Chiral Ligand Design



Dong Lab Literature Talk February 19, 2014

Overview

- Background
- DIOP and Sons: C₂ Symmetry
- C₁ Symmetry
- Non-symmetrical
- Other Chiral Ligands
- Conclusions

The Nobel Prize in Chemistry 2001



William S. Knowles

Ryoji Noyori

K. Barry Sharpless

The Nobel Prize in Chemistry 2001 was divided, one half jointly to William S. Knowles and Ryoji Noyori *"for their work on chirally catalysed hydrogenation reactions"* and the other half to K. Barry Sharpless *"for his work on chirally catalysed oxidation reactions"*.

Ligands and Other Inventions

- Paul Ehrlich: "Father of Chemotherapy"
 - 1. Geist- Good idea
 - 2. Geld- Money
 - 3. Geduld- Patience
 - 4. Gluck- Luck



Chirality in Medicine

- A common morning sickness medication in the 1950s was prescribed racemically
 - (R)-Thalidomide was a sedative
 - (S)-Thalidomide was teratogenic
- As late as the early 1990s, about 90% of synthetic chiral drugs were still racemic



Noyori, R., Adv. Synth. Catal., **2003**, 345, 15.

Pre-Asymmetric Catalysis Chiral Synthesis

- Before the advent of enantioselective reactions, chiral compounds had to be biosynthetically made or resolved
 - This was an expensive and time consuming process, especially for industrial applications



- Chiral ligands show a broad scope not seen with enzymes
 - Privileged ligands work for variety of rxns

Privileged Ligands



X=OH BINOL X=PPh₂ BINAP Diels-Alder Mukaiyama aldol aldehyde allylation hydrogenation alkene isomerization Heck reaction



MeDuPhos

hydrophosphination hydroacylation hydrosilylation Bayer-Villager oxidation

hydrogenation



Brintzinger's

ligand

t-Bu

t-Bu

alkene reduction imine reduction alkene carbometallation Ziegler-Natta polymerization

t-Bu

H

t-Bu

Salen complexes

imine cyanation

conjugate addition

epoxide ring-opening

epoxidation

Diels-Alder



Diels-Alder aldehyde alkylation ester alcoholysis iodolactonization

TADDOLate ligand



Diels-Alder Mukaiyama aldol conjugate addition cyclopropanation t-Bu aziridination

Bis(oxazoline)



dihydroxylation acylation heterogeneous hydrogenation phase transfer catalysis

Cinchona alkaloid derivatives

Jacobsen, E.N., Science, 2003, 299, 1691.

Modular Structures

• Ligand backbones need to be variable in order to quickly and efficiently find the best conditions



First Chiral Heterogenous Catalyst

- Akabori first synthesized Pd catalyst in 1956
- Adsorbed PdCl₂ on silk fibroin fibers and reduced with H₂.



The Road to Chiral Phosphines

- 1966: After success of Wilkinson's catalyst, chiral derivatives wanted
- 1968: PAMP/CAMP-Knowles
- 1971: DIOP first bidentate- Kagan
- 1977: DIPAMP next Knowles
 L-Dopa synthesis
- Industry driven, so asymmetric hydrogenations very important

First Chiral Homogenous Catalyst

 Knowles replaced PPh₃ with a chiral phosphine, leading to first example of asymmetric hydrogenation



DIOP: The Game Changer

• Kagan and Dang introduced DIOP in 1971





Kelley, C.J., J.Org.Chem., **1968**, 2171. Kagan, H.B., J. Chem. Soc. Chem. Commun., **1971**, 481.

Design Features

- C₂ Symmetry- Many of the privileged ligands today exhibit
 - Equivalent P atoms reduce the number of possible isomers and reaction pathways
 - Also reduces substrate/catalyst arrangements
 - Helpful for mechanistic studies due to simplicity
- Greatly influenced ligand development from this point



DiPAMP and L-Dopa

• Knowles developed the first industrially useful catalytic asymmetric process



CAMP and DiPAMP Synthesis

 Synthesis starts from trimethyl phosphite and uses (-)-Menthol as a recyclable chiral resolving agent



CAMP and DiPAMP Synthesis

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Design Features

- DiPAMP more stable than
 CAMP
 - Also exhibits important C₂ symmetry
- Why is OMe important?
 - Only made successful ligands with anisole group, but others have had little success with anisole
- Common intermediate important for screening



BINAP Comes On the Scene

• BINAP first synthesized as a new Rh hydrogenation ligand



BINAP Synthesis

• Synthesis more difficult than expected from 1974-1978



Design Features

- Fully aromatic, axially C₂ symmetric
- Steric and electronic properties easily tuned by substituents on the rings



DuPhos

• While working at DuPont, Burk synthesized a new type of C2 symmetrical chiral diphosphine ligand



Burk, M.J., JACS, 1993, 115, 10125.

