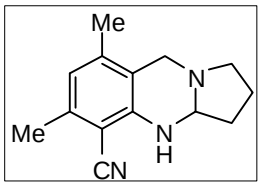
Methyl 3-amino-4-formyl benzoate (36): Starting with methyl 3-nitro-4-formyl benzoate, the reaction was carried out in analogy to the preparation of **1h**. After purification by column chromatography, the title compound was obtained as a solid in 70% yield. (R_f = 0.48 in 20% EtOAc/Hex); mp: 119-121 °C; IR (KBr) 3463, 3360, 3066, 2961, 2827, 2745, 1712, 1666, 1626, 1598, 1545, 1492, 1435, 1310, 1262, 1186, 995, 812, 759, 522 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.94 (s, 1H), 7.55 (d, 1H, *J* = 8.4 Hz), 7.36-7.32 (comp, 2H), 6.22 (br s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 194.2, 166.6, 149.6, 135.9, 135.7, 121.1, 117.8, 116.8, 52.7; *m/z* (ESIMS) 180.2 $[M + H]^+$.



General Procedure for the Reaction between Aminobenzaldehydes and Amines:

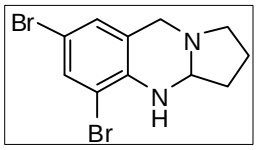
To a stirred solution of aminoaldehyde (1 mmol) in 4 mL of EtOH was added the secondary amine (3 mmol), followed by heating at reflux. The reaction mixture was monitored by TLC. After the completion of the reaction, the solvent was evaporated off and the crude product was purified by column chromatography.

Preparation of 10: The reaction was carried out according to the general procedure (18



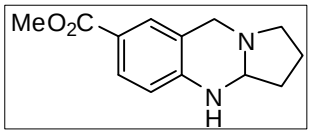
h). The product was obtained as a white solid in 95% yield. (R_f = 0.47 in 2% MeOH/EtOAc); mp: 138-140 °C; IR (KBr) 3363, 2942, 2922, 2842, 2209, 1598, 1580, 1508, 1477, 1460, 1333, 1291, 1267, 1190, 1123, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.38 (s, 1H), 4.53 (br s, 1H), 4.33 (dd, 1H, *J* = 3.0 Hz, *J* = 5.0 Hz), 3.87 (d, 2H, *J* = 3.8 Hz), 2.88 (app dt, 1H, *J* = 6.5 Hz, *J* = 8.9 Hz), 2.81 (app dt, 1H, *J* = 4.8 Hz, *J* = 8.8 Hz), 2.36 (s, 3H), 2.14-2.27 (m, 1H), 2.14 (s, 3H), 1.89-2.07 (comp, 2H), 1.72-1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.9, 140.7, 139.5, 120.3, 117.2, 114.3, 93.9, 70.1, 50.1, 47.0, 32.0, 21.2, 20.3, 18.9; *m/z* (ESIMS) 228.1 $[M + H]^+$.

Preparation of 14: The reaction was carried out according to the general procedure (23



h). The product was obtained as a white solid in 92% yield. (R_f = 0.19 in 40% EtOAc/Hex); mp: 122-124 °C; IR (KBr) 3403, 3052, 2971, 2938, 2907, 2839, 1768, 1692, 1575, 1438, 1349, 1258, 1119, 980, 927, 861, 747, 722, 637 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 7.37 (d, 1H, *J* = 1.7 Hz), 6.99 (d, 1H, *J* = 0.9 Hz), 4.37 (ddd, 1H, *J* = 5.2 Hz, *J* = 2.8 Hz, *J* = 0.8 Hz), 4.23 (br s, 1H), 4.09 (d, 1H, *J* = 16.2 Hz), 3.78 (d, 1H, *J* = 16.3 Hz), 2.82-2.75 (comp, 2H), 2.20-2.11 (m, 1H), 2.04-1.87 (comp, 2H), 1.73 (dddd, 1H, *J* = 2.8 Hz, *J* = 4.2 Hz, *J* = 9.9 Hz, *J* = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 139.6, 132.5, 129.2, 121.7, 109.0, 108.3, 71.3, 49.9, 49.6, 32.7, 21.7; *m/z* (ESIMS) 333.0 $[M + H]^+$.

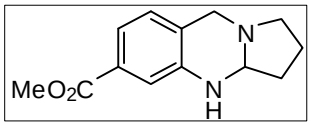
Preparation of 11. To a stirred solution of methyl 4-amino-3-formyl benzoate (1 mmol)



in 4 mL of methanol was added pyrrolidine (3 mmol). The mixture was heated at 100°C in a sealed tube for 24 h.

