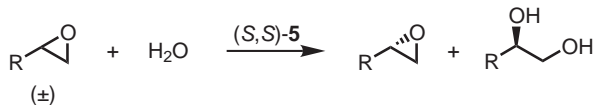
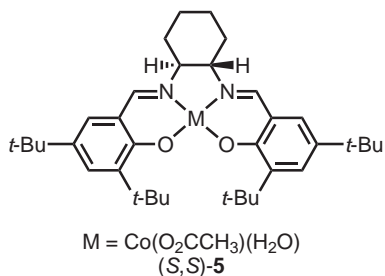
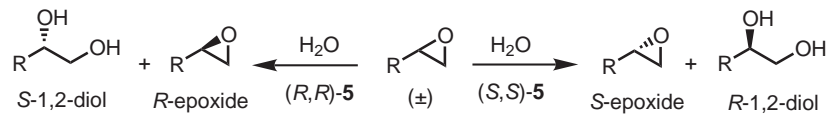
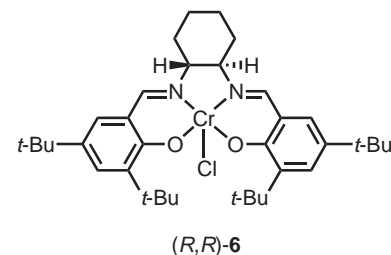
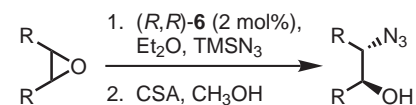


## Hydrolytic Kinetic Resolution (HKR):



R	5 (mol %)	water (equiv)	time (hours)	Epoxide		Diol		<i>k</i> <sub>rel</sub>
				ee (%)	isolated yield (%)	ee (%)	isolated yield (%)	
CH <sub>3</sub>	0.2	0.55	12	>98	44	98	50	>400
CH <sub>2</sub> Cl	0.3	0.55	8	98	44	86	38	50
(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	0.42	0.55	5	98	46	98	48	290
Ph	0.8	0.70	44	98	38	98	39	20
CH=CH <sub>2</sub>	0.64	0.50	20	84	44	94	49	30

## Enantioselective Opening of Meso Epoxides:



substrate	product	yield (%)	ee (%)
		72	81
		80	95
		65*	82

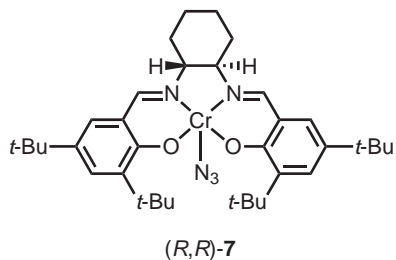
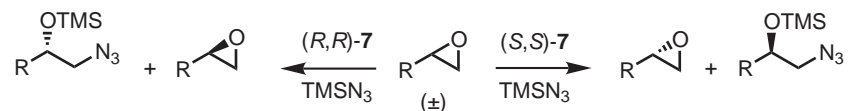
\*Isolated yield of silyl ether.

- Epoxides fused to 5-membered rings show higher enantioselectivity than 6-membered-ring and acyclic substrates.

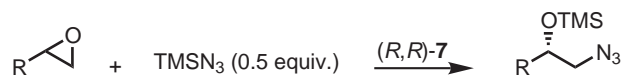
From: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, 277, 936-938.

Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5897-5898.

### Kinetic Resolution of Terminal Epoxides with Trimethylsilyl Azide:



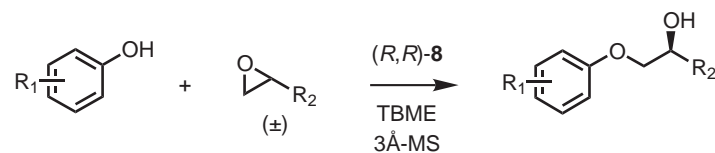
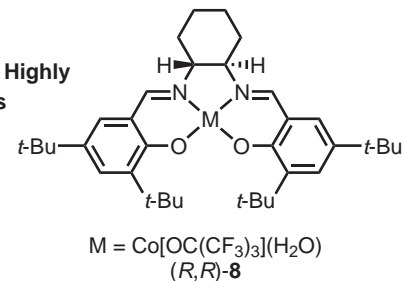
- High yields and ee's with a variety of substituents.



R	7 (mol %)	yield (%)	ee (%)	$k_{rel}$
CH <sub>2</sub> Cl	2.0	94	95	100
CH <sub>2</sub> CN	2.0	80	92	45
CH(OEt) <sub>2</sub>	2.0	96	89	44
CH <sub>2</sub> Ph	2.0	94	93	71

Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420-7421.

