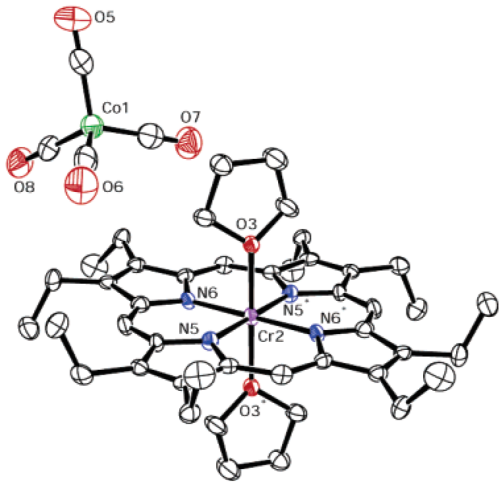
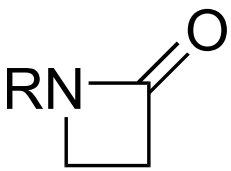
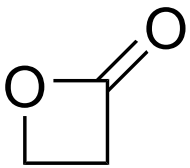
Catalytic Carbonylative Ring Expansion of Epoxides and Aziridines







Andrew J. Hoover

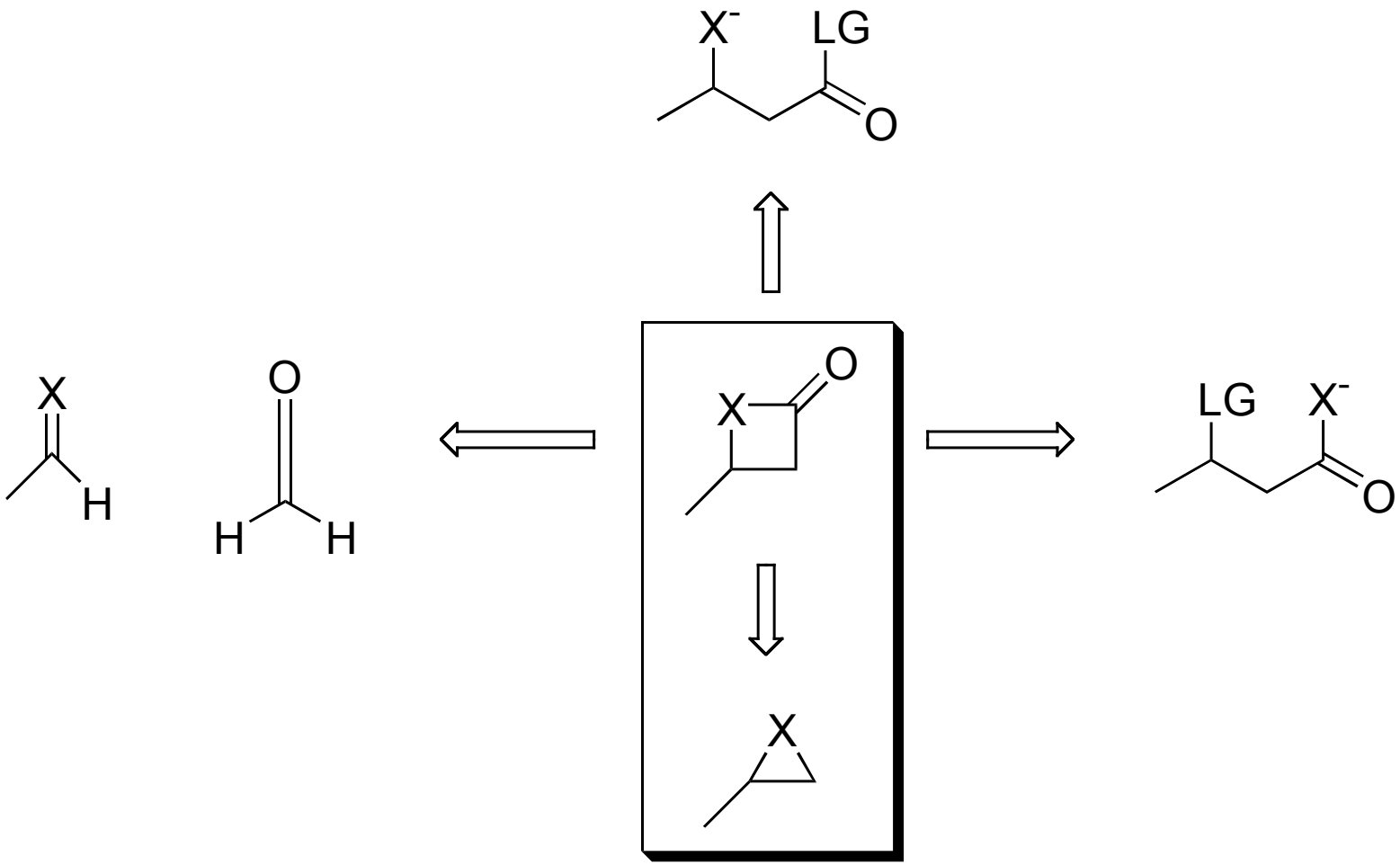
Denmark Research Group Meeting

June 10, 2008

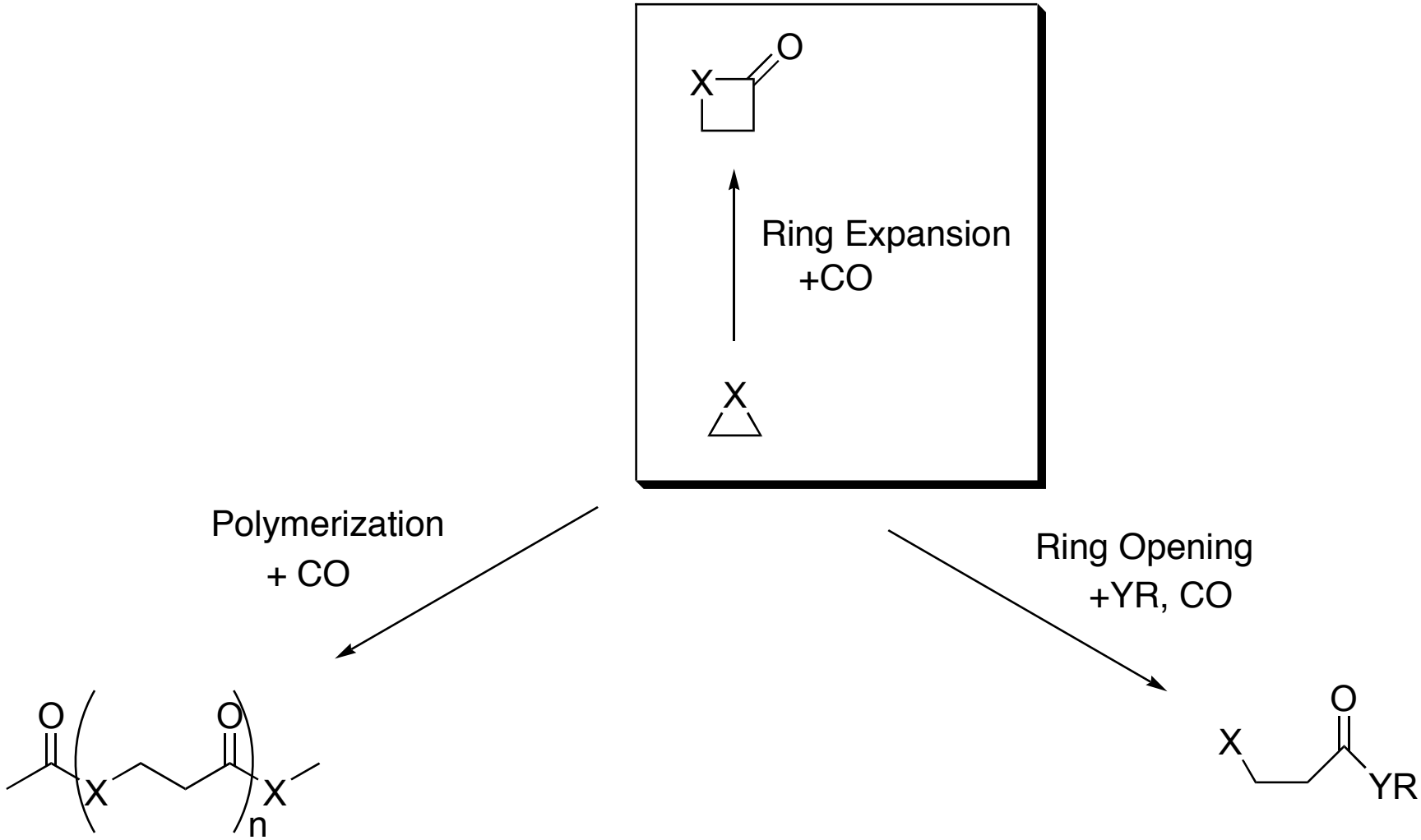
Outline

- Carbonylation overview, history, modern catalyst development
- Mechanism of Carbonylative Ring Expansion of Epoxides
- Refinement of Epoxide Ring Expansion Chemistry
- Double (Tandem) Epoxide Carbonylation
- Carbonylative Ring Expansion of Aziridines

Carbonylation Chemistry

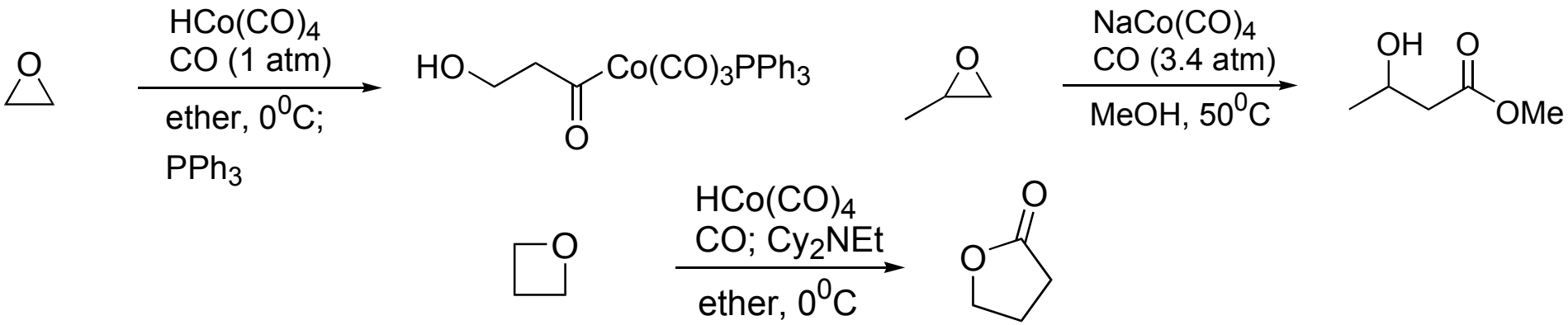


Carbonylation Chemistry



Epoxide Carbonylation: Historical Development

R. F. Heck, 1963: Opening of epoxides and oxetanes with (stoichiometric) $Co(CO)_4^-$



Drent and Kragtwijk, 1994: $Co_2(CO)_8$ / 3-hydroxypyridine catalyst

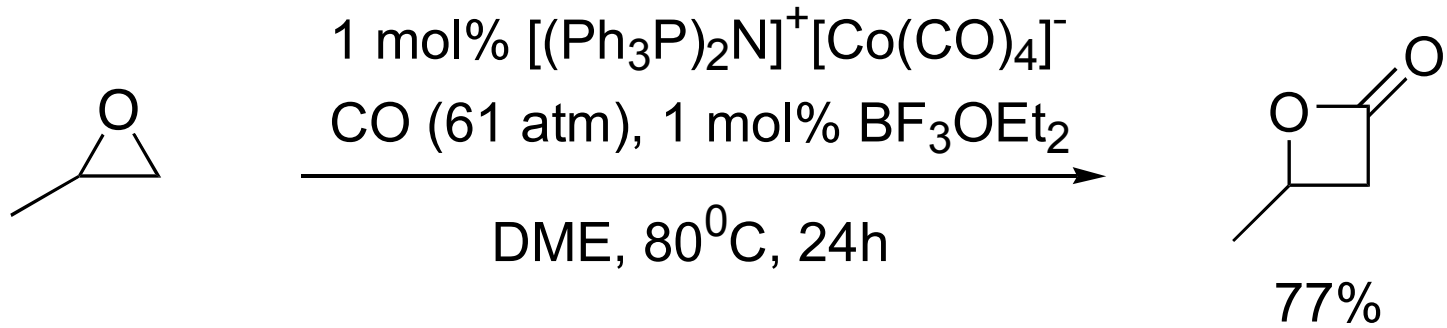
Also demonstrated polymerization under similar conditions

