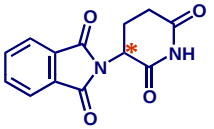
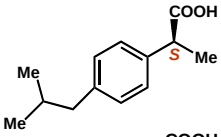
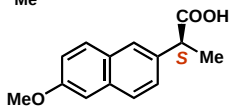
Importance of Chirality



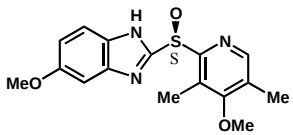
Thalidomide was prescribed to pregnant women for morning sickness during 1957-1962. But, it turned out to be a teratogen (creating malinformation in Embryos) having caused serious birth defects to more than10,000 babies. Later, it was confirmed that (*S*)-enantiomer was the culprit.



(±)-Ibuprofen, an anti-inflammatory and analgesic drugs can be used as body converts inactive (*R*)-enantiomer into (S)-one, but it takes time. For example, *S*-isomer reaches therapeutic conc. in body in 12 min whereas racemic one takes 30 min.

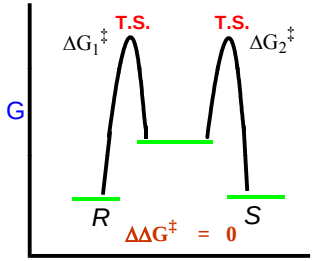


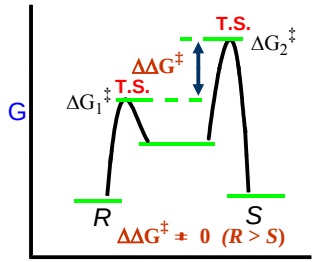
(*S*)-Naproxen is active, but the (*R*)-enantiomer has some undesirable side effects.



Racemic Switching (use of chirality for patent protection): **Omeprazole** (antiulcer drug; AstraZeneca) marketed in U.S. as a racemic form in 1995. The patent ran out in 2002. Since the pharmacological property lied in (*S*)-enantiomer, the company patented the (*S*)-enantiomer.

Principle of Enantioselectivity



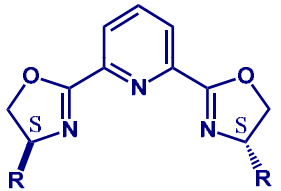


ΔΔG‡	% ***R*** (-78 °C)	% ***R*** (+25 °C)
1.0	93	84
1.5	98	93
2.0	99.4	97

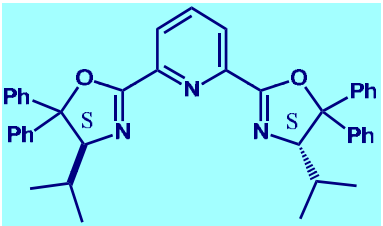
Ways to Synthesize Chiral Molecules

1. Asymmetric Induction
   - a. Internal Auxiliary
   - b. External Auxiliary
2. Chiron Approach
3. Resolution
   - a. Enzymatic
   - b. Non-enzymatic

PYBOX and PYBOX–DIPH Ligands

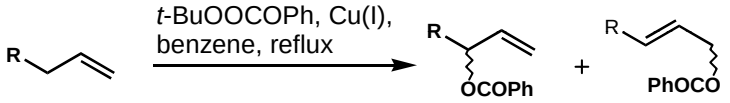


Nishiyama introduced in asymm. hydrosilylation (1989), and later used in asymmetric cyclopropanation (1994) and other reactions.
Evans and others used it extensively.



Singh introduced in enantioselective cyclopropanation (1994), and later used in allylic oxidation of olefins, propargylation of imines, and Friedel-Crafts Reactions (1994-2010).
Loh used in asymm. allylation to aldehydes and ketones (2005).

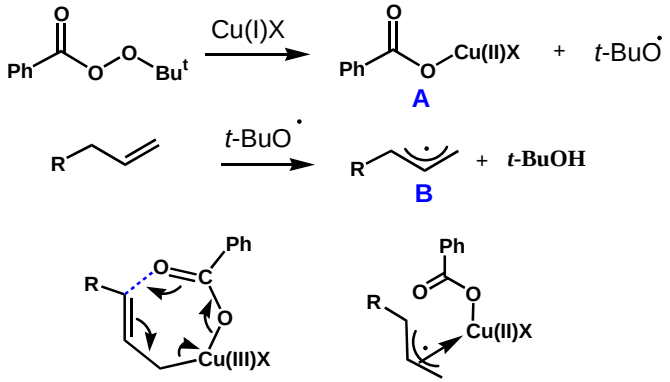
Allylic Oxidation of Olefins (Kharasch Reaction)



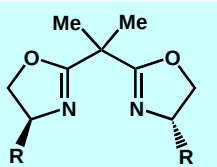
Major

Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 5756.

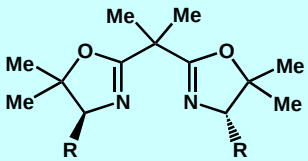
Mechanism of the Kharasch reaction



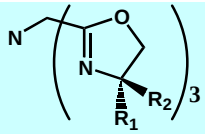
Beckwith *et al. J. Am. Chem. Soc.* **1986**, *108*, 8230.
Kochi *et al. J. Org. Chem.* **1965**, *30*, 1862.



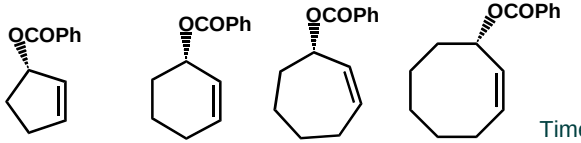
Pfaltz *et al.*
Tetrahedron Lett.
1995, *36*, 1831.



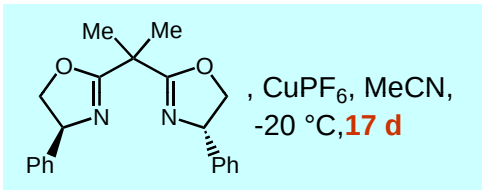
Andrus *et al.*
Tetrahedron Lett.
1995, *36*, 2945.

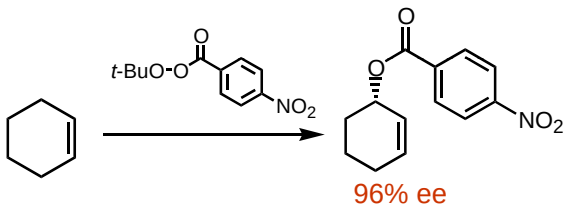


Katsuki *et al. Synlett*
1995, 1245;
Tetrahedron **1997**, *53*, 6337; *TL*, **2000**, *41*, 3941.



					Time
Pfaltz	84% ee	77% ee	82% ee	---	14 - 22 days
Andrus	81% ee	80% ee	---	13% ee	5 days
Katsuki	93% ee	88% ee	60% ee	64% ee	3 - 10 days

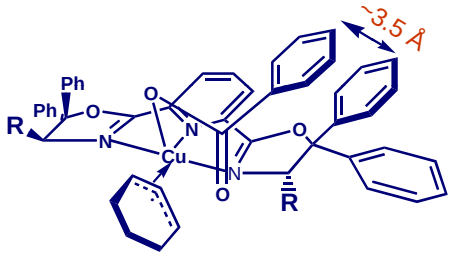




96% ee

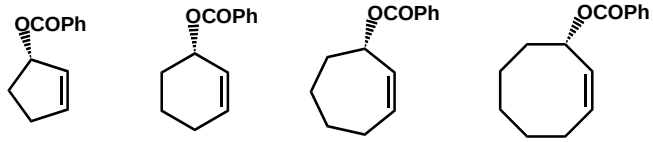
M. B. Andrus and Z. Zhou *J. Am. Chem. Soc.***2002**, *124*, 8806.

Assumption of Transition State Model



Early Results

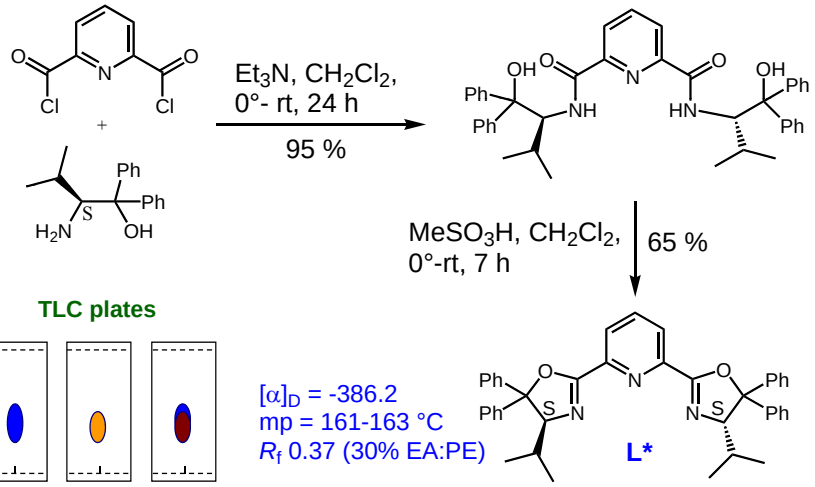
Reagents:
5 Mole % L* - $Cu(OTf)_2$, $PhNHNH_2$,
$PhCO_3t$-Bu, 4 Å MS, acetone, rt



60% ee 86% ee 81% ee 82% ee

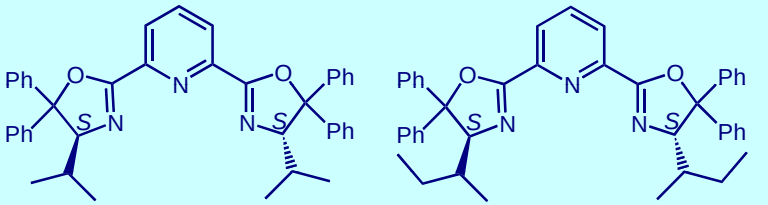
Tetrahedron Lett **1996**, *37*, 2633.
J. Org. Chem. **1998**, *63*, 2961.

Synthesis & Purification of Pybox Ligand



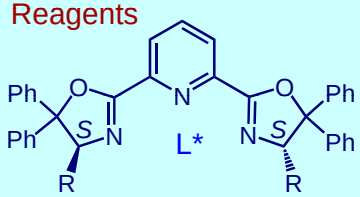
Tetrahedron, **2006**, *62*, 3573.

