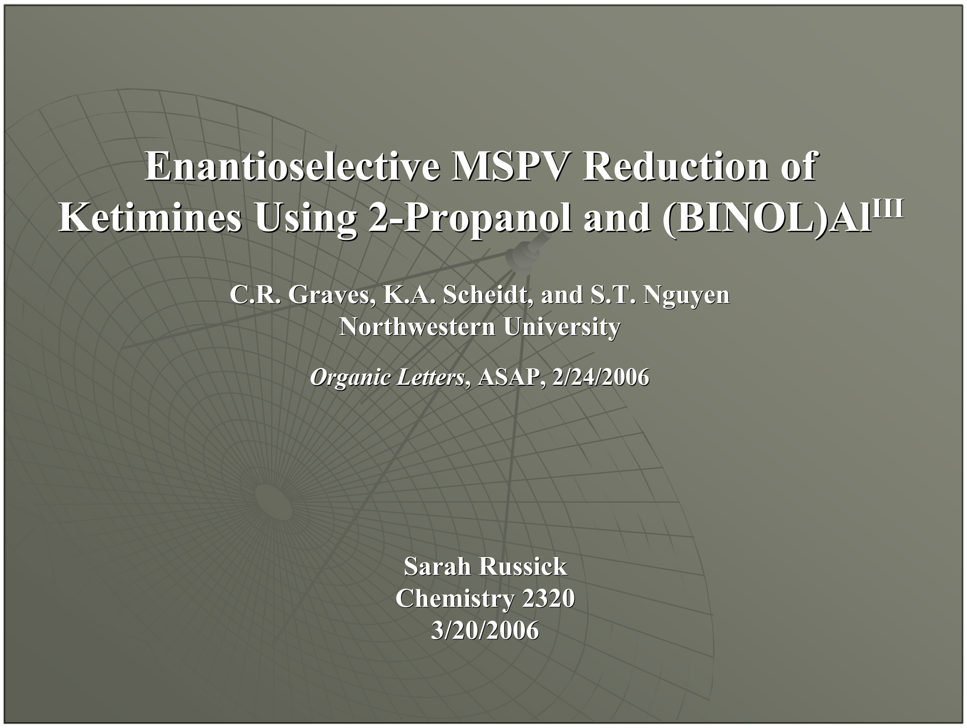

Enantioselective MSPV Reduction of Ketimines Using 2-Propanol and (BINOL)Al^{III}

