The Tishchenko Reaction: Recent Advances, Modifications and Applications

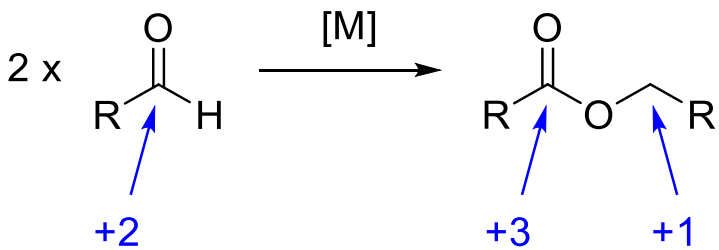
Kevin A. Robb

S.E.Denmark Group Meeting

Tues. 11/29/2016

Tishchenko Reaction

- Described by Russian chemist V. E. Tishchenko in 1906 in a series of four publications
- Dimerization of aldehydes to form esters in the presence of metal alkoxides
  - Disproportionation reaction
  - One aldehyde moiety is oxidized, the other is reduced
  - [M] = $Al(OR)_3$ (most common), NaOR, LiOR, $Mg(OR)_2$, others



- Reactivity first observed by Claisen in 1887 (Na alkoxides)

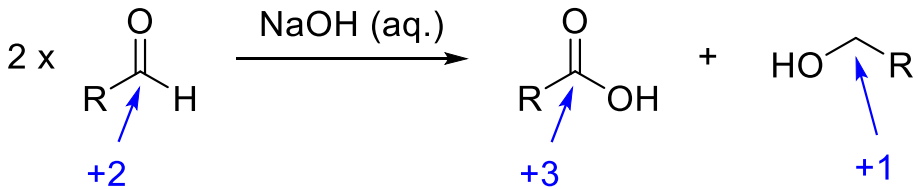
ru.wikipedia.org

Kataja, A. O. and Koskinen, A. M. P. "The Tishchenko Reaction" in *Organic Reactions*, **2015**, 86(2), 107-409

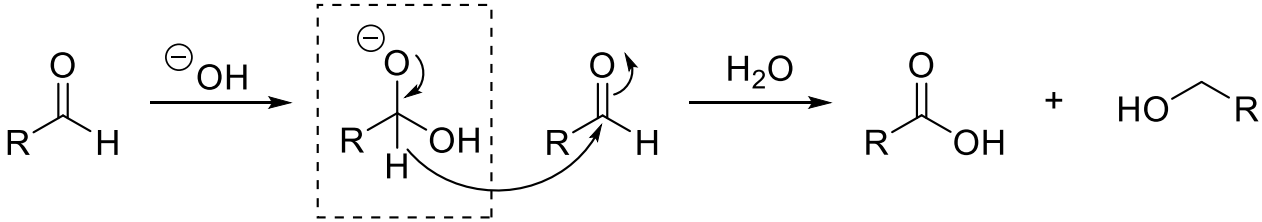
Tishchenko, V. E. *J. Russ. Phys. Chem. Soc*. **1906**, 38, 355
Tishchenko, V. E. *J. Russ. Phys. Chem. Soc*. **1906**, 38, 482
Tishchenko, V. E. *Chem. Zentralbl*. **1906**, 77, 1309
Tishchenko, V. E. *Chem. Zentralbl*. **1906**, 77, 1552

Aside: Cannizzaro Reaction

- Reaction of aldehydes to form corresponding alcohol and carboxylic acid (1853)
- Carried out in presence of aqueous base