Selected Ligands

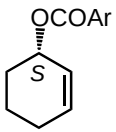


Different peresters

Reagents



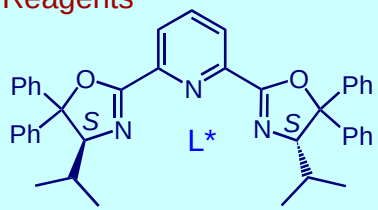
5 Mol% L*-Cu(OTf)$_2$, PhNHNH$_2$, **Ar**CO$_3$^{t}Bu, acetone, rt



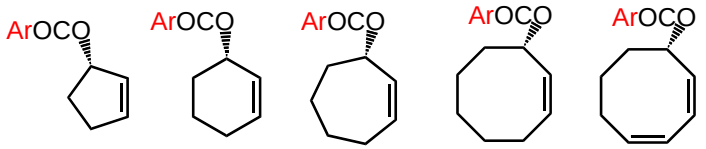
	R =	*i*-Pr	*s*-Bu
Ar = phenyl:		91% ee	91% ee
Ar = *p*-nitrophenyl:		86% ee	87% ee
Ar = *o*-nitrophenyl:		82% ee	83% ee
Ar = *m*-nitrophenyl:		88% ee	86% ee
Ar = *m*-methoxyphenyl:		91% ee	90% ee
Ar = *p*-methoxyphenyl:		92% ee	92% ee
Ar = *o*-methoxyphenyl:		91% ee	98% ee
Ar = *p*-isopropylphenyl:		91% ee	89% ee
Ar = 2,6-difluorophenyl:		72% ee	79% ee
Ar = pentafluorophenyl:		40% ee	52% ee

Best results with “ip-pybox-diph” Ligand

Reagents



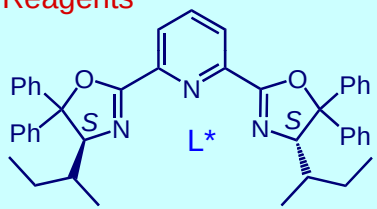
5 Mol% L*-Cu(OTf)$_2$, PhNHNH$_2$, ArCO$_3$^{t}Bu, acetone, rt



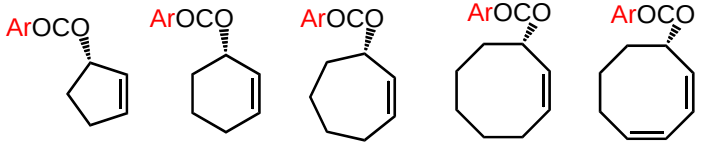
Ar					
Ph	70% ee	91% ee	86% ee	94% ee	80% ee
p-NO$_2$Ph	62% ee	86% ee	85% ee	91% ee	66% ee
p-OMePh	77% ee	93% ee	91% ee	96% ee	95% ee
o-OMePh	80% ee	91% ee	91% ee	91% ee	86% ee

Best results with “sb-pybox-diph” Ligand

Reagents



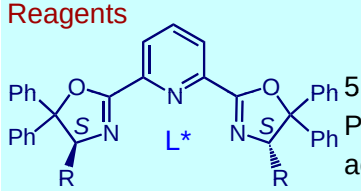
5 Mol% L*-Cu(OTf)$_2$, PhNHNH$_2$, ArCO$_3$^{t}Bu, acetone, rt



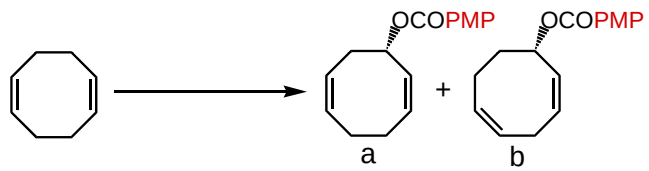
Ar					
Ph	65% ee	91% ee	-	95% ee	-
p-NO$_2$Ph	58% ee	87% ee	90% ee	88% ee	65% ee
p-OMePh	72% ee	92% ee	94% ee	90% ee	96% ee
o-OMePh	80% ee	98% ee	87% ee	92% ee	82% ee

1,5 Cyclooctadiene

Reagents



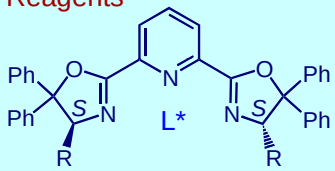
5 mol % L*-Cu(OTf)$_2$, PhNHNH$_2$, PMPCO$_3$^{t}Bu, acetone, rt



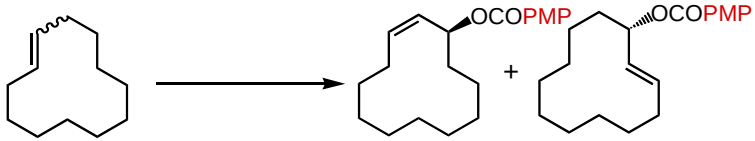
Ligand (R)	Time (h)	Ratio (a:b)	Yield (%)	ee (a / b)%	
i-Pr	12	3 : 2	68	93	94
s-Bu	05	1 : 1	70	93	93

cis and *trans* mixture of Cyclododecene

Reagents



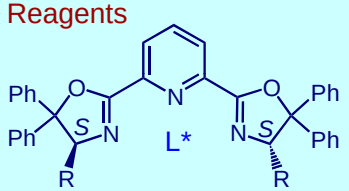
5 mol % L*-Cu(OTf)$_2$, PhNHNH$_2$, PMPCO$_3$^{t}Bu, acetone, rt



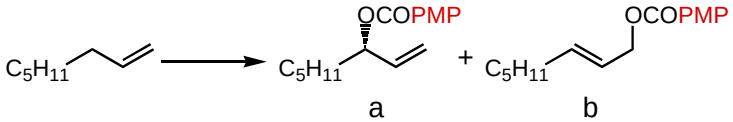
Ligand (R)	Time (h)	Yield (a / b)%		ee (a / b)%	
		a			**b**
i-Pr	12	37	13	56	17
s-Bu	05	40	14	57	06

Acyclic Substrate (1-Octene)

Reagents

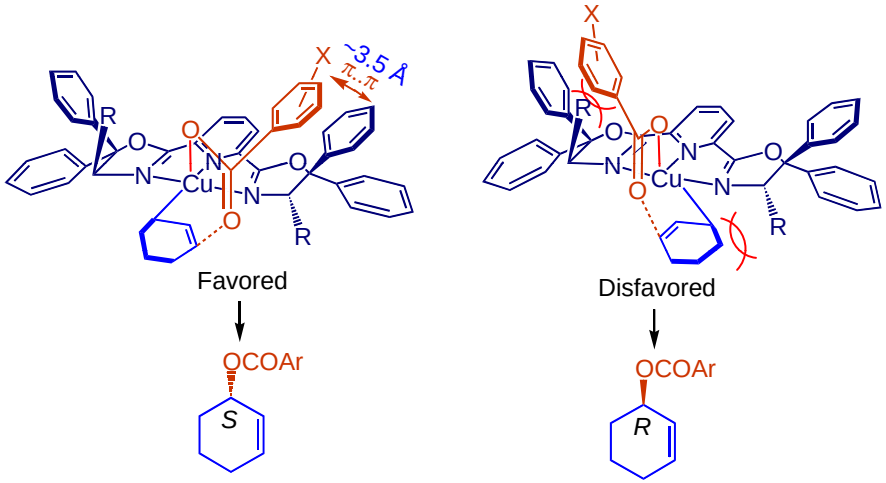


5 mol % L*-Cu(OTf)$_2$, PhNHNH$_2$, PMPCO$_3$^{t}Bu, acetone, rt



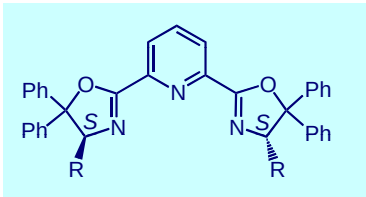
Ligand (R=)	Time (h)	Ratio (a/b)	Yield (%)	ee (a)%
i-Pr	39	7:3	39	31
s-Bu	39	6:4	35	28

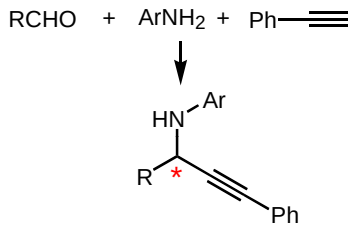
Proposed Transition State Model



Org. Biomol. Chem. **2006**, *4*, 4370.

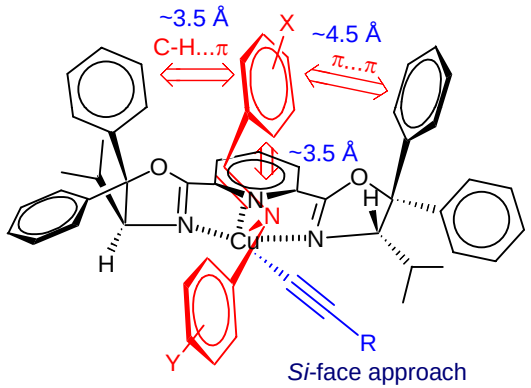
Enantioselective One-pot Three-Component Coupling Reaction



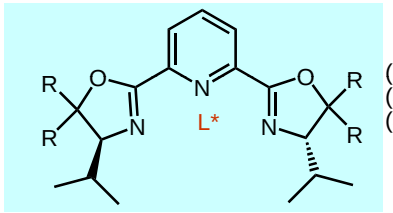


Org. Lett. **2006**, 8, 2405.

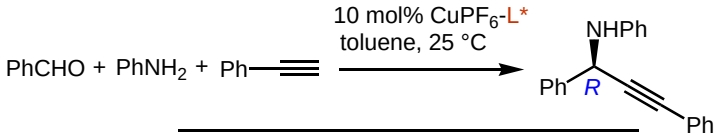
Basis of ‘ip-pybox-diph’ ligand



C_2-Symmetric ip-Pybox Ligands



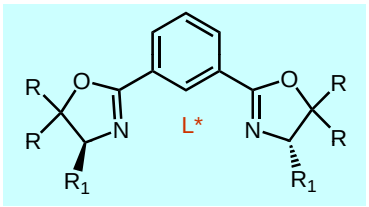
(*R*,*R*)-**1**: R = H
(*S*,*S*)-**2**: R = Et
(*S*,*S*)-**3**: R = Ph



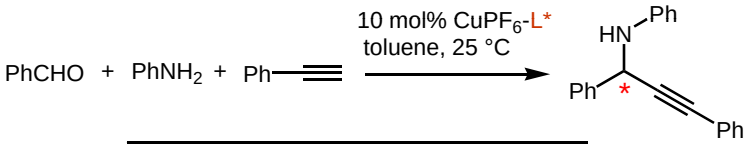
Ligand	time	yield (%)	ee (%)
(*R*,*R*)-**1**	5 d	32	38 (*S*)
(*S*,*S*)-**2**	4 d	43	56
(*S*,*S*)-**3**	5 h	95	85

Li *et al.*
JACS, **2002**, *124*, 5638.
PNAS **2004**, *101*, 5749.

