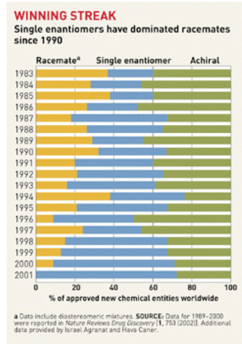
Metal-bis(oxazoline) Complexes in Asymmetric Catalysis: Concepts and Applications

Oliver Reiser
Oliver.Reiser@chemie.uni-regensburg.de
University of Regensburg

Importance of Chiral Compounds

Market Value for chiral fine chemicals (2000)

Total	6600 Mill US$
Pharmaceutics	5400 Mill US$
Other (Agro, Flavors etc)	1200 Mill US$



Any new drug that's chiral is likely to be developed and marketed as a single enantiomer. You win more than you lose with single enantiomers.

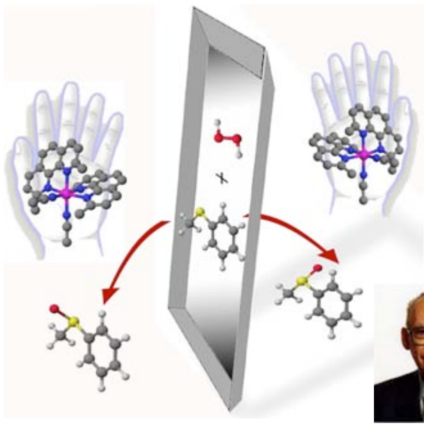
Chem. Eng. News ***2003***

Top Asymmetric Catalysis Reactions in Industry

Transformation	Production > 5t/y	Production <5 t/y	Pilot >50 kg	Pilot <50 kg	Bench scale
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C-COOR / -CH-OH	1	0	3	4	6
Hydrogenation of other C=C	1	0	1	2	2
Hydrogenation of α and β funct. C=O	1	2	3	6	4
Hydrogenation / reduction of other C=O	0	0	0	1	4
Hydrogenation of C=N	1	0	1	0	0
Dihydroxylation of C=C	0	1	0	0	4
Epoxidation of C=C, oxidation of sulfide	2	1	2	0	2
Isomerization, epoxide opening, addition	2	0	3	0	1
Total	10	5	15	19	27

Adapted from H.U-Blaser, Solvias

Principles of Enantioselective Catalysis



Principles of Enantioselective Catalysis

Catalyst design: Metal–chiral ligand combination

- more than 2000 chiral ligands to choose from
  - enhancement of selectivity
    - regio- / chemoselectivity
    - diastereoselectivity
    - enantioselectivity
  - enhancement of reactivity
    - LAC - Ligand Accelerated Catalysis

Give me reactivity, and I will give you selectivity later

B. Sharpless, nobel laureate 2001

Ligand Accelerated Catalysis

- change of the electronic properties
  - ✓ donor / acceptor (σ and π)

Complex	pKa (MeCN)
H–Co(CO)$_4$	8.4
H–Co(CO)$_3$[P(OPh)$_3$]	11.4
H–Co(CO)$_3$[PPh$_3$]	15.4

↑ Increasing ability of the ligands to stabilize the conjugate base by back bonding

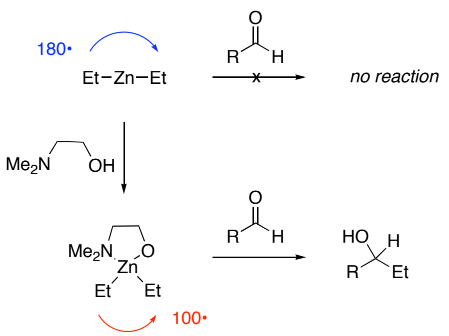
Complex	ν_{CO} (cm^{-1})
(CO)$_5$W←OEt$_2$	1908
(CO)$_5$W←PMe$_3$	1947
(CO)$_5$W←P(OPh)$_3$	1965
(CO)$_5$W← CH_2=CH_2	1973

↓ CO Bindung becomes stronger, since back bond to CO becomes weaker

⇒ back bonding to other ligand (not CO) becomes stronger

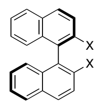
Ligand Accelerated Catalysis

- change of reagent geometry



Privileged Ligand Classes

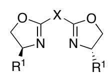
Binaphthyls



X = OH
X = PPh$_2$
X = OPPh$_2$
X = P(O)Ph$_2$
X = NH$_2$
X = NHPPh$_2$
X = N=CHAr
X = AsPh$_2$

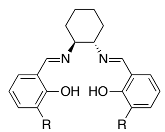
Noyori

Bis(oxazolines)



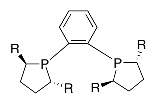
Evans, Pfaltz, Masamune, Corey

Salen



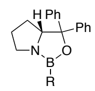
Jacobsen, Katsuki

DUPHOS



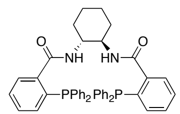
Burk

Oxabor



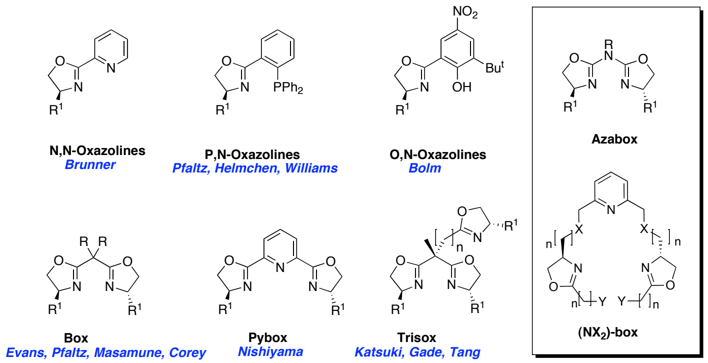
Corey

PNNP



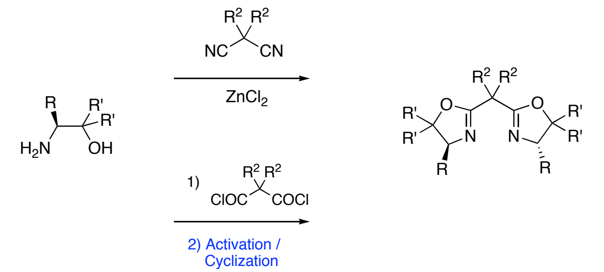
Trost

Oxazoline-Ligands for Catalysis



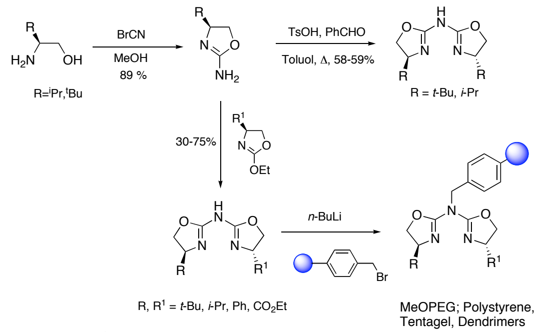
Excellent Reviews: P. Guiry, *Chem. Rev.* **2004**, *104*, 4151
G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561

