Development of Practical Catalytic C-C Bond Forming Reactions & Applications to Organic Synthesis

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Catalysis for Organic Synthesis: Challenges & Goals 2002

Allow scientists to prepare any chiral molecule with:

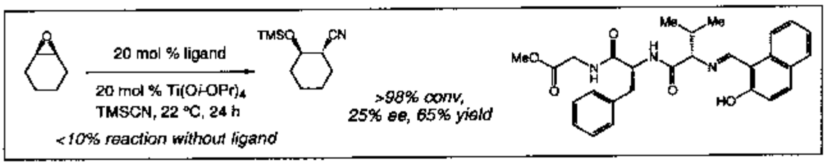
- 100% effiency and selectivity
- Minimum production of waste (including solvents)

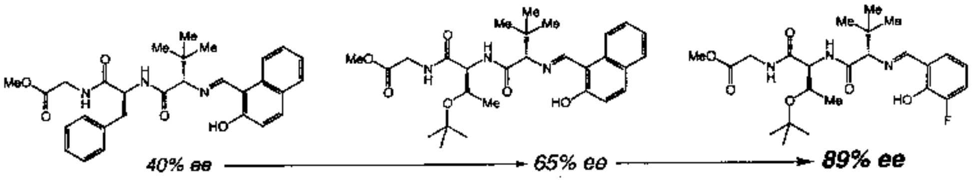
Through reactions promoted by ***catalysts*** that are:

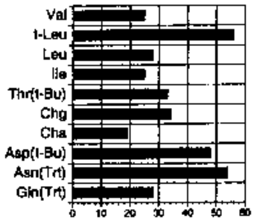
- Readily accessible
- Can be easily handled
- Afford high TON and TOF
- Can be applied to various method in chemical synthesis (e.g., large scale synthesis, library synthesis)

Sophisticated Enantioselective Synthesis Practiced by Non-Specialists

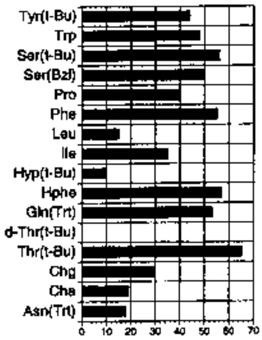
Ti-Catalyzed CN Addition to *Meso* Epoxides

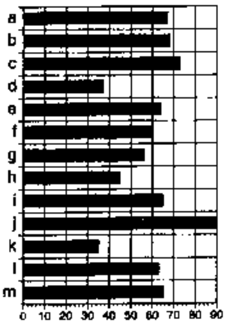


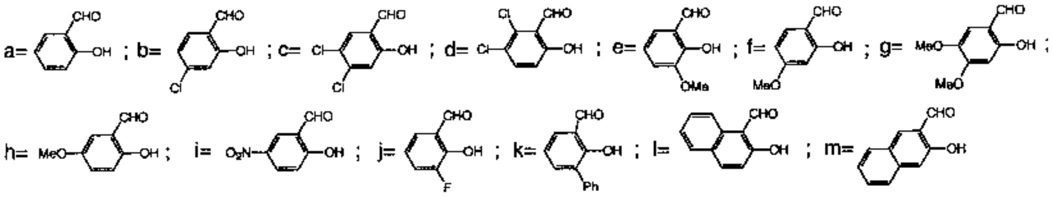




Angew. Chem. Int. Ed. **1996**, 1668

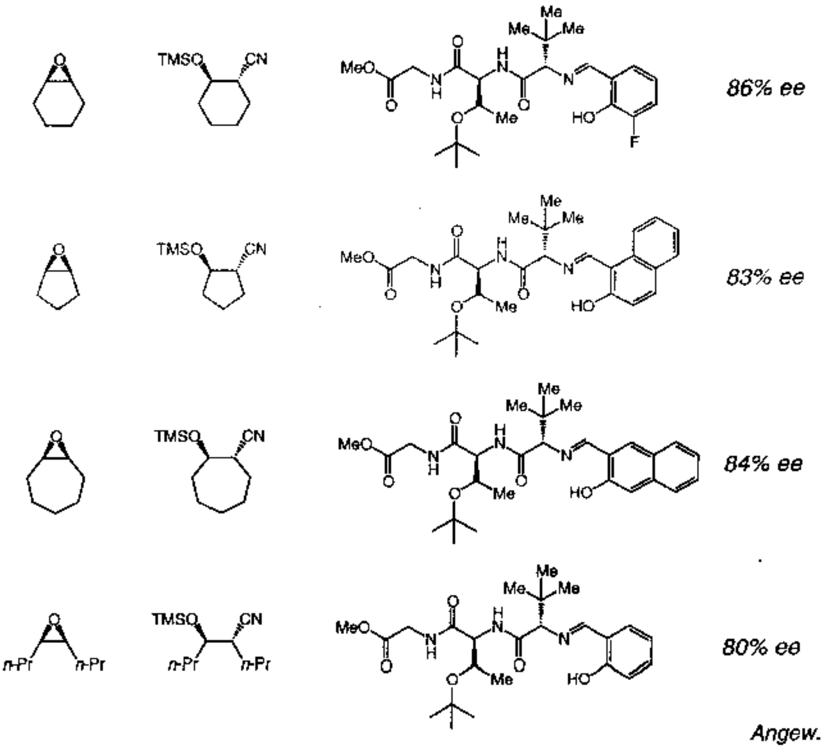






Ti-Catalyzed CN Addition to *Meso* Epoxides

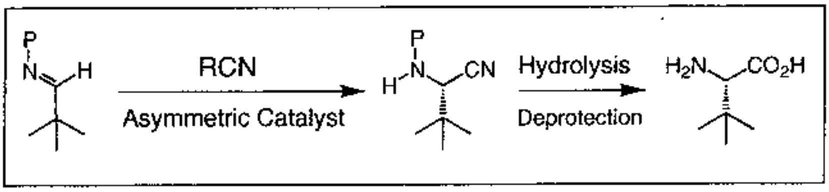
Different substrate; Different ligands

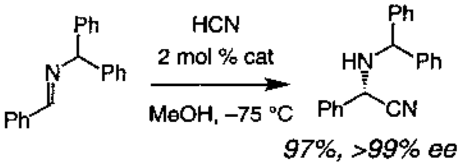


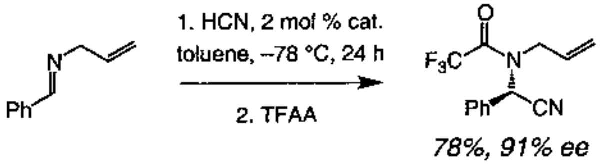
20 mol % ligand,
20 mol % Ti(O*i*-OPr)$_4$
TMSCN, 22 °C, 24 h

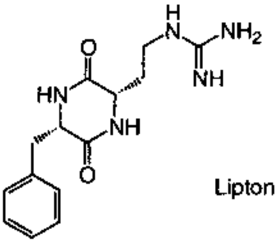
Angew. Chem. Int. Ed. **1997**, 1704

Ti-Catalyzed CN Addition to Imines: Asymmetric Strecker

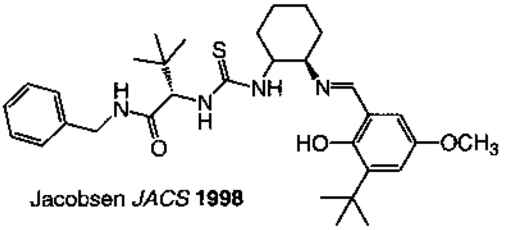








Lipton *JACS* **1996**

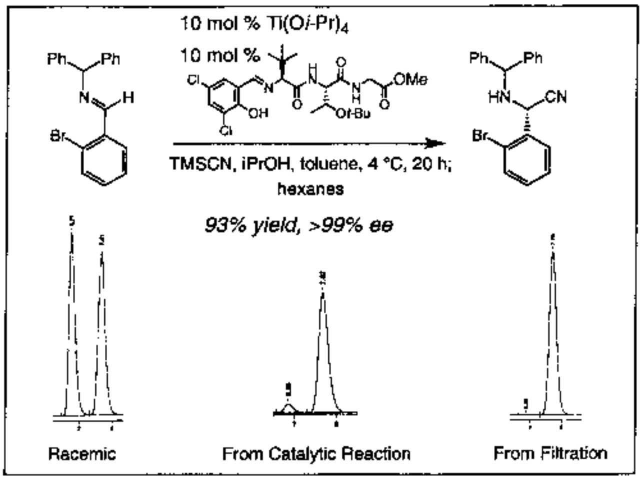


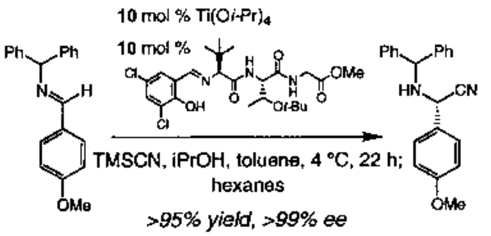
Jacobsen *JACS* **1998**

Later developments by Corey, Kobayashi and Shibasaki

Ti-Catalyzed CN Addition to Imines: Asymmetric Strecker

Optically pure amino nitrile readily available

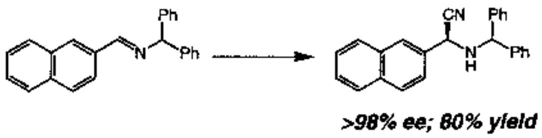


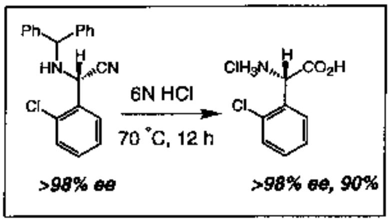


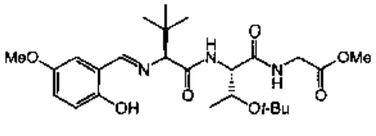
with **5.0** mol % catalyst (22 h) 98% conv., 94% ee

with **2.5** mol % catalyst (42 h) 99% conv., 94% ee

Without added i-PrOH: 15% conv, 84% ee in 22 h

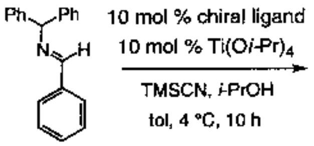






JACS **1999**, 4284

Mechanism of Ti-Catalyzed Cyanide Addition to Imines



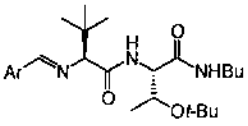
Rate = k_{obs} [Ti•L]^1 [imine]^0 [TMSCN]^0 [*i*-PrOH]^0

$\Delta H^{\ddagger} = 8.98 \pm 1.5$ kcal•mol^{-1}

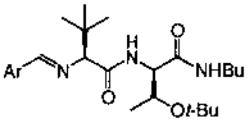
$\Delta S^{\ddagger} = -45.6 \pm 4.1$ cal•K^{-1}•mol^{-1}