Importance of ‘N’ of Pyridine

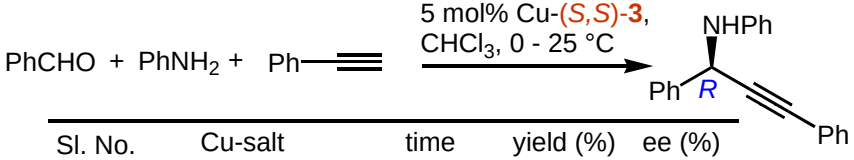


(*S*,*S*)-**4**: R_1 = *i*-Pr, R = H
(*R*,*R*)-**5**: R_1 = Ph, R = H
(*S*,*S*)-**6**: R_1 = *i*-Pr, R = Ph



Ligand	time	yield (%)	ee (%)
(*S*,*S*)-**4**	5 d	22	10.4 (*S*)
(*R*,*R*)-**5**	5 d	42	0.0
(*S*,*S*)-**6**	3 d	81	0.0

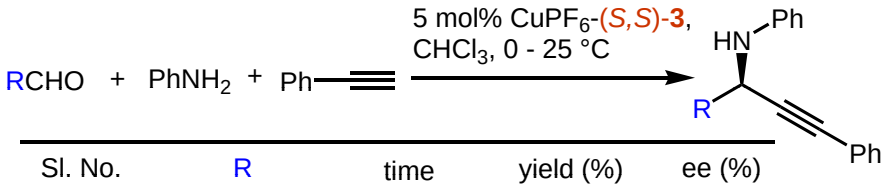
Different Cu-Lewis acids



Sl. No.	Cu-salt	time	yield (%)	ee (%)
1.	$Cu(MeCN)_4PF_6$	12 h	90	96[a]
2.	$Cu(MeCN)_4PF_6$	12 h	88	96
3.	$(CuOTf)_2.PhMe$	12 h	95	95[a]
4.	$(CuOTf)_2.PhMe$	18 h	94	96
5.	$(CuOTf)_2.PhH$	12 h	92	95[a]
6.	$(CuOTf)_2.PhH$	18 h	91	96
7.	$Cu(OTf)_2$	24 h	95	94[a]
8.	$Cu(OTf)_2$	72 h	85	94

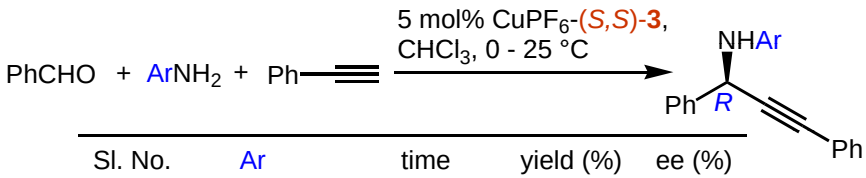
[a]10 mol% catalyst was used.

Different Aldehydes



Sl. No.	R	time	yield (%)	ee (%)
1.	phenyl	12 h	80	96 (*R*)
2.	4-*i*-Pr-phenyl	20 h	89	95 (*R*)
3.	4-Cl-phenyl	24 h	94	96 (*R*)
4.	3,5-di Me-phenyl	12 h	98	95 (*R*)
5.	3-Br-phenyl	26 h	92	91 (*R*)
6.	3-Me-phenyl	12 h	91	96 (*R*)
7.	3-F-phenyl	28 h	85	93 (*R*)
8.	4-NO_2-phenyl	28 h	82	94 (*R*)
9.	2-Cl-phenyl	12 h	93	98 (*S*)

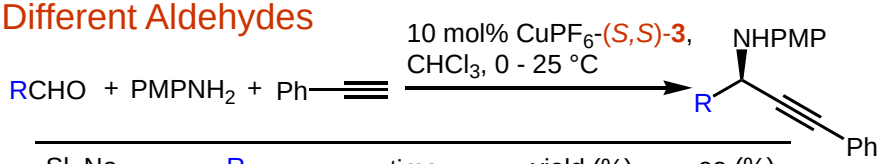
Different Aromatic amines



Sl. No.	Ar	time	yield (%)	ee (%)
1.	Ph-	12 h	88	96
2.	3-F-Ph-	24 h	93	95
3.	4-Br-Ph-	24 h	86	93
4.	3-Cl-Ph-	24 h	93	95
5.	4-MeO-Ph- (PMP)	16 h	98	90[a]

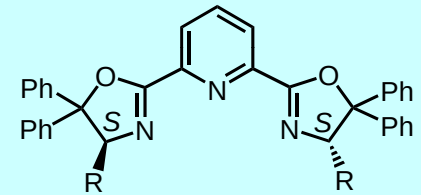
[a] 10 mol% catalyst was used.

Different Aldehydes

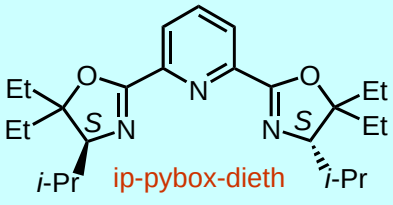


Sl. No.	R	time	yield (%)	ee (%)
1.	Ph-	16 h	98	90 (*R*)
2.	4-Cl-Ph-	28 h	91	90 (*R*
3.	4-*i*-Pr-Ph-	22 h	87	83 (*R*
4.	3,5-di Me-Ph-	16 h	98	93 (*R*)
5.	3-Br-Ph-	26 h	96	80 (*R*)
6.	3-Me-Ph-	22 h	99	92 (*R*)
7.	3-F-Ph-	26 h	90	85 (*R*)
8.	4-F-Ph-	24 h	95	91 (*R*)
9.	3-Cl-Ph-	16 h	92	82 (*R*
10.	2-Cl-Ph-	16 h	94	**97** (*S*)
11.	4-NO_2-Ph-	46 h	90	90 (*R*)
12.	2,4-di Me-Ph-	18 h	97	**99** (*S*)

Ligands used in propargylamine synthesis

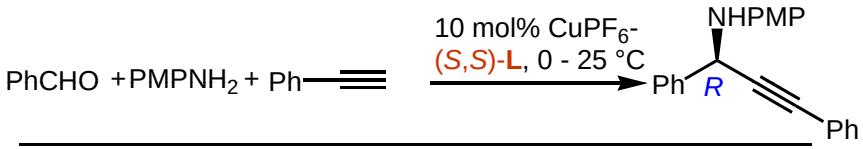


R = *i*-Pr (ip-pybox-diph)
R = Me (me-pybox-diph)
R = Ph (ph-pybox-diph)
R = Bn (bn-pybox-diph)
R = *i*-Bu (ib-pybox-diph)
R = *s*-Bu (sb-pybox-diph)
R = *t*-Bu (tb-pybox-diph)



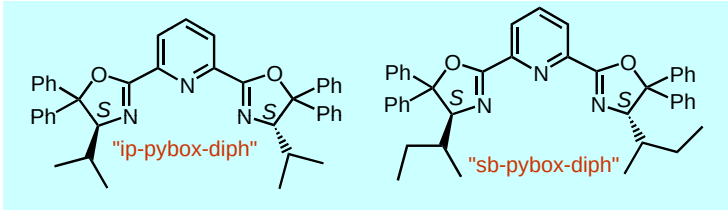
ip-pybox-dieth

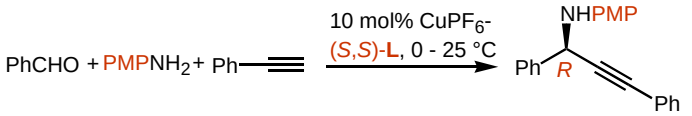
Screening of Different Ligands



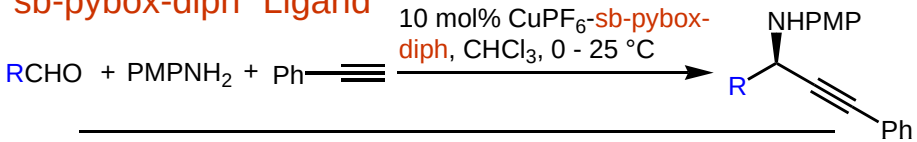
Sl. No.	Ligands	time	yield (%)	ee (%)
1.	ip-pybox-diph	16 h	98	**90**
2.	me-pybox-diph	4 days	51	53
3.	ph-pybox-diph	28 h	96	75
4.	bn-pybox-diph	5 days	45	64
5.	ib-pybox-diph	4 days	56	63
6.	sb-pybox-diph	18 h	97	**93**
7.	tb-pybox-diph	22 h	90	68
8.	ip-pybox-dieth	6 days	46	68

Best Ligands



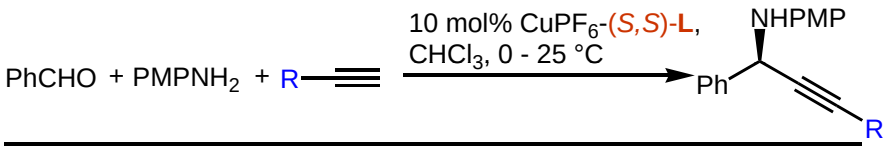


"sb-pybox-diph" Ligand



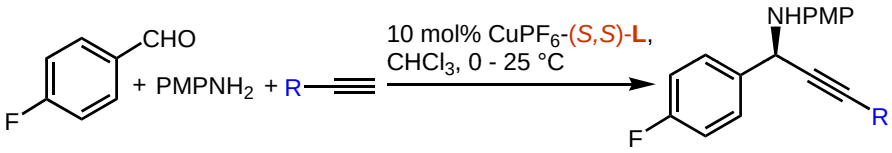
Sl. No.	R	time	yield (%)	ee (%)
1.	Ph	18 h	97	93 (*R*)
2.	4-Cl-Ph	20 h	93	95 (*R*)
3.	4-*i*-Pr-Ph	20 h	92	96 (*R*)
4.	3,5-di Me-Ph	18 h	96	96 (*R*)
5.	3-Br-Ph	23 h	90	87 (*R*)
6.	3-Me-Ph	22 h	98	95 (*R*)
7.	3-F-Ph	22 h	97	92 (*R*)
8.	4-F-Ph	20 h	97	96 (*R*)
9.	3-Cl-Ph	30 h	97	89 (*R*
10.	2-Cl-Ph	24 h	90	**97** (*S*)
11.	4-NO_2-Ph	46 h	89	**97** (*R*)
12.	2,4-di Me-Ph	18 h	97	**99** (*S*)