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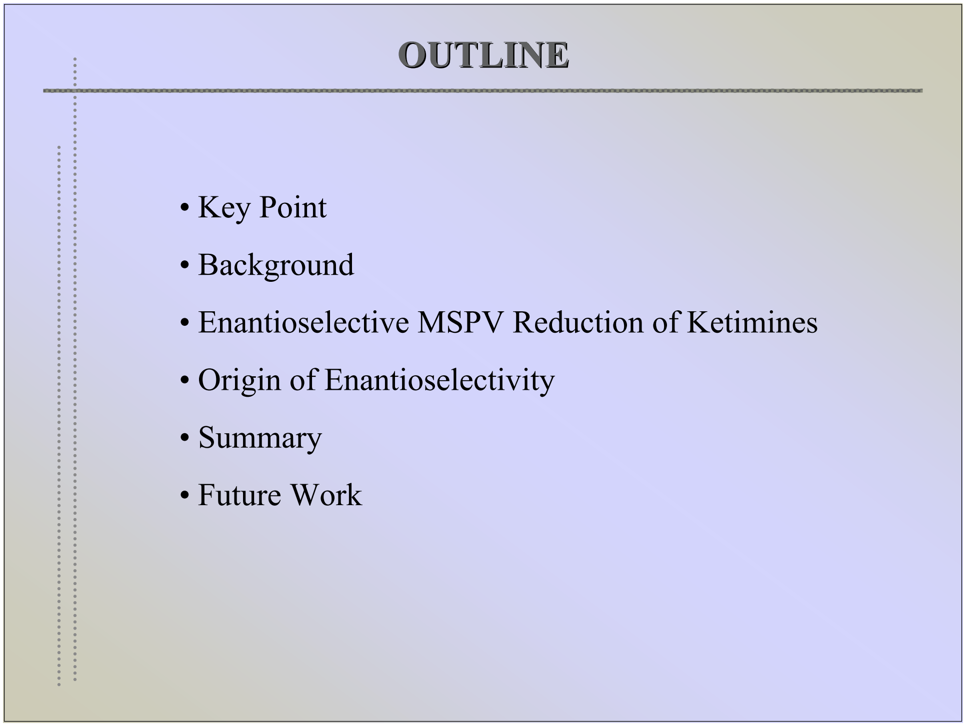
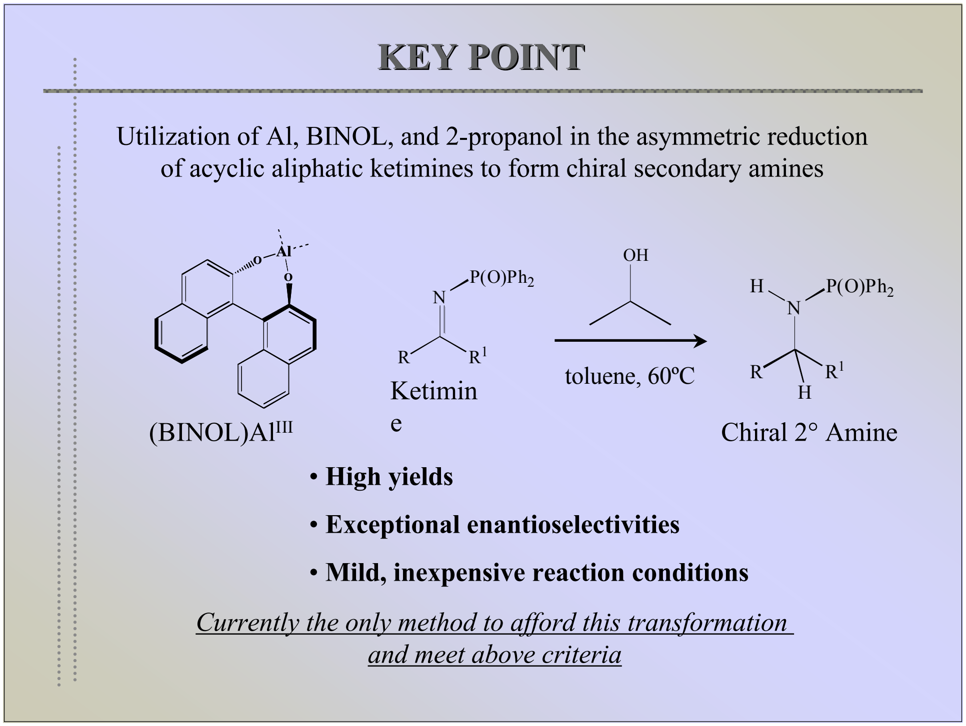
***Organic Letters*, ASAP, 2/24/2006**

Sarah Russick
Chemistry 2320
3/20/2006



OUTLINE

- Key Point
- Background
- Enantioselective MSPV Reduction of Ketimines
- Origin of Enantioselectivity
- Summary
- Future Work



KEY POINT

Utilization of Al, BINOL, and 2-propanol in the asymmetric reduction of acyclic aliphatic ketimines to form chiral secondary amines