Slow Addition of HCN: Identical ee and conv

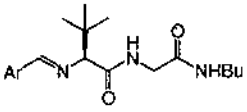
$k_H / k_D = 1.0 \pm 0.08$



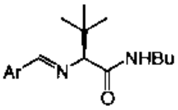
>98% conv, 95% ee



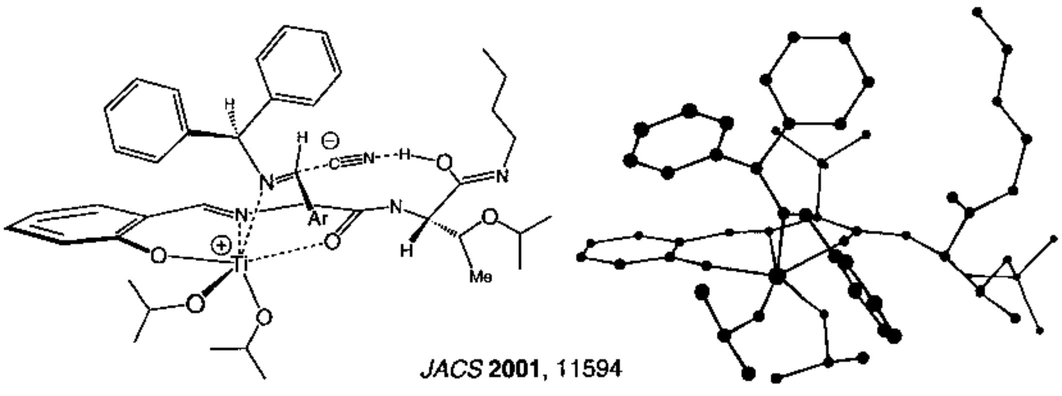
10% conv, <10% ee



44% conv, -15% ee

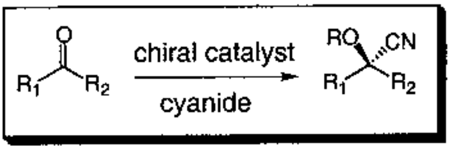


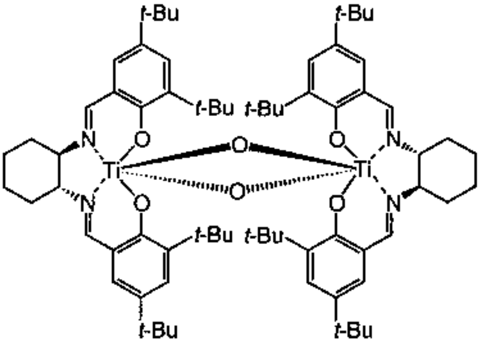
<5% conv, <5% ee



JACS **2001**, 11594

Catalytic Asymmetric Cyanide Addition to Ketones: Enantioselective Synthesis of Tertiary Cyanohydrins

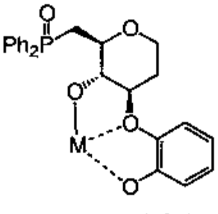




with TMSCN

with aryl ketones: up to 72% ee
10-50 mol % loading, >1 day

Belokon, *TL* **1999**, 8147

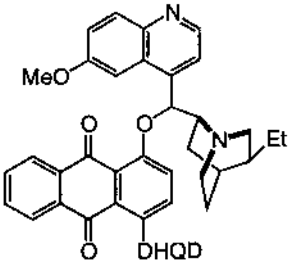


M=Al and Gd

with TMSCN

aryl ketones: up to 95% ee
alkyl ketones: up to 91% ee

Shibasaki, *JACS* **2000**, 7412
Shibasaki, *JACS* **2001**, 9908

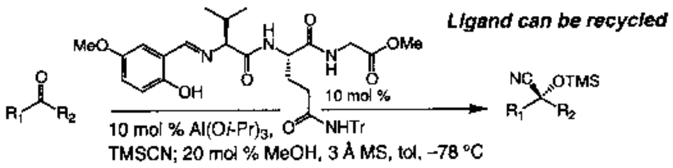


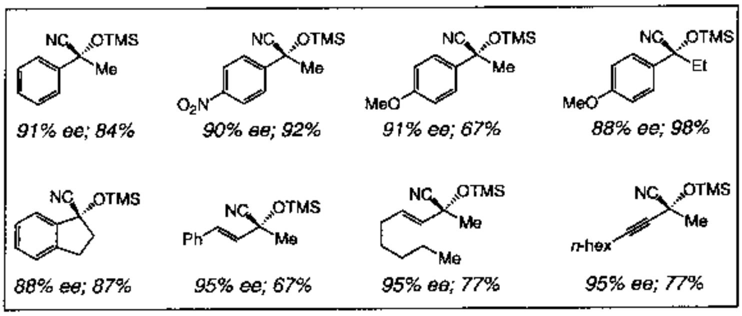
with ethylcyanoformate

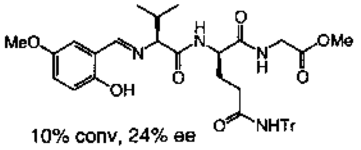
with sterically differentiated aliphatic: up to 97% ee

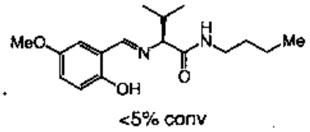
Deng, *JACS* **2001** 6195

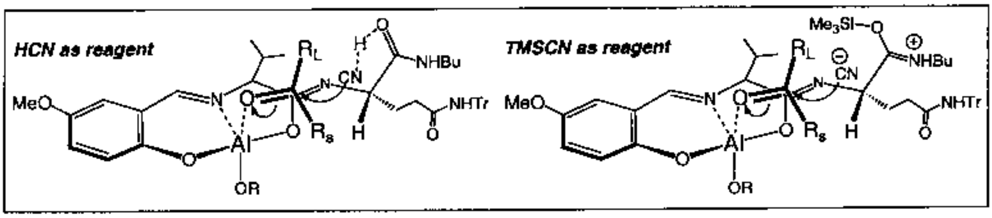
Al-Catalyzed Asymmetric Cyanide Addition to Ketones









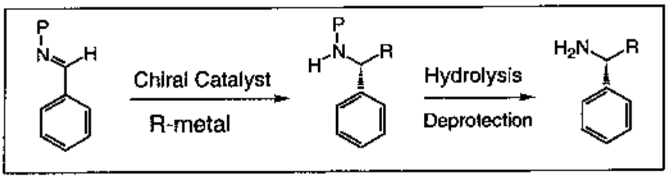


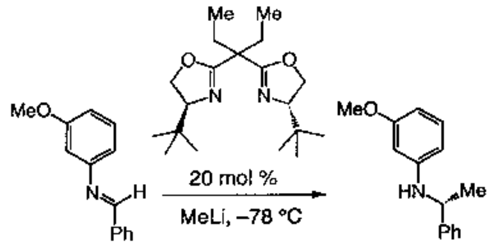
Low conversion (~60%) in the absence of MeOH and MS

Addition of HCN instead of MeOH gives same ee and conv as in reaction without either MeOH or HCN

Angew. Chem. Int. Ed. **2002**, 1009

Catalytic Alkylation of Imines: Asymmetric Amine Synthesis

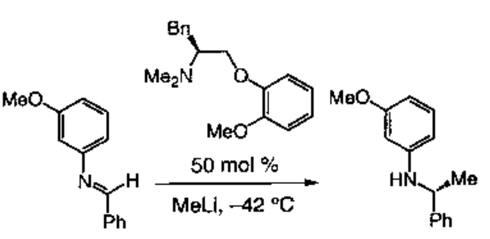




82% ee, 81%

(range: 51-82% ee)

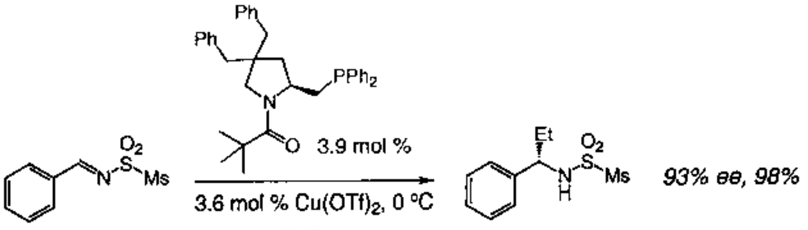
Denmark, *JACS* **1994**, 8797



62% ee, 96%

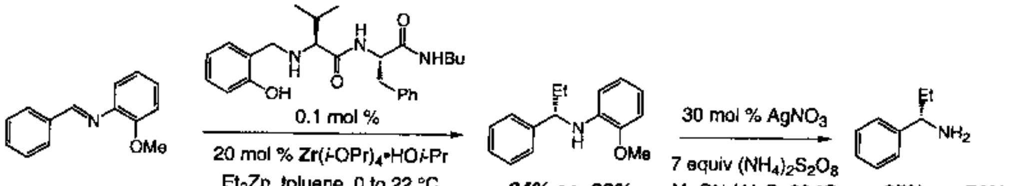
(range: 25-62% ee)

Tomioka, *TL* **1991**, 3095



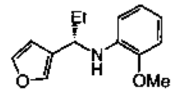
Tomioka, *JACS* **2000**, 12055

Zr-Catalyzed Alkylation of Imines: *Asymmetric Amine Synthesis*

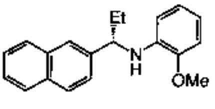


94% ee, 82%

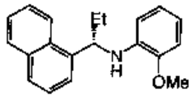
95% ee, 70%



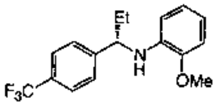
97% ee, 87%



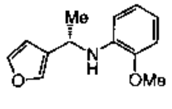
92% ee, 69%



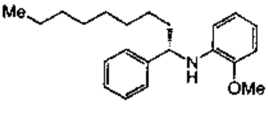
91% ee, 86%



90% ee, 71%



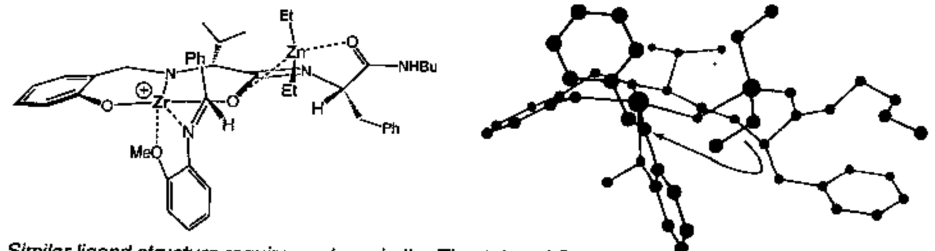
84% ee, 98%



96% ee, 87%

<10% conv with Schiff base ligand

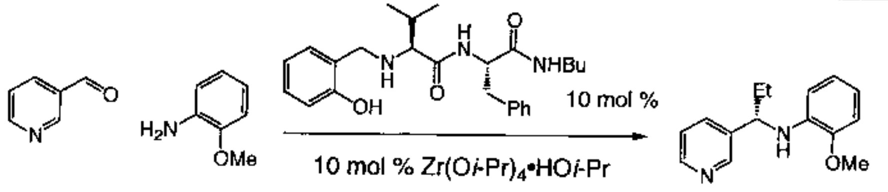
JACS **2001**, 984



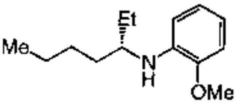
Similar ligand structure requirements as in the Ti-catalyzed Strecker