Different Terminal alkynes



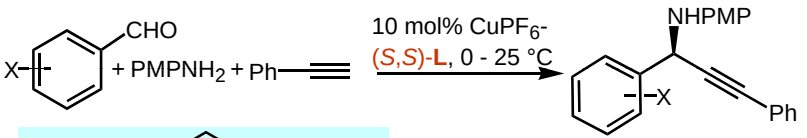
Sl. No.	R	ip-pybox-diph time	ip-pybox-diph yield (%)	ip-pybox-diph ee (%)	sb-pybox-diph time	sb-pybox-diph yield (%)	sb-pybox-diph ee (%)
1.	$PhCH_2CH_2$	42 h	86	84 (*R*)	48 h	66	88 (*R*)
2.	*n*-Bu	28 h	67	87 (*R*)	70 h	71	90 (*R*)
3.	*p*-MePh	18 h	98	93 (*R*)	17 h	99	94 (*R*)
4.	*p*-pentylPh	18 h	92	92 (*R*)	21 h	92	95 (*R*)
5.	*p*-BrPh	18h	93	90 (*R*)	20 h	94	91 (*R*)
6.	*p*-OMePh	20 h	96	93 (*R*)	23 h	94	94 (*R*)

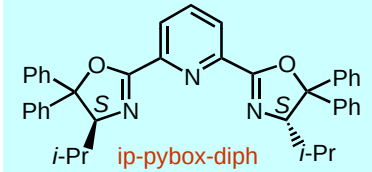
Different Terminal alkynes with *p*-F-Benzaldehyde



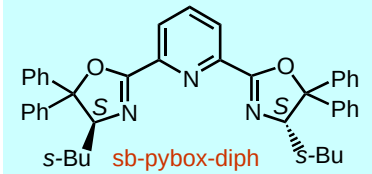
Sl. No.	R	ip-pybox-diph time	ip-pybox-diph yield (%)	ip-pybox-diph ee (%)	sb-pybox-diph time	sb-pybox-diph yield (%)	sb-pybox-diph ee (%)
1.	$PhCH_2CH_2$	62 h	80	82 (*R*)	72 h	70	89 (*R*)
2.	*n*-Bu	62 h	67	84 (*R*)	72 h	65	91 (*R*)
3.	4-Me-Ph	18 h	94	93 (*R*)	22 h	88	96 (*R*)
4.	4-*n*-Pentyl-Ph	20 h	91	93 (*R*)	22 h	90	97 (*R*)
5.	4-Br-Ph	20 h	93	90 (*R*)	24 h	93	94 (*R*)
6.	4-OMe-Ph	24 h	98	92 (*R*)	26 h	97	96 (*R*)

Effect of *ortho*-substitution on aromatic aldehydes



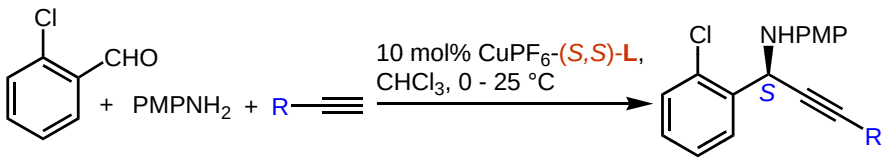


X = 2-Cl, 16 h, 94% yield, 97% *ee*
X = 2,4-di Me, 18 h, 97% yield, 99% *ee*



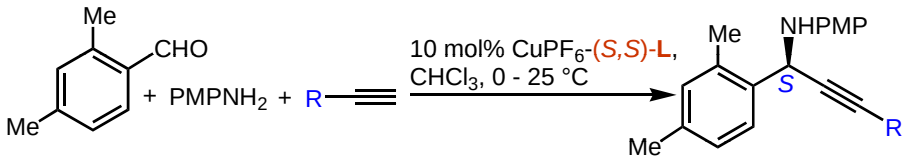
X = 2-Cl, 24 h, 90% yield, 97% *ee*
X = 2,4-di Me, 16 h, 98% yield, 99% *ee*

Study with 2-Chlorobenzaldehyde



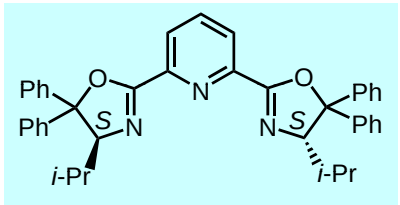
Sl. No.	R	ip-pybox-diph time	ip-pybox-diph yield (%)	ip-pybox-diph ee (%)	sb-pybox-diph time	sb-pybox-diph yield (%)	sb-pybox-diph ee (%)
1.	$PhCH_2CH_2$	48 h	61	85	68 h	61	91
2.	*n*-Bu	48 h	67	87	68 h	63	87
3.	4-Me-Ph	22 h	97	**98**	25 h	89	**98**
4.	4-Br-Ph	22 h	95	**97**	22 h	93	**97**
5.	4-OMe-Ph	24 h	91	**98**	26 h	95	**99**

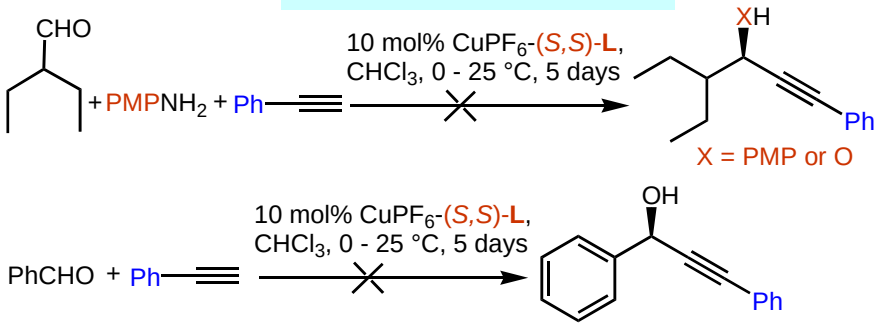
Study with 2,4-dimethylbenzaldehyde



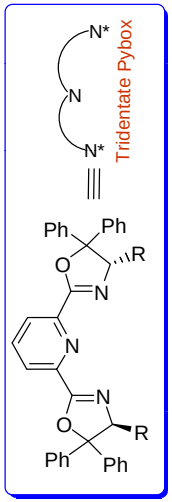
Sl. No.	R	ip-pybox-diph time	ip-pybox-diph yield (%)	ip-pybox-diph ee (%)	sb-pybox-diph time	sb-pybox-diph yield (%)	sb-pybox-diph ee (%)
1.	$PhCH_2CH_2$	62 h	92	97	70 h	75	97
2.	4-Me-Ph	18 h	94	**98**	22 h	90	**98**
3.	4-OMe-Ph	22 h	92	87	25 h	95	87
4.	4-Br-Ph	24 h	95	**98**	22 h	96	**99**

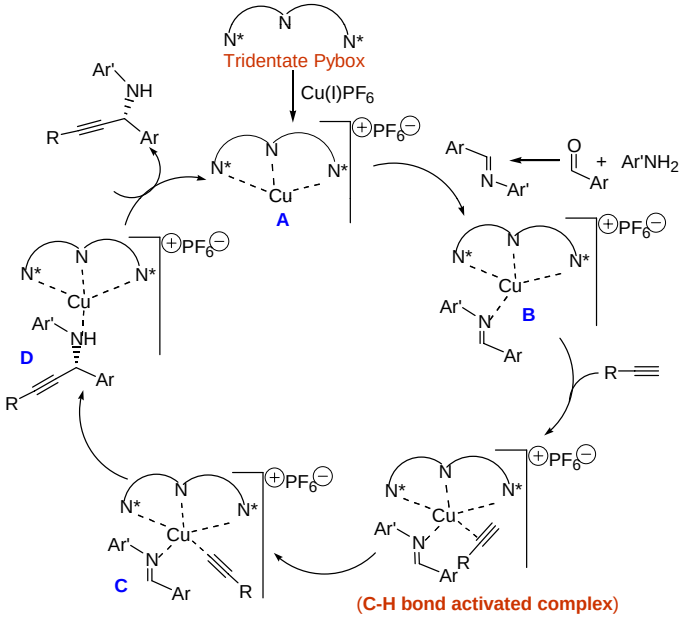
Limitations



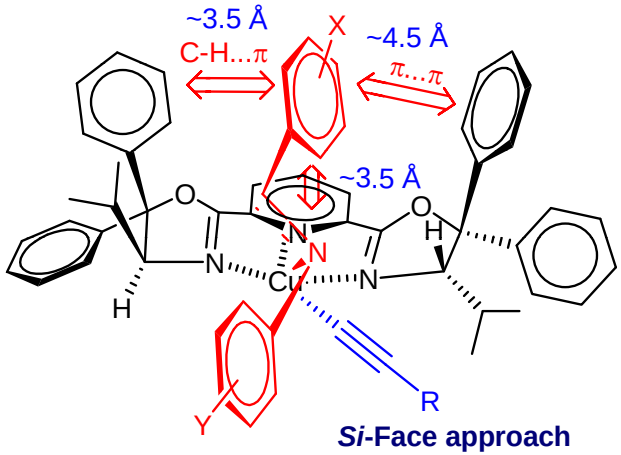


Proposed Catalytic Cycle for Propargylation Reactions



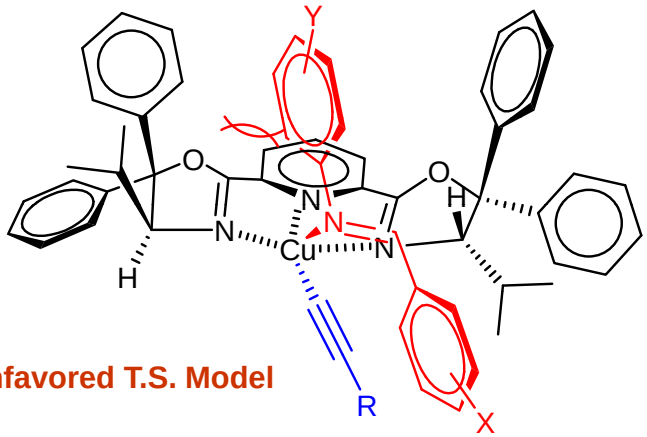


Proposed Transition State Models



***Si*-Face approach**

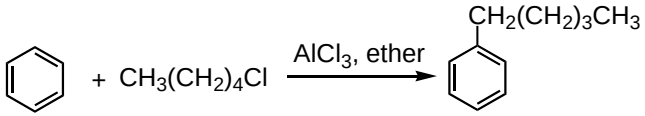
Favored T.S. Model



Unfavored T.S. Model

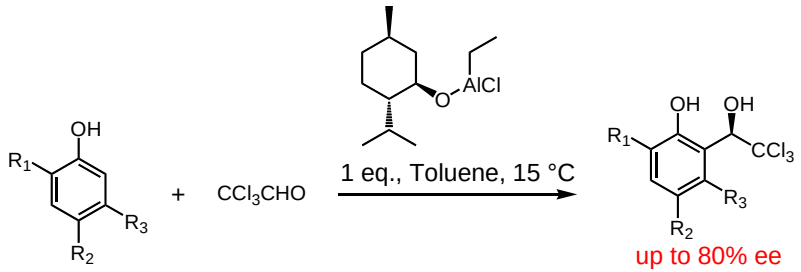
Org. Lett. **2006**, *8*, 2405.

