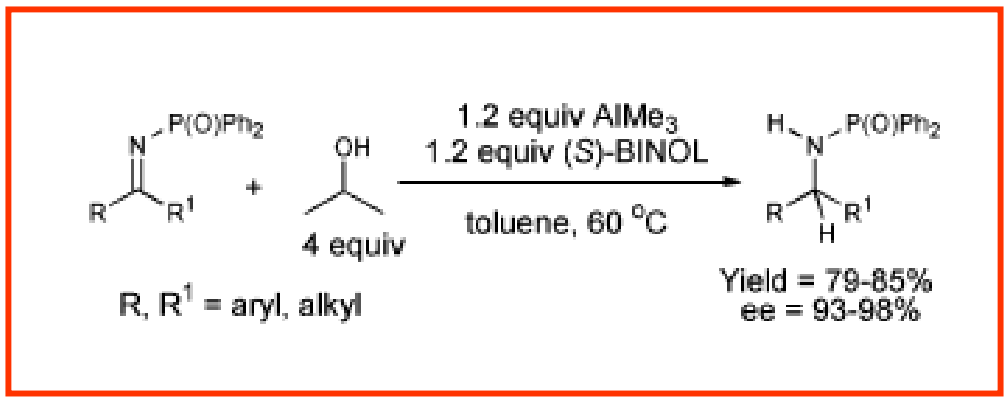
Enantioselective Meerwein-Schmidt-Ponndorf-Verley (MSPV) Reduction of Ketimines Using 2-Propanol and (BINOL)Al^{III}



Christopher R. Graves, Karl A. Scheidt, and SonBinh T. Nguyen

Department of Chemistry and Institute for Environmental Catalysis, Northwestern University

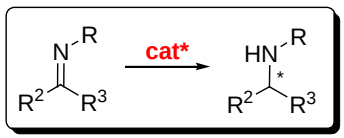
Organic Letters **2006**, *ASAP*

Topic Outline

Transition Metal-Catalyzed Hydrogenation

Iridium-Catalyzed Asymmetric Hydrogenation
Osborn, J.A. and *et al*. *JACS* **1990**, *112*, 9400.

Rh-Catalyzed Asymmetric Hydrogenation
Cullen, W. R. and *et al*. *Inorg. Chem*. **1991**, *30*, 5002.



Transition Metal-Catalyzed Hydrosilylation

Titanocene-Catalyzed Asymmetric Hydrogenation
Buchwald, S.L. and *et al*. *JACS* **1994**, *116*, 11703.
Buchwald, S.L. and *et al*. *OL* **2000**, *2,* 713.

Cu(I)-Catalyzed Asymmetric Hydrosilylation
Lipshutz, B. H. and *et al*. *ACIE* **2004**, *43*, 2228.

Ir-Catalyzed Asymmetric Hydrosilylation
Hidai, M. and *et al*. *Organometallics* **1999**, *18*, 2271.

Re-Catalyzed Asymmetric Hydrosilylation
Toste, F. D. and *et al*. *JACS* **2005**, *127*, 12462.

Asymmetric Hydroboration

Reduction by Asymmetric Hydroboration
Sakito, Y. and *et al*. *TL* **1988**, *29,* 223.
Fujisawa, T. and *et al*. *TL* **1995**, *36,* 8607.

Organocatalytic Reduction

Asymmetric Reduction derived from N-formylpyrrolidine
Matsumura, Y. and *et al*. *TL* **2001**, *42*, 2525.

Asymmetric Reduction derived from N-Methylamino Acids
Kocovsky, P. and *et al*. *Tetrahedron* **2006** *63,* 265.

Asymmetric Reduction derived from Binaphthyl Array
Hosomi, A. and *et al*. *Synlett* **2003**, *36*, 8607.

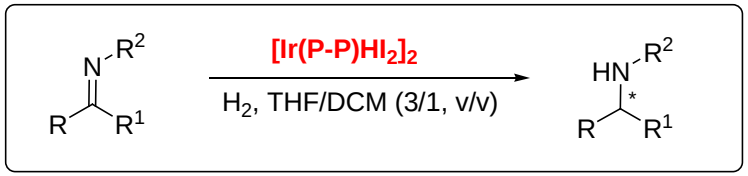
Enantioselective Organocatalytic Reductive Amination
MacMillan, D. W. C. and *et al*. *JACS* **2006**, *128*, 84.