Following solvent removal and purification of the crude product by column chromatography, the product was obtained as a white solid in 76% yield. (R_f = 0.43 in 5% MeOH/EtOAc); mp: 118-120 °C; IR (KBr) 3375, 2942, 2874, 2804, 1685, 1608, 1513, 1436, 1381, 1363, 1321, 1293, 1237, 1198, 1142, 1111, 1096, 1002, 989, 908, 832, 768, 443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.66 (dd, 1H, *J* = 1.9 Hz, *J* = 8.4 Hz), 7.62 (s, 1H), 6.40 (d, 1H, *J* = 8.4 Hz), 4.38 (dd, 1H, *J* = 2.8 Hz, *J* = 5.1 Hz), 4.31 (br s, 1H), 4.10 (d, 1H, *J* = 15.9 Hz), 3.83 (d, 1H, *J* = 16.1 Hz), 3.81 (s, 3H), 2.82 (app dt, 1H, *J* = 6.6 Hz, *J* = 8.9 Hz), 2.76 (app dt, 1H, *J* = 4.9 Hz, *J* = 8.8 Hz), 2.15-2.07 (m, 1H), 2.01-1.85 (m, 2H), 1.64 (dddd, 1H, *J* = 2.9 Hz, *J* = 4.3 Hz, *J* = 9.8 Hz, *J* = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6, 147.5, 129.7, 129.6, 118.6, 117.2, 113.1, 70.9, 51.7, 49.8, 49.5, 32.5, 21.7; *m/z* (ESIMS) 233.1 $[M + H]^+$.

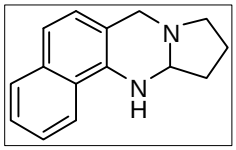
Preparation of 12. To a stirred solution of methyl 3-amino-4-formyl benzoate (1 mmol)



in 4 mL of methanol was added pyrrolidine (3 mmol). The mixture was heated at 100°C in a sealed tube for 24 h. Following solvent removal and purification of the crude product by column chromatography, the product was obtained as a white solid in 60% yield. (R_f = 0.43 in 5% MeOH/EtOAc); mp: 119-120 °C; IR (KBr) 3400, 2970, 2942, 2842, 1713, 1614, 1581, 1499, 1479, 1459, 1439, 1342, 1312, 1289, 1278, 1230, 1216, 1101, 1018, 854, 755, 440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32 (dd, 1H, *J* = 1.6 Hz, *J* = 7.8 Hz), 7.18 (d, 1H, *J* = 1.5 Hz), 6.97 (d, 1H, *J* = 7.8 Hz), 4.21 (dd, 1H, *J* = 4.0 Hz, *J* = 5.1 Hz), 4.06 (d, 1H, *J* = 16.3 Hz), 3.96-3.87 (comp, 2H), 3.86 (s, 3H), 2.94 (app dt, 1H, *J* = 5.8 Hz, *J* = 8.9 Hz), 2.71 (app dt, 1H, *J* = 5.3 Hz, *J* = 8.8 Hz), 2.13 (ddd, 1H, *J* = 5.6 Hz, *J* = 11.0 Hz, *J* = 18.0 Hz), 2.04-1.85 (comp, 2H), 1.66 (app tdd, 1H, *J* = 4.2 Hz, *J* = 10.2 Hz, *J* =

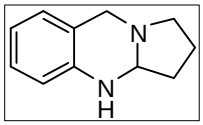
12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6, 143.3, 129.3, 127.5, 124.5, 119.2, 115.8, 71.3, 52.1, 50.6, 50.4, 32.2, 21,5; *m/z* (ESIMS) 233.2 $[M + H]^+$.