Zr-Catalyzed Alkylation of Aliphatic Imines: *Asymmetric Amine Synthesis*

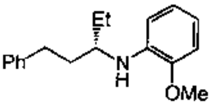
In situ Three-Component EnantioselectiveSynthesis



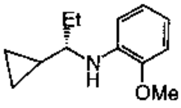
85% ee, >98%



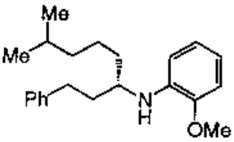
97% ee, 69%



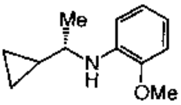
94% ee, >98%



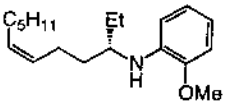
98% ee, 83%



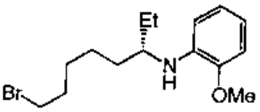
97% ee, 80%



88% ee, 54%



>98% ee, 60%



>98% ee, 60%

Deprotection delivers derived amine in 65-75% yield

Development of Effective Methods for Catalytic Enantioselective Conjugate Additions to Enones

- ■ Reactions of "Hard Nucleophiles"
- ■ Reaction of Cyclic and Acyclic Enones

■ Reactivity

Additions to Trisubstituted Enones

Additions to Unsaturated Ketones, Esters, Amides, etc

■ Enantioselectivity

■ Practicality

Minimal Waste

Readily Available Catalyst

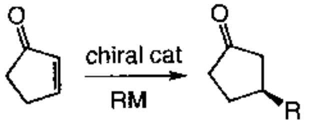
Modular Catalyst

Recyclable Catalyst

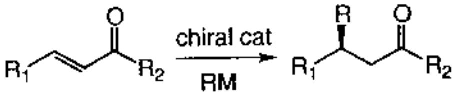
Applicable to Library Synthesis

1. Background

2.



3.



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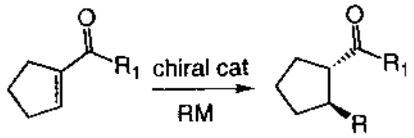
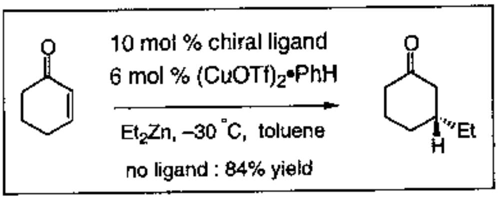


Peptidic Ligands in Reactions of Alkylmetals

Optimal ligand Schiff base



10 mol % chiral ligand

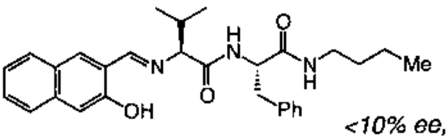
6 mol % $(CuOTf)_2$•PhH

Et_2Zn, –30 °C, toluene

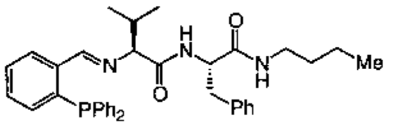
no ligand : 84% yield

Cu salts examined:

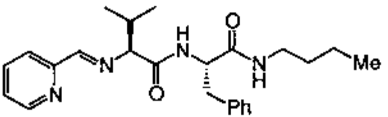
CuCN, CuCl, CuBr•Me_2S, CuI, Cu(OAc), $Cu(OTf)_2$, $Cu(OTf)_2$•PhH



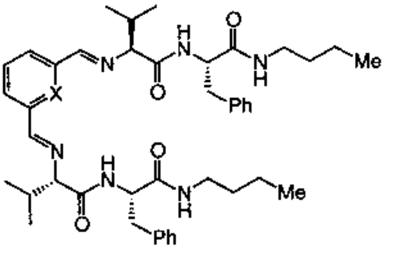
<10% ee, 93% conv



95% ee, >98% conv

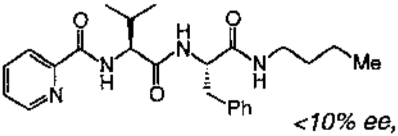


<10% ee, 39% conv



X = CH, <10% ee, 34% conv

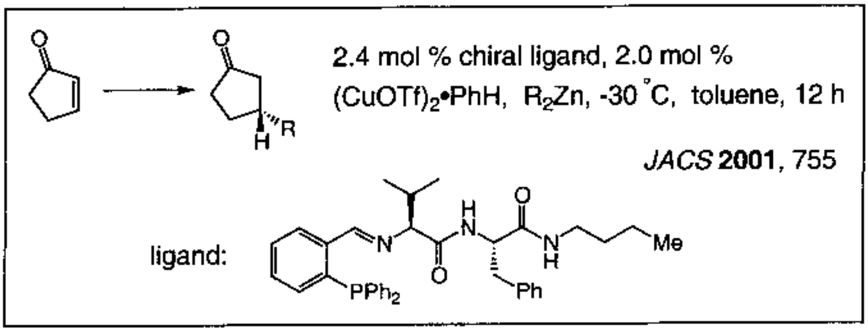
X = N, <10% ee, 65% conv



<10% ee, 78% conv

Peptidic Ligands in Reactions of Alkylmetals

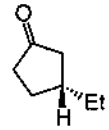
Can same ligand be used for cyclopentenones?



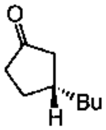
2.4 mol % chiral ligand, 2.0 mol % $(CuOTf)_2$•PhH, R_2Zn, -30 °C, toluene, 12 h

JACS **2001**, 755

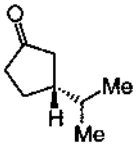
ligand:



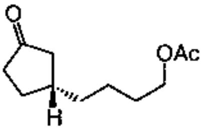
97% ee, 78%



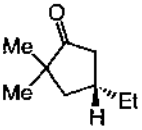
98% ee, 92%



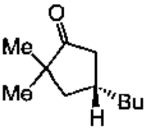
85% ee, 75%



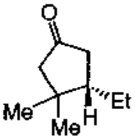
99% ee, 56%



>98% ee, 72%

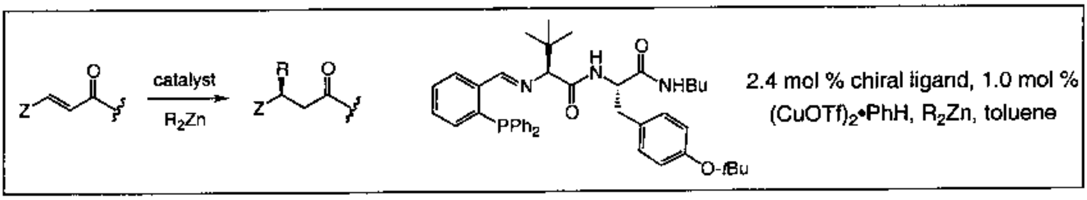


>98% ee, 64%

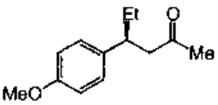


97% ee, 56%

Cu-Catalyzed Asymmetric Conjugate Addition to *Acyclic* Enones

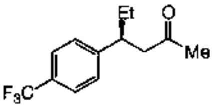


2.4 mol % chiral ligand, 1.0 mol % $(CuOTf)_2$•PhH, R_2Zn, toluene



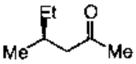
94% ee, 93%

–20 °C, 3 h



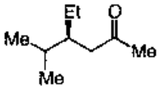
90% ee, 86%

–20 °C, 3 h



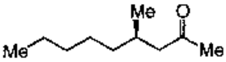
90% ee, 87%

22 °C, 1 h



91% ee, 70%

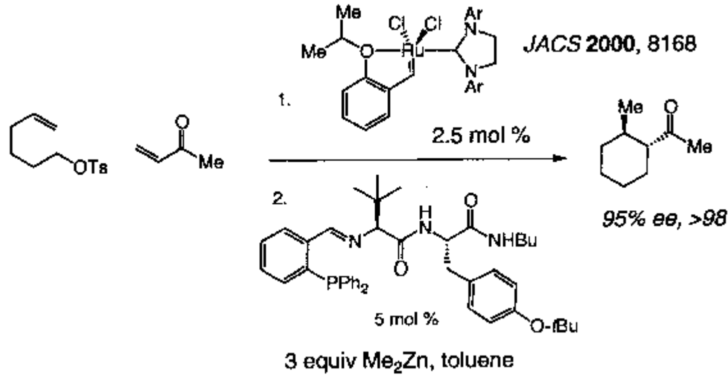
22 °C, 1 h



95% ee, 85%

22 °C, 5 h

Sequential Ru-Catalyzed Cross Metathesis/Asymmetric Cu-Catalyzed Conjugate Addition



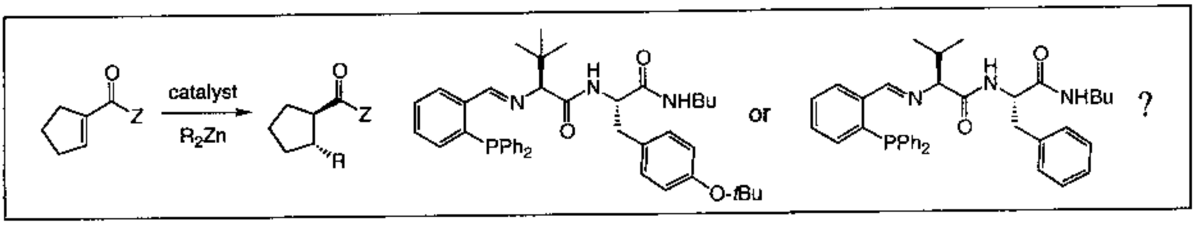
JACS **2000**, 8168

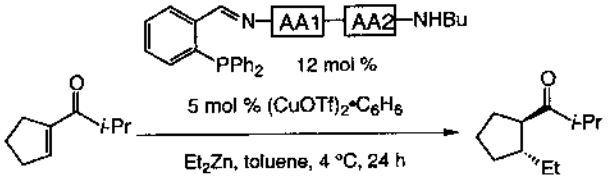
3 equiv Me_2Zn, toluene

95% ee, >98% anti, 75%

JACS **2002**, 779

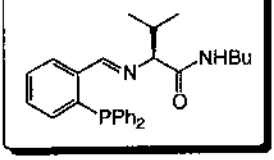
Cu-Catalyzed Asymmetric Conjugate Addition to *Trisubstituted* Enones