Metal-Catalyzed transfer Hydrogenation

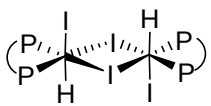
Asymmetric Transfer Hydrogenation Using Ru-Catalyst and Formic acid-TEA
Noyori, R.and *et al*. *JACS* **1996**, *118*, 4916.
Mao, J. and Baker, D. C. *OL* **1999**, *1*, 841

Asymmetric Reduction Using 2-Propanol and (BINOL)Al^{III}
Nguyen, S. T. and *et al*. *OL* **2006**, *asap.*

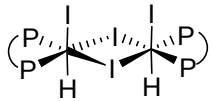
Iridium(III) Hydride Complexes for the Enantioselective Hydrogenation of Imine



Ir(III)-diphosphine-monohydrido complex

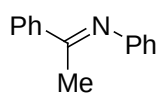


transoid-1

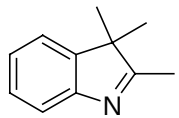


cisoid-1

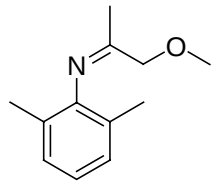
Substrate Scope



I



II

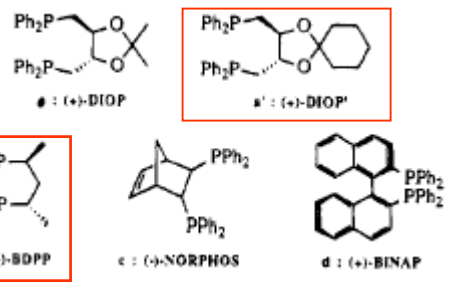


III

Table I. Hydrogenation of Imines **1–3** Catalyzed by $[Ir(P–P)HI_2]_2$

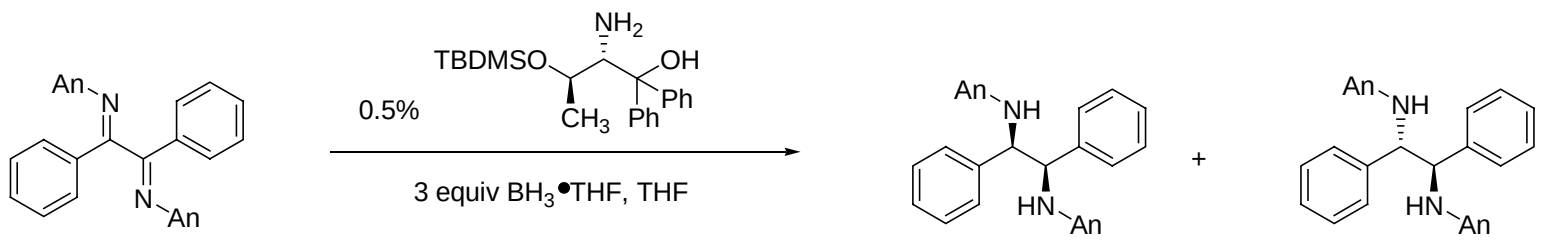
entry	S	P–P	S/[Ir$_2$]	H_2(bar), T (°C)	time (h)	ee (%)
1	I	(−)-BDPP	1000	40, 30	2	40 (*S*)
2	I	(+)-DIOP	1000	28, 30	5	11 (*S*)
3	II	(−)-BDPP	1000	40, 30	43	80 (+)
4	II	(+)-DIOP	1000	40, 30	21	51 (−)
5	II	(−)-NORPHOS	1000	40, 30	13	47 (−)
6	III	(+)-DIOP	1000	40, 30	8	54 (*S*)
7	III	(+)-DIOP	4000	100, 20	40	63 (*S*)
8	III	(−)-BDPP	1000	40, 30	6.5	34 (*R*)
9	III	(−)-NORPHOS	1000	40, 30	4	25 (*S*)
10	III	(+)-BINAP	1000	40, 30	145	22 (*S*)

- Modest enantioselectivity.
- Relatively harsh conditions.
- Limited substrate scope and lack of generality.



Osborn, J. A.; *et al*. *JACS* **1990**, *112*, 9400.

Via Asymmetric Hydroboration



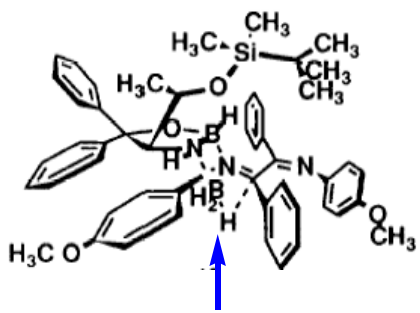
1

An = 4-MeOPh

Chiral-1

Meso-2

Entry	Ligand **3** (mol%)	BH_3•THF (eq)	Yield of **2** (%)[b]	*chiral* : *meso*[c]	%ee[d]
1	0.1	3.0	71	95 : 5	73
2	0.5	3.0	90	95 : 5	99
3	1	3.0	82	95 : 5	99
4	2	3.0	81	95 : 5	99
5	5	3.0	86	95 : 5	99
6	10	3.1	93	96 : 4	99
7	25	3.3	89	96 : 4	99
8	50	3.5	96	96 : 4	99
9	100	4.0	90	>99 : <1	99