(BINOL)Al^{III}

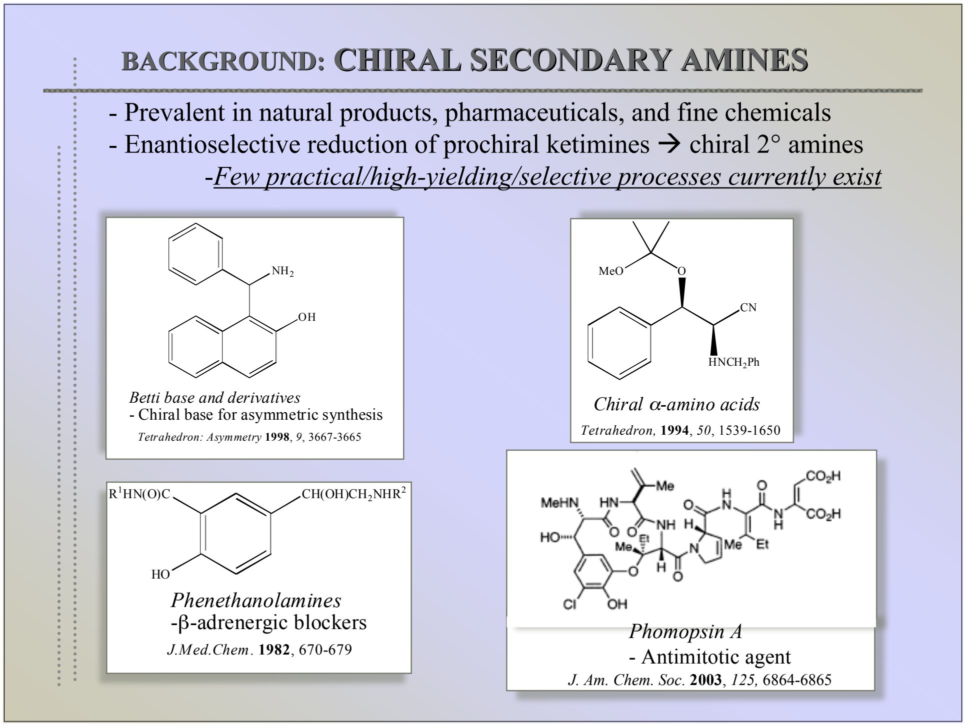
Ketimine

toluene, 60ºC

Chiral 2° Amine

- **High yields**
- **Exceptional enantioselectivities**
- **Mild, inexpensive reaction conditions**

Currently the only method to afford this transformation and meet above criteria



BACKGROUND: CHIRAL SECONDARY AMINES

- Prevalent in natural products, pharmaceuticals, and fine chemicals
- Enantioselective reduction of prochiral ketimines → chiral 2° amines
  - *Few practical/high-yielding/selective processes currently exist*

Betti base and derivatives
- Chiral base for asymmetric synthesis

Tetrahedron: Asymmetry **1998**, *9*, 3667-3665

Chiral α-amino acids

Tetrahedron, **1994**, *50*, 1539-1650

Phenethanolamines
-β-adrenergic blockers

J.Med.Chem. **1982**, 670-679

Phomopsin A
- Antimitotic agent

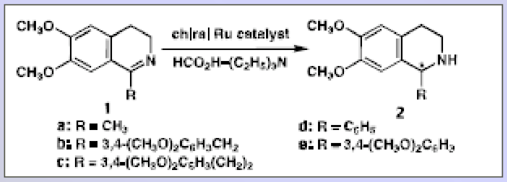
J. Am. Chem. Soc. **2003**, *125,* 6864-6865

BACKGROUND: Ru-CATALYZED KETIMINE REDUCTION

- Noyori's "state of the art" asymmetric reduction of ketimines

Conditions: chiral Ru(II) complex and formic acid-triethyl amine mixture

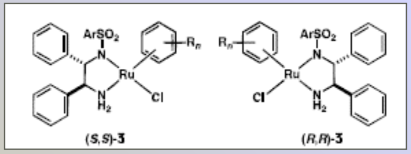
Model Reaction



Highlights:

- Catalytic
- High yields (>90%)
- High ee's (>95%)
- Proceeds at 28ºC
- Works well for cyclic *N*-benzylic imines

Ru(II) catalysts



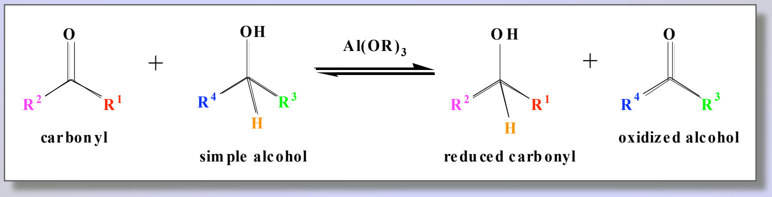
Limitations:

- Poor selectivity for exocyclic and acylic ketimines
- Conditions cleave many *N*-protecting groups

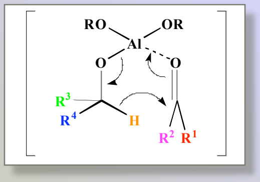
J. Am. Chem. Soc. **1996**, *118*, 4916-4917

BACKGROUND: MSPV REDUCTION

- Independently discovered by Meerwein and Schmidt, Ponndorf, and Verley in mid-1920's
- Al catalyzed hydride reduction of a carbonyl
- Hydride donated by alcohol component
- Mild, inexpensive, environmentally friendly



- Occurs via concerted 6- member T.S.

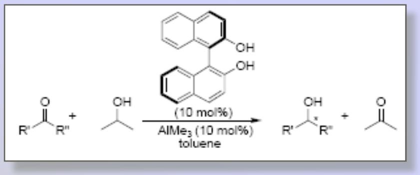


Drawbacks:

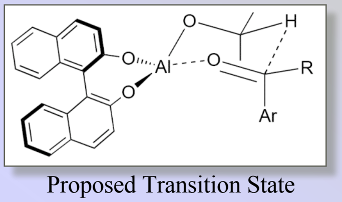
- Excess $Al(OR)_3$ required; High aggregation state of Al alkoxides

BACKGROUND: ENANTIOSELECTIVE MSPV REDUCTION

- First reported Al-catalyzed asymmetric MSPV reduction of carbonyls using an achiral hydrogen source
- Yields and *ee*’s ≥ 80%



Model Reaction



Proposed Transition State

- Neutral reaction conditions

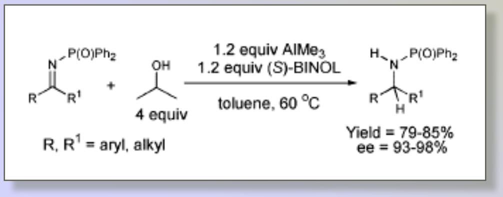
Related Work:

- Noyori’s and Evans’ asymmetric MSPV reductions utilized achiral hydrogen sources and chiral transition metal catalysts

Angew. Chem. Int. Ed. ***2002,*** *41*, 1020-1022

ENANTIOSELECTIVE MSPV REDUCTION OF KETIMINES

Model Reaction:
N-phosphinoyl ketimines



R, R^1 = aryl, alkyl

Yield = 79-85%
ee = 93-98%

I. Reaction Optimization

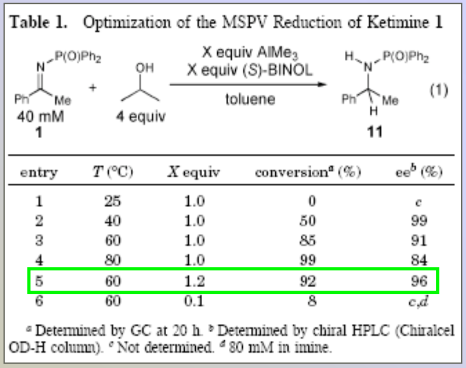


Table 1. Optimization of the MSPV Reduction of Ketimine **1**

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*

[a] Determined by GC at 20 h. [b] Determined by chiral HPLC (Chiralcel OD-H column). [c] Not determined. [d] 80 mM in imine.

Reaction Notes:

- Does not proceed at RT
  - *Optimal Temp is 60°C*
- $AlMe_3$: BINOL ratio is 1:1
- Optimal $AlMe_3$/BINOL: Substrate ratio is 1.2:1
  - *Indicates single turnover event*

ENANTIOSELECTIVE MSPV REDUCTION OF KETIMINES

II. Reaction Scope

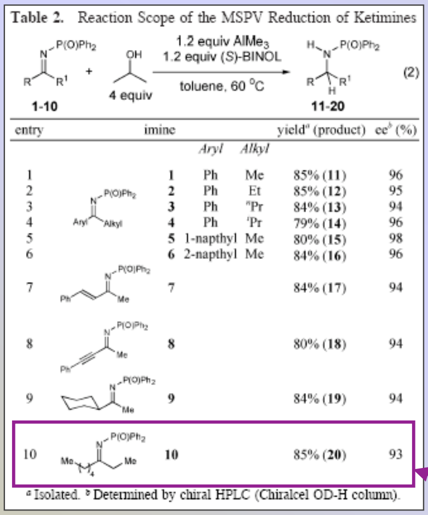


Table 2. Reaction Scope of the MSPV Reduction of Ketimines

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

[a] Isolated. [b] Determined by chiral HPLC (Chiralcel OD-H column).

- Wider scope than Noyori reduction
- Excellent yields and ee's maintained

Aryl/alkyl ketimines

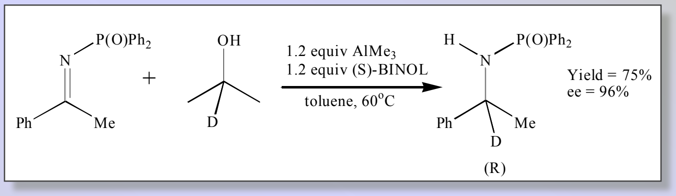
***α,β**-unsaturated ketimines*

Doubly aliphatic ketimines

Asymmetric environment even distinguishes between primary alkyl groups

ENANTIOSELECTIVE MSPV REDUCTION OF KETIMINES

III. Preparation of Deuterated Secondary Amines

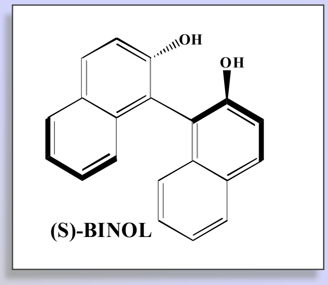


Yield = 75%
ee = 96%

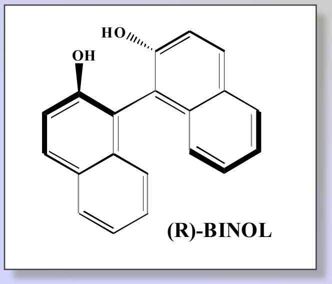
- Isotope labeling
- Kinetic studies

ENANTIOSELECTIVE MSPV REDUCTION OF KETIMINES

IV. Ligand Recycling



(S)-BINOL

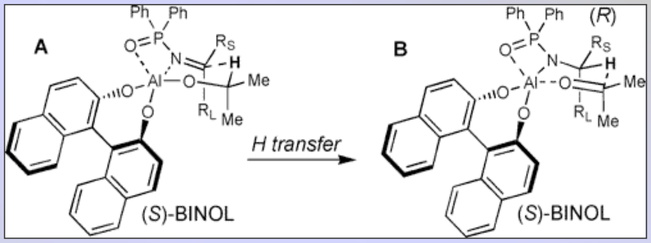


(R)-BINOL

- Inexpensive in bulk
  - ~$1.86/g on kg scale
- Acid/base extraction/ recovery procedure
  - ~93% recovery

ORIGIN OF ENANTIOSELECTIVITY

Highly organized metal-substrate complex:



- 4-member chelation of Al by iminophosphinoyl
- 5th coordination to Al by phosphinoyl oxygen
  - (^{27}Al NMR indicates pentacoordinate Al)
- Hydride transferred via concerted 6-member T.S.
- R_L of ketimine is pseudo-axial and R_S is pseudo-equitorial

ORIGIN OF ENANTIOSELECTIVITY

Predictability of absolute configuration:

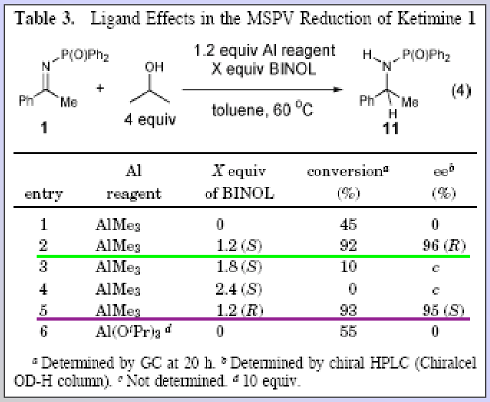


Table 3. Ligand Effects in the MSPV Reduction of Ketimine 1

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

[a] Determined by GC at 20 h. [b] Determined by chiral HPLC (Chiralcel OD-H column). [c] Not determined. [d] 10 equiv.

For ketimine 1:
(S)-BINOL → (R)-amide
(R)-BINOL → (S)-amide

- 1:1 $AlMe_3$: BINOL is optimal
  - increasing ligand ratio decreases yield

SUMMARY

- High yielding and highly enantioselective MSPV reduction of ketimines to form secondary amines
- Mild, neutral reaction conditions
- 1:1 ratio of $AlMe_3$:BINOL and excess propanol used as reagents
- Reagents must be used stoichiometrically
- Inexpensive and environmentally friendly process
- Wide range of ketimines can be reduced

FUTURE WORK

- Examine further application of reagents on different substrates
  - *Is N-phosphinoyl group necessary for selectivity?*
- Develop conditions for catalytic amounts of Al/BINOL reagents
  - *Necessary if reagents are inexpensive and recyclable?*
- Explore full mechanistic details

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Thank You