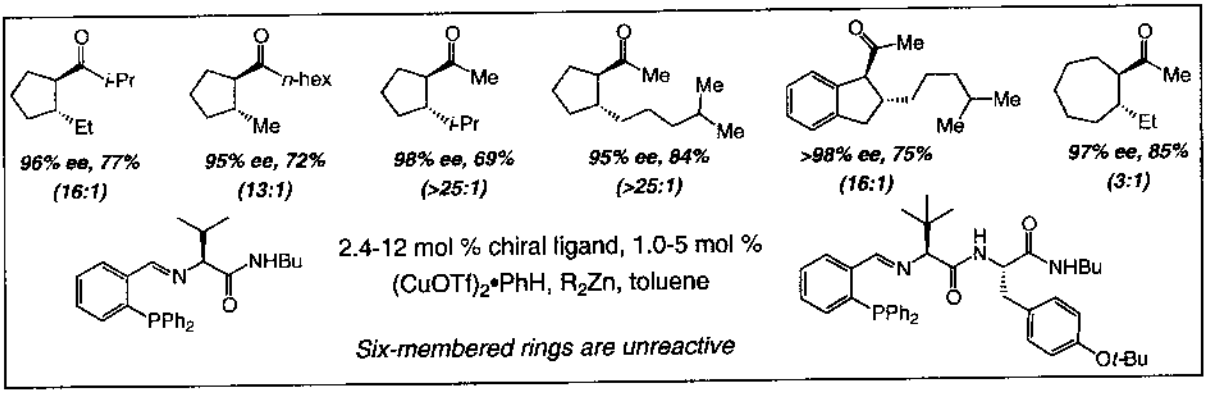
AA1	AA2	conv (%)	ee (%)
L-*t*-Leu	L-Phe	93	85
L-Val	L-Phe	32	76
L-*t*-Leu	Gly	87	93
L-Val	Gly	92	91
L-*t*-Leu	–	>98	83
L-Val	–	97	96

optimal ligand:



Evidence of cooperativity between AA1 and AA2 residues

Cu-Catalyzed Asymmetric Conjugate Addition to *Trisubstituted* Enones



96% ee, 77% (16:1)

95% ee, 72% (13:1)

98% ee, 69% (>25:1)

95% ee, 84% (>25:1)

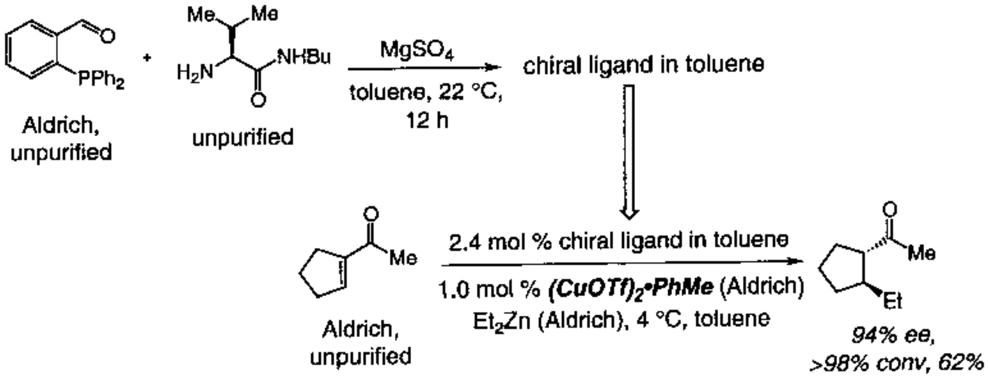
>98% ee, 75% (16:1)

97% ee, 85% (3:1)

2.4-12 mol % chiral ligand, 1.0-5 mol % $(CuOTf)_2 \cdot PhH$, R_2Zn, toluene

Six-membered rings are unreactive

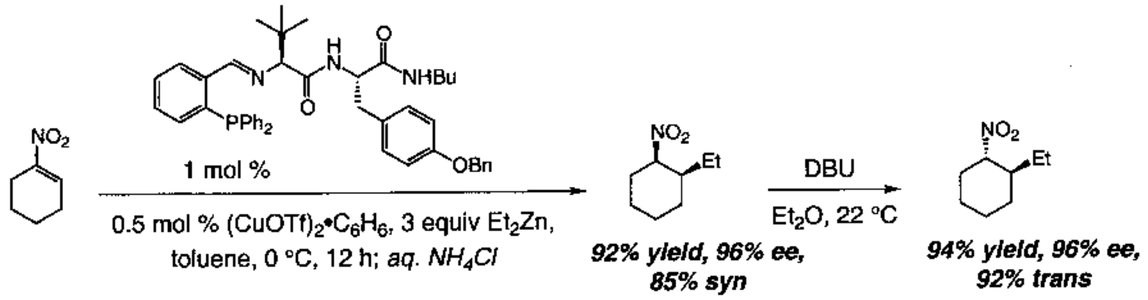
Ease of Operation:

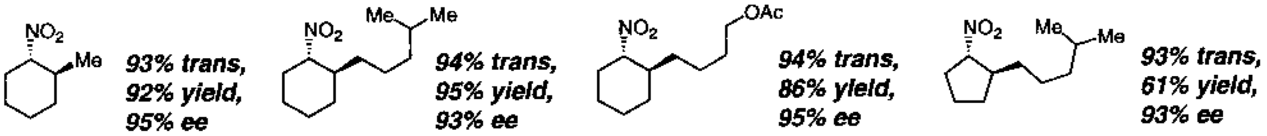


94% ee, >98% conv, 62%

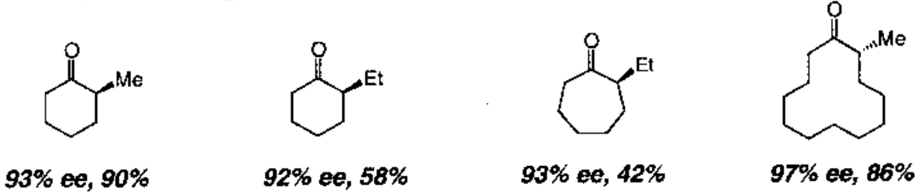
Cu-Catalyzed Asymmetric Conjugate Addition to Nitroalkenes

Catalytic Asymmetric Synthesis of α-Substituted Ketones





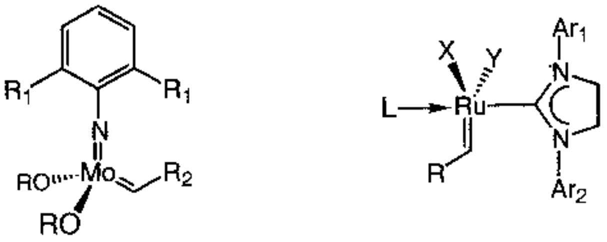
Workup with 20% H_2SO_4 leads to in situ Nef:



JACS **2002**, in press

New Catalysts for Efficient, Selective and Practical Organic and Combinatorial Synthesis

Development of New Catalysts for Olefin Metathesis



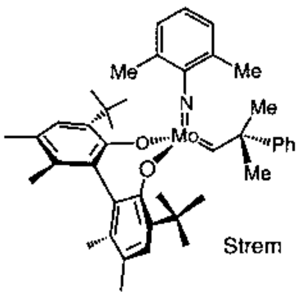
1) Reactivity

2) Selectivity:
Regio- and ***Enantioselectivity***

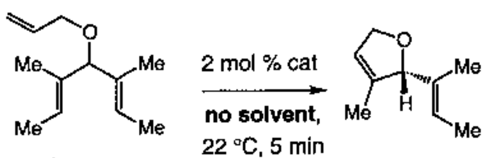
3) Practicality:
Recyclable
Minimal Use of Solvents
Minimal Product Purification
Applicable to Library Format

Catalytic Enantioselective Desymmetrization by ARCM

Enantioselective C–C Bond Formation Without Solvent Waste

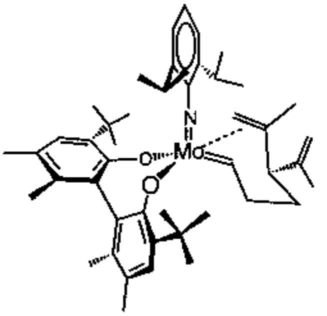


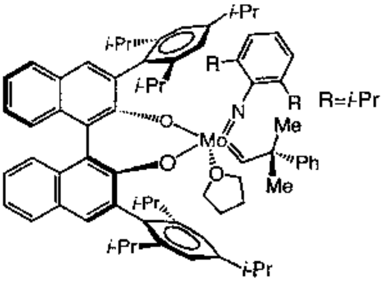
JACS **1998**, 9720



>98% ee, 93%

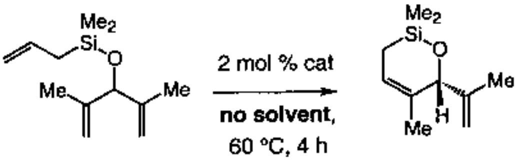
Alexander & La





JACS **1999**, 8251

Zhu & Cefalo

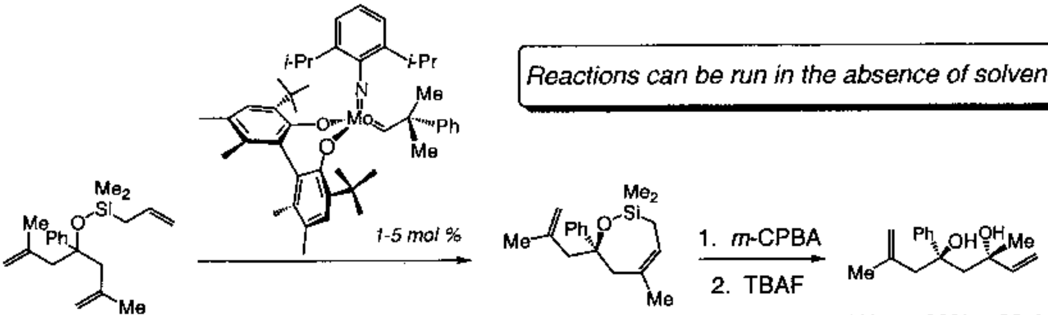


>98% ee, 98%

20% monomer, 30% dimer
with biphen catalysts (in C_6H_6), 65-87% ee

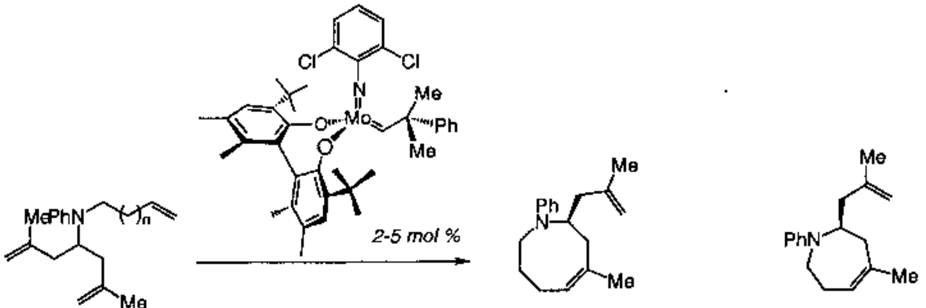
Enantioselective Synthesis of *Medium Rings* By Catalytic Asymmetric Ring-Closing Metathesis