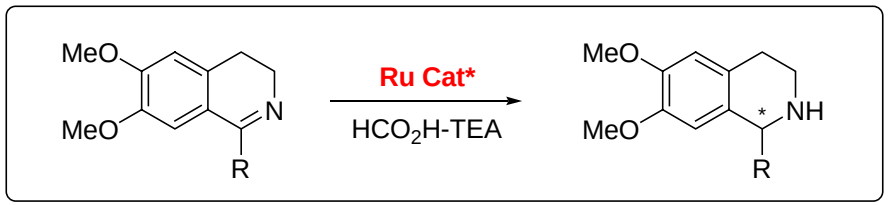


6-membered cyclic TS

- High diastereo- and enantioselectivity.
- Catalytic amount of oxazaborolidine is utilized.
- Undesirable meso-isomer can be completely suppressed with 100 mol% ligand.
- Extremely limited substrate scope.

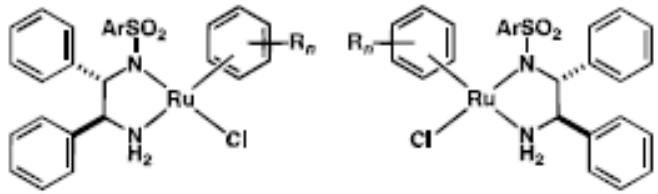
Fujisawa, T.; *et al*. *TL* **1995**, *36*, 8607.

Asymmetric Transfer Hydrogenation of Imines



1a: R = CH_3
1b: R = 3,4-$(CH_3O)_2C_6H_3CH_2$
1c: R = 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$
1d: R = Ph
1e: R = 3,4-$(CH_3O)_2C_6H_3$

2

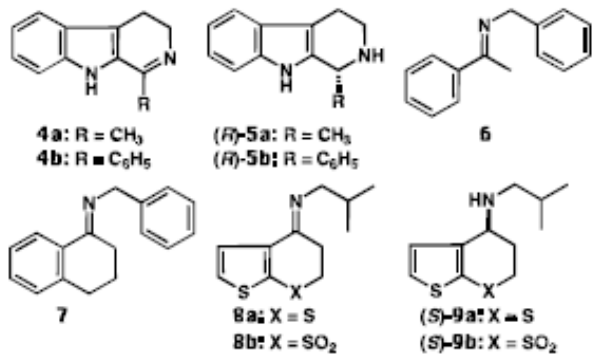


a: η^6-arene = *p*-cymene; Ar = 4-$CH_3C_6H_4$
b: η^6-arene = *p*-cymene; Ar = 2,4,6-$(CH_3)_3C_6H_2$
c: η^6-arene = benzene; Ar = 2,4,6-$(CH_3)_3C_6H_2$
d: η^6-arene = benzene; Ar = 1-naphthyl

imine	catalyst	S/C	solvent	time, h	amine % yield[b]	amine % ee[c]	amine config[d]
1a	(*S*,*S*)-**3a**	200	CH_3CN	3	>99	95	*R*
1a[e]	(*S*,*S*)-**3a**	1000	CH_3CN	12	97	94	*R*
1b	(*R*,*R*)-**3b**	200	$(CH_3)_2NCHO$	7	90	95	*S*
1c	(*R*,*R*)-**3b**	200	CH_2Cl_2	12	99	92	*S*
1d	(*S*,*S*)-**3d**	200	CH_2Cl_2	8	99	84	*R*[f]
1e	(*R*,*R*)-**3d**	100	CH_2Cl_2	12	>99	84	*S*
4a	(*S*,*S*)-**3a**	200	$(CH_3)_2NCHO$	5	86	97	*R*
4a[e]	(*S*,*S*)-**3a**	1000	$(CH_3)_2NCHO$	12	89	93	*R*
4b	(*S*,*S*)-**3a**	200	$(CH_3)_2NCHO$	5	83	96	*R*[f]
6[g]	(*S*,*S*)-**3c**	200	CH_2Cl_2	36	72	77[h]	*S*
7	(*S*,*S*)-**3d**	100	CH_2Cl_2	6	90	89[i]	*S*[j]
8a	(*S*,*S*)-**3d**	100	CH_3CN	12	82	85	*S*[k]
8b	(*S*,*S*)-**3d**	100	CH_3CN	5	84	88	*S*