R. F. Heck, *J. Am. Chem. Soc.*, **1965**, *85*, 1460.

E. Drent, E. Kragtwijk, *Eur. Pat. Appl.*, EP 577206 (**1994**)

Discrete Lewis Acid Catalyst

Alper, 2001:

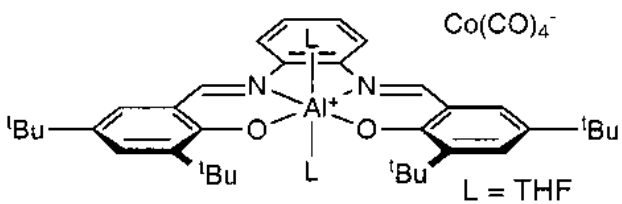


Under the same conditions in the absence of BF_3OEt_2, no product was formed.
11 examples, limited scope, modest to good yields.

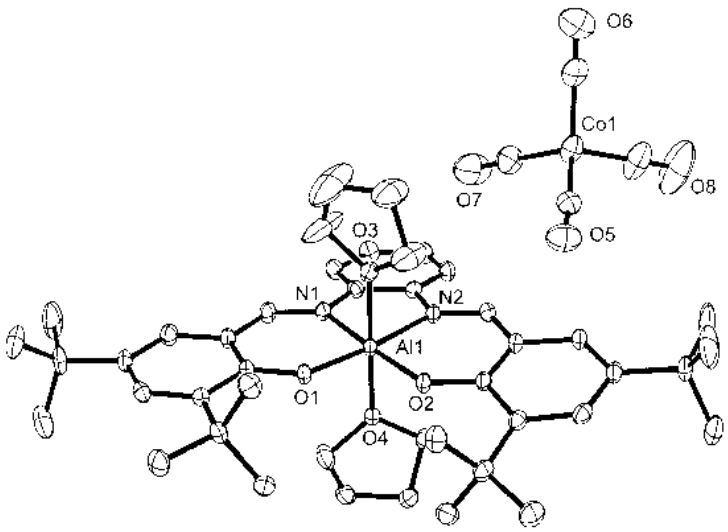
Alper et. al., *J. Org. Chem.*, **2001**, *66*, 5424.

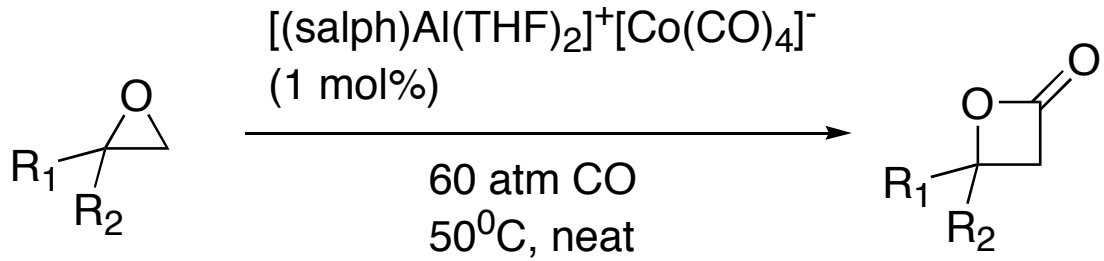
Coates's First Heterobimetallic Catalyst

A well-defined, highly active carbonylation catalyst



[(salph)Al(THF)$_2$][Co(CO)$_4$]





R_1	R_2	time (h)	yield (%)
H	Me	1	95
H	(*R*)-Me	1	95
H	Et	2.5	>99
H	CH_2Cl	9.5	73
Me	Me	1	83

Configurational purity of (R)-propylene oxide was maintained.

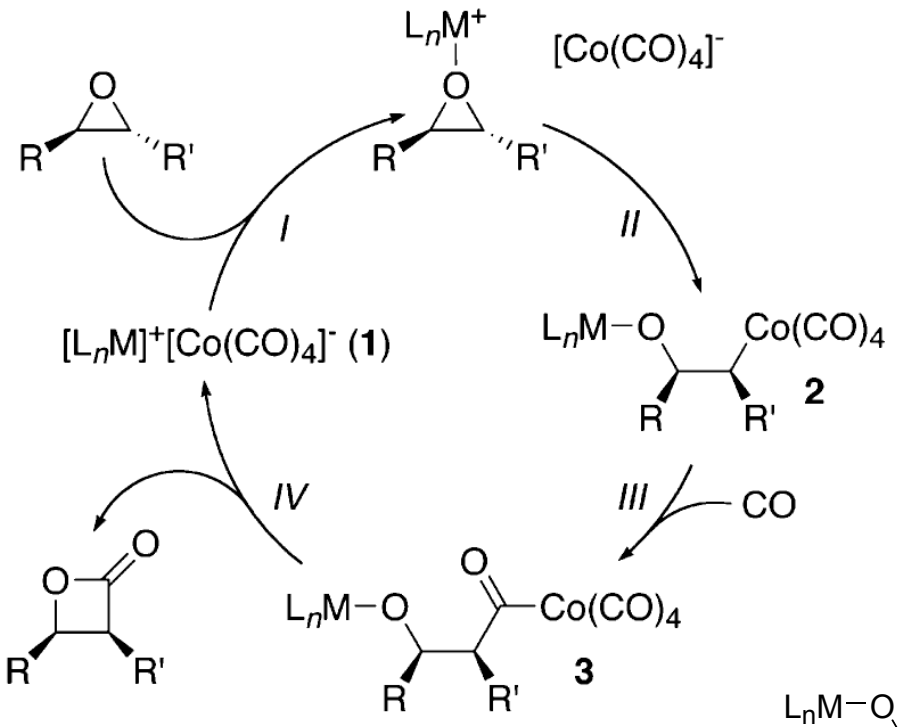
"… a well defined catalyst is a discrete metal complex or organic compound with either a known structure or exact molecular stoichiometry (or both) that, with minimal chemical or physical change, acts as the active catalytic species for a given transformation. Typically, such a metal complex features a permanent ligand set, and operates by a reproducible mechanism in which the active species is regenerated after each cycle."

Coates et. al., *J. Am. Chem. Soc.*, **2002**, *124*, 1174.

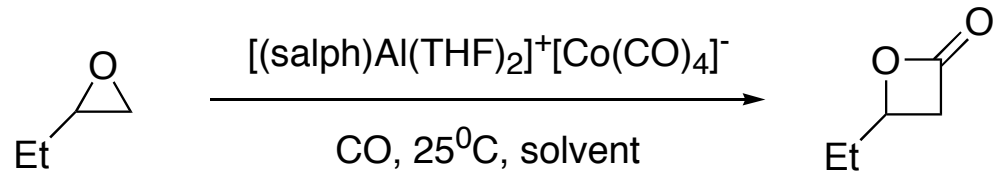
Coates et. al., *Chem. Comm.*, **2007**, 657.

Epoxide Carbonylation: Mechanism Overview

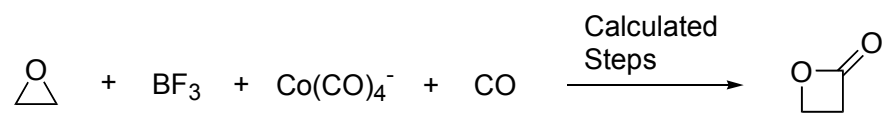
Overview:



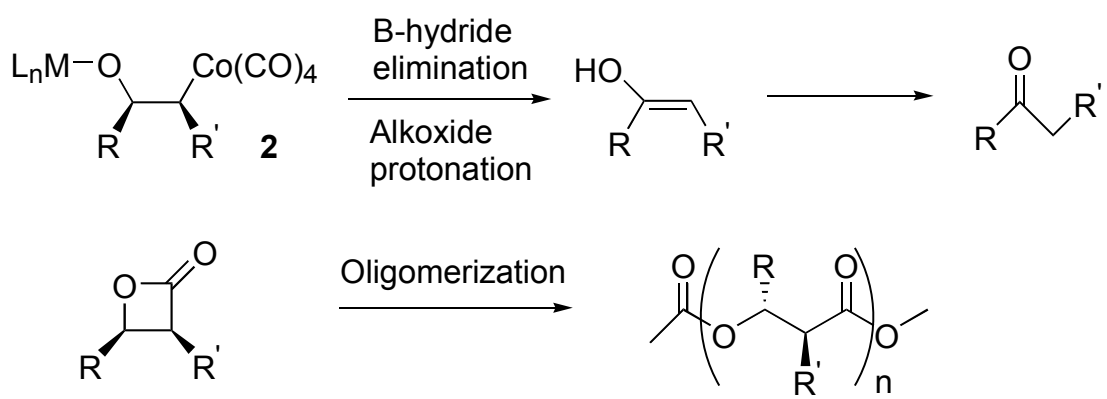
Coates: IR spectroscopy, Kinetics



Stirling, Molnar:
DFT and Metadynamics calculations

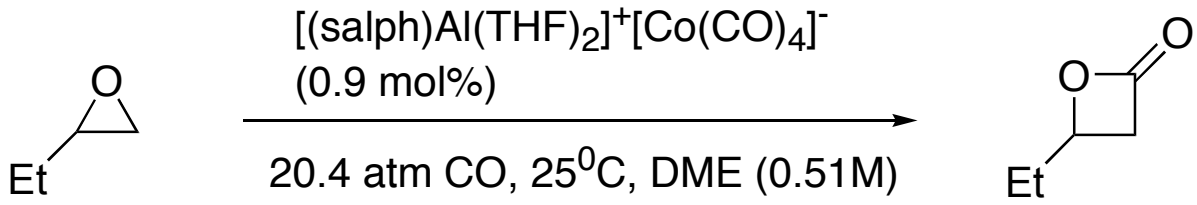


Important (Problematic) Side Reactions:

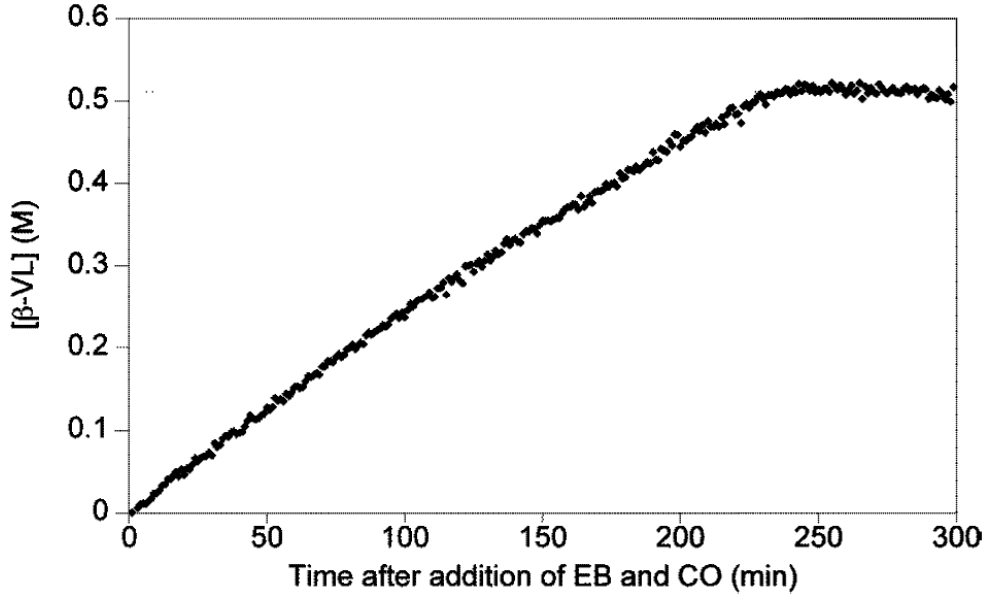


Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125. Molnar et. al., *Chem. Eur. J.*, **2003**, *9,* 1273.
Stirling et. al., *Organometallics*, **2005**, *24*, 2533.