Reactions can be run in the absence of solvent



93% ee, 92% ***93% ee, 86%, >20:1***

JACS **2002**, 2868 *Jernelius & Keily*

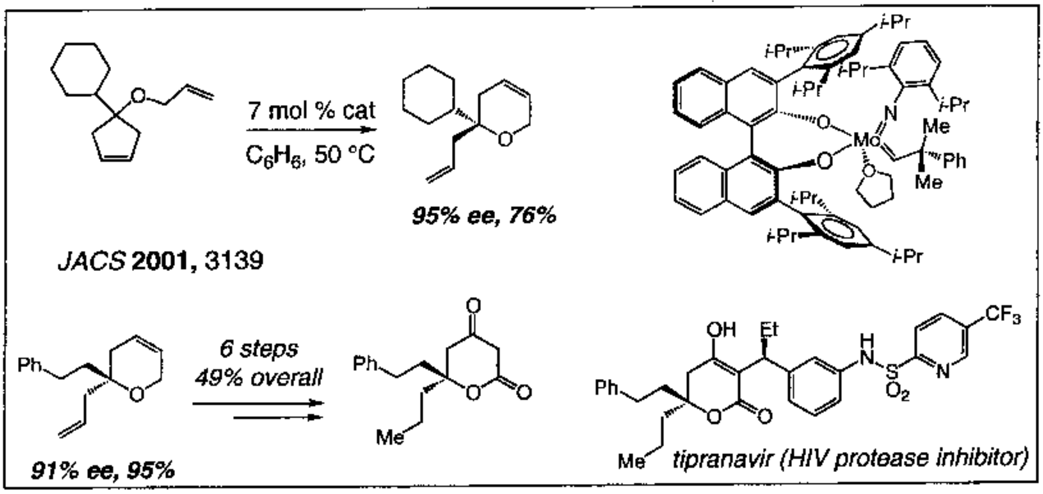


>98% ee, 90% ***95% ee, 90%***

JACS **2002**, 6991 *Dolman & Sattely*

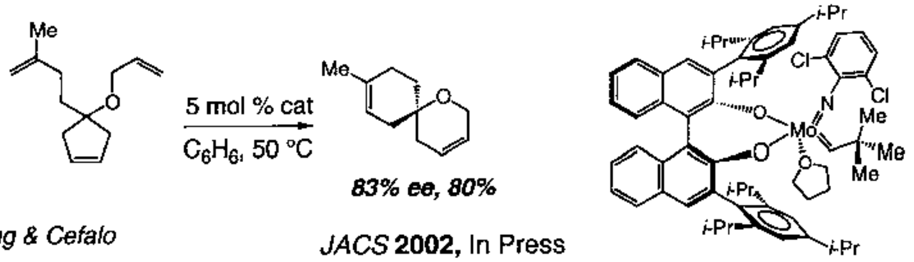
Catalytic Asymmetric Synthesis of Pyrans Bearing a Tertiary Ether Site

Application to Tipranavir Synthesis



JACS **2001,** 3139

Catalytic Enantioselective Synthesis of Spirocycles

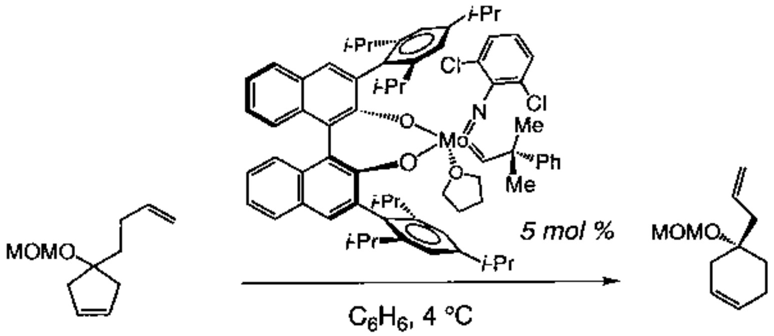


Teng & Cefalo

JACS **2002,** In Press

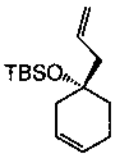
Catalytic Asymmetric Rearrangement Through Metathesis

Unexpected Effect of THF as Additive

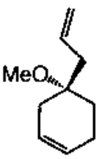


no additive	78% ee; >98% conv
2 equiv THF	85% ee; >98% conv
10 equiv THF	***92% ee, 86% yield***

~60% ee with (i-Pr)$_2$ catalyst for which no change was observed



no additive	58% ee; >98% conv
10 equiv THF	***96% ee, 94% yield***

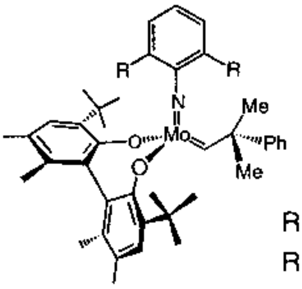


no additive	80% ee; >98% conv
10 equiv THF	***90% ee, 88% yield***

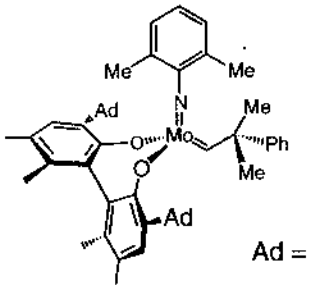
JACS **2002**, In Press

Teng & Cefalo

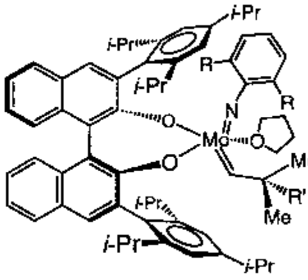
Collection of Chiral Catalysts: Variations in Diolate and Imido Sites



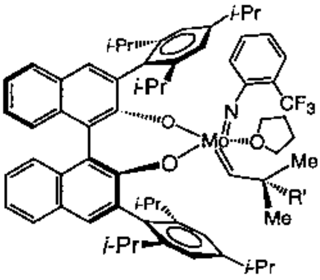
R = *i*-Pr
R = Me
R = Cl

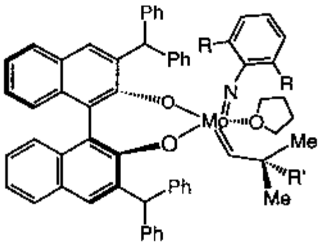


Ad = adamantyl



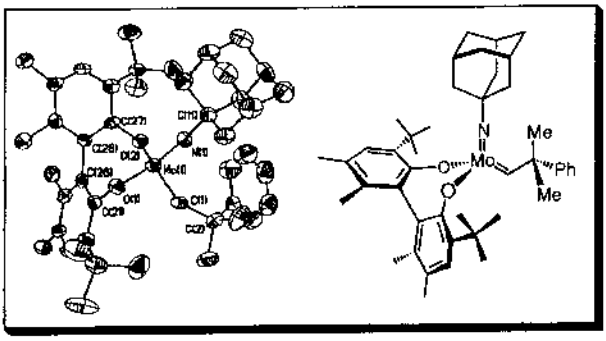
R = *i*-Pr R' = Ph
R = Cl R' = Me

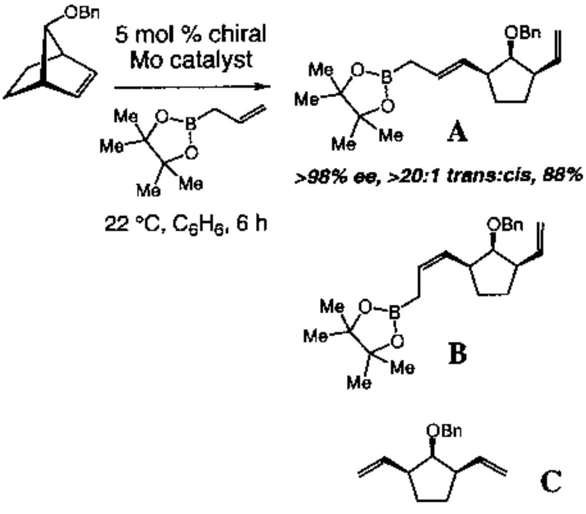


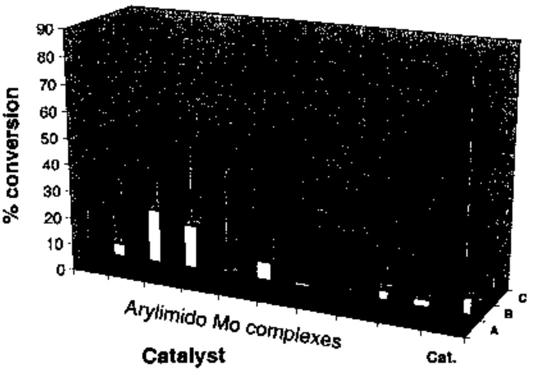


R = *i*-Pr$_2$

New Chiral Mo Catalyst: Alkylimido Ligand

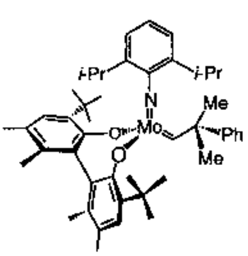


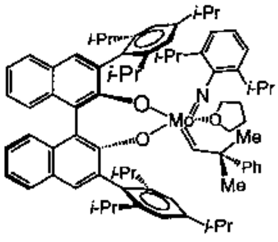


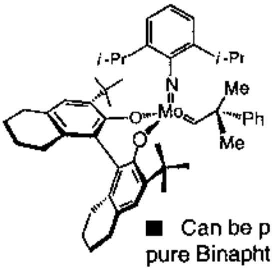


Tsang & Jemelius

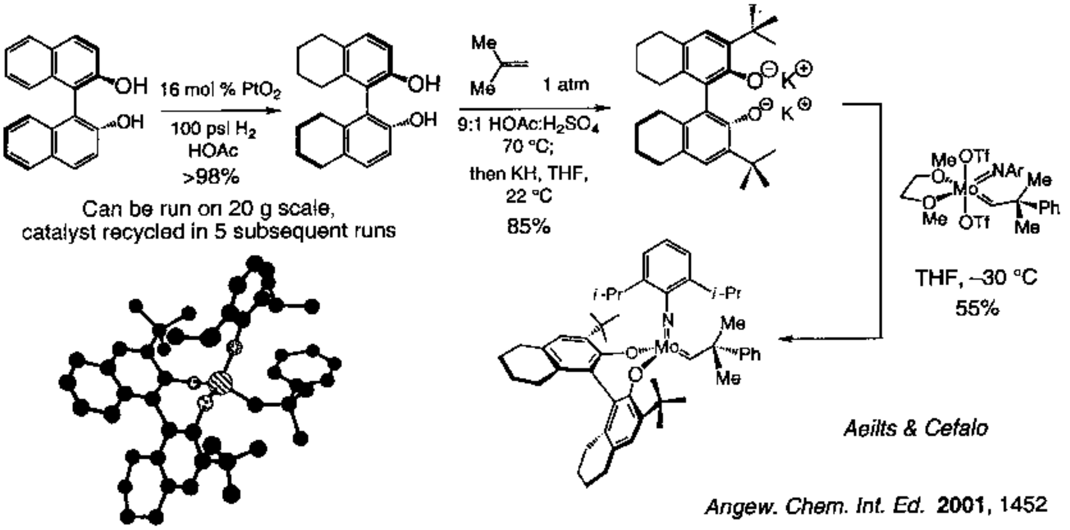
A *Hybrid* Mo-Based Chiral Catalyst for Asymmetric Metathesis