Synthesis of bis(oxazoline) ligands



Activation / Cyclization: $ZnCl_2$; NEt_3 /TsCl; $SOCl_2$/NaOH; Burgess-Reagent…

Synthesis of azabis(oxazoline) ligands



Org. Lett. **2000**, *2*, 2045
J. Org. Chem. **2003**, *68*, 10166

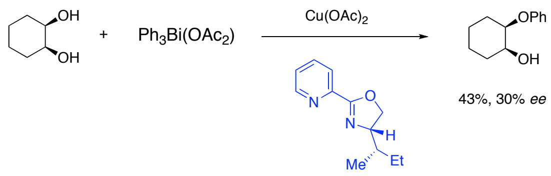
For a related approach towards pentadentate box ligands see *Tetrahedron* **2006**, *62*, 9973

Catalysis - Concepts and Applications

- C_1- vs. C_2- vs. C_3-symmetry
  - ✓ steric and electronic aspects
  - ✓ ligand / metal ratio
- Tricoordination
- Tetracoordination
  - ✓ tetrahedral or square planar geometries
- Pentacoordination
  - ✓ trigonal bipyrimidal vs. tetragonal pyrimidal
- Hexacoordination

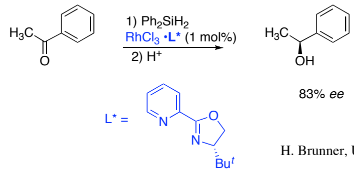
Coord. Chem. Rev. **2008**, *252*, 702

Oxazoline Ligands in Catalysis - The Beginning

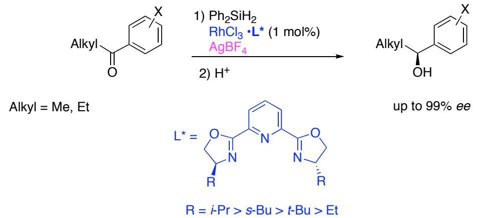


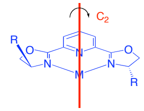
H. Brunner. U. Obermann. P. Wimmer. *J. Organonmet. Chem.* **1986**, *316*, C 1

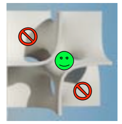
Rh(III)-catalyzed hydrosilylation: C_1- vs C_2-symmetry



H. Brunner, U. Obermann, *Chem. Ber.* **1989**, *122*, 499

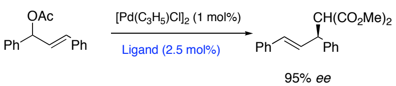


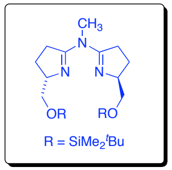




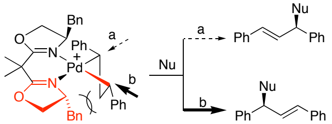
H. Nishiyama et al., *Organometallics* **1989**, *8*, 846; *Organometallics* **1991**, *10*, 500; *J. Org. Chem.* **1992**, *57*, 4306

Semicorrins in Catalysis – Pd(0)-catalyzed Allylations





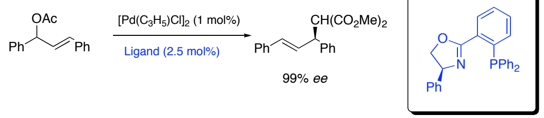
H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem.* **1986**, *98*, 1005

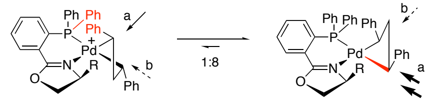


X-ray structure

A. Pfaltz et al., *Helv. Chim. Acta* **1995**, *78*, 265

P, N-oxazolines – Pd(0)-catalyzed Allylations

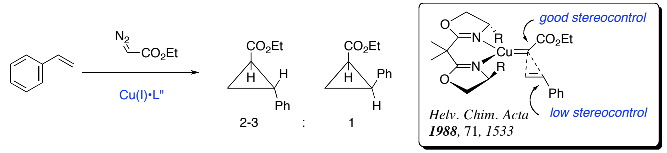


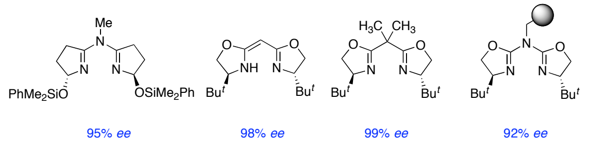


Attack via *a* is observed but
stereoelectronics should favor attack via *b*

Original report: A. Pfaltz et al., *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 566; b) J. G. Helmchen et al., *Tetrahedron Lett.* **1993**, *34*, 1769-1772; c) J. M. J. Williams et al., *Tetrahedron Lett.* **1993**, *34*, 3149
Mechanistic discussion: O. Reiser, *Angew. Chem. Int. Engl. Ed.*, **1993**, *32*, 547-549
Mechanism: G. Helmchen, *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2687

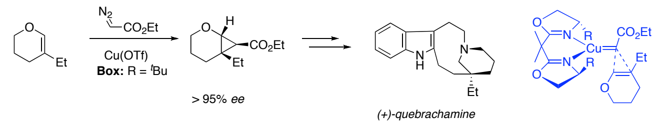
Cu(I)-box catalyzed cyclopropanation



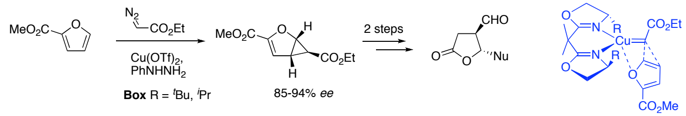


Tetrahedron **1992**, *48*, 2143 — *Tetrahedron Lett.* **1990**, *31*, 6005 — *J. Am. Chem. Soc.* **1991**, *113*, 726 — *Org. Lett.* **2000**, *2*, 2045