Epoxide Carbonylation Mechanism: Kinetics



Monitored by IR
(lactone C=O stretch:
1827 cm^{-1})



Linear formation of lactone from 0 to 240 min (ca. 100% yield)

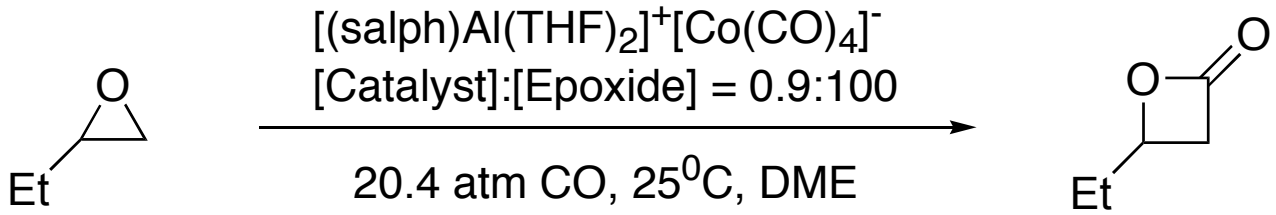
Separate experiment: 0.32M lactone present at beginning of reaction, no effect on rate or conversion.

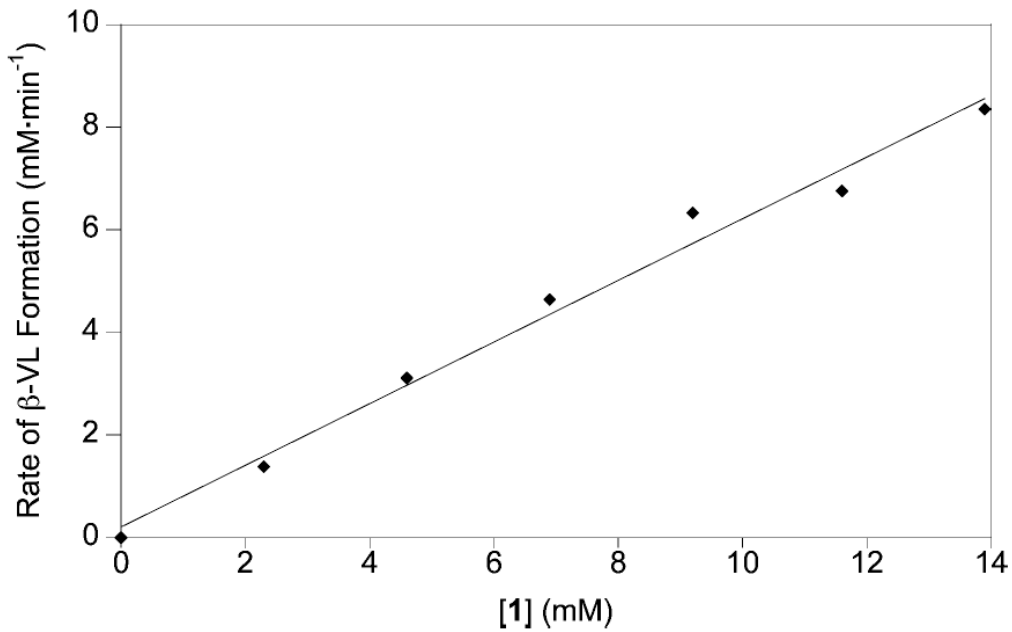
Zero-order in epoxide (and lactone produced).

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Epoxide Carbonylation Mechanism: Kinetics

Varied cat. Concentration, measured rate:





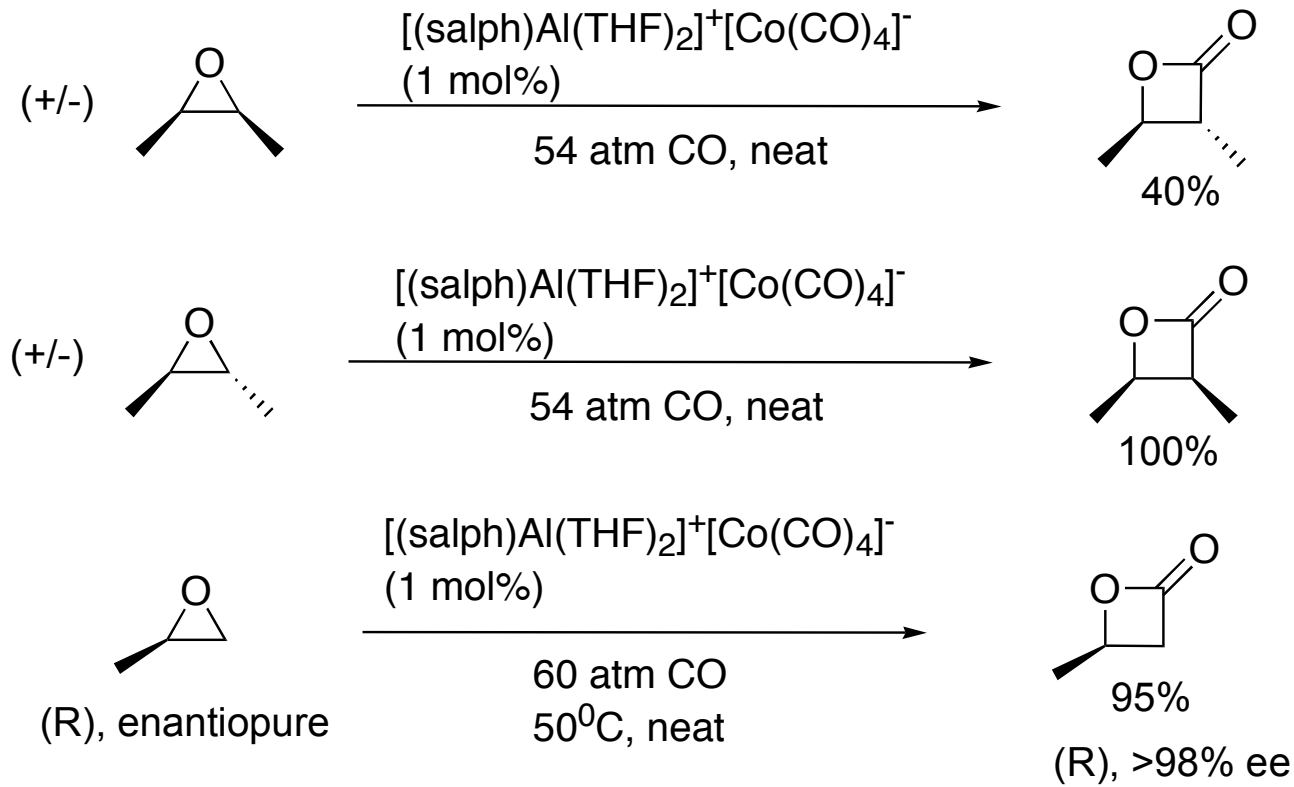
Also varied CO pressures between 15 and 71 atm, no effect on rate.

First order in catalyst, zeroth order in CO

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Epoxide Carbonylation Mechanism: Ring Opening

Previous experiments:



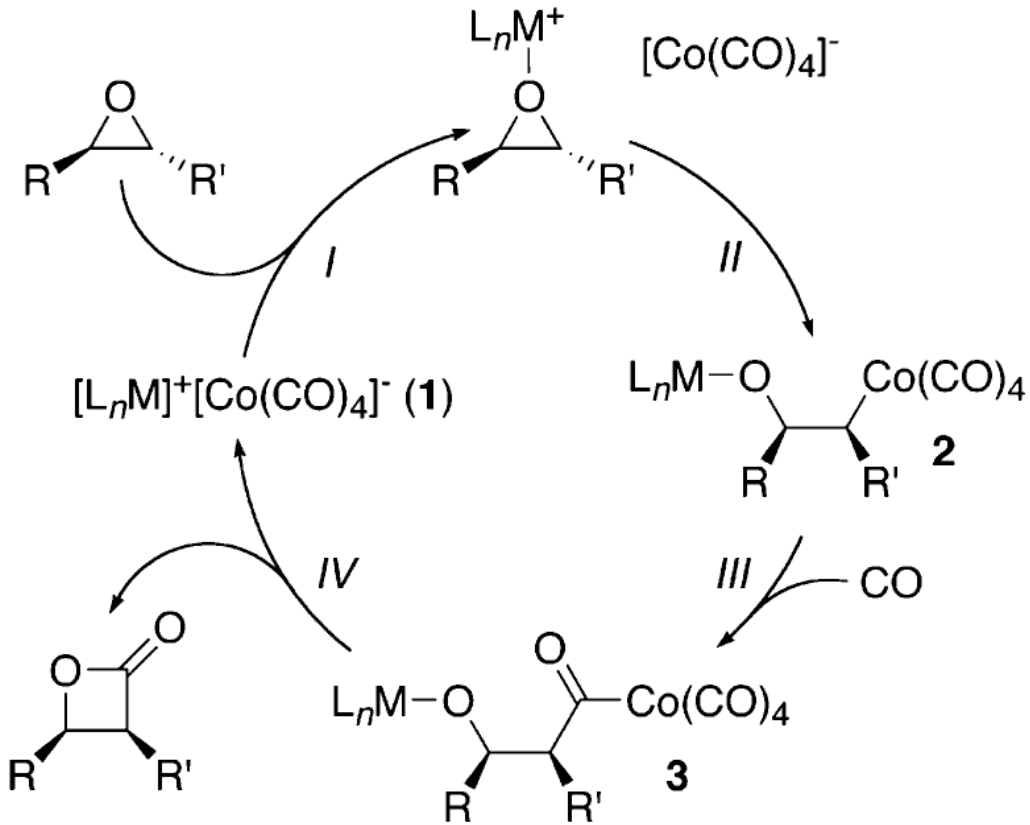
Conclusion: S_N2 attack of cobalt on epoxide

- Addition of excess $[(salph)Al(THF)_2]^+[BPh_4]^-$, or addition of excess $[PPh_4]^+[Co(CO)_4]^-$ has no effect on the reaction rate.
- $[Co(CO)_4]^-$ IR stretch disappears quickly and quantitatively at the beginning of reaction.
- ***Epoxide opening, which occurs in an S_N2 fashion, is not rate-limiting.***

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125. Coates et. al., *Angew. Chem. Int. Ed.*, **2002**, *41*, 2781.
Coates et. al., *Pure Appl. Chem.*, **2004**, *76*, 557.