Friedel-Crafts Alkylation Reaction



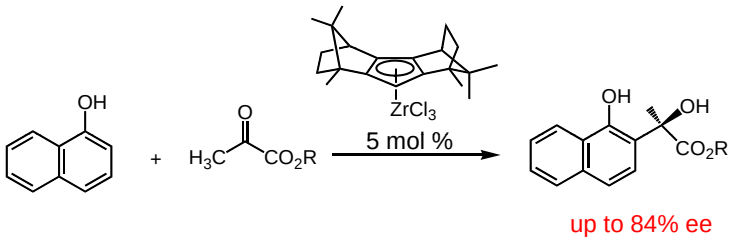
Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, *84*, 1392 &1450.

First Enantioselective Friedel-Crafts Reaction



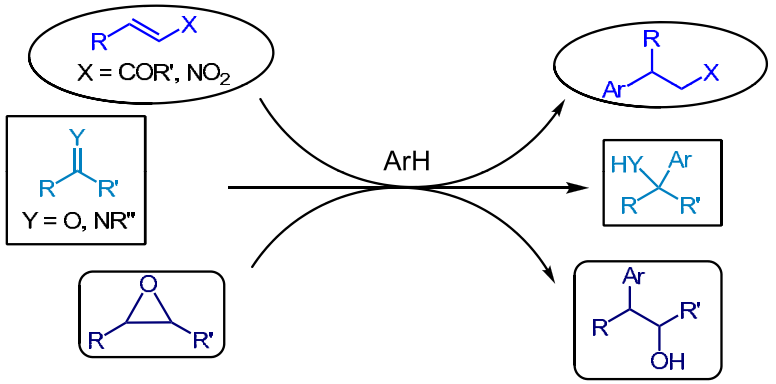
Casiraghi *et al. J. Org. Chem.* **1985**, *50*, 5018.

First Catalytic Enantioselective Friedel-Crafts Reaction



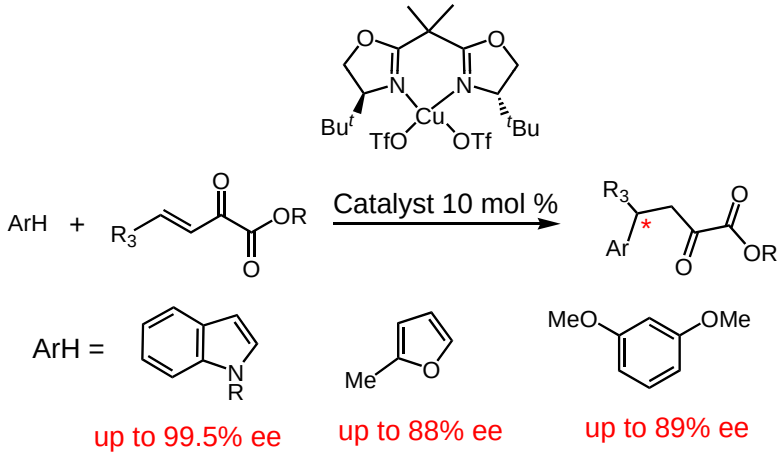
Erker *et al. Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 512.

Approaches for Enantioselective Friedel-Crafts Alkylation



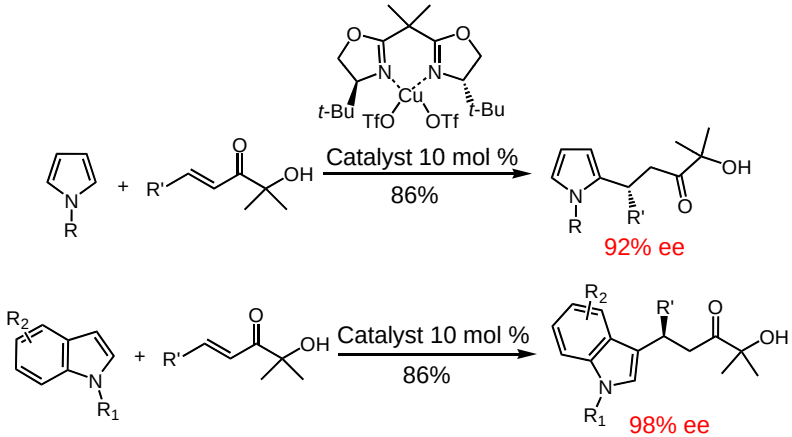
Bandini *et al. Helv. Chim. Acta* **2003**, *86*, 3753.

Bis(oxazoline)–Cu(II) Complex

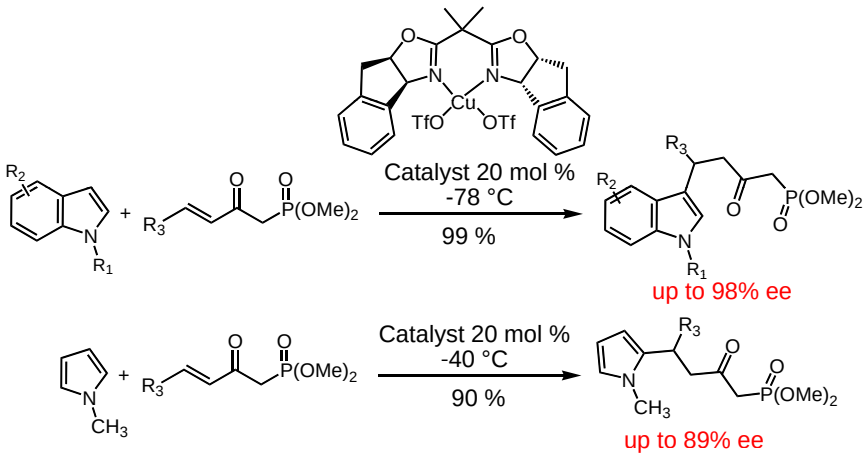


Jørgensen *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 160.

Bis(oxazoline)–Cu(II) Complex------

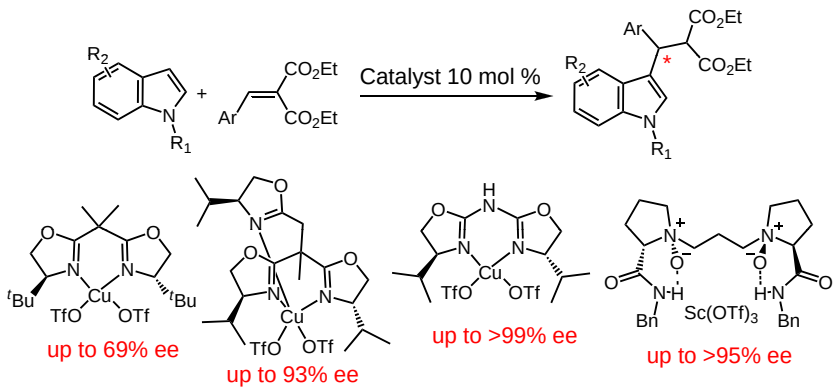


Palomo *et al. J. Am. Chem. Soc.* **2005**, *127*, 4154.



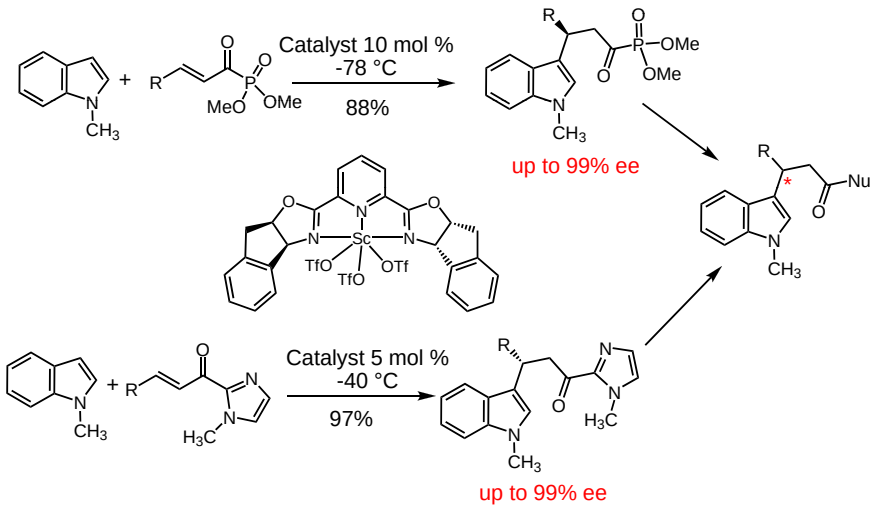
Kim *et al. Org. Lett.* **2007**, *9*, 2281.