Cu(I)-box catalyzed cyclopropanation - Applications

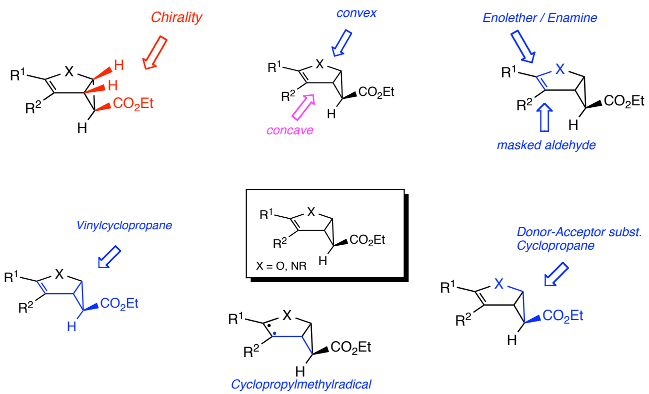


O. Temme, S.-A. Taj, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 6007.



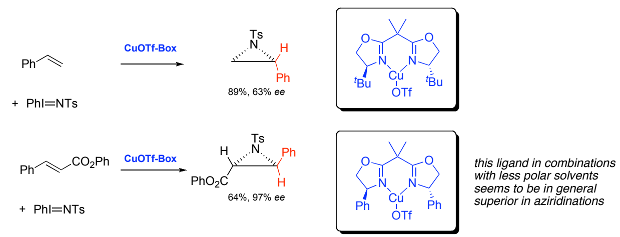
Eur. J. Org. Chem. **2000**, 2955

Cyclopropanated Furans and Pyrrols - Versatile Building Blocks in Organic Synthesis

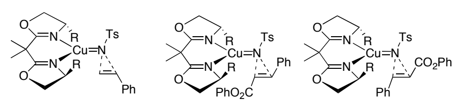
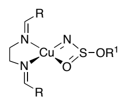


Org. Lett. **2001**, *3*, 1315; *Chem. Eur. J.* **2003**, *9*, 260; *Org. Lett.* **2003**, *5*, 914; *Synlett* **2005**, 915; *Org. Lett.* **2005**, *7*, 5353; Curr. Opn. Chem. Biol. **2005**, *9*, 285; Angew. *Chem. Int. Ed.* **2007**, *46*, 6361

Cu(I)-box catalyzed aziridination

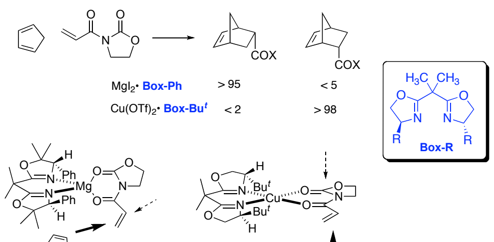


D. A. Evans et al., *J. Am. Chem. Soc.* **1993**, *115*, 5328

Mechanistic Studies: E. N. Jacobsen et al., *J. Am. Chem. Soc.* **1994**, *115*, 5326;
P. G. Andersson et al., *J. Am. Chem. Soc.* **2000**, *122*, 8013.

Cu(II) or Mg(II)-catalyzed Diels-Alder reactions: tetrahedral vs. square planar

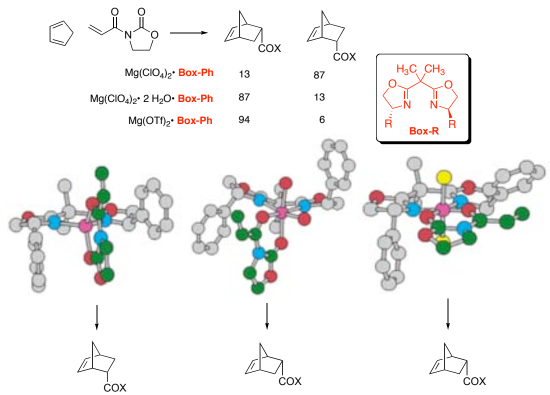


Square planar vs. tetrahedral coordination reverses enantioselectivity!

D. A. Evans et al., *J. Am. Chem. Soc.* **1993**, *115*, 6460

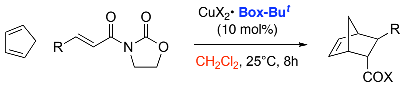
E. J. Corey et al., *Tetrahedron Lett.* **1992**, *33*, 6807

Mg(II)-catalyzed Diels-Alder reactions: tetrahedral vs. octahedral

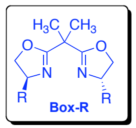


Octahedral vs. tetrahedral coordination reverses enantioselectivity!

Cu(II)-catalyzed Diels-Alder reaction - role of the counter ion and solvent



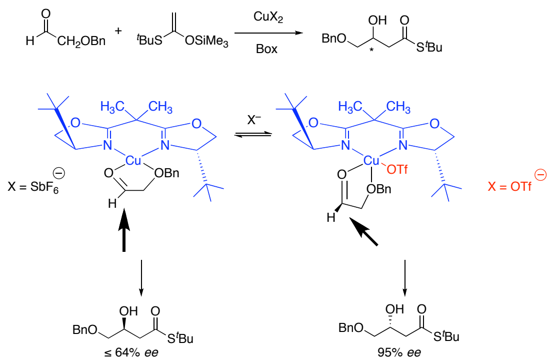
	counterion	*endo ee*	yield
R = Me	X = TfO$^-$	94% *ee*	95%
	X = SbF_6^-	96% ee	98%
R = Ph	X = TfO$^-$	90% *ee*	85%
	X = SbF_6^-	96% ee	95%
R = Cl	X = TfO$^-$	53% *ee*	–
	X = SbF_6^-	94% ee	95%



J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325

Further increase of reactivity in nitromethane: K. A. Jørgenson et al., *J. Perk. Trans. 2*, **1997**, 1183