Epoxide Carbonylation: Mechanism Review

Overview:



Summary so far:
$d[lactone]/dt = k[epox]^0 P_{CO}^0 [cat]^1$

Epoxide opening not rate limiting

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Epoxide Carbonylation Mechanism: Catalyst Resting State

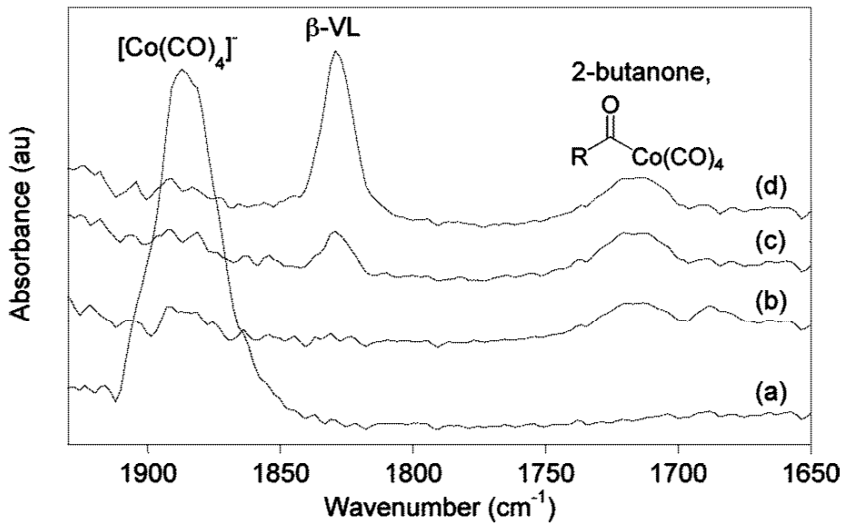
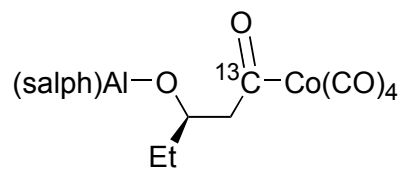


Figure 3. IR spectra of (a) catalyst **1** in 1,2-dimethoxyethane solution, (b) immediately following addition of 1,2-epoxybutane and CO ($t = 0$ min), (c) $t = 1$ min, and (d) $t = 5$ min.

Use of ^{13}CO demonstrated intermediacy of Co-acyl intermediate: ketone $^{12}C{=}O$ stretch overlaps with putative Co-acyl $^{12}C{=}O$ stretch (1715 cm^{-1}). However,

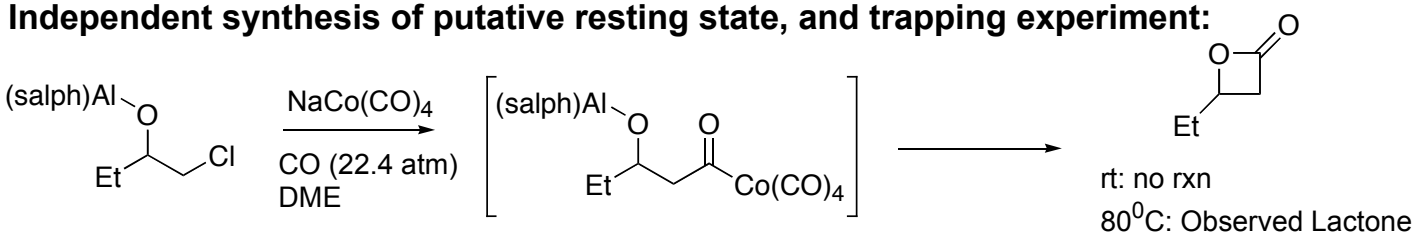


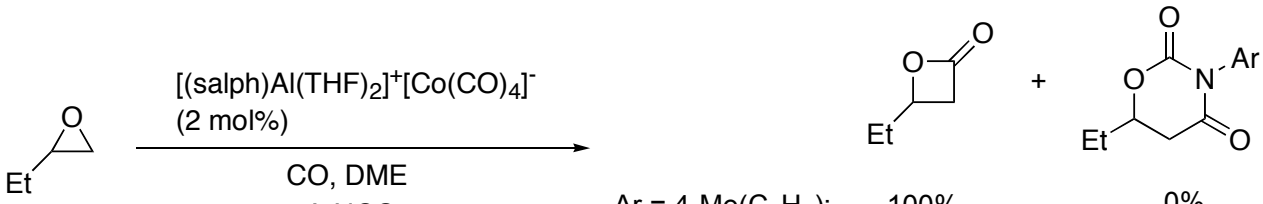
Calc. $^{13}C{=}O$ stretch: 1677 cm^{-1}

New Peak Observed when reaction conducted under $^{13}C{=}O$ atm: 1677 cm^{-1}; 1715 cm^{-1} (ketone $^{12}C{=}O$) also observed

Co-acyl is likely the catalyst resting state.

Independent synthesis of putative resting state, and trapping experiment:





Ar = 4-Me(C_6H_5):	100%	0%
Ar = 4-F(C_6H_5):	93%	7%

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Full paper on oxazoline synthesis from epoxides: Coates et. al., *J. Am. Chem. Soc.*, **2007**, *129*, 8156.

Epoxide Carbonylation Mechanism: Solvent Effects

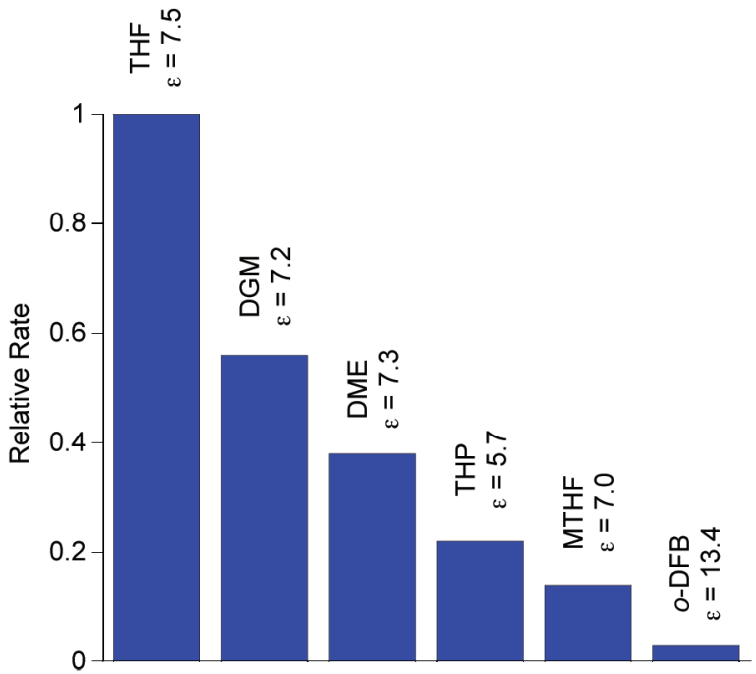


Figure 4. Comparison of the rate of carbonylation of 1,2-epoxybutane (EB) by catalyst **1** in various solvents. ϵ = dielectric constant.[76] [**1**] = 11.6 ± 0.1 mM, $[EB]_0$ = 1.25 ± 0.01 M, P_{CO} = 300 ± 10 psi, T = 25.0 ± 0.5 °C. THF = tetrahydrofuran, DGM = diglyme, DME = 1,2-dimethoxyethane, THP = tetrahydropyran, MTHF = 2-methyltetrahydrofuran, *o*-DFB = 1,2-difluorobenzene.

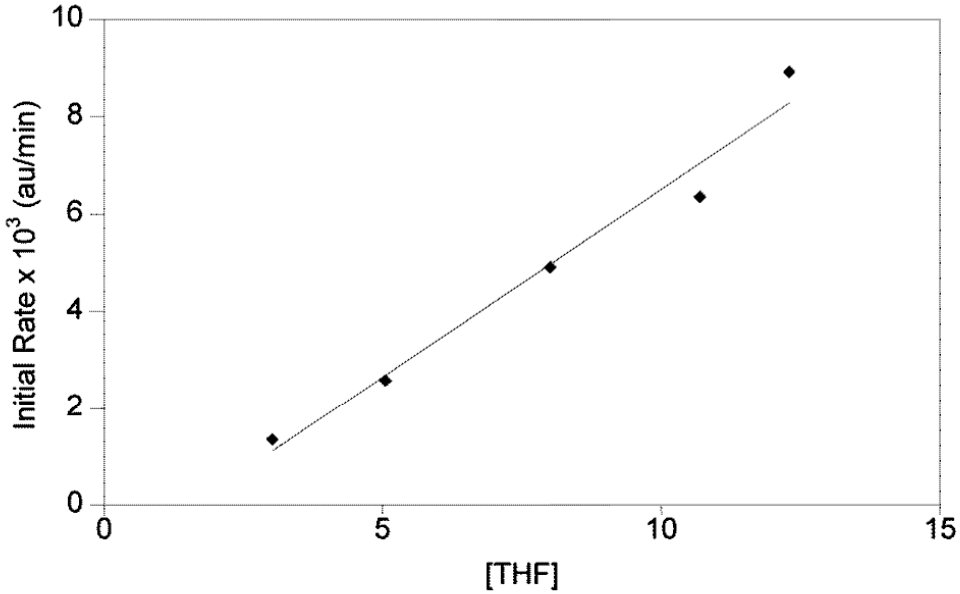


Figure 5. Effect of tetrahydrofuran (THF) concentration on the rate of carbonylation of 1,2-epoxybutane (EB) to β-valerolactone, in mixtures of THF/2,5-dimethylTHF. Reaction was monitored by in situ IR spectroscopy, and initial rates taken for 5 to 15% conversion. [**1**] = 11.5 ± 0.1 mM, [EB] = 1.27 ± 0.01 M, P_{CO} = 300 ± 10 psi, T = 25.0 ± 0.5 °C.