Friedel-Crafts Reaction with Alkylidene Malonate

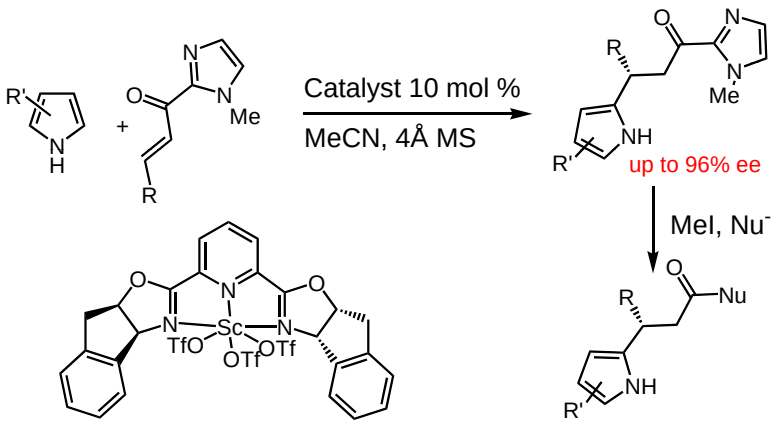


Jørgensen *et al. Chem. Commun.* **2001**, 347.
Tang *et al. J. Am. Chem. Soc.* **2002**, *124*, 9030.
Reiser *et al. Org. Lett.* **2006**, *8*, 6099.
Liu *et al. Chem. Eur. J.* **2009**, *15*, 2055.

Pybox–Sc(III) Complex----

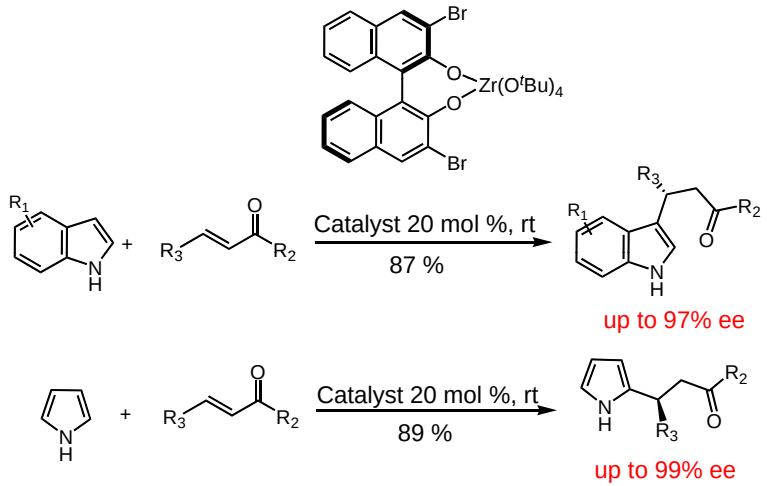


Evans *et al. J. Am. Chem. Soc.* **2003**, *125*, 10780
Evans *et al. J. Am. Chem. Soc.* **2005**, *127*, 8942



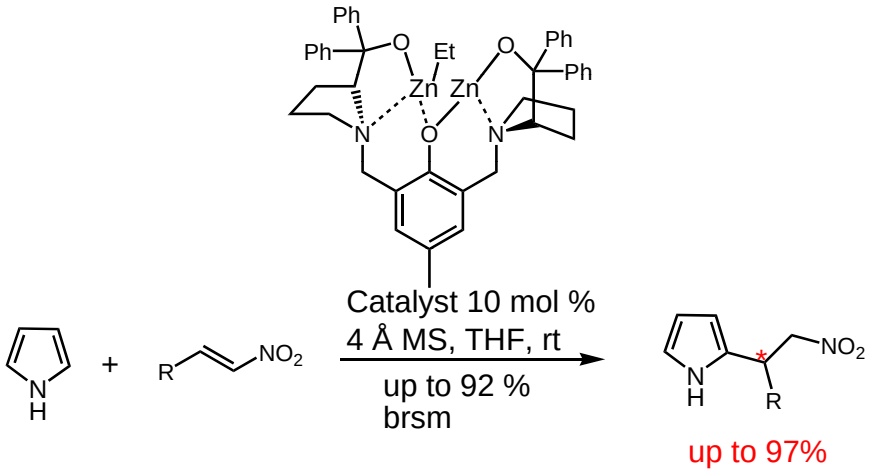
Evans *et al. Org. Lett.* **2006**, *8*, 2249.

BINOL–Zirconium(IV) Complex



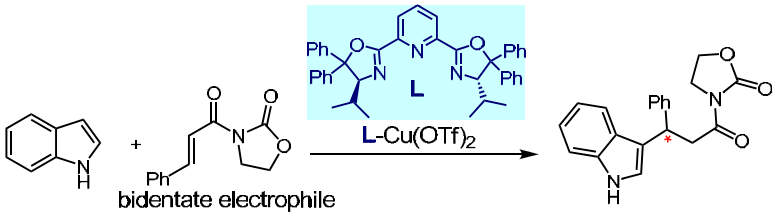
Pedro *et al. Org. Lett.* **2007**, *9*, 2601.

Dinuclear Zinc Complex

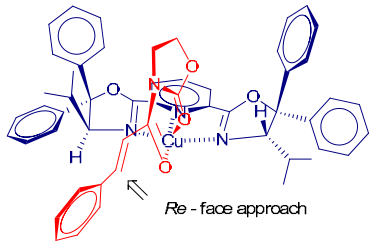


Trost *et al. J. Am. Chem. Soc.* **2008**, *130*, 2438.

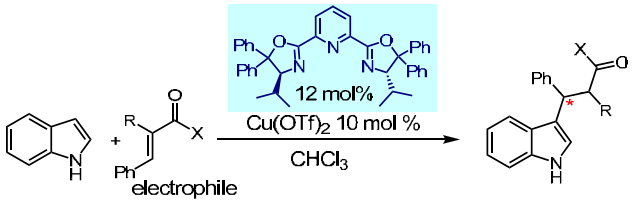
Our Approach

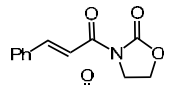
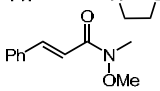
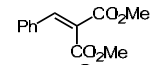
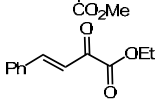


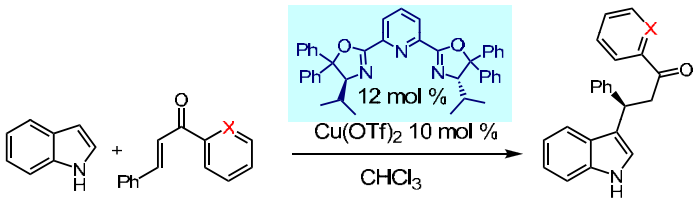
Assumed Transition State Model



Different Bidentate Electrophile

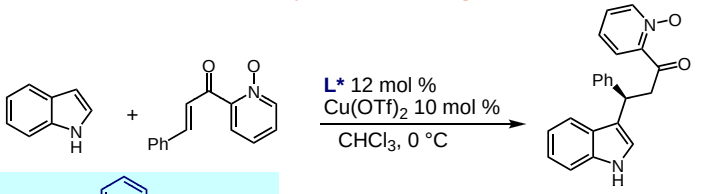


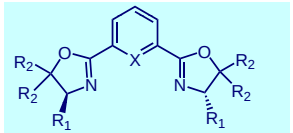
electrophile	temp.	time	yield (%)	ee (%)
	rt	7 d	nr	nr
	rt	7 d	nr	nr
	rt	7 d	nr	nr
	rt	1 h	80	26
	0 °C	12 h	58	21



entry	X	temp	time	yield (%)	ee (%)
1	N	0 °C	24 h	89	16 (*S*)
2	N–O	0 °C	15 min	96	96 (*R*)
3	CH	rt	7 d	nr	nr

Catalyst Screening

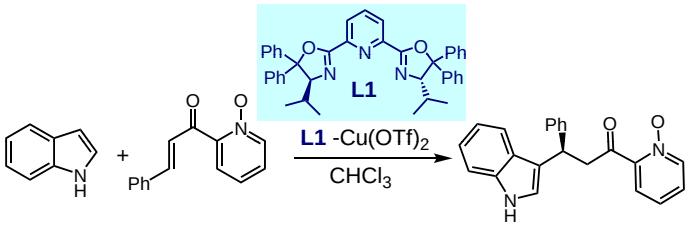




L1: R_1 = *i*-Pr; R_2 = Ph; X = N
L2: R_1 = *t*-Bu; R_2 = Ph; X = N
L3: R_1 = Me; R_2 = Ph; X = N
L4: R_1 = *s*-Bu; R_2 = Ph; X = N
L5: R_1 = *i*-Bu; R_2 = Ph; X = N
L6: R_1 = Ph; R_2 = Ph; X = N
L7: R_1 = Bn; R_2 = Ph; X = N
L8: R_1 = *i*-Pr; R_2 = Ph; X = CH
L9: R_1 = *i*-Pr; R_2 = Bn; X = N
L10: R_1 = *i*-Pr; R_2 = Et; X = N
L11: R_1 = *i*-Pr; R_2 = H; X = N

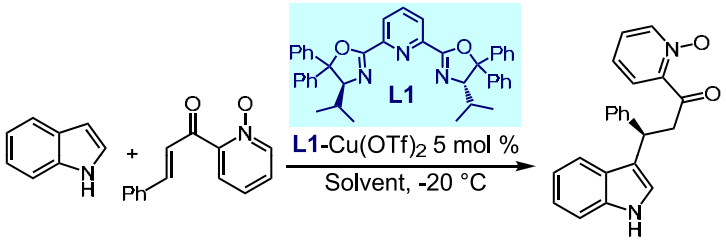
entry	Ligand	time	yield (%)	ee (%)
1	**L1**	15 min	96	96
2	**L2**	15 min	95	94
3	**L3**	15 min	89	17
4	**L4**	15 min	86	94
5	**L5**	15 min	98	5
6	**L6**	15 min	65	6
7	**L7**	15 min	87	1
8	**L8**	12 h	84	1
9	**L9**	15 min	97	65
10	**L10**	8 h	93	59
11	**L11**	48 h	92	25

Effect of Temperature and Catalyst Loading



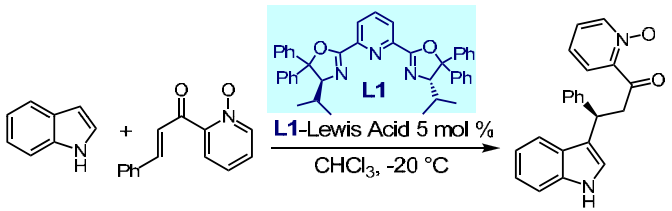
entry	Catalyst	temp	time	yield (%)	ee (%)
1	10 mol %	rt	15 min	90	88
2	10 mol %	0 °C	15 min	96	96
3	10 mol %	-20 °C	15 min	97	99
4	5 mol %	-20 °C	15 min	96	99
5	2 mol %	-20 °C	5 h	94	96
6	1 mol %	-20 °C	12 h	89	82