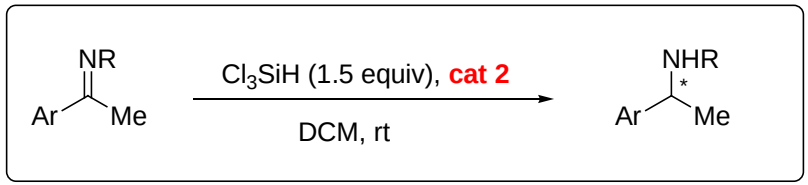
Noyori, R.; *et al*. *JACS* **1996**, *118*, 4916.

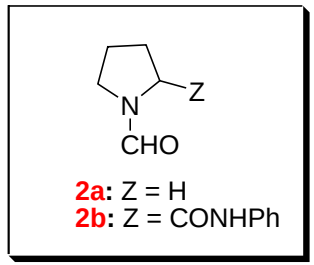
Substrate Scope

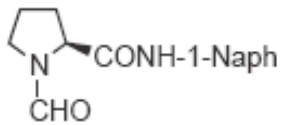


- Usage of stable and organic hydrogen atom.
- The rate and enantioselectivity of the reaction are influenced by η^6-arene and 1,2-diamine ligand.
- Chemoselective for imine vs. ketone.
- Inexpensive and less hazardous reagents.
- Simple performance.
- Limited to cyclic and aromatic imines.

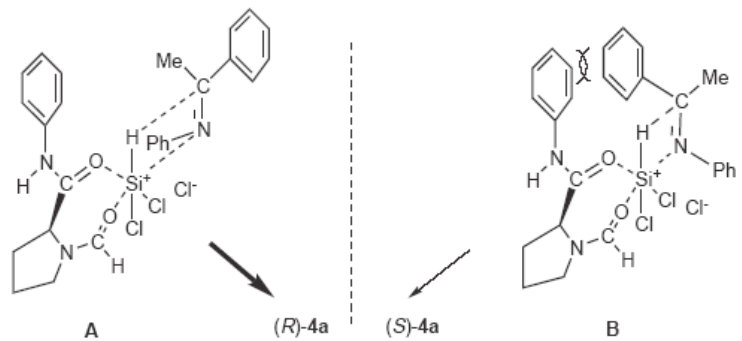
Organocatalytic Asymmetric Reduction of Imine using Trichlorosilane activated with N-formylpyrrolidine derivatives





Entry	Activator (mmol)	Substrate	Ar	R		Yield of 4 (%)	% Ee[a]	*R* or *S*
1	(*S*)-**2b** (0.1)	**3a**	Ph	Ph	**4a**	91	55	*R*
2	(*S*)-**2b** (0.1)	**3b**	Ph	Bn	**4b**	97	55	*R*
3	(*S*)-**2b** (0.2)	**3c**	4-NO_2Ph	Ph	**4c**	>99	49	–[b]
4	(*S*)-**2b** (0.2)	**3d**	4-ClPh	Ph	**4d**	95	54	–[b]
5	(*S*)-**2b** (0.2)	**3e**	2-Naph	Ph	**4e**	56	49	–[b]
6	 (*S*)-**2c** (0.1)	**3a**	Ph	Ph	**4a**	52	66	*R*

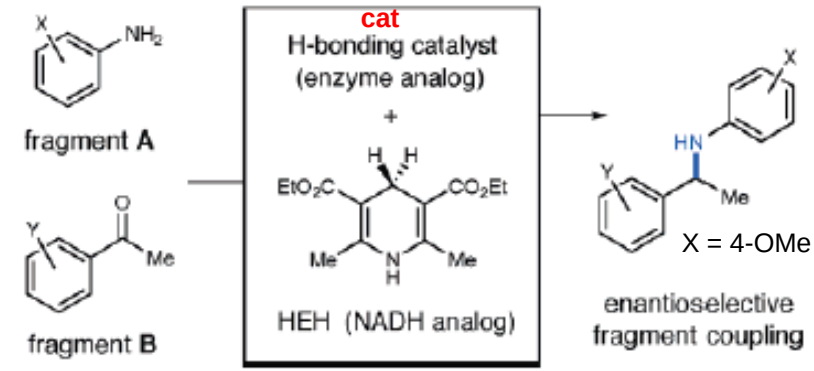
- Cl_3SiH as a reducing reagent.
- Inexpensive and environmentally friendly reagents.
- Modest enantioselectivity.
- Low substrate scope.