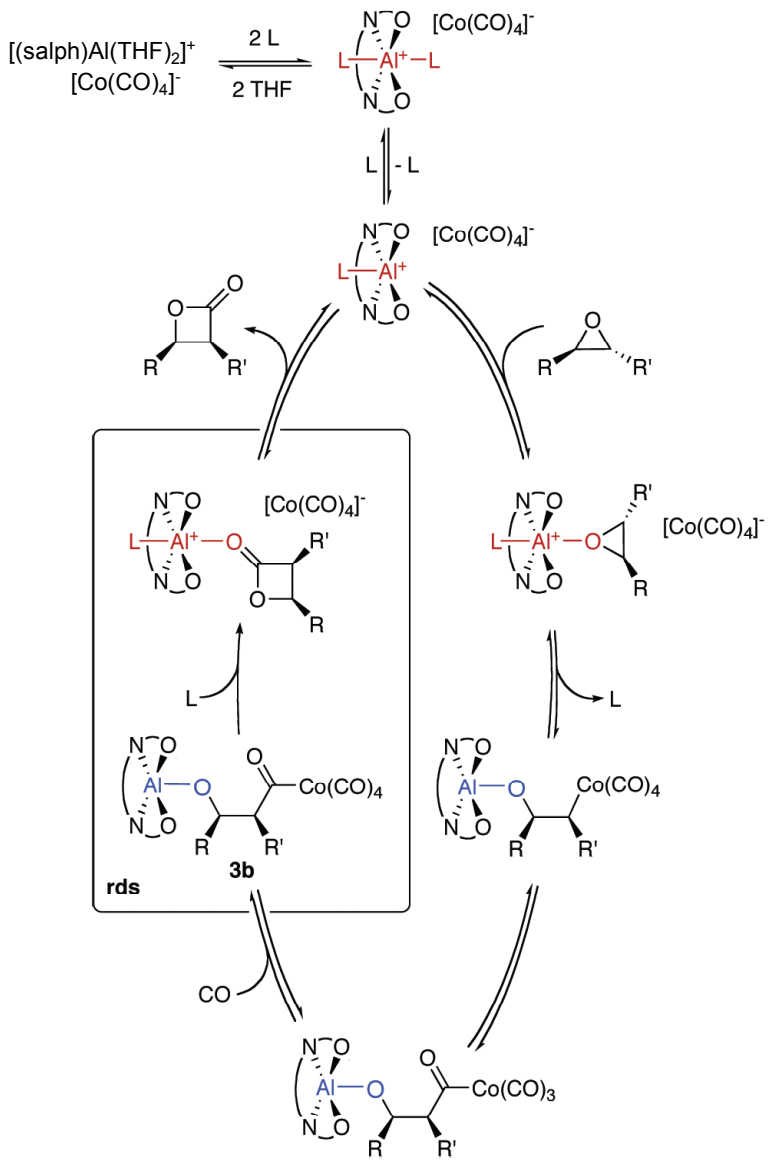
- Reaction is zero-order in epoxide in above solvents.
- Reaction in acetonitrile is slow and first order in epoxide;
- Reaction in neat epoxide is first order in epoxide.

First order in THF.
Reaction in DME / 2,5-dimethylTHF is slower than in DME.

Conclusion: rate-limiting ring-closure is assisted by Lewis base stabilization of Al^+ cation thus generated.

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Epoxide Carbonylation: Mechanism Summary



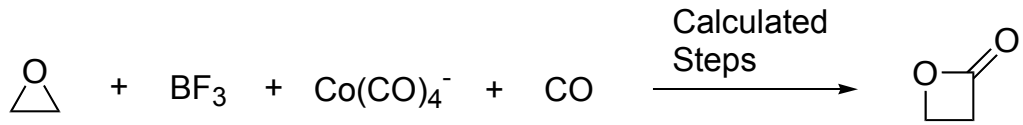
$$d[\text{lactone}]/dt = k[\text{epox}]^0 P_{CO}{}^0 [\text{cat}]^1 [\text{solvent}]^1$$

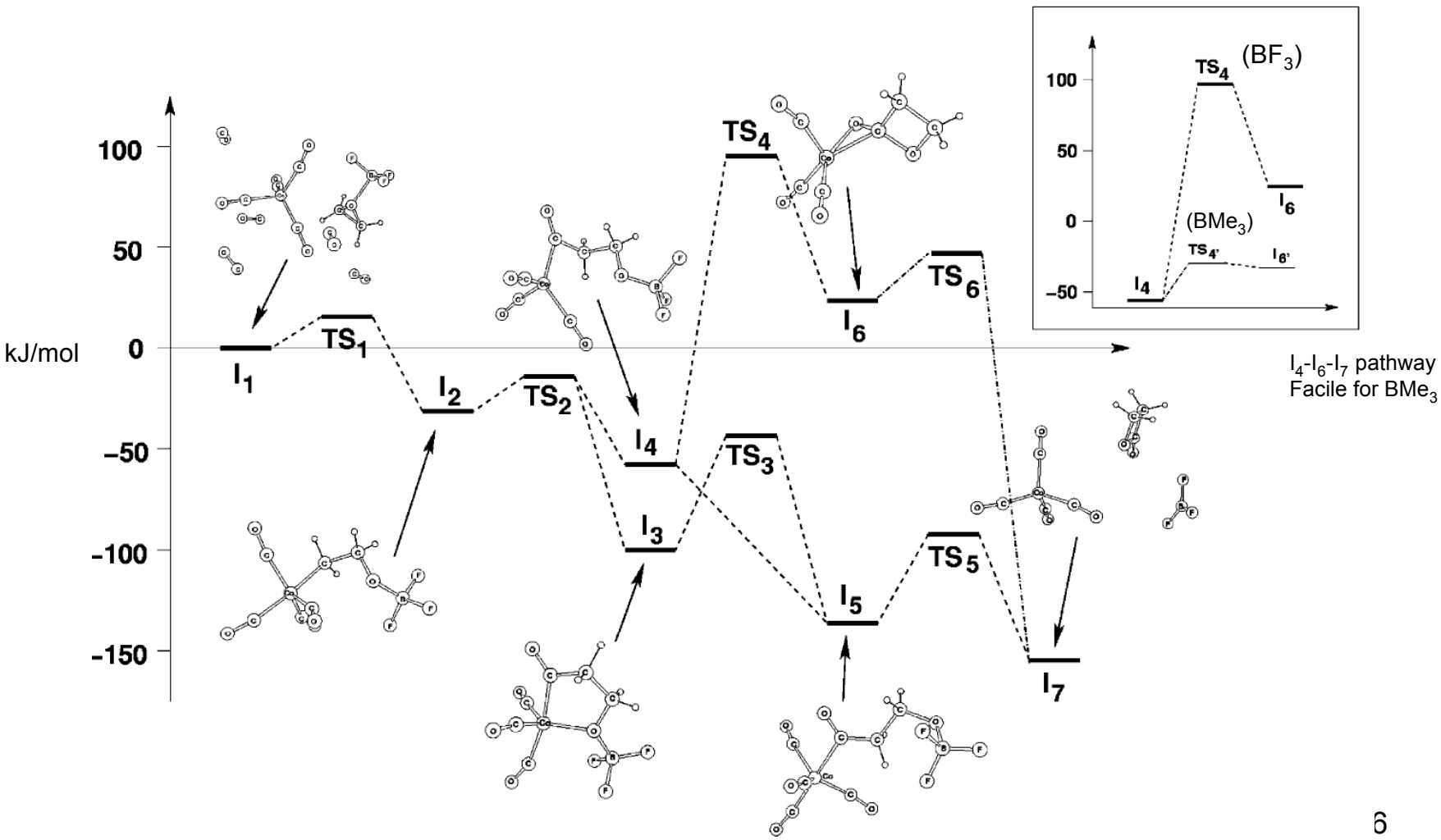
(in moderately Lewis basic solvents)

Coates et. al., *J. Am. Chem. Soc.*, **2006**, *128*, 10125.

Epoxide Carbonylation: Calculations

Theoretical reaction pathways, elucidated by the metadynamics approach

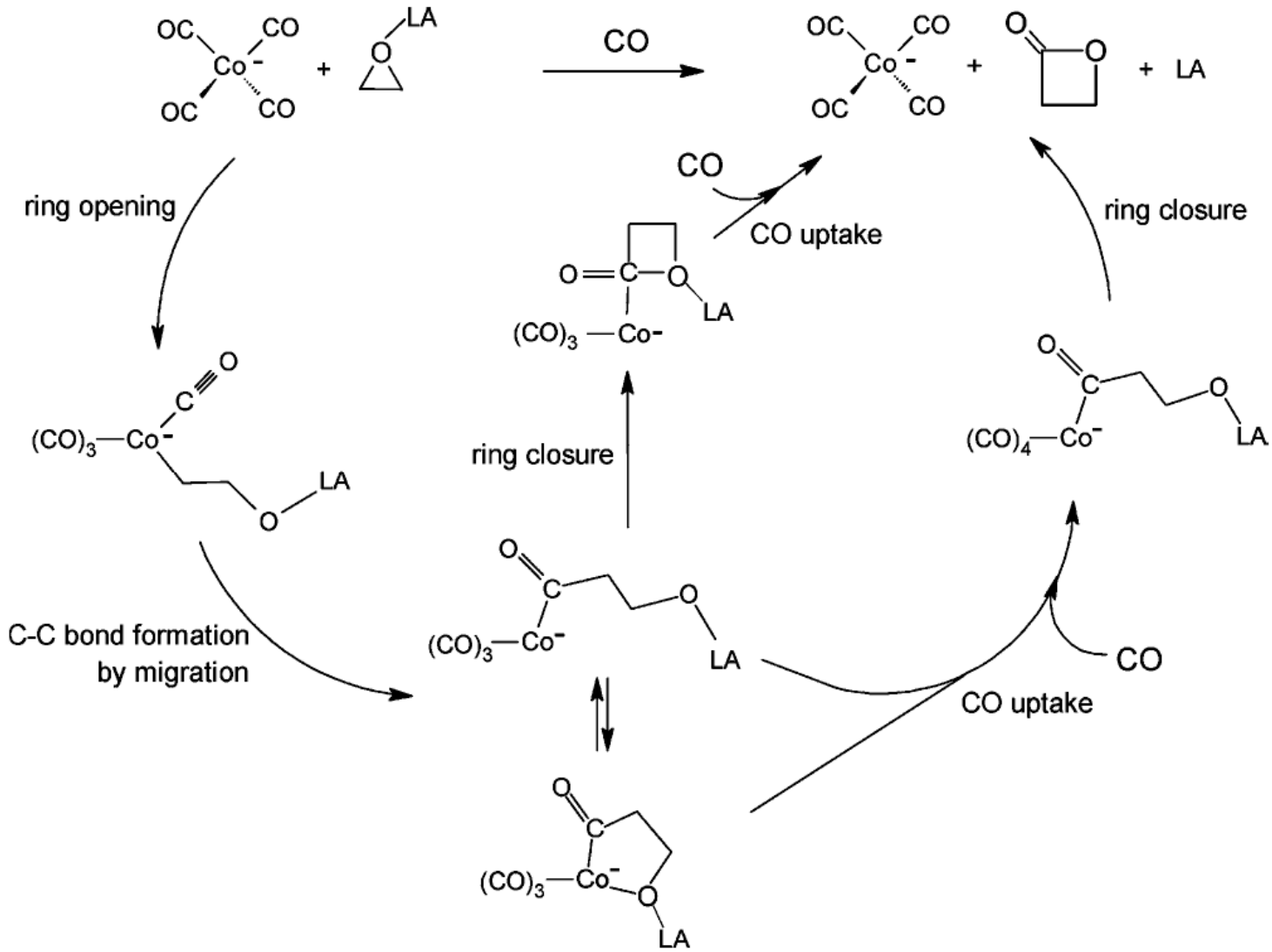




Stirling et. al., *Organometallics*, **2005**, *24,* 2533.

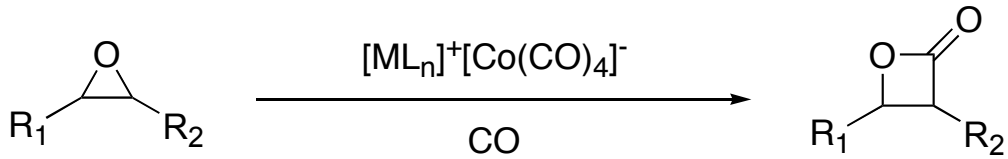
Epoxide Carbonylation: Calculations

Calculations support this amended mechanism:



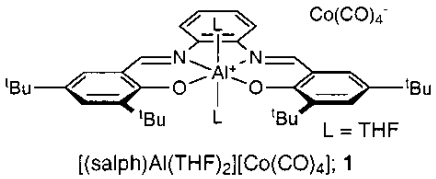
Stirling et. al., *Organometallics*, **2005**, *24,* 2533.