Preparation of 13: The reaction was carried out according to the general procedure (48



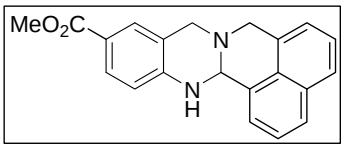
h). The product was obtained as a white solid in 58% yield. (R_f = 0.27 in 5% MeOH/EtOAc); mp: 130-133 °C; IR (KBr) 3227, 3062, 2977, 2956, 2915, 2856, 1576, 1520, 1487, 1407, 1363, 1340, 1325, 1304, 1260, 1120, 1093, 775, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.82-7.75 (comp, 2H), 7.47-7.40 (comp, 2H), 7.30 (d, 1H, *J* = 8.3 Hz), 7.11 (d, 1H, *J* = 8.3 Hz), 4.19-4.11 (comp, 3H), 4.06 (d, 1H, *J* = 15.6 Hz), 3.14 (app dt, 1H, *J* = 5.1 Hz, *J* = 8.8 Hz), 2.69 (app dt, 1H, *J* = 6.1 Hz, *J* = 8.8 Hz), 2.30 (app dtd, 1H, *J* = 5.5 Hz, *J* = 10.8 Hz, *J* = 16.1 Hz), 2.12-2.03 (m, 1H), 2.02-1.92 (m, 1H), 1.88-1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.6, 133.3, 128.6, 126.0, 125.5, 125.2, 124.3, 120.0, 118.9, 115.2, 72.4, 51.9, 50.9, 31.9, 21.3; *m/z* (ESIMS) 225.1 $[M + H]^+$.

Preparation of 51: The reaction was carried out according to the general procedure (72



h). The product was obtained as a white solid in 73% yield. (R_f = 0.25 in 5% MeOH/EtOAc); mp: 63-64 °C [lit. 69-70 °C][12]; IR (KBr) 3246, 2966, 2826, 1608, 1585, 1478, 1383, 1255, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.02 (app t, 1H *J* = 7.6 Hz), 6.95 (d, 1H *J* = 7.4 Hz), 6.70 (app dt, 1H, *J* = 0.9 Hz, *J* = 7.4 Hz), 6.54 (d, 1H, *J* = 7.9 Hz), 4.15 (m, 1H), 4.04 (d, 1H, *J* = 15.6 Hz), 3.90 (d, 1H, *J* = 15.6 Hz), 3.67 (br s, 1H), 3.03 (app dt, 1H, *J* = 5.5 Hz, *J* = 8.9 Hz), 2.68 (app dt, 1H, *J* = 5.6 Hz, *J* = 8.8 Hz), 2.18-2.09 (m, 1H), 1.97-2.07 (m, 1H), 1.96-1.87 (m, 1H), 1.66 (app tdd, 1H, *J* = 4.4 Hz, *J* = 10.2 Hz *J* = 12.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)142.9, 127.2, 127.0, 119.4, 118.1, 114.9, 71.2, 50.5, 50.3, 31.8, 21.1; *m/z* (ESIMS) 175.1 $[M + H]^+$.

Preparation of 43: The reaction was carried out according to the general procedure (48 h). The product was obtained as a white solid in 80% yield. (R_f = 0.32 in 20% EtOAc/Hex); mp: 176-179 °C; IR (KBr) 3338, 3043, 2944, 2839, 1694, 1608, 1512, 1433, 1333, 1294, 1249, 1187, 1125, 1012, 780, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.86 (d, 1H, *J* = 8.3 Hz), 7.77-7.70 (comp, 3H), 7.51-7.43 (comp, 2H), 7.40 (d, 1H, *J* = 6.9 Hz), 7.28 (d, 1H, *J* = 7.2 Hz), 6.40 (d, 1H, *J* = 8.3 Hz), 5.75 (s, 1H), 4.68 (d, 1H, *J* = 16.5 Hz), 4.37-4.31 (comp, 2H), 3.99 (d, 1H, *J* = 16.5 Hz), 3.94 (d, 1H, *J* = 14.7 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.5, 146.6, 133.6, 133.0, 132.9, 129.9, 129.8, 128.8, 126.6, 126.4, 126.3, 125.7, 123.2, 123.1, 119.5, 117.1, 113.2, 69.3, 54.6, 51.9, 49.3; *m/z* (ESIMS) 331.1 $[M + H]^+$



Preparation of 48: The reaction was carried out according to the general procedure (48 h). The product was obtained as a white solid in 55% yield. (R_f = 0.32 in 5% MeOH/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 – 6.96 (m, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 4.16 (dd, *J* = 5.2, 3.7 Hz, 1H), 4.00 (d, *J* = 15.9 Hz, 1H), 3.91 – 3.58 (m, 1H), 2.91 (td, *J* = 8.9, 5.9 Hz, 1H), 2.68 (td, *J* = 8.8, 5.2 Hz, 1H), 2.18 – 1.77 (m, 2H), 1.77 – 1.45 (m, 2H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.24, 130.11, 121.37, 116.47, 109.71, 71.32, 50.32, 50.11, 32.26, 21.50.