- Can be prepared from optically pure Binaphthol
- May represent a hybrid catalyst

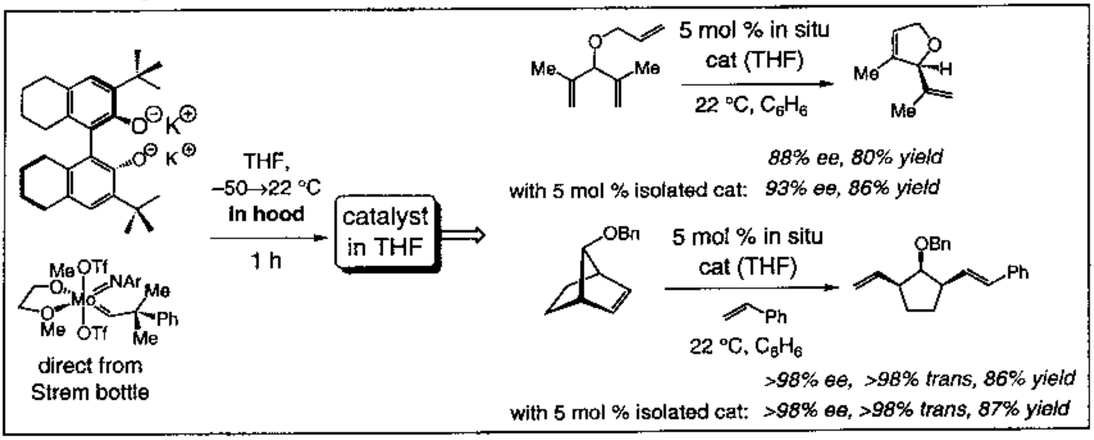


Can be run on 20 g scale, catalyst recycled in 5 subsequent runs

Aeilts & Cefalo

Angew. Chem. Int. Ed. **2001**, 1452

A Readily Available and General Class of Chiral Metathesis Catalysts



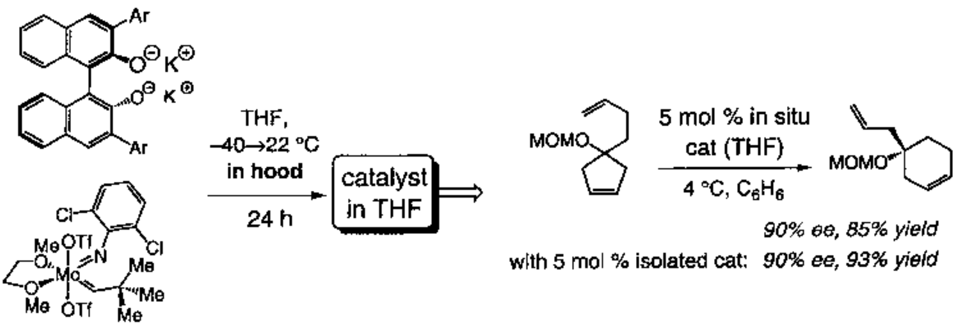
direct from Strem bottle

88% ee, 80% yield

with 5 mol % isolated cat: *93% ee, 86% yield*

>98% ee, >98% trans, 86% yield

with 5 mol % isolated cat: *>98% ee, >98% trans, 87% yield*



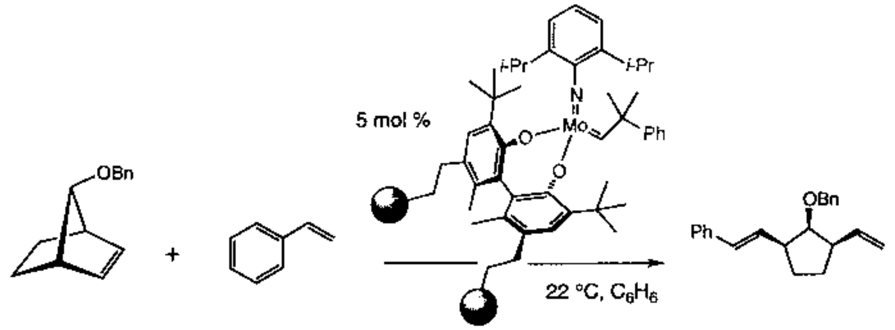
90% ee, 85% yield

with 5 mol % isolated cat: *90% ee, 93% yield*

- Stock solutions active for at least two weeks
- Use of drybox not required

Angew. Chem. Int. Ed. **2001**, 1452

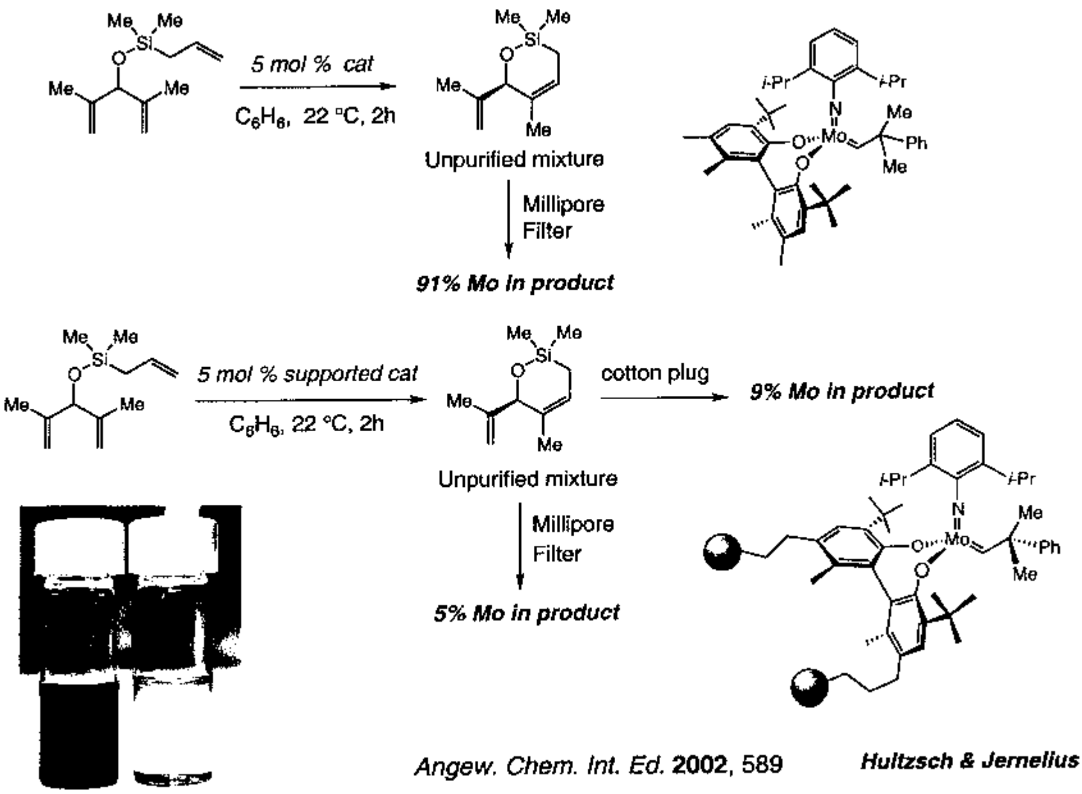
Recyclable Solid-Supported Mo-Based Chiral Metathesis Catalysts



100% styrene/ 0% DVB	**45 mol % styrene/ 55 mol % DVB**
Cycle1: 30 min, 97% ee, >98% *product contains 3% of tot. Mo (5 mol % loading)*	***Cycle1:*** 30 min, 98% ee, 80% conv., *product contains 3% of tot. Mo (5 mol % loading)*
Cycle 2: 30 min, 98% ee, 98% *product contains 10% of tot. Mo (5 mol % loading)*	***Cycle 2:*** 30 min, 98% ee, >98% conv *product contains 7% of tot. Mo (5 mol % loading)*
Cycle 3: 16h, 89%ee, 55% *product contains 16% of tot. Mo (5 mol % loading)*	***Cycle 3:*** 16h, 88% ee, 55% conv *product contains 11% of tot. Mo (5 mol % loading)*

Hultzsch & Jernelius

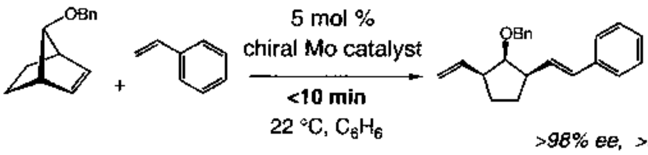
Supported vs Solution Phase: Higher Purity Products



Angew. Chem. Int. Ed. **2002**, 589

Hultzsch & Jernelius

Complementarity of Mo– and Ru–Based Systems

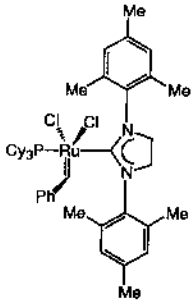


>98% ee, >98% trans, 86% yield

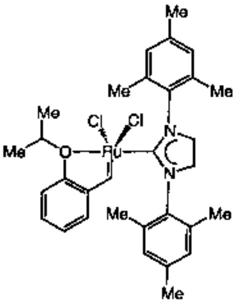
with 5 mol % isolated cat: *>98% ee, >98% trans, 87% yield*

<5% reaction with the following Ru catalysts

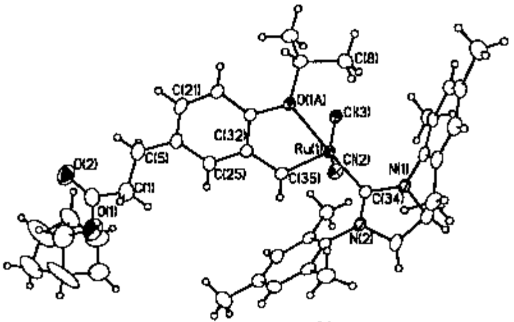
(100 mol % at 70 °C)

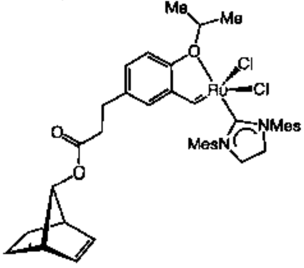


Grubbs, *Org. Lett.* **1999**, 953

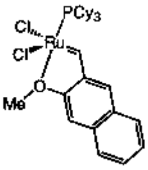


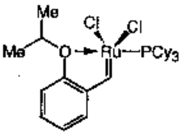
Hoveyda, *JACS* **2000**, 8168

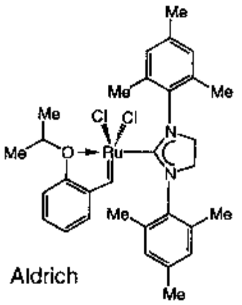




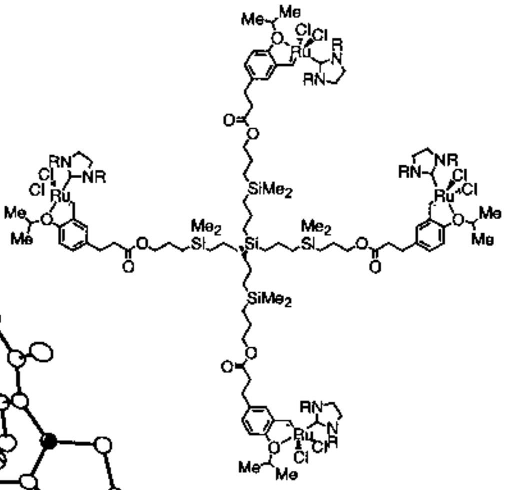
Recyclable Ru-Based Metathesis Catalysts