Evolution of Epoxide Carbonylation with Coates's Catalysts



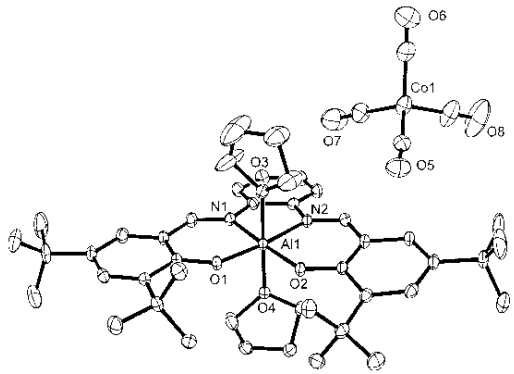
In all cases, the conditions given are typical. For most substrates under given conditions, yields > 90%

2002:



[(salph)Al(THF)$_2$][Co(CO)$_4$]; **1**

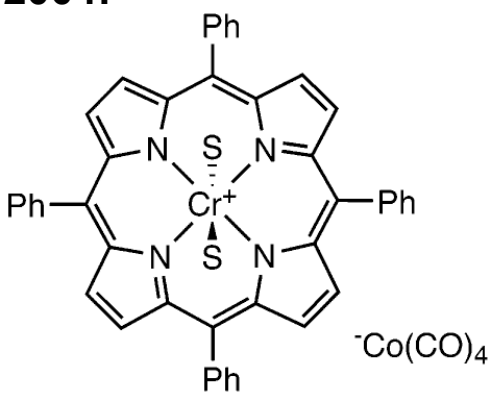
Also [Cp$_2$Ti(THF)$_2$][Co(CO)$_4$]



(salph)Al$^+$ cat: 60 atm CO, 1 mol% cat, 50^{0}C, 1-3h
4 examples, R_2=H; R_1=Me, Et, CH_2Cl, gem-Me_2

Cp_2Ti^+ cat: 61 atm CO, 5 mol% cat, 60^{0}C, 3-5h
Now R_1=homoallyl, cis/trans 2,3-epoxybutane possible

2004:



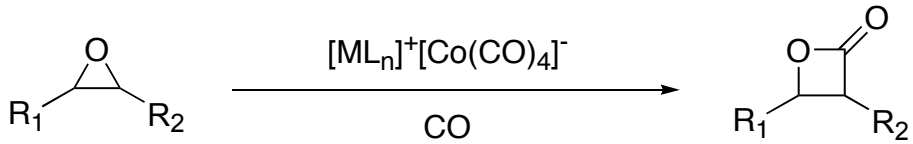
[(TPP)Cr(THF)$_2$][Co(CO)$_4$]
(No X-ray)

61 atm CO, **<1 mol% cat**, 60^{0}C, 6h
Now R_1=longer alkyl, CH_2OR, CH_2OTBS, tBu, 8,10-rings (fused) possible

G. W. Coates

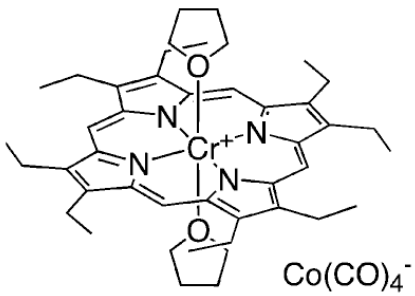
Coates et. al., *J. Am. Chem. Soc.*, **2002**, *128*, 10125.
Coates et. al., *Angew. Chem. Int. Ed.*, **2002**, *41*, 2781.
Coates et. al., *Org. Lett.*, **2004**, *6*, 373.

Evolution of Epoxide Carbonylation with Coates's Catalysts

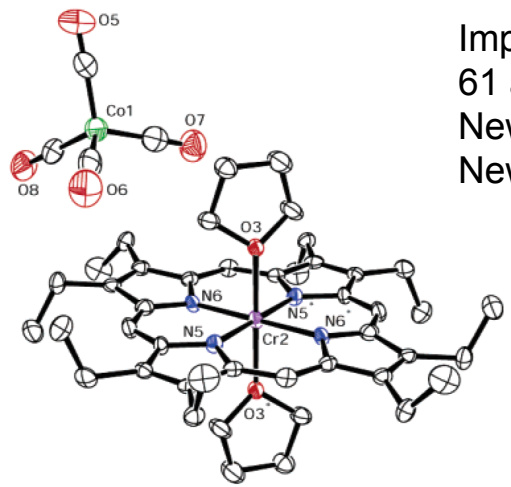


In all cases, the conditions given are typical. For most substrates under given conditions, yields > 90%

2005:

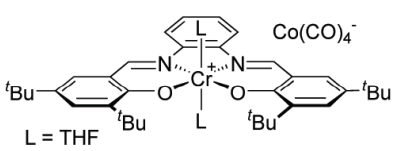


[(OEP)Cr(THF)$_2$][Co(CO)$_4$]

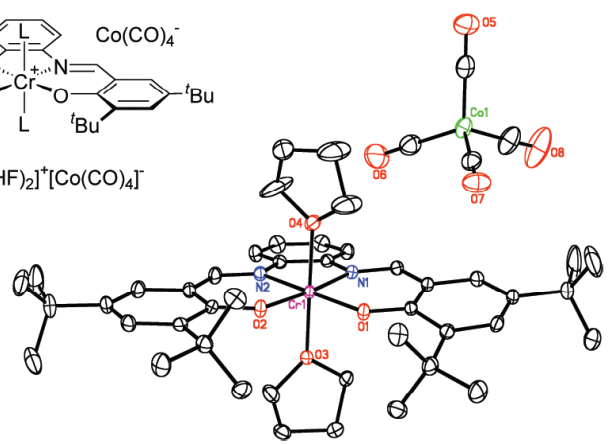


Improved rates (**<0.1 mol% cat**) for previous substrates
61 atm CO, 60^{0}C, 6h
New substrates: R_1= CH_2OCOR, distant amides
New route to five-membered lactones

2006:



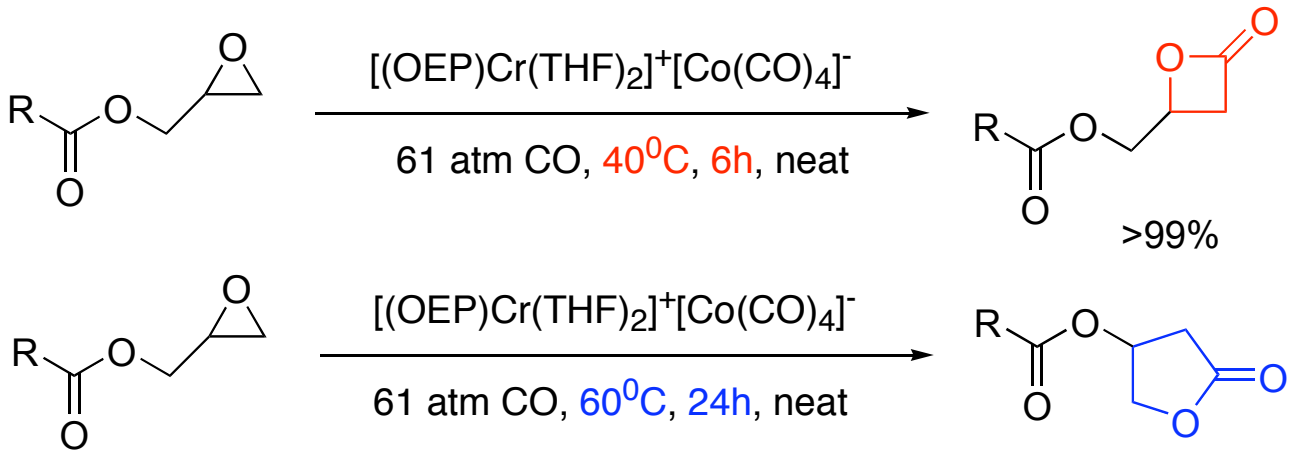
[(salph)Cr(THF)$_2$]$^+$[Co(CO)$_4$]$^-$



6.8 atm CO, 22^{0}C, 1-3h, 1 mol% cat
OR **1 atm CO**, 22^{0}C, 6h, 2 mol% cat
Versatile substrate scope (most previous examples)

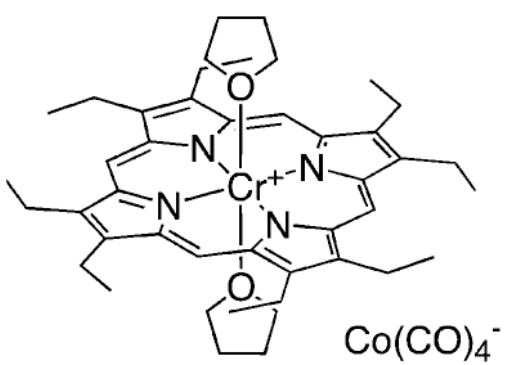
Coates et. al., *J. Am. Chem. Soc.*, **2005**, *127*, 11426.
Coates et. al., *Org. Lett.*, **2006**, *8*, 3709.

γ-Lactone Synthesis

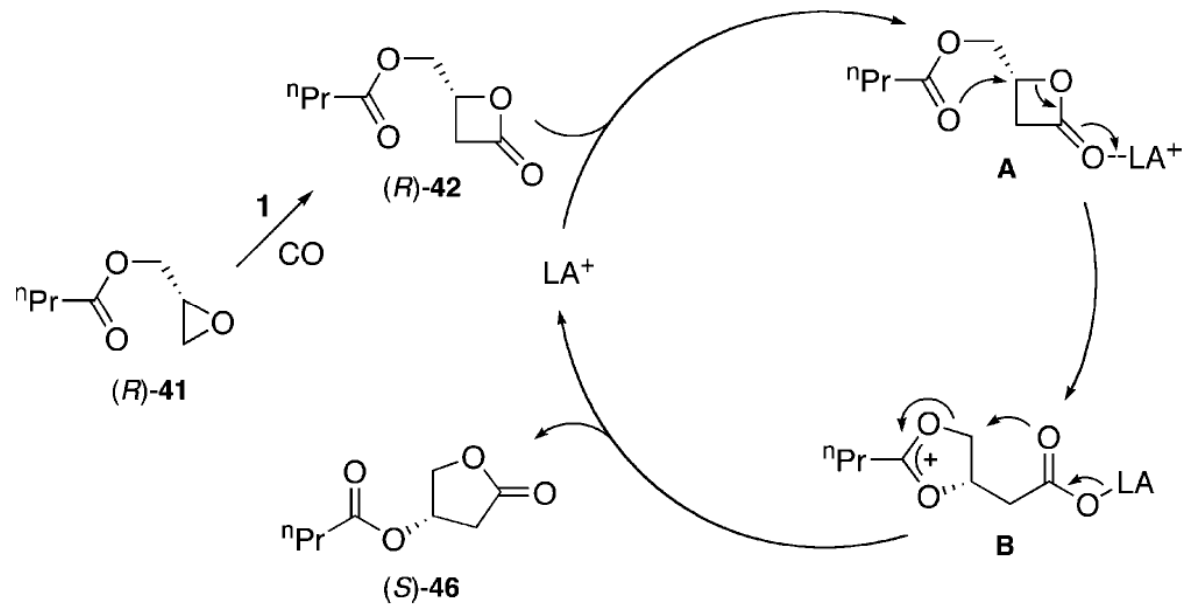


R = alkyl, Ph

Proposed Mechanism:

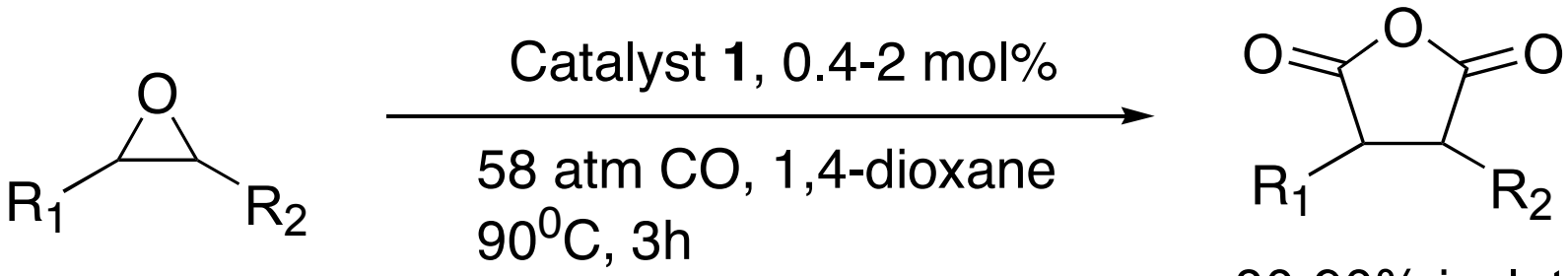


[(OEP)Cr(THF)2][Co(CO)4]



Coates et. al., *J. Am. Chem. Soc.*, **2005**, *127*, 11426.