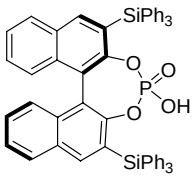


Matsumura, Y.; *et al*. *TL* **2001**, *42*, 2525.

Enantioselective Organocatalytic Reductive Amination

Enantioselective Organocatalytic Reductive Amination (Coupling)



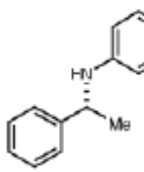
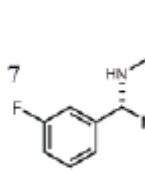
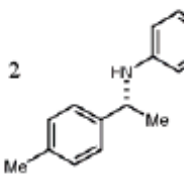
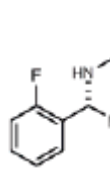
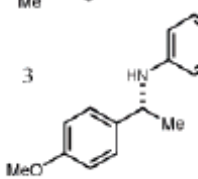
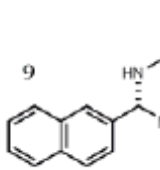
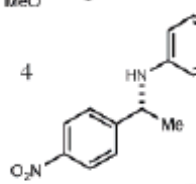
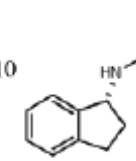
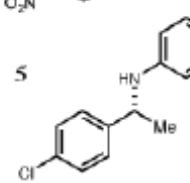
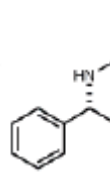
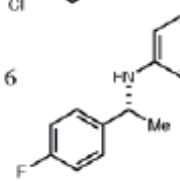
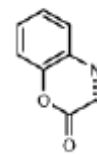


- First organocatalytic reductive amination allowing the asymmetric coupling using H-bonding catalyst and Hantzsche ester.
- HEH is NADH analog, catalyze reaction by H-bonding to a substrate (like an enzyme).

- Selective for methyl ketones.
- High substrate scope. Also aliphatic imines are reduced with high enantioselectivity (not shown). *p*-Anisidine group can be replaced with heterocycles without the lose of ee.

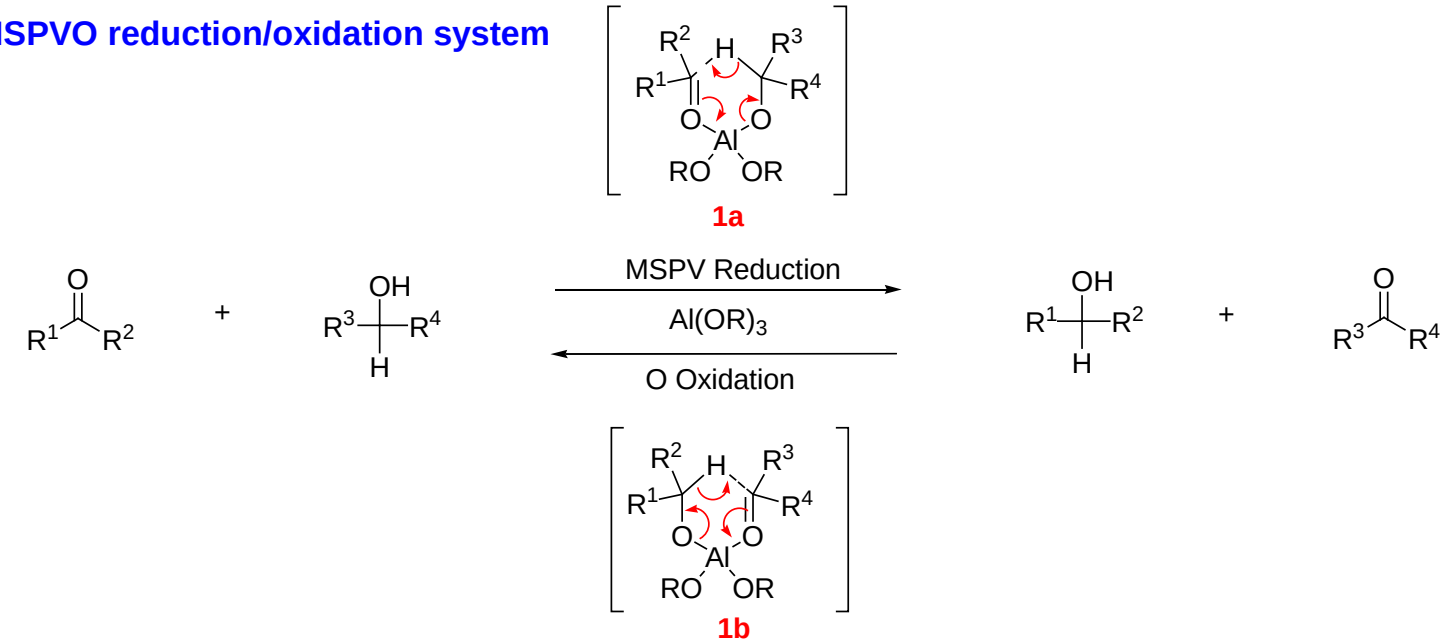
MacMillan, D. W. C.; *et al*. *JACS* **2006**, *128*, 84.