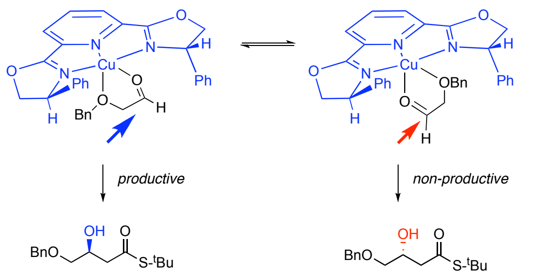
Box-catalyzed aldol reactions - tetra- vs. pentacoordination



Evans, D. A. et al., *J. Am. Chem. Soc.* **1999**, *121*, 669

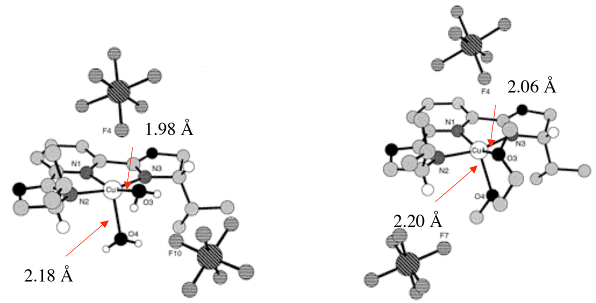
cf. pybox ligands ligands (pyridimal square planar as well) gives opposite selectivity

Pybox-ligands: axial vs. equatorial coordination



D. A. Evans et al., *J. Am. Chem. Soc.*, **1999**, *121*, 669

Pybox-ligands: axial vs. equatorial coordination

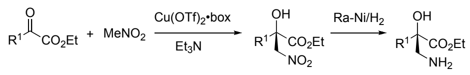


$[Cu(pybox)(H_2O)_2](SbF_6)_2$ $[Cu(pybox)(DME)](SbF_6)_2$

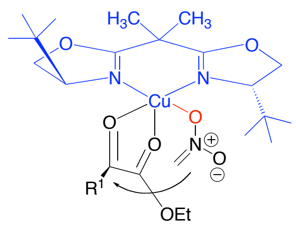
equatorial coordination more effective = better carbonyl activation

D. A. Evans et al., *J. Am. Chem. Soc.*, **1999**, *121*, 669

Cu(II)-box catalyzed nitroaldol reactions

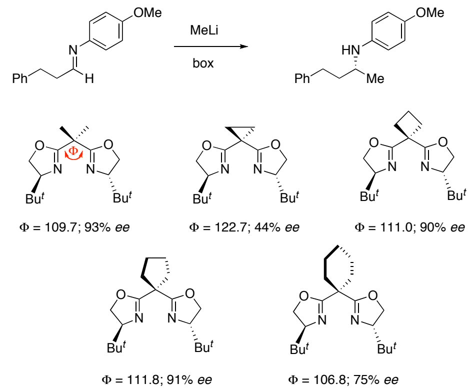


R^1 = Alkyl, Vinyl, Aryl: 57-93% *ee*



K. A. Jørgensen et al. *Chem. Commun.* **2001**, 2222; *J. Org. Chem.* **2002**, *67*, 4875

Bite angle

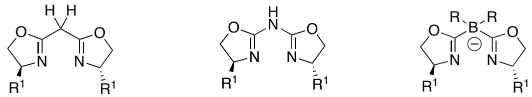


S. E. Denmark et al., *J. Org. Chem.* **2000**, *65*, 5875

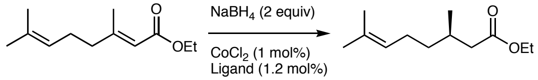
Neutral or anionic box ligands - does it matter?

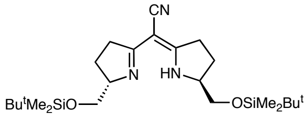
Neutral

Anionic

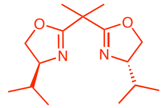


Co(II)-catalyzed conjugate reduction





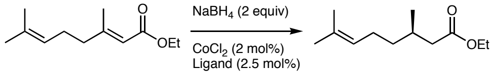
95% yield, 94% ee

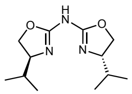


No reaction!

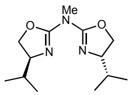
A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 60

Conjugate Reduction with NaBH$_4$

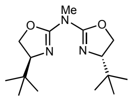




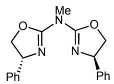
12%, *racemic*



82%, 96% *ee*



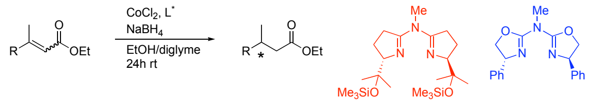
no reaction

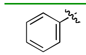
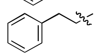
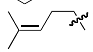


86%, 96% *ee*
81%, 94% *ee* (1 mol%)

Adv. Synth. Catal. **2005**, *347*, 259

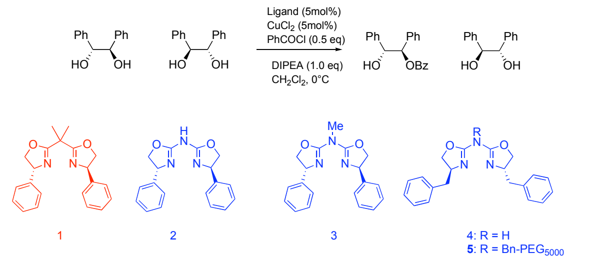
Co(II)-catalyzed conjugate reduction



R		yield	% ee	% ee	Konfiguration
	(E)	86	95	90	S
	(Z)	89	81	73	R
	(E)	86	93	94	R
	(Z)	86	97	94	S
	(E)	88	96	94	R
	(Z)	87	96	94	R
TBDMSO	(E)	85	95	–	S

A. Pfaltz et al., *Angew. Chem.* **1989**, *101*, 61
C. Geiger, P. Kreitmeier, O. Reiser, *Adv. Synth. Catal.* **2005**, *347*, 249