Solvent Study



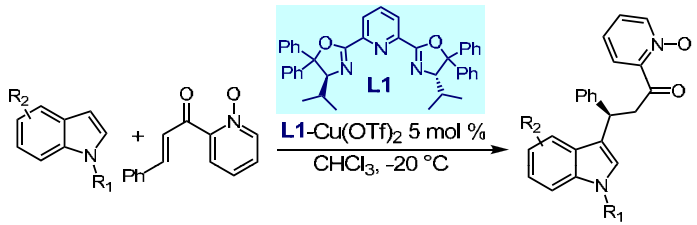
entry	Solvent	time	yield (%)	ee (%)
1	$CHCl_3$	15 min	96	99
2	CH_2Cl_2	15 min	92	95
3	$(CH_2Cl)_2$	15 min	96	92
4	THF	15 min	95	98
5	CH_3CN	5 h	94	64
6	Toluene	24 h	91	94
7	CCl_4	7 d	nr	nr

Lewis Acid Study



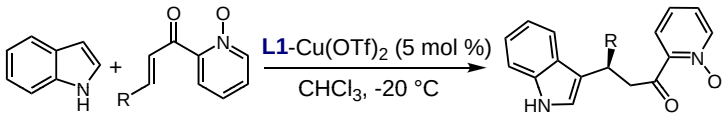
entry	Lewis acid	time	yield (%)	ee (%)
1	$Cu(OTf)_2$	15 min	96	99
2	$Cu(ClO_4)_2{\cdot}6H_2O$	15 min	95	99
3	$Cu(BF_4)_2{\cdot}xH_2O$	15 min	94	99
4	$Cu(CH_3CN)_4{\cdot}PF_6$	7 d	nr	nr
5	$(CuOTf)_2{\cdot}PhH$	3 d	88	96
6	$Zn(OTf)_2$	36 h	91	96
7	$Sc(OTf)_3$	15 min	91	8
8	$In(OTf)_3$	30 min	96	3
9	$Yb(OTf)_3$	1 h	97	3
10	$Sn(OTf)_2$	2 h	95	10
11	$Mg(OTf)_2$	5 d	nr	nr
12	$CuCl_2$	5 d	nr	nr

Different Indoles

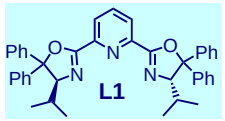


entry	R_1	R_2	time	yield (%)	ee (%)
1	H	H	15 min	96	99
2	H	5-F	1 h	97	97
3	H	5-Cl	1 h	92	96
4	H	5-Br	6 h	93	97
5	H	5-OCH_3	15 min	98	95
6	H	5-CN	7 d	86	83
7	CH_3	H	30 min	97	86
8	Bn	H	3 h	94	87
9	H	2-CH_3	15 min	97	67

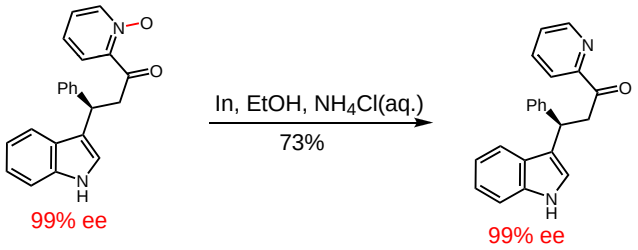
Different 2-Enoylpyridine *N*-Oxides



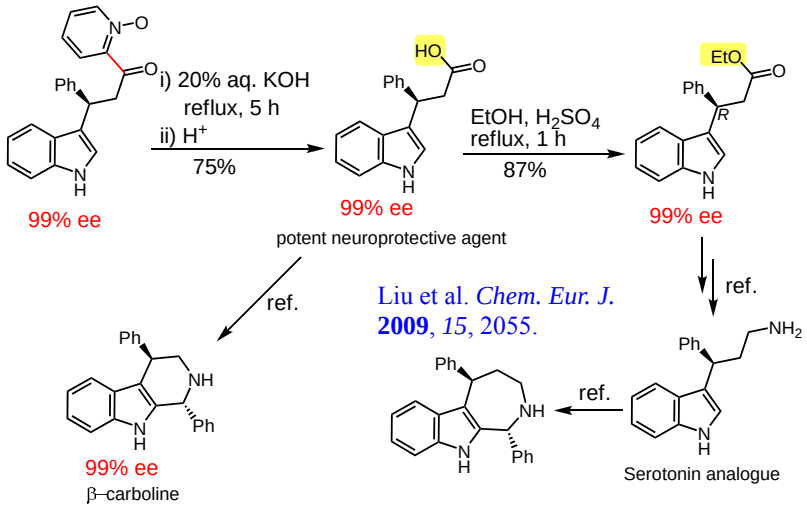
entry	R	time	yield (%)	ee (%)
1	Ph	15 min	96	96
2	4-FC_6H_4	15 min	96	95
3	4-$CH_3OC_6H_4$	3 h	97	94
4	4-$NO_2C_6H_4$	15 min	95	99
5	3-$NO_2C_6H_4$	15 min	97	98
6	2-$NO_2C_6H_4$	15 min	96	97
7	4-ClC_6H_4	15 min	97	94
8	3-ClC_6H_4	15 min	98	93
9	2-ClC_6H_4	15 min	96	91
10	2-naphthyl	2 h	83	89
11	2-furyl	3 h	97	87
12	*n*-C_5H_{11}	2 h	70	27
13	Cyclohexyl	3 d	75	5



Cleavage of N-O Bond



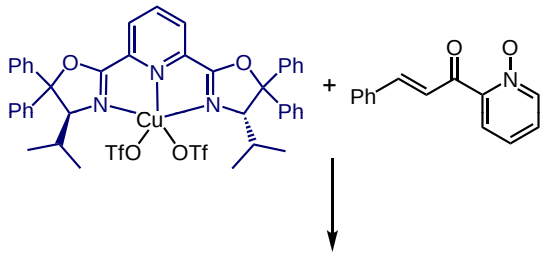
Determination of Absolute Stereochemistry



Liu et al. *Chem. Eur. J.* **2009**, *15*, 2055.

Org. Lett. **2008**, *10*, 4121.

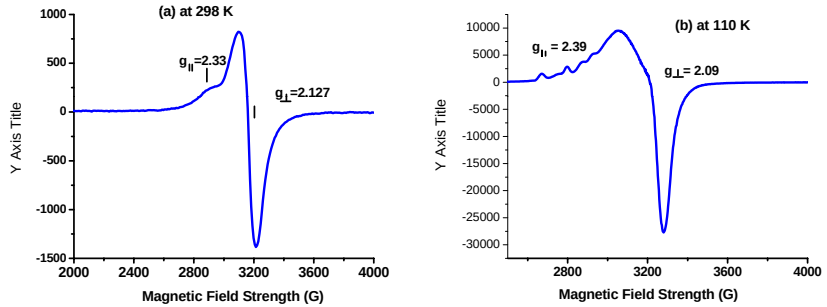
Structure Study of the Complex



Five Coordinated Complex

Trigonal bipyramidal vs. Square pyramidal

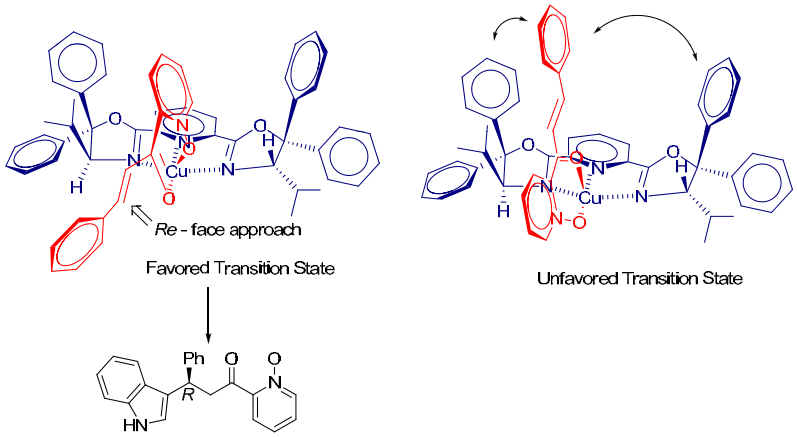
EPR spectra of Cu(II)-(IP-PYBOX-DIPH)(2-Enoylpyridine-*N*-oxide) Complex



$g_{\parallel} > g_{\perp} \Longrightarrow$ Sqare pyramidal

Garribba *et al. J. Chem. Edu.* **2006**, *83*, 1229.

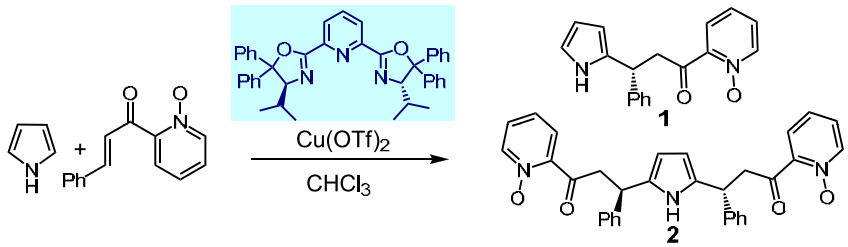
Proposed Transition State Model



Pyrrole alkylation

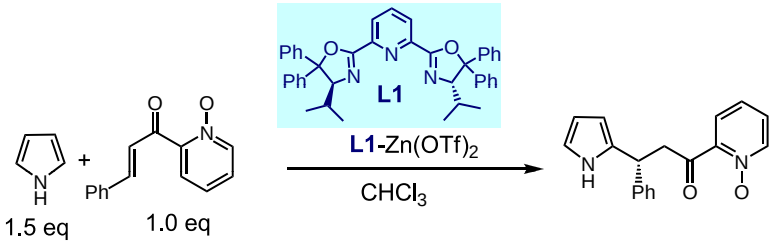
Limitation

- Tendency of dialkylation
- Limited substrate scope (most of the literature known methods can not tolerate substitutions at pyrrole)
- Instability towards acids



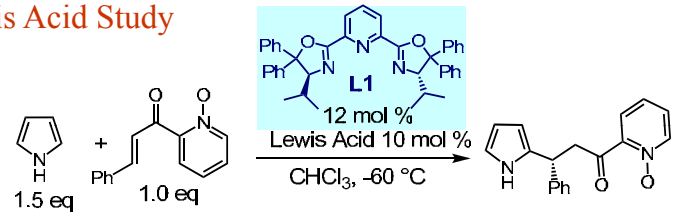
entry	pyrrole	catalyst loading	temp	time	yield (%) 1	yield (%) 2	ee (%) 1
1	1.5 eq	5 mol %	-20 °C	15 min	63	36	95
2	1.5 eq	10 mol %	-20 °C	15 min	48	46	95
3	1.5 eq	10 mol %	-40 °C	30 min	65	42	96
4	1.5 eq	10 mol %	-60 °C	3 h	42	40*	96
5	5 eq	10 mol %	-60 °C	2 h	69	17	93
6	10 eq	10 mol %	-60 °C	2 h	75	12	85
7	20 eq	10 mol %	-60 °C	2 h	90	--	85

* Dimer consisted of a 77:23 mixture of C_2-symmetric (>99% ee):meso isomer.