Double (Tandem) Epoxide Carbonylation

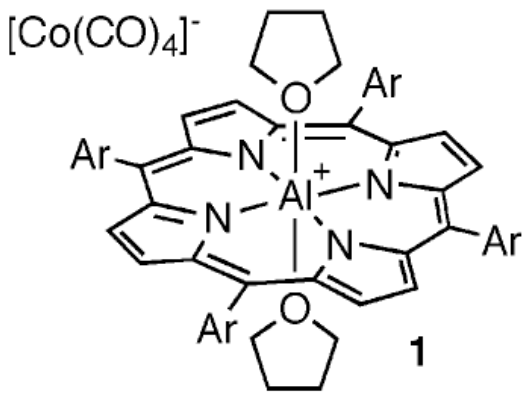


80-90% isolated

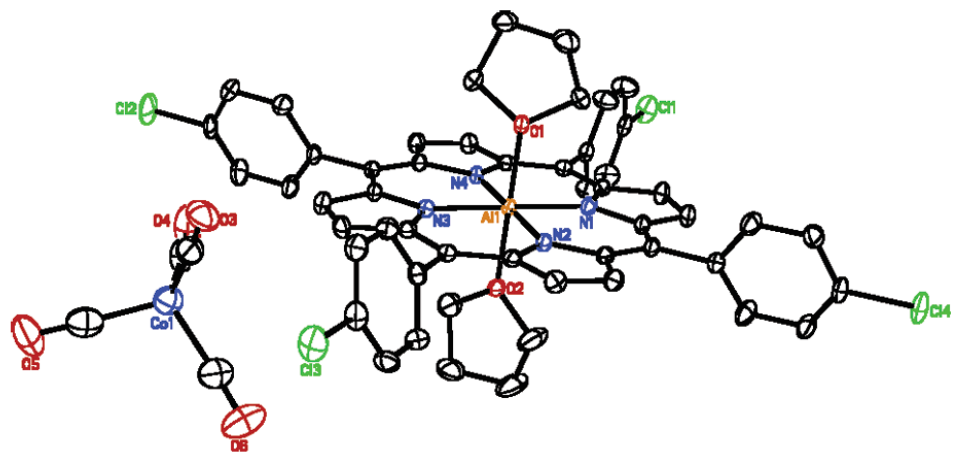
Good scope:
Monosubstituted: alkyl, Bn, Ph, CH_2OR, distant olefins, amide, ester, nitrile, alcohol

Disubstituted: 2,3-alkyl;
trans epoxide = trans anhydride
Cis epoxide = cis anhydride
Configuration of epoxide centers preserved

New Catalyst:

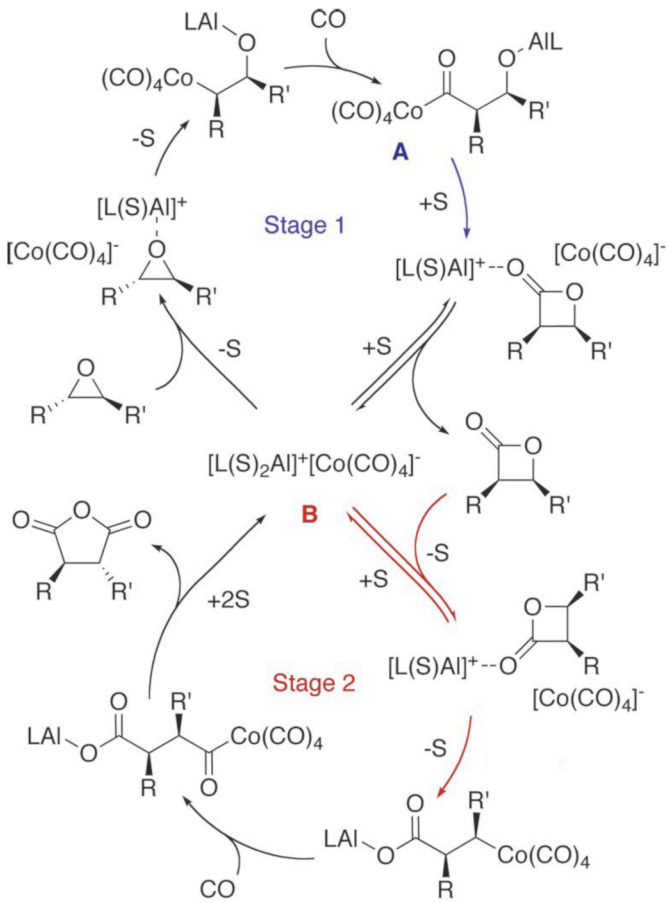


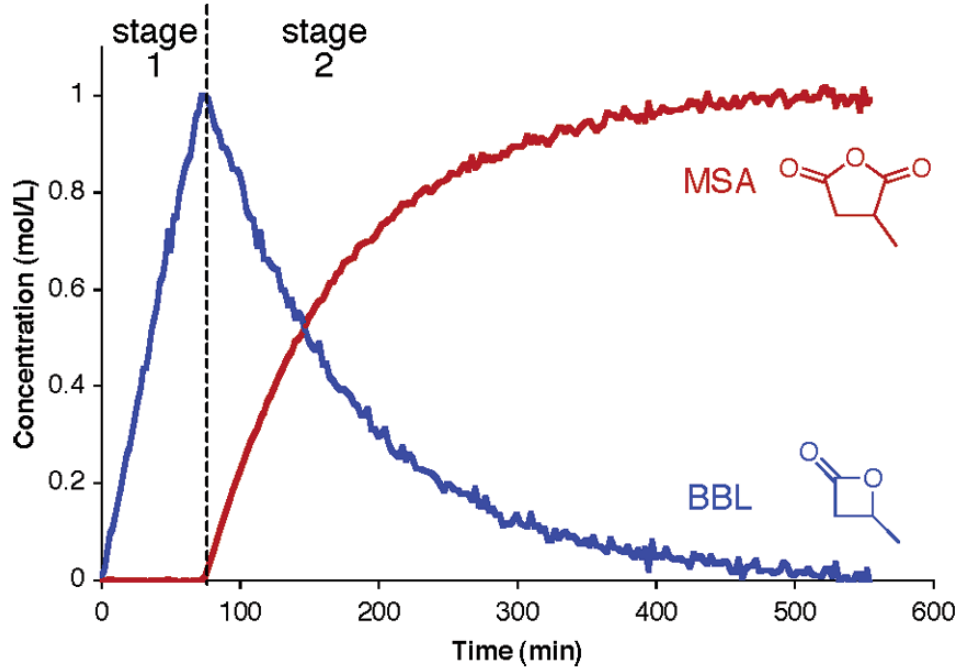
Ar = 4-Cl phenyl



Coates et. al., *J. Am. Chem. Soc.*, **2007**, *129*, 4948.

Double (Tandem) Epoxide Carbonylation Mechanism: Overview





Although carbonylation of epoxide and lactone likely follow similar pathways, there are striking differences in reaction kinetics

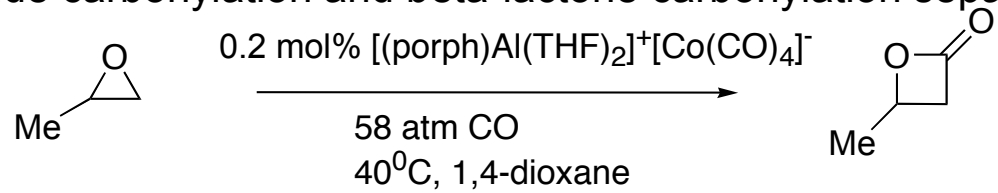
Group Question: Explain the origin of the two stage phenomenon.

Coates et. al., *J. Am. Chem. Soc.*, **2007**, *129*, 4948.

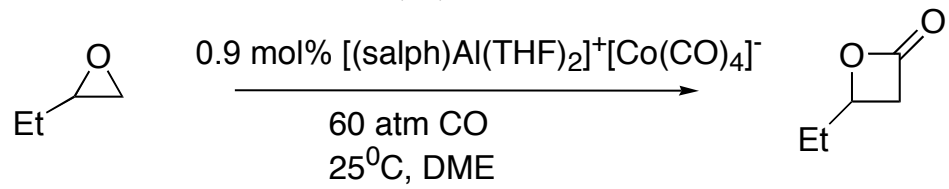
Double (Tandem) Epoxide Carbonylation Mechanism: Summary

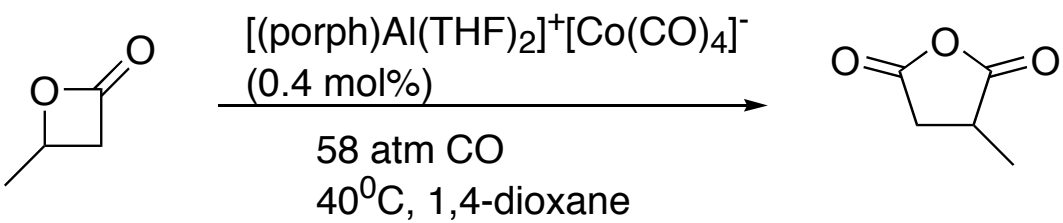
Coates studies the mechanisms of epoxide carbonylation and beta-lactone carbonylation separately.