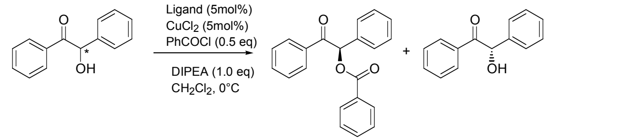
Cu(II)-catalyzed benzoylations

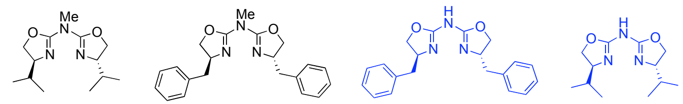


Ligand	Time [h]	Yield (%)	ee (%)	Configuration
1	2	48	≥99	(*R*,*R*)
2	3	48	86	(*R*,*R*)
3	3	46	93	(*S*,*S*)
4 (0.5 mol%)	3	44	97	(*S*,*S*)
5 (0.7 mol%; 5 cycles)	3	40-44	92-97	(*R*,*R*)

Y. Matsumura et. al., *J. Am. Chem. Soc.*, **2003**, *125*, 20523 *Org. Lett.* **2005**, *7*, 2325

Cu(II)-catalyzed benzoylations

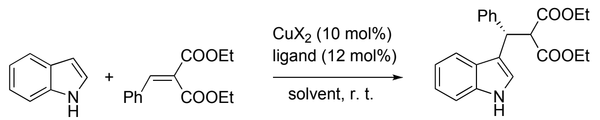


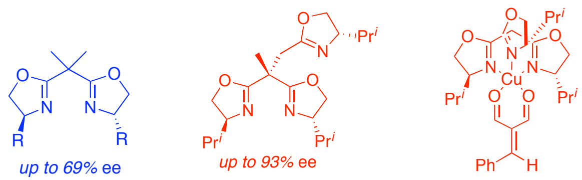


36%, 10% *ee* 32, 27%*ee* 32, 77%*ee* 38%, 81% *ee*

Org. Lett. **2005**, *7*, 2325

Ligand / Metal ratio - does it matter?



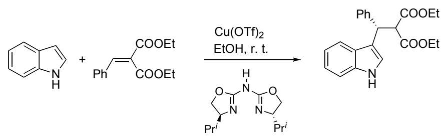


up to 69% ee *up to 93% ee*

Jørgensen et al.
Chem. Commun. **2001**, 347

Y. Tang et al. *J. Am. Chem. Soc.* **2002**, *124*, 9030;
J. Comb. Chem. **2004**; 6, 301; *J. Org. Chem.* **2005**

Conjugate Additions of Indoles to Benzylidenemalonates



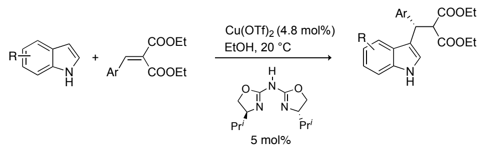
	Mol% Cu / ligand	Yield (%)	% *ee*
1:1.3	0.050:0.065	98	81
1:1.1	0.050:0.055	93	88
1:1.04	0.050:0.052	95	98
1:1	0.050:0.050	96	≥99
1:0.9	0.050:0.045	96	96
1:0.7	0.050:0.035	95	91

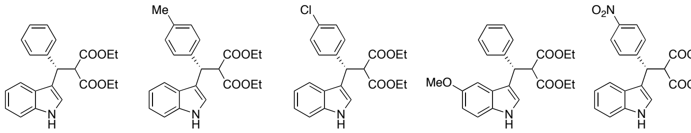
Ligand excess can be disadvantageous for enantioselectivity in metal-box catalyzed reactions

Org. Lett. **2006**, *8*, 6099

Cu-pybox cat. addition of Nu to imines: A. S. Chan et al., *Adv. Synth. Catal.* **2007**, *349*, 2375

Conjugate Additions of Indoles to Benzylidenemalonates



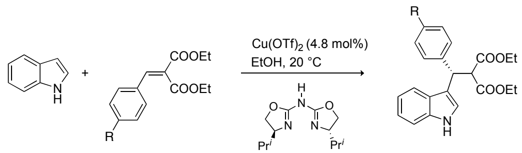


97%, 99% *ee* / 84%, 89% *ee* — 80%, 93% *ee* — 91%, 98% *ee* / 84%, 90% *ee* — 80%, 90% *ee* / 73%, 91% *ee* — 94%, 80% *ee* / 99%, 91% *ee*

*i*Pr-trisox @ –20 °C, taken from
Y. Tang et al. *J. Am. Chem. Soc.* **2002**, *124*, 9030

Org. Lett. **2006**, *8*, 6099

Conjugate Additions of Indoles to Benzylidenemalonates

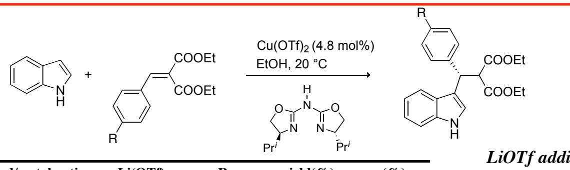


Chem. Eur. J. **2008**, *14*, 7259

Excess ligand

ligand/metal-ratio	R	yield(%)	ee(%)
1.04/1.0	4-Me	80	93
1.3/1.0	4-Me	78	76
1.04/1.0	H	97	>99
1.3/1.0	H	98	81
1.5/1.0	H	94	71
1.04/1.0	2-Br	89	85
1.3/1.0	2-Br	86	86
1.05/1.0	4-NO_2	92	82
1.3/1.0	4-NO_2	83	94
1.5/1.0	4-NO_2	73	93

Conjugate Additions of Indoles to Benzylidenemalonates

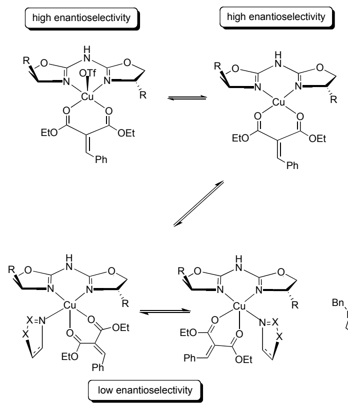


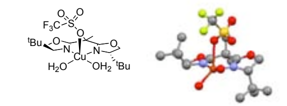
LiOTf additive

ligand/metal-ratio	Li(OTf)	R	yield(%)	ee(%)
1.04/1.0	–	H	97	>99
1.05/1.0	5	H	93	93
1.3/1.0	–	H	98	81
1.3/1.0	5	H	97	96
1.04/1.0	-	2-Br	89	85
1.04/1.0	5	2-Br	84	82
1.3/1.0	–	2-Br	86	86
1.3/1.0	5	2-Br	78	85
1.05/1.0	–	4-NO_2	92	82
1.05/1.0	5	4-NO_2	89	96
1.3/1.0	–	4-NO_2	83	94
1.3/1.0	5	4-NO_2	73	93