Excellent Enantioselectivity

 Showed amazing results with a steric optimum at Pr-DuPhos



• All showed > 99% ee



Burk, M.J., JACS, 1993, 115, 10125.

Design Features

- 1. Electron-rich Phosphorous
- 2. Rigid Backbone
- 3. Tight Binding
- 4. Ordered Asymmetric Environment
- 5. Variable/Optimizable Steric Environment



DIOCP: Desymmetrizing DIOP

 Achiwa showed the two phosphorous atoms did not play identical roles



- P1 (cis) : enantioselection
- P2 (trans) : electron-rich
 - acceleration of the oxidative addition of molecular hydrogen

higher catalytic activity (d-o* interaction)

 rigid chelation of rhodium with electrondeficient olefins or ketones

higher enantioselection (d-n+ back-donation)

Achiwa, K., Synlett., 1992, 169.



(R,R)-DIOP



Table	IV.	Asymmetric H	lydrogenation ^{a)}	of	Ketop	antlacton
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1. S.			A REAL PROPERTY AND A REAL	
Ligand	[Subst.]/[Rh]	atm/°C/h	Convn./%	e.e./%
DIOP	100	50/50/45	100	52(<i>R</i>)
	1000	50/50/45	45	37(<i>R</i>)
DIOCP	1000	50/50/45	100	72(<i>R</i>)
	1000	15/50/70	100	75(<i>F</i>)
Cy-DIOP	50	15/1/12	100	45(<i>R</i>)
a) in THE				194 (1

Non-symmetrical P,N

- A drastic take on desymmetrizing P,P or N, N ligands
- Plays off of soft P, hard N concepts
- Helmchen, Williams, and Pfaltz developed PHOX ligands



PHOX Ligands

• In AAA reactions, regioselectivity of nucleophilic attack determines the ratio of products



• Using different X and Y groups allowed for excellent selectivity



Modulation of PHOX

- Although large substrates showed excellent ee's, smaller substrates such as methyl had poor results
- Helmchen made many derivatives quickly due to the modular character of PHOX



Salen Complexes





Salen-Inspired Complexes

• Chromium bound salen complex showed some selectivity for heterocyclic reactions, so backbone modified



Cinchona Alkaloid Derivatives

Cinchona alkaloids, including quinine, have a tertiary • quinuclidine nitrogen that makes them interesting ligands



auinuclidine

Sharpless utilized derivatives for osmium-catalyzed asymmetric dihydroxylation





Cinchona Derivative Features

• Ligand Design Features:



Dimeric Derivatives

• Sharpless optimized extensively, finally coming up with dimeric derivatives that proved very successful



Sharpless, K.B., Chem. Rev., 1994, 94, 2483.

Chiral Phase Transfer Catalysts

 Corey showed cinchona derivatives could also function as PTCs when reacted with benzyl halides





PhCH ₂ Br	-78 °C, 23 h	94	87
Ph ₂ CHBr	-78 °C, 22 h	99.5	73
Me Br	-78 °C, 24 h	96	81
MeO OTBS	-78 °C, 24 h	97	67

Chiral Dienes

 Inspired by COD's ability to catalyze many background reactions, new class of ligand developed







• Followed closely by Carreira in 2004



Hayashi, T. J. Amer. Chem. Soc., **2003**, 125, 11508. Carreira, E. J. Amer. Chem. Soc., **2004**, 126, 1628.

Chiral Diene Synthesis

Needs expensive chiral ligand and low yielding



Chiral Diene Synthesis

• More modular and easily accessible than Hayashi's



Led to easy synthesis of derivatives



Future Outlook and Conclusions

- Chiral ligands have enjoyed over 50 years of success, but are by no means exhausted
- The search is always on for the ultimate ligand the works for every reaction
- Most new chiral catalysts are still found empirically, with chance, intuition, and systematic screening
- Mechanistic insights and general concepts that have been developed aid ligand design, however
- New ligand ideas?

Thank You for Your Attention

• Questions or comments?



Question 1



• B)



Question 2









Question 3



Properties

- Excellent sigma donors and weak p-acceptors (binap, DuPhos, etc.).
- p-Accepting ligands are also of considerable importance in catalysis, however the classic paccepting ligands used in inorganic chemistry (CO, bipy) cannot be trivially reconstituted into "chiral versions" for asymmetric catalysis.

Asymmetric Hydrogenation

• Halpern first showed accepted mechanism



Knowles, W.S., Adv. Synth. Catal., 2003, 345, 3.

BOX Ligands: Nitrogen is Good Too