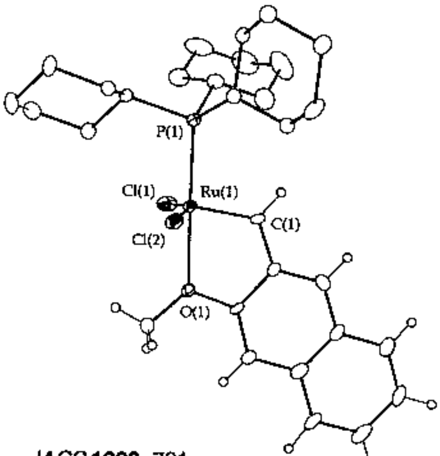






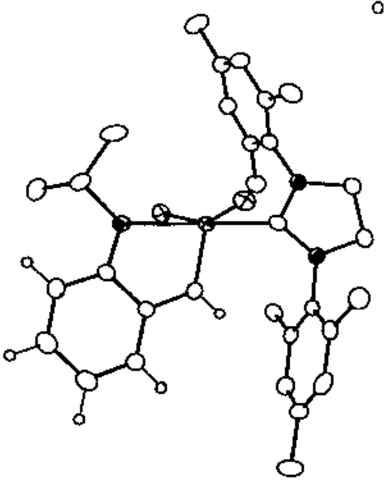
Aldrich





JACS **1999**, 791

Harrity & Kingsbury

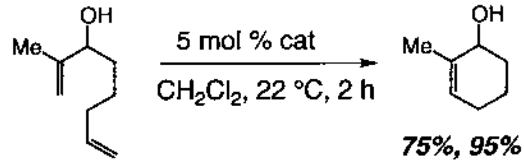


JACS, **2000**, 8168

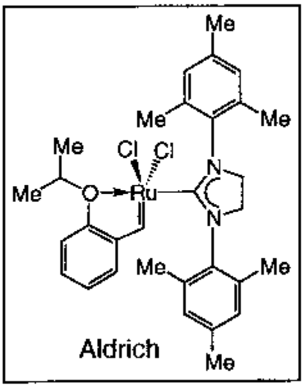
Kingsbury & Garber

Not Just a Recyclable Metathesis Catalyst!

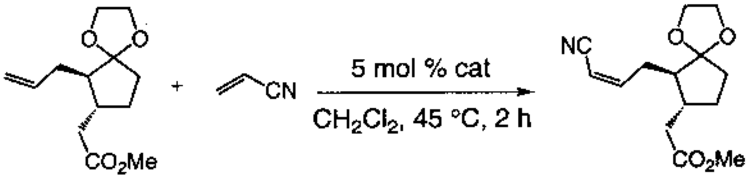
Superior Catalyst for CM with Electron Deficient Olefins



75%, 95% cat recovery

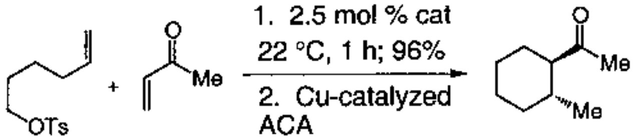


Aldrich



Blechert *Synlett* **2001**, 430 ***83%, 90% Z***

<10% conv with PCy$_3$ catalyst

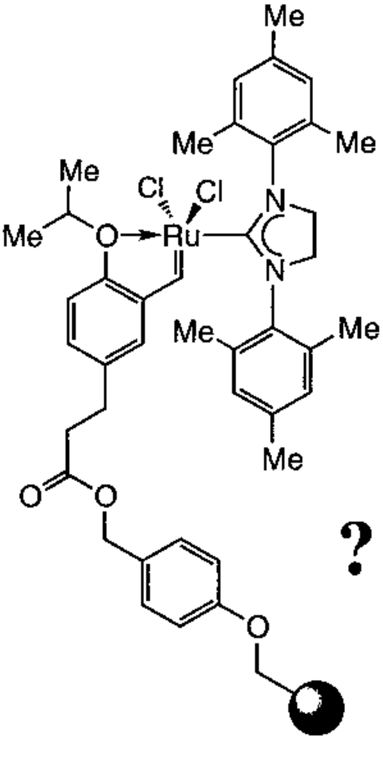


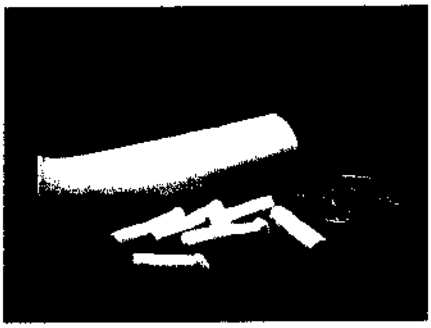
JACS **2002**, 779 ***95% ee, >98% anti, 75%***

mixture of products with PCy$_3$ catalyst

An Alternative Strategy for Catalyst Recycling

Selecting a suitable solid support

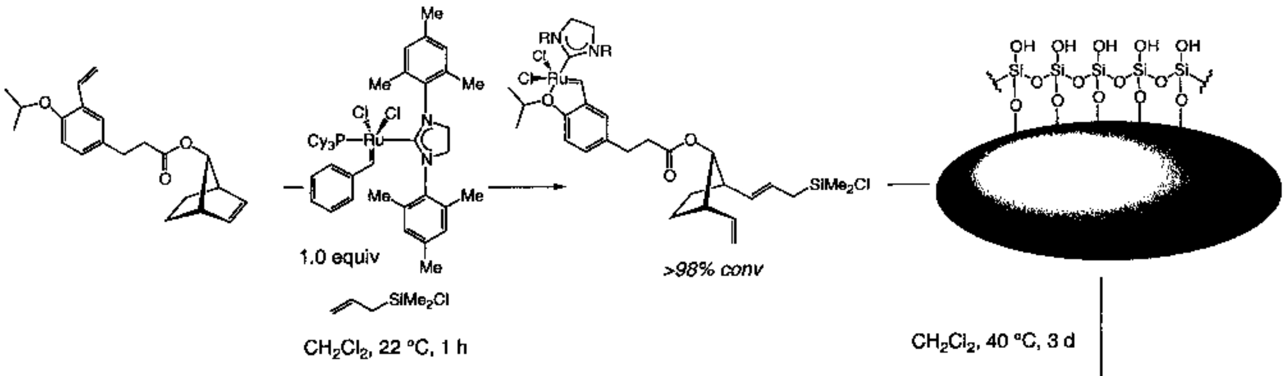


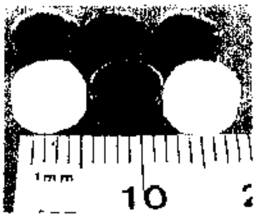


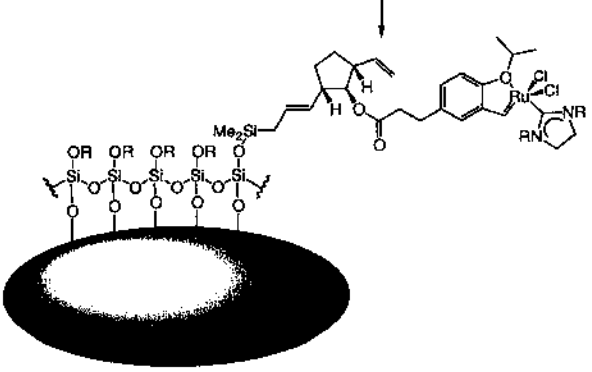
Advantages of Sol-Gel as Solid Support:

1) Rigid, highly exposed surface area (typically 300-1000 m^2/g)
2) No shrinking or swelling in solvents
3) Bulk sample eliminates filtration
4) Mold chosen for processing determines size and shape

Recyclable Ru Catalyst on Glass: Efficient & Practical



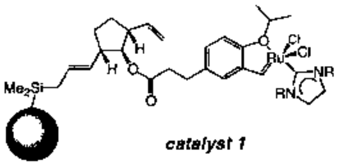




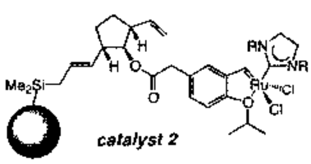
Kingsbury *Angew. Chem. Int. Ed.* **2001**, 4251

- ■ 1-2 x10^{-3} mmol Ru / mg glass
- ■ 200 Å pores

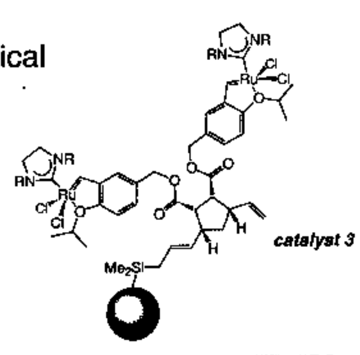
Recyclable Ru Catalysts on Glass: Efficient & Practical



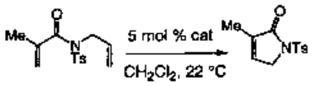
catalyst 1



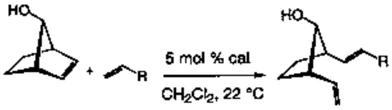
catalyst 2



catalyst 3



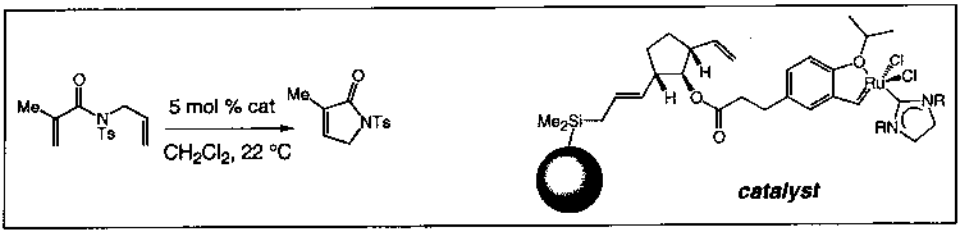
catalyst	cycle 1 (3 h)	cycle 2 (3 h)	cycle 3 (3 h)	cycle 4 (3 h)
1	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y
2	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y
3	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y



	styrene	*1-octene*	*vinylferrocene*
catalyst	cycle 5 (1 h)	cycle 6 (1 h)	cycle 7 (1 h)
1	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y
2	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y
3	>98% c, 99% y	>98% c, 99% y	>98% c, 99% y