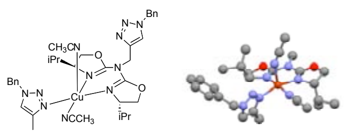
Chem. Eur. J. **2008**, *14*, 7259

Square Planar vs. Square Pyramidal Box-Complexes





D. A. Evans et al., *J. Am. Chem. Soc.* **1999**, *121*, 7599; *ibid.* **2000**, *122*, 9134



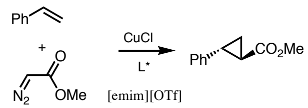
Org. Lett. **2006**, *8*, 6099
Chem. Eur. J. **2008**, *14*, 7259
Coord. Chem. Rev. **2008**, *252*, 702

Immobilization of Catalysts

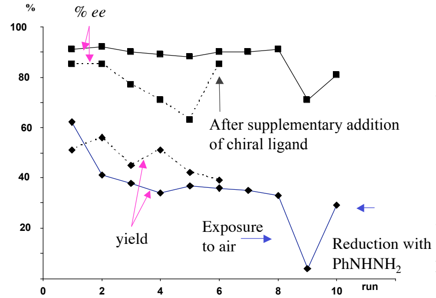
✓ Facile Separation of the Catalyst from Reagents/Products
✓ Recycling and Reuse of Catalysts
✓ Continuous Processes / Flow Reactors

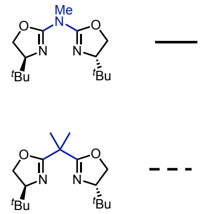
↓ Additional Synthetic Steps for Immobilization
↓ Loading / Catalyst Concentration
↓ Heterogenization: Reduced Reaction Kinetics
↓ Metal Leaching

Immobilization in ionic liquids



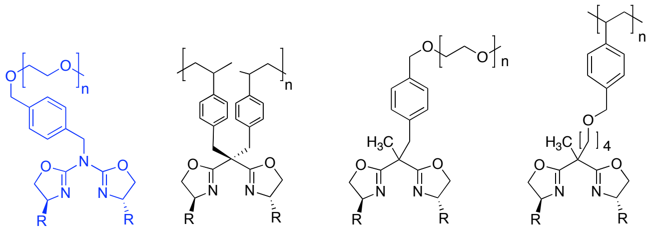
Ligand leaching results in drop of enantioselectivity





In collaboration with J. Mayoral, *Tetrahedron Lett*. **2004**, *45*, 6765

Polymer-supported Bis(oxazoline) ligands



Reiser et al. *Org. Lett.* **2000**, *2*, 2048

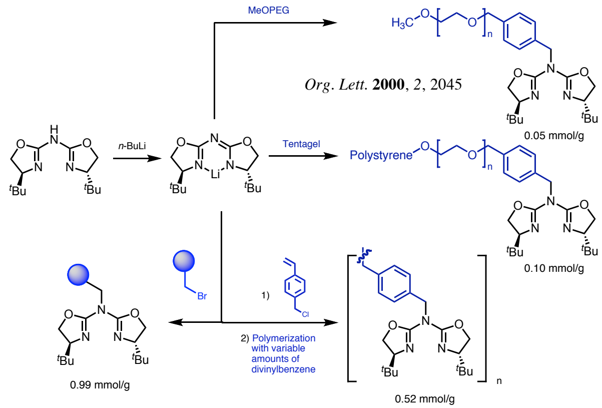
Fraile, Mayoral et al. *Org. Lett.* **2000**, *2*, 3905

Cozzi et al. *JOC* **2001**, *66*, 3160

Salvadori et al. *ACIE* **2001**, *40*, 2519

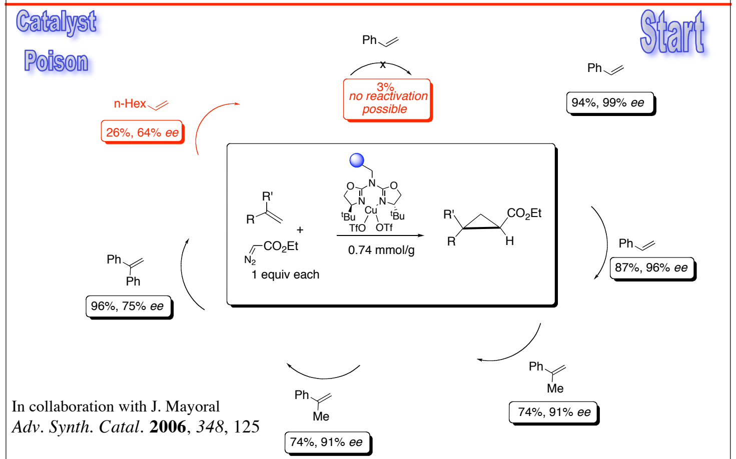
Review: Le Maire et al., *Chem. Rev*. **2002**, *102*, 3467

Polystyrene bound Aza(bisoxazolines)



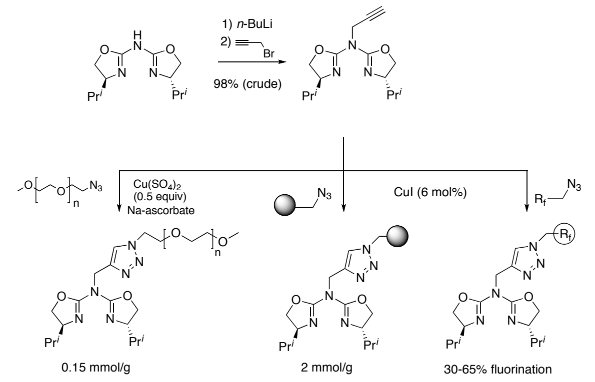
With J. Mayoral; *Adv. Synth. Catal*. **2006**, *348*, 125

Polystyrene bound Aza(bisoxazolines)