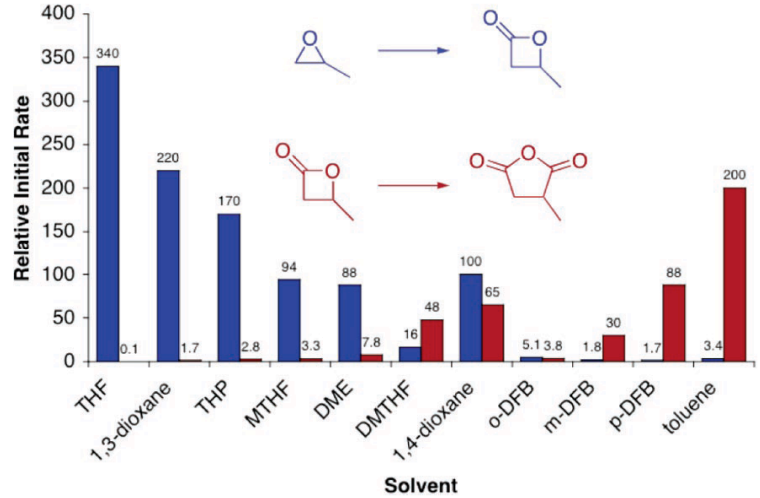
Kinetic orders, solvent effects, etc. identical for this carbonylation:



As were reported previously for slightly different substrate, catalyst, solvent:





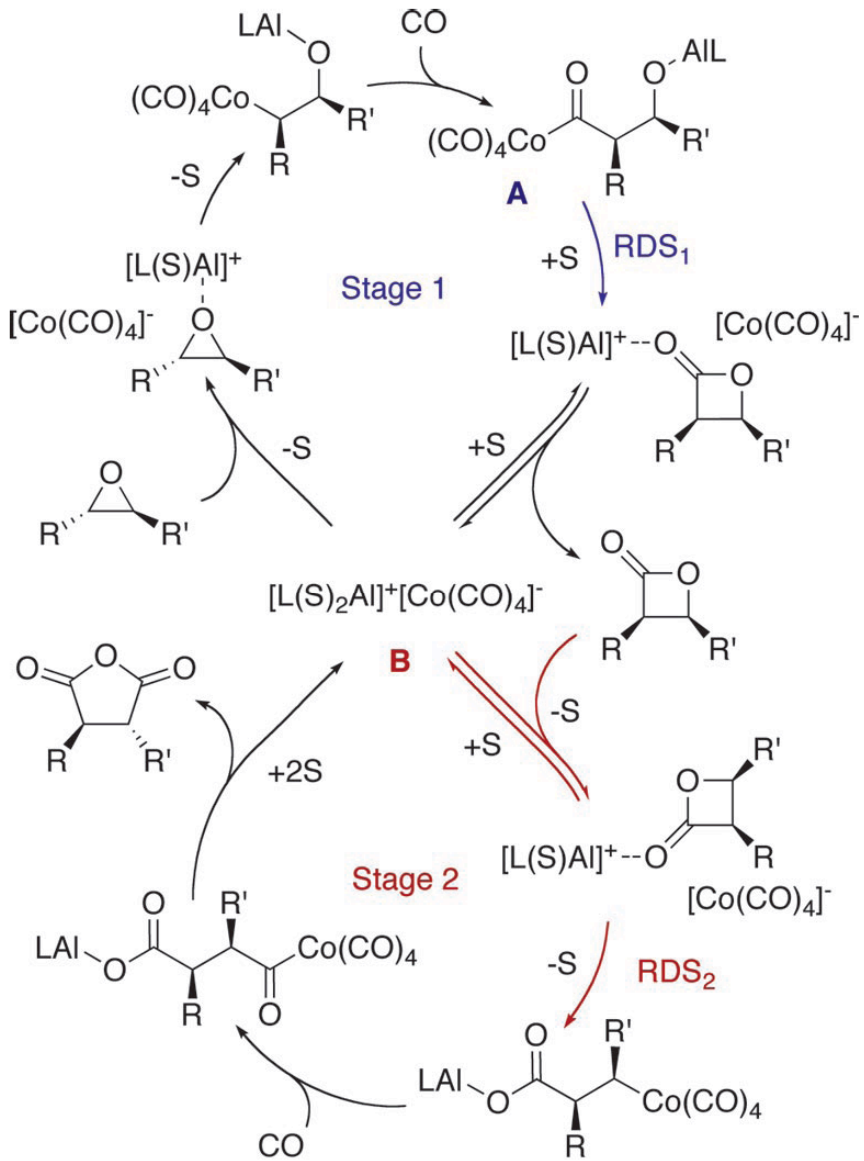


Kinetics profile very different:

- **First order in lactone,**
- **Inverse first order in THF (solvent = 2,5-dimethylTHF)**
- First order in catalyst, zeroth order in CO
- Independently varied $[(porph)Al(THF)_2]^+$ and $[Co(CO)_4]^-$ concentrations. No effect.
- **Increasing substitution at beta-position decreased rate.**
- **Careful balance of solvent polarity and Lewis basicity required for good rates**

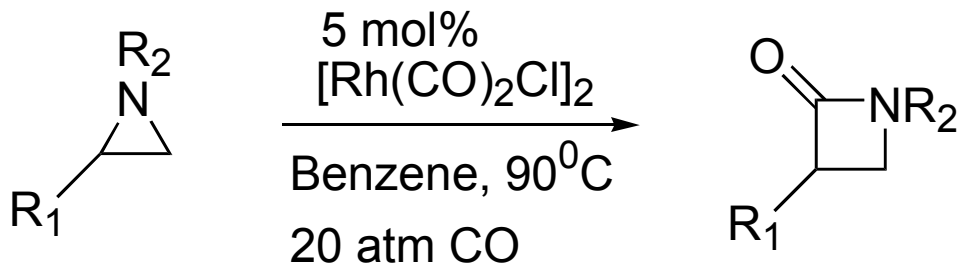
Coates et. al., *J. Am. Chem. Soc.*, **2007**, *129*, 4948.

Double (Tandem) Epoxide Carbonylation Mechanism: Conclusion



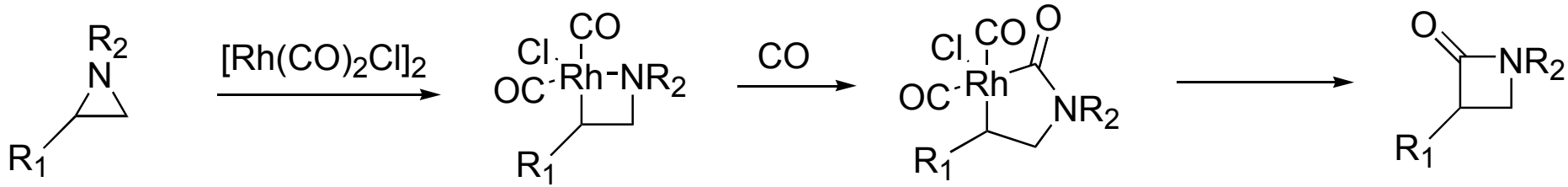
Coates et. al., *J. Am. Chem. Soc.*, **2007**, *129*, 4948.

Rh-Cat. Aziridine Carbonylative Ring Expansion

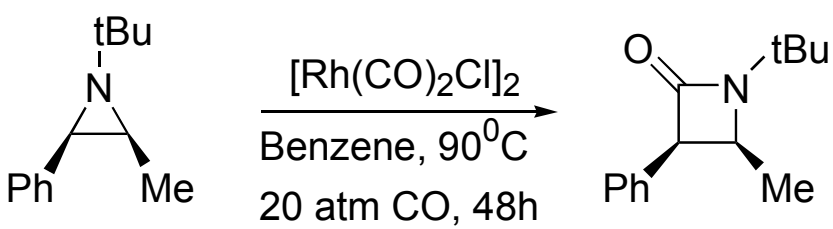


R_1= Aryl, R_2 = tBu, adamantyl

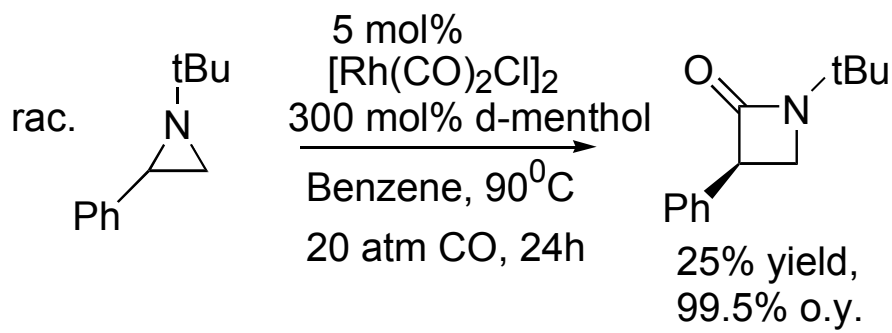
Mechanistic Proposal:



Retentive:



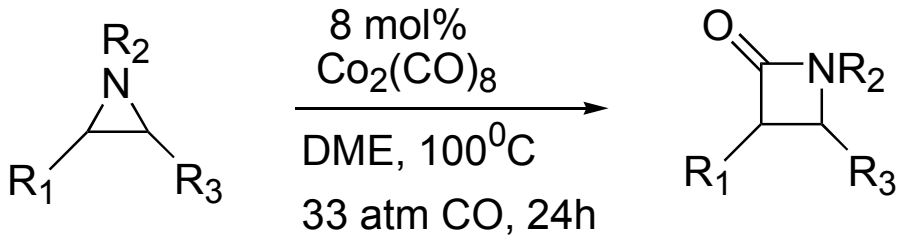
Kinetic Resolution:



Alper et. al., *J. Am. Chem. Soc.*, **1983**, *105*, 6737.
Alper et. al., *J. Am. Chem. Soc.*, **1989**, *111*, 931.

Co-Cat. Aziridine Carbonylative Ring Expansion

Alper, 1996:



R_2=$PhCH_2CH_2$, p-MeOPh, iPr, tBu

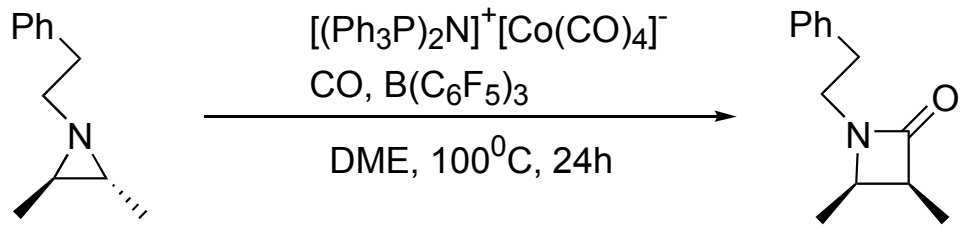
Carbonylation at less substituted position (R_1=H, R_3=alkyl) except when R_3=Ph

Proposed mechanism is analogous to epoxides. Inversion of stereochemistry observed.

Alper, 1999; Prati, 2001:

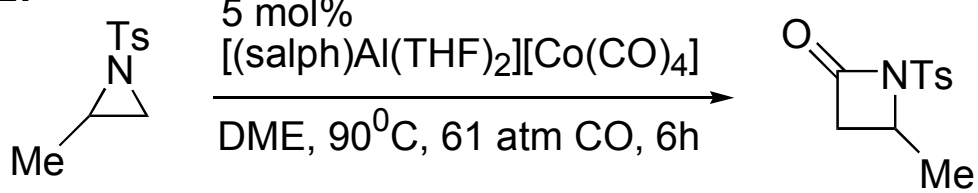
Under the above Co-catalyzed conditions of Alper, extended scope to R_1 = Ph
R_3 = CH_2OAc, CH_2OTBS, CH_2OH, CH_2NH_2, R_2 = Bn

Alper, 2001:



81%

Coates, 2002:



99%

Alper et. al., *J. Am. Chem. Soc.*, **1996**, *118*, 111.; Prati et. al., *Tetrahedron,* **2001**, *57*, 1801.
Alper et. al., *J. Org. Chem.*, **1999**, *64*, 518.; Alper et. al., *J. Org. Chem.*, **2001**, *66*, 5424.
Coates et. al., *Angew. Chem. Int. Ed.*, **2002**, *41*, 2781.

Conclusions

- Epoxide carbonylative ring expansion is advancing steadily (catalysts, reactions, mechanistic understanding)
- Aziridine carbonylative ring expansion is lagging
- Kinetic resolution methods very undeveloped