Substrate Scope

entry	product[a]	yield, % ee[b]	entry	product[a]	yield, % ee[b]
1		87% yield 94% ee	7		81% yield 95% ee
2		79% yield 91% ee	8		60% yield 83% ee
3		77% yield 90% ee	9		73% yield 96% ee
4		71% yield 95% ee	10		75% yield 85% ee
5		75% yield 95% ee	11[c]		70% yield 88% ee
6		75% yield 94% ee	12[d]		82% yield 97% ee

Meerwein-Schmidt-Ponndorf-Verley Reduction

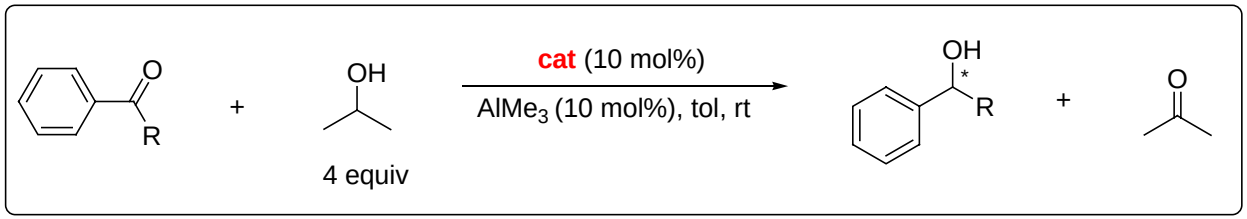
MSPVO reduction/oxidation system

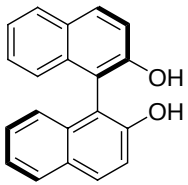


- First reported in 1920's by three independent groups.
- The aluminum-catalyzed hydride shift from the α-carbon of an alcohol component to the carbonyl carbon of other component, which proceeds via a six-membered transition state.
- Isopropanol is generally used as a hydride donor mediated by $Al(OR)_3$.
- In 1950's, MSPV reduction was improvised by using boro- and aluminum hydride.
- While the MSPV reduction has many practical advantages, such as being chemoselective, simple performance and environmentally friendly, it has been relatively less exploited.

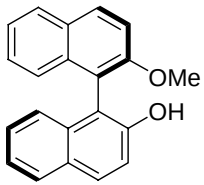
Meerwein, H.; Schmeidt, R. *Liebigs Ann. Chem.* **1925**, *444*, 221. Ponndorf, W. Z. *Angew. Chem.* **1926**, *39*, 138. Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871.Oppenauer, R. V. *Rec. Tav. Chim.* **1937**, *56*, 137.

Earlier Work: Meerwein-Ponndorf-Verley Reduction of Ketones with iPrOH Catalyzed by Aluminum Catalysts