In collaboration with J. Mayoral
Adv. Synth. Catal. **2006**, *348*, 125

Click-attachment of Azabox-Ligands to Supports

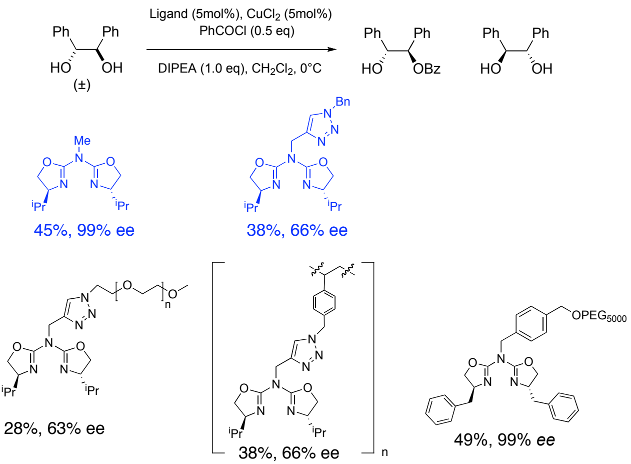


Org. Lett. **2005**, *7*, 2325

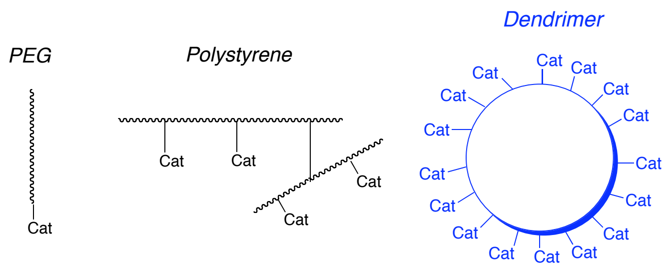
Org. Lett. **2006**, *8*, 6099
Org. Lett. **2007**, *9*, 2895

unpublished

Cu(II)-catalyzed benzoylations



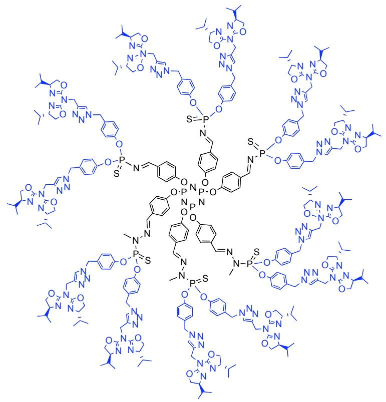
Globular or linear polymeric support?

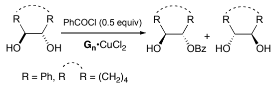


Exposure of linker and ligand during complexation and during the reaction

Exposure of ligand during complexation and during the reaction

Azabox-Dendrimers





1st or 2nd generation:
35-45% yield, 95-99% ee

catalyst recovery by
precipitation from hexanes

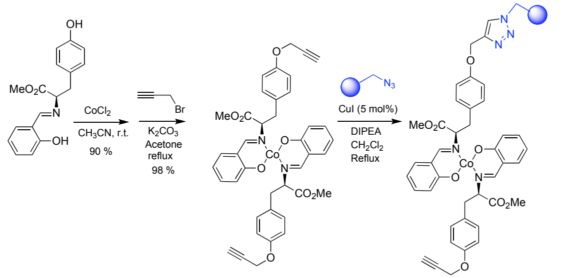
multiple cycles possible
without reloading of copper

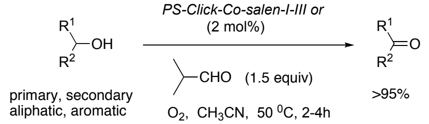
Continuous reactor (nanofiltration)
under development