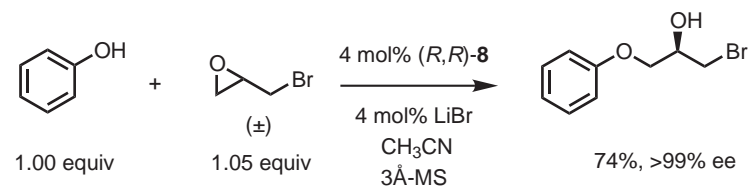
### Kinetic Resolution of Terminal Epoxides via Highly Enantioselective Ring-Opening with Phenols



R <sub>1</sub>	R <sub>2</sub>	8 (mol %)	temp. (°C)	yield (%) <sup>a</sup>	ee (%)
H	CH <sub>2</sub> Cl	4.4	-15	97	99
H	CH <sub>2</sub> OCH <sub>2</sub> CH=CH <sub>2</sub>	4.4	4	93	97
H	COCH <sub>2</sub> CH <sub>3</sub>	8.8	-20	96	96
H	CO <sub>2</sub> CH <sub>3</sub>	4.4	-20	98	96
<i>p</i> -CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	4.4	25	95	97
<i>m</i> -CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	4.4	25	99	99
<i>o</i> -CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	4.4	25	<5	NA
<i>o</i> -Br	C <sub>4</sub> H <sub>9</sub>	8.8	-30	98	92
<i>p</i> -NO <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	8.8	-20	93	91

<sup>a</sup>2.2 equivalents of epoxide was used.

- With the exception of styrene oxide and ortho-substituted alkyl phenols, excellent yields and ee's are obtained with a wide range of substrates.

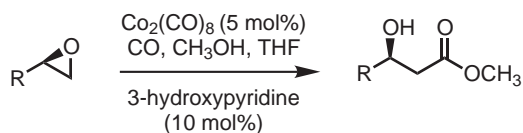


- A remarkable dynamic kinetic resolution was achieved using epibromohydrin.

Ready, J. M.; Jacobsen E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086-6087.

## Carbomethoxylation of Chiral Terminal Epoxides

- The coupling of Jacobsen's HKR of terminal epoxides with Drent's protocol (Drent, E.; Kragtwijk, E. Eur. Pat. Appl. 577206, 30 Mar. 1994; *Chem Abstr.* **1994**, 120, 191517c) for catalytic carbonylation of aliphatic epoxides provides a route to enantiomerically enriched acetate aldol products.



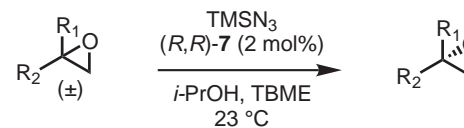
substrate	temperature (°C)	yield (%) <sup>a</sup>	ee (%)
	65	92	>99
	55	96	>99
	60	95	>99
	55	86	>99
	60	91 <sup>b</sup>	>99

<sup>a</sup>Reactions conducted in CH<sub>3</sub>OH-THF (1:1) at [epoxide]<sub>0</sub> = 0.5 M and a final CO pressure of 600 psi for 9 h. <sup>b</sup>CO pressure of 670 psi.

- Terminal epoxides bearing sp<sup>2</sup> substituents (e.g., styrene oxide and 1,3-butadiene monoepoxide) undergo carbomethoxylation in low yield (10-15%) and with poor regioselectivity (linear/branched ~1:1).
- The stereochemical integrity of the epoxide substrates is retained in the β-hydroxy ester products, even when the stereogenic center is enolizable.
- Preliminary experiments indicate that addition of *N,O*-dimethylhydroxylamine to the reaction mixture results in the direct formation of β-hydroxy Weinreb amides in 70-90% yield.

Hinterding, K.; Jacobsen, E. N. *J. Org. Chem.* **1999**, *64*, 2164-2165.

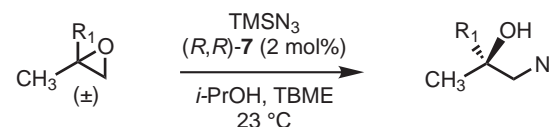
## Chromium-Catalyzed Kinetic Resolution of 2,2-Disubstituted Epoxides:



R <sub>1</sub>	R <sub>2</sub>	HN <sub>3</sub> (equiv) <sup>a</sup>	yield of epoxide (%)	ee (%)
TBSOCH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub>	0.55	42	99
PhCH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub>	0.60	44	97
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	CH <sub>3</sub>	0.55	42	99
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	CH <sub>3</sub>	0.50	46	98
<i>t</i> -BuO <sub>2</sub> C <sup>b</sup>	CH <sub>3</sub>	0.55	46	85
<i>c</i> -C <sub>6</sub> H <sub>11</sub> <sup>b,c</sup>	TMSC≡C	0.70	48	80

<sup>a</sup>Generated by combining equimolar amounts of TMSN<sub>3</sub> and *i*-PrOH. <sup>b</sup>Reaction conducted neat. <sup>c</sup>Used 5 mol% of (*R,R*)-**7**.

- Catalyst **7** can efficiently differentiate between methyl groups and alkyl chains but fails to distinguish between an ethyl and a phenethyl side chain.
- Sterically hindered epoxides (i.e. R<sub>1</sub>=*i*-Pr, R<sub>2</sub>=*n*-Bu) are not reactive.
- This kinetic resolution may be used to prepare enantiomerically enriched azido alcohols as well.



R <sub>1</sub>	yield of azido alcohols (%) <sup>a</sup>	ee (%)
TBSOCH <sub>2</sub> CH <sub>2</sub>	47	90
PhCH <sub>2</sub> CH <sub>2</sub>	45	92
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	44	95
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	40	99

<sup>a</sup>0.50 equivalents of HN<sub>3</sub> was used.

Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **2000**, *40*, 7303-7306.

M. Movassaghi