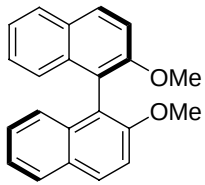




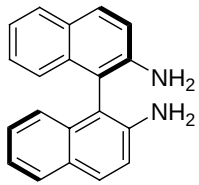
BINOL



cat-1



cat-2



cat-3

Ligand Effect

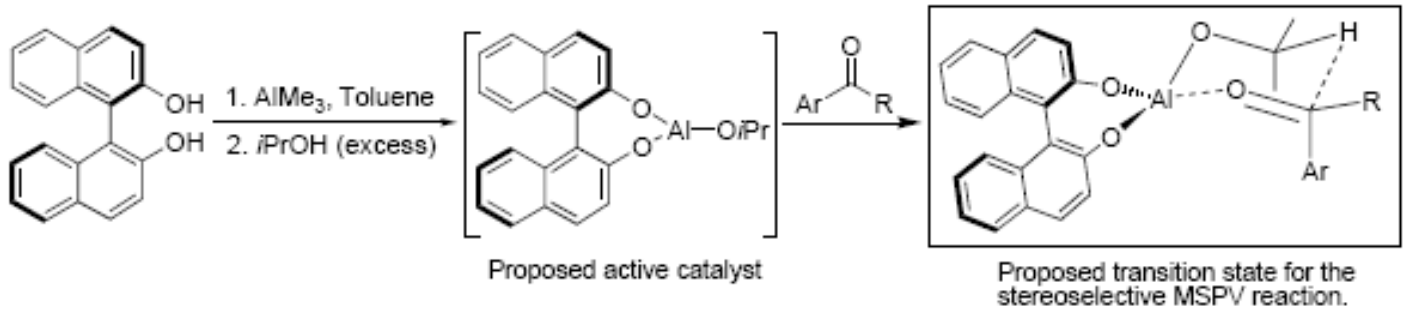
Ligand	R = Me Ligand:$AlMe_3$	Yield [%]	*ee* [%]	Ligand	R = CH_2Cl Ligand:$AlMe_3$	Yield [%]	*ee* [%]
BINOL	1:1	54	30	BINOL	1:1	99	80
BINOL	2:1	0	–	BINOL	2:1	0	–
1	1:1	58	0	**1**	1:1	99	15
1	2:1	40	0	**1**	2:1	90	12
1	4:1	20	0	**1**	4:1	60	0
2	1:1	25	0	**2**	1:1	90	10
3	1:1	7	0	**3**	1:1	25	0

Substrate Scope

Entry	R	2-Propanol (equivalents[b])	Product Yield [%]	Product *ee* [%]
1	CH_2Cl	4	99	80 (*R*)[c]
		4	99	80 (*S*)[d]
2	CH_2Br	4	99	83 (*S*)[d]
3	CH_2CH_3	4	30	50 (*R*)[c]
		15	80	46 (*R*)[c]
4	$CH_2CH(CH_3)_2$	4	32	53 (*S*)[d]
		15	35	35 (*S*)[d]
5	$CH(CH_3)_2$	4	20	61 (*S*)[d]
		15	46	50 (*S*)[d]
6	CH_3	4	54	30 (*R*)[c]
		4	58	28 (*S*)[d]
		15	80	25 (*R*)[c]
7	CH_2OCH_3	4	95	8 (*R*)[c]
8	acetonaphthone[e]	4	41	48 (*S*)[d]
		15	43	46 (*S*)[d]

Nguyen, S. T.; *et al*. *OL* **2001**, *3*, 2391. Nguyen, S. T.; *et al*. *ACIE* **2002**, *41*, 1020.
Nguyen, S. T.; *et al*. *JACS* **2004**, *126*, 14796.

Earlier Work: Meerwein-Ponndorf-Verley Reduction of Ketones with iPrOH Catalyzed by Aluminum Catalysts



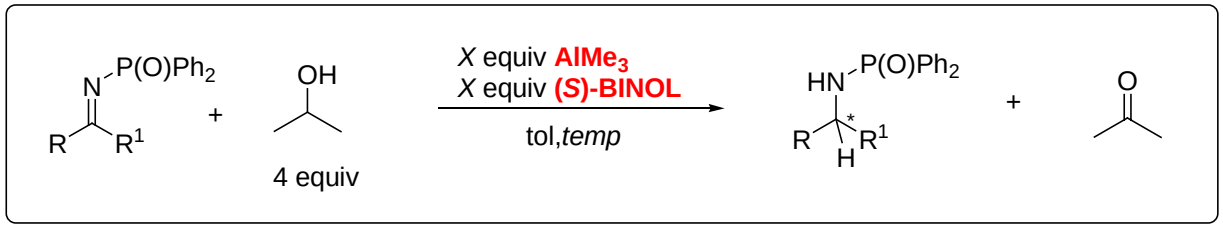
Proposed active catalyst

Proposed transition state for the stereoselective MSPV reaction.

- First example of asymmetric MSPV reduction using an achiral hydride source and a chiral aluminum alkoxide catalyst.
- Reaction proceeds through an active chiral aluminum alkoxide catalyst.
- Proposed transition state shows a tetradentate aluminum species and a hydride is transferred from *i*PrOH by a highly organized six-membered ring system.

Nguyen, S. T.; *et al*. *OL* **2001**, *3*, 2391. Nguyen, S. T.; *et al*. *ACIE* **2002**, *41*, 1020.
Nguyen, S. T.; *et al*. *JACS* **2004**, *126*, 14796.