1st generation

With J.-P-Majoral, Org. Lett. **2007**, *9*, 2895

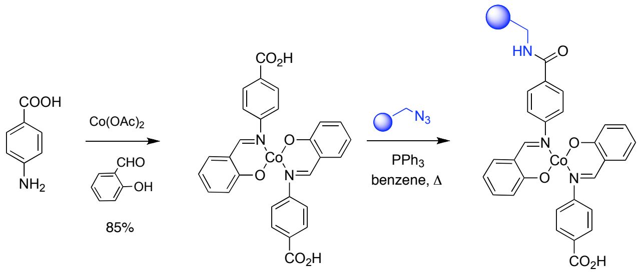
Immobilized Co-Schiff base complexes

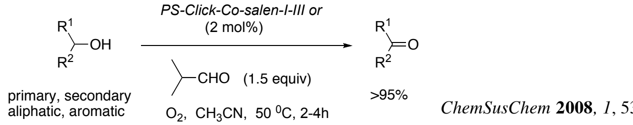




ChemSusChem **2008**, *1*, 534

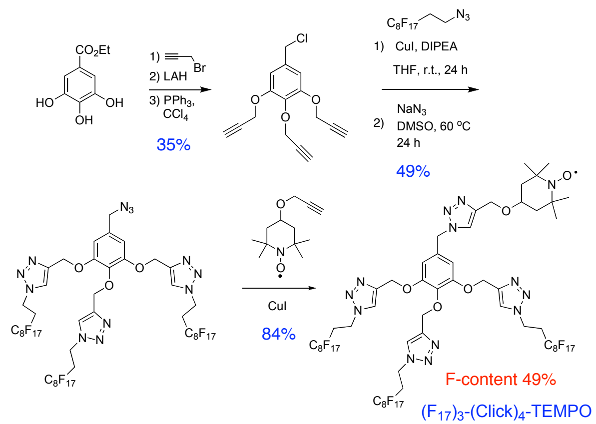
Immobilized Co-Schiff base complexes





ChemSusChem **2008**, *1*, 534

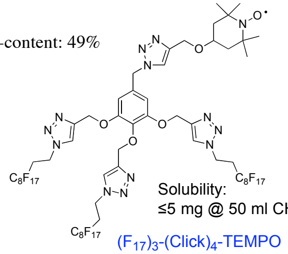
$(F_{17})_3$-(Click)$_4$-TEMPO



$(F_{17})_3$-(Click)$_4$-TEMPO

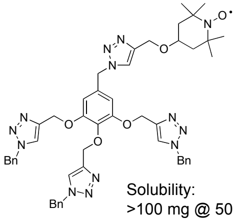
$CH_2Cl_2/NaOCl_{aq}$

F-content: 49%



Solubility:
≤5 mg @ 50 ml CH_2Cl_2

$(F_{17})_3$-(Click)$_4$-TEMPO

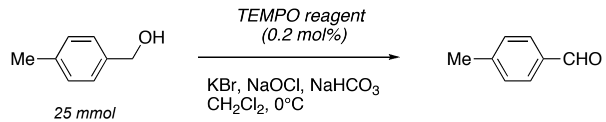


Solubility:
>100 mg @ 50 ml CH_2Cl_2

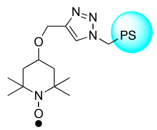
$(Bn)_3$-(Click)$_4$-TEMPO

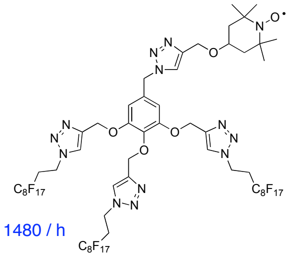
Org. Lett. **2008**, ASAP

Oxidation of Alcohols



heterogeneous

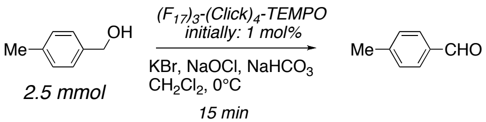


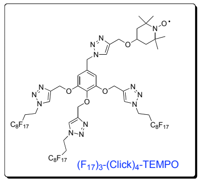


TOF	450 / h	1480 / h

Org. Lett. **2008**, ASAP

Recovery of Catalyst

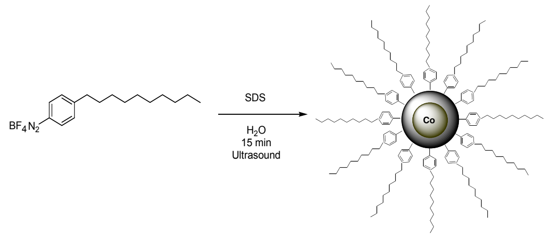




Run	Conversion (%)	Isolated Yield (%)	Purity (%)	Recovery of **$(F_{17})_3$-(Click)$_4$-TEMP O** (%)
1	>98	98	>98	98
2	>98	99	>98	94
3	>98	97	>98	80
4	>98	92	>98	70

Org. Lett. **2008**, ASAP

Carbon Coated Cobalt Nanoparticles

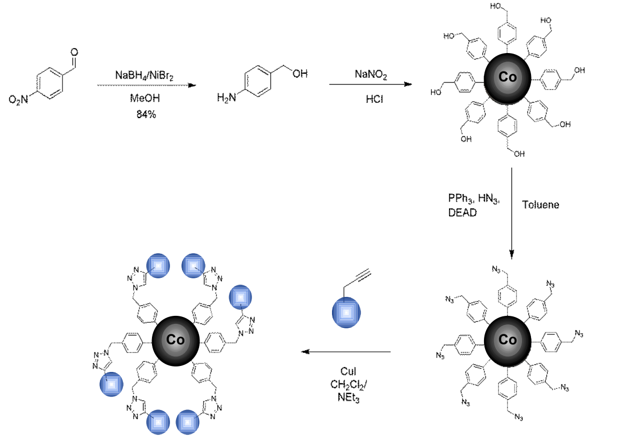


Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

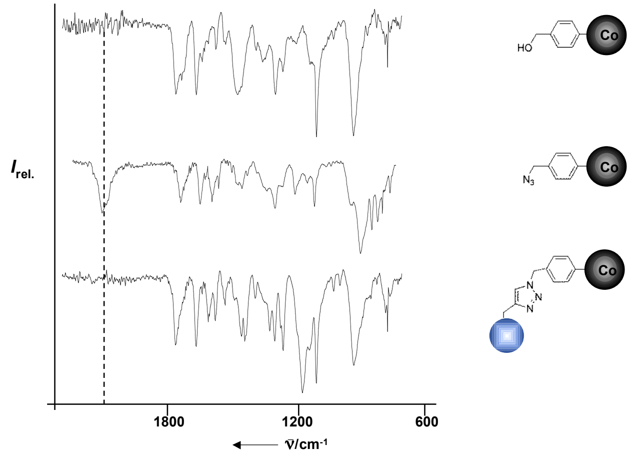
- Stable against air and water
- Synthesis on large scale (> 30 g h^{-1})

Grass, R. N.; Athanassiou, E. K.; Stark, W. J. *Angew. Chem.* **2007**, *119*, 4996.

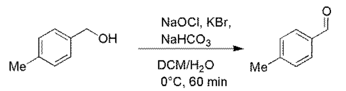
Click-Reaction on Carbon coated Co-NPs

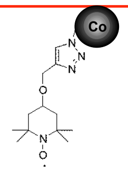


Monitoring of the Functionalization Chemistry via IR

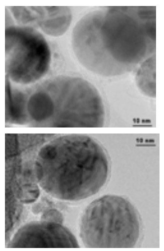


Oxidation of Alcohols by TEMPO/Bleach





entry	conversion [%][b]	yield [%][c]	purity [%][b]
1	> 98	89	> 98
2	> 96	92	> 96
3	> 98	95	> 98
4	> 98	87	> 98
5	> 93	90	> 93
6	> 98	96	> 98



[a]Alcohol (3 mmol) in CH_2Cl_2 (6 mL), KBr (1 mmol), CoNP-TEMPO (2.5 mol%), NaOCl (3.9 mmol), $NaHCO_3$ (0.6 mmol), 0°C, 60 min. [b]Determined by ^1H and ^{13}C NMR; >98% indicates that no starting material or by-products could be detected. [c]Yields of isolated products.

with W. Stark, *Chem. Eur. J.* **2008**, *14*, 8262

Acknowledgement

This lecture is aimed to present some concepts of bis(oxazoline) catalysis, not to give an overview of the field. I am aware that many outstanding contributions from other groups are not covered here, the examples presented here are chosen on my own personal reflection to provide some useful rules on how to approach (asymmetric) catalysis.

I am indebted to all my co-workers who have contributed to the developments coming from our group presented in this lecture.

Support from the Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie und Degussa Rexim, Degussa AG is gratefully acknowledged.