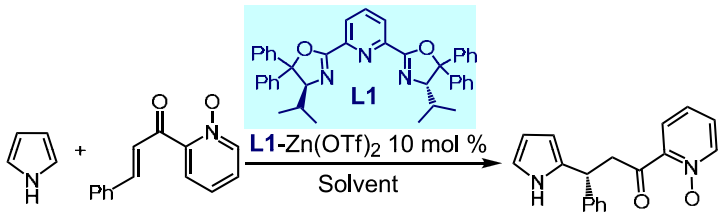
entry	catalyst loading	temp	time	yield (%)	ee (%)
1	10 mol %	-20 °C	30 min	85	96
2	10 mol %	-40 °C	1.5 h	84	98
3	10 mol %	-60 °C	9 h	95	>99
4	5 mol %	-60 °C	24 h	59	99
5	2 mol %	-60 °C	4 d	59	85

Lewis Acid Study



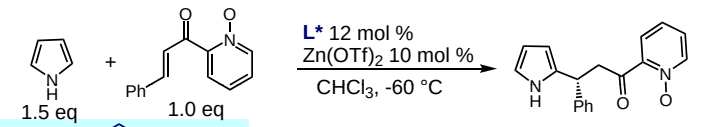
entry	Lewis acid	time	yield (%)	ee (%)
1	$Zn(OTf)_2$	9 h	97	>99
2	$Cu(OTf)_2$	3 h	42	96
3	$(CuOTf)_2 \cdot PhCH_3$	2.5 h	89	95
4	$Cu(CH_3CN)_4 \cdot PF_6$	7 d	nr	nr
5	$(CuOTf)_2 \cdot PhH$	1 h	86	94
6	$Cu(ClO_4)_2 \cdot 6H_2O$	30 min	51	96
7	$Cu(BF_4)_2 \cdot xH_2O$	30 min	67	95
8	$Sc(OTf)_3$	3 h	38	0
9	$In(OTf)_3$	30 min	34	6
10	$Yb(OTf)_3$	30 min	38	37
11	$Sn(OTf)_2$	2 h	29	2
12	$Mg(OTf)_2$	5 d	nr	nr

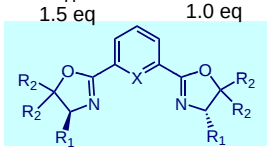
Solvent Study



entry	Solvent	temp	time	yield (%)	ee (%)
1	$CHCl_3$	-60 °C	9 h	97	>99
2	CH_2Cl_2	-60°C	9 h	77	97
3	THF	-60 °C	3 d	nr	nr
4	THF	-20 °C	10 h	56	97
5	CH_3CN	-60 °C	3 d	nr	nr
6	CH_3CN	-20 °C	6 h	72	48
7	Toluene	-60 °C	3 d	nr	nr

Catalyst Screening

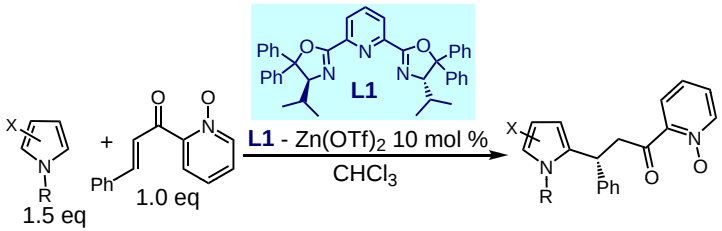


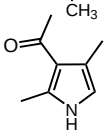


L1: R_1 = *i*-Pr; R_2 = Ph; X = N
L2: R_1 = *t*-Bu; R_2 = Ph; X = N
L3: R_1 = Me; R_2 = Ph; X = N
L4: R_1 = *s*-Bu; R_2 = Ph; X = N
L5: R_1 = *i*-Bu; R_2 = Ph; X = N
L6: R_1 = Ph; R_2 = Ph; X = N
L7: R_1 = Bn; R_2 = Ph; X = N
L8: R_1 = *i*-Pr; R_2 = Ph; X = CH
L9: R_1 = *i*-Pr; R_2 = Bn; X = N
L10: R_1 = *i*-Pr; R_2 = Et; X = N
L11: R_1 = *i*-Pr; R_2 = H; X = N

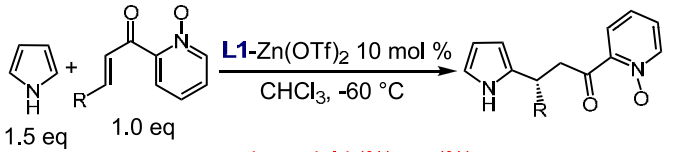
entry	Ligand	time	yield (%)	ee (%)
1	**L1**	9 h	96	>99
2	**L2**	3 h	75	96
3	**L3**	24 h	82	44
4	**L4**	3 h	92	98
5	**L5**	5 d	61	78
6	**L6**	24 h	69	7
7	**L7**	36 h	72	74
8	**L8**	3 d	31	5
9	**L9**	24 h	75	92
10	**L10**	24 h	67	95
11	**L11**	40 h	79	79

Substrate Scope



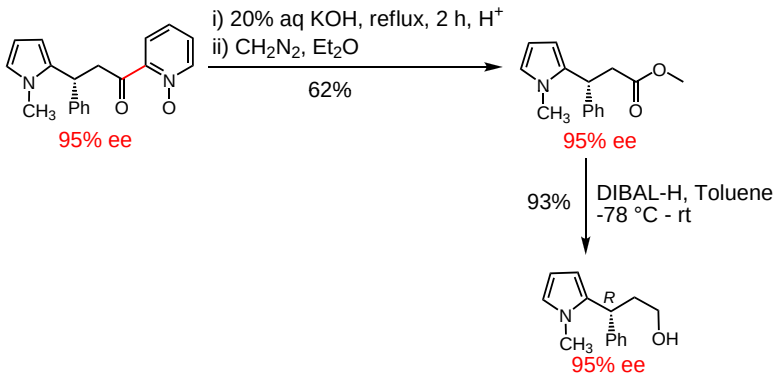
entry	pyrrole	temp.	time	yield (%)	ee (%)
1		-60 °C	9 h	96	>99
2		-30 °C	3 d	87	95
3		-60 °C	20 h	97	>99

Substrate Scope

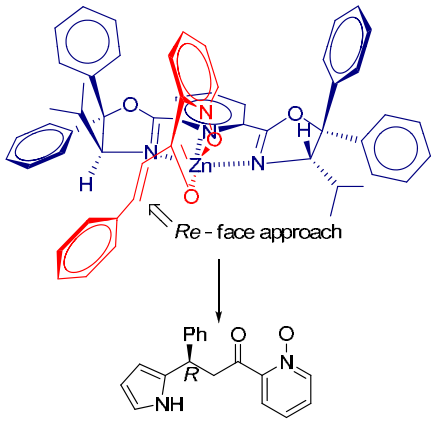


entry	R	time	yield (%)	ee (%)
1	Ph	9 h	96	>99
2	4-FC_6H_4	3 h	90	98
3	4-$CH_3OC_6H_4$	18 h	54	99
4	4-$NO_2C_6H_4$	3 h	96	88
5	3-$NO_2C_6H_4$	3 h	99	99
6	2-$NO_2C_6H_4$	5 h	98	97
7	4-ClC_6H_4	3 h	86	98
8	3-ClC_6H_4	5 h	96	>99
9	2-ClC_6H_4	5 h	88	97
10	1-naphthyl	9 h	71	98
11	2-furyl	18 h	82	97
12	*n*-C_5H_{11}	5 h	74	94
13	*c*-C_6H_{11}	12 h	76	94

Determination of Absolute Stereochemistry

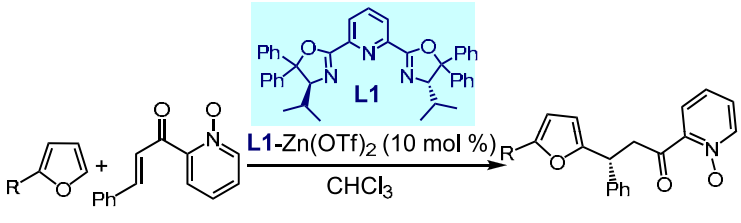


Proposed Transition State Model



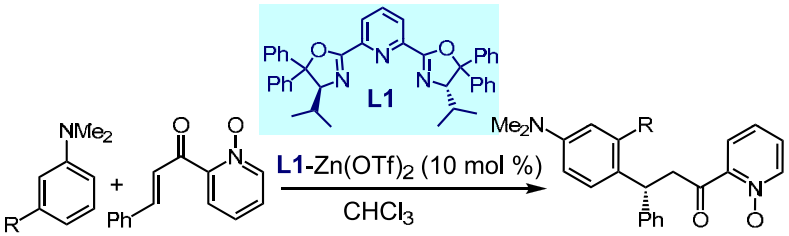
Org. Lett. **2010**, *12*, 80.

Friedel-Crafts Alkylation of Furan



entry	R	temp	time	yield (%)	ee (%)
1	H	rt	5 d	nr	nr
2	OMe	-20 °C	1 h	79	66
3	OMe	-60 °C	36 h	84	85

Friedel-Crafts Alkylation of Anilines



entry	R	temp	time	yield (%)	ee (%)
1	H	rt	3 d	90	91
2	H	10 °C	7 d	87	93
3	OMe	0 °C - rt	9 h	93	82
4	OMe	-30 °C	3 d	88	93