Title Paper: Enantioselective MSPV Reduction of Ketimines Using 2-Propanol and (BINOL)Al^{III}

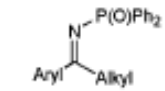
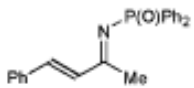
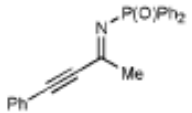
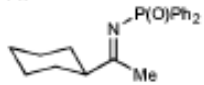
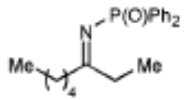


Reaction Condition Optimization

entry	T (°C)	X equiv	conversion[a] (%)	ee[b] (%)
1	25	1.0	0	*c*
2	40	1.0	50	99
3	60	1.0	85	91
4	80	1.0	99	84
5	60	1.2	92	96
6	60	0.1	8	*c,d*

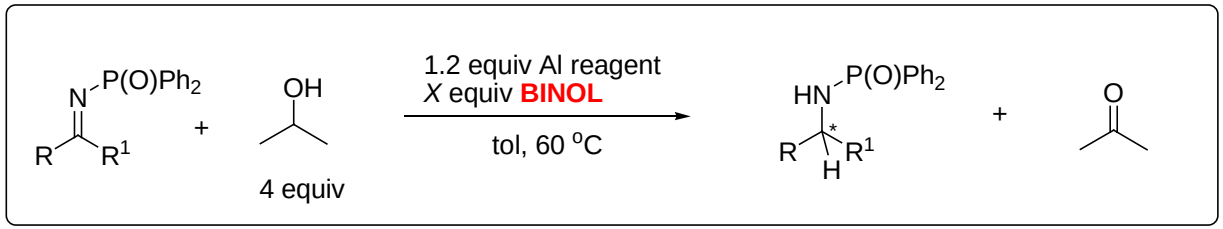
- Excellent enantioselectivity.
- High substrate scope: able to discriminate two different primary alkyl groups (entry 10, right).
- Although BINOL is inexpensive, it can be recovered (up to 93%, 1g scale) and can be reused without the lose of enantioselectivity.
- Reaction is a single turnover event (entry 6, above).

Substrate Scope

entry	imine		*Aryl*	*Alkyl*	yield[a] (product)	ee[b] (%)
1		**1**	Ph	Me	85% (**11**)	96
2		**2**	Ph	Et	85% (**12**)	95
3		**3**	Ph	^{n}Pr	84% (**13**)	94
4		**4**	Ph	^{i}Pr	79% (**14**)	96
5		**5**	1-napthyl	Me	80% (**15**)	98
6		**6**	2-napthyl	Me	84% (**16**)	96
7		**7**			84% (**17**)	94
8		**8**			80% (**18**)	94
9		**9**			84% (**19**)	94
10		**10**			85% (**20**)	93

Nguyen, S. T.; *et al*. *OL* **2006**, *asap.*

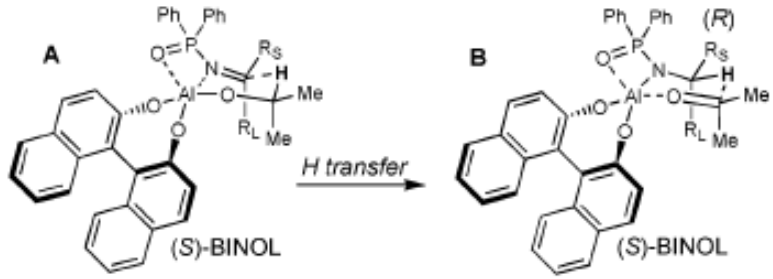
Title Paper: Enantioselective MSPV Reduction of Ketimines Using 2-Propanol and (BINOL)Al^{III}



Ligand Effect

entry	Al reagent	*X* equiv of BINOL	conversion[a] (%)	ee[b] (%)
1	$AlMe_3$	0	45	0
2	$AlMe_3$	1.2 (*S*)	92	96 (*R*)
3	$AlMe_3$	1.8 (*S*)	10	*c*
4	$AlMe_3$	2.4 (*S*)	0	*c*
5	$AlMe_3$	1.2 (*R*)	93	95 (*S*)
6	$Al(O^iPr)_3$[d]	0	55	0

Proposed TS



- Highly organized metal-substrate complex.
- R_L is pseudoaxial position.
- Hydride transfer in intermediate A is via concerted and six-membered TS.

Nguyen, S. T.; *et al*. *OL* **2006**, *asap.*

Summary

- Although asymmetric reductions of ketones are widely explored, the imine variant of this chemistry is much less prevalent. Therefore, more general and practical protocol for asymmetric reduction of imine is highly desired.

- First example of asymmetric MSPV reduction of imine is reported using an achiral hydride source and a chiral aluminum alkoxide catalyst.

- While still stoichiometric, MSPV reduction of ketimine gave both high yield and enantioselectivity and works well for a wide range of imine substrates.

- Reaction condition is mild and neutral reductant, *iso*-propanol, was employed to carry out the reduction of imines containing the acid-sensitive *N*-phosphinoyl group.