Kingsbury

Recyclable Ru Catalyst on Glass: Efficient & Practical

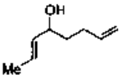
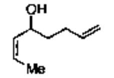
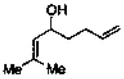
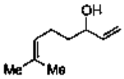
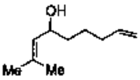
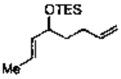
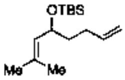
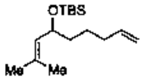
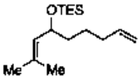
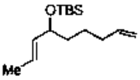
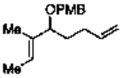
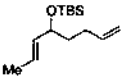
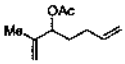
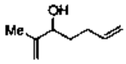
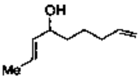
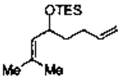
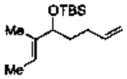
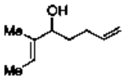
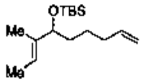
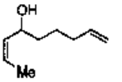
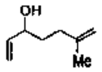


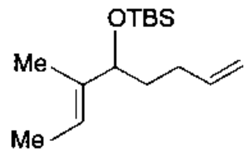
cycle 1 (3 h)	cycle 2 (3 h)	cycle 3 (3 h)	cycle 4 (4 h)	cycle 5 (5 h)	cycle 6 (6 h)
>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y
cycle 7 (6 h)	cycle 8 (7 h)	cycle 9 (8 h)	cycle 10 (8 h)	cycle 11 (9 h)	cycle 12 (10 h)
>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y
cycle 13 (12 h)	cycle 14 (14 h)	cycle 15 (14 h)	cycle 16 (16 h)	cycle 17 (18 h)	cycle 18 (20 h)
>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y	>98% c, >98% y
		cycle 19 (22 h)	cycle 20 (24 h)		
		>98% c, >98% y	>98% c, >98% y		

Remove glass, evaporate solvent: analytically pure product,
no coloring (0.04-0.05% Ru residue)

Kingsbury & Giftos

Ring-Closing Metathesis Library-1

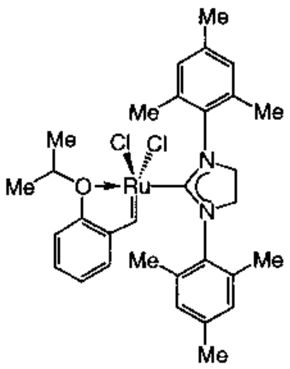
	1	2	3	4	5
A	 >98% conv. MS: 85.0653 (85.0653)	 60% conv. MS: 85.0653 (85.0653)	 >98% conv. MS: 85.0653 (85.0653)	 >98% conv. MS: 85.0649 (85.0653)	 96% conv. MS: 98.0729 (98.0732)
B	 96% conv. MS: 198.1440 (198.1440)	 98% conv. MS: 199.1526 (199.1518)	 98% conv. MS: 211.1519 (211.1518)	 >98% conv. MS: 212.1592 (212.1596) C, 66.93 (67.86) H, 10.92 (11.39)	 >98% conv. MS: 211.1522 (211.1518)
C	 74% conv. MS: 218.1301 (218.1307) Ru impurity: 0.13%	 >98% conv. MS: 199.1520 (199.1518) C, 66.95 (66.60) H, 10.99 (11.18) Ru impurity: 0.03%	 48% conv. MS. No M+ for High Res Ru impurity: 0.68%	 50% conv. MS: 97.0656 (97.0653) Ru impurity: 1.2%	 >98% conv. MS: 98.0732 (98.0732) C, 71.21 (73.43) H, 9.68 (10.27)
D	 91% conv. MS: 199.1526 (199.1518) Ru impurity: 0.44%	 >98% conv. MS: 211.1521 (211.1518) C, 67.74 (67.86) H, 10.86 (11.39) Ru impurity: 0.07%			 89% conv. MS: 98.0730 (98.0732) Ru impurity: 1.2%
E	 >98% conv. MS: 225.1672 (225.1675) C, 69.21 (68.76) H, 11.31 (11.57) Ru impurity: 0.13%	 >98% conv. MS: 98.0730 (98.0732) C, 68.80 (73.43) H, 9.63 (10.27)			 >98% conv. MS: 97.0652 (97.0653) C, 71.53 (73.43) H, 9.39 (10.27)



>98% conv.
MS: 211.1521 (211.1518)
C, 67.74 (67.86)
H, 10.86 (11.39)
Ru impurity: 0.07%

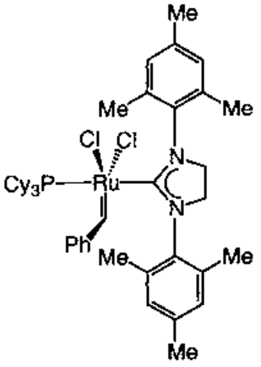
Chiral Ru Catalyst for Olefin Metathesis?

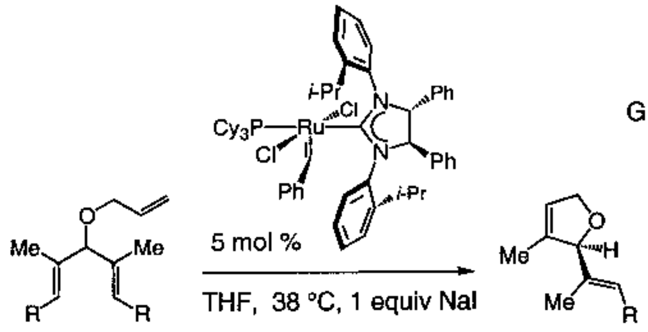
Can Complement Mo Catalysts and Enhance Practicality



Mono- or bidentate chiral ligand?
Replacement of Cl can reduce activity

Chiral bidentate ligand: stereogenic Ru center
& problem of diastereoselectivity



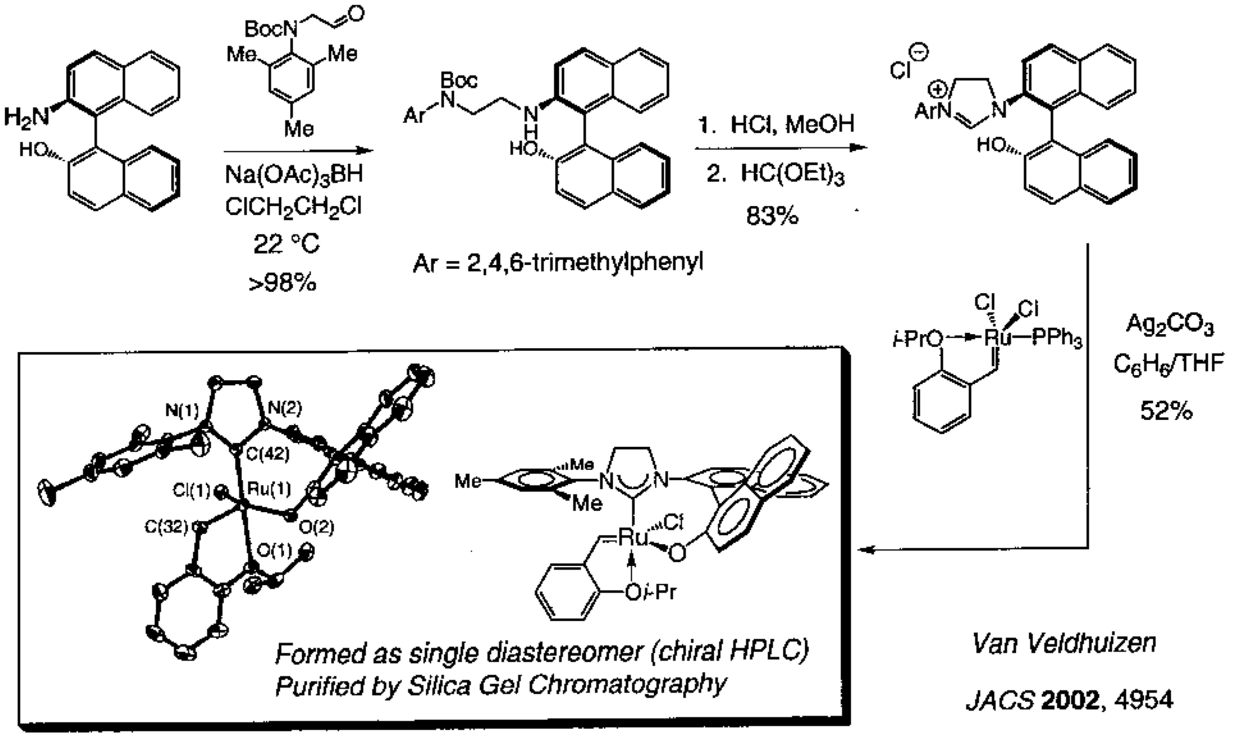


Grubbs *Org. Lett.* **2001**, 3225

a R = H 39% ee, 22% conv
b R = Me 90% ee, 82% conv

Chiral Bidentate IMES: Chiral Ru Catalyst for Olefin Metathesis

Diastereoselective Synthesis of Air–Stable Chiral Catalyst



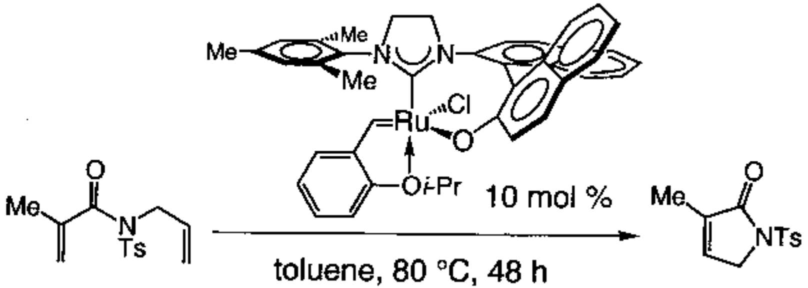
Formed as single diastereomer (chiral HPLC)
Purified by Silica Gel Chromatography

Van Veldhuizen

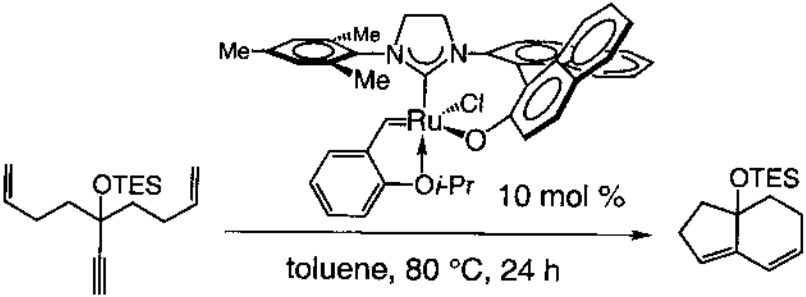
JACS **2002**, 4954

Chiral Ru Catalyst for Olefin Metathesis

Reactive & Recyclable



>98% conv., 98% yield
91% recovered catalyst



>98% conv., 97% yield
90% recovered catalyst

Dienyne Tandem RCM Cannot be Promoted by Mo Catalysts

JACS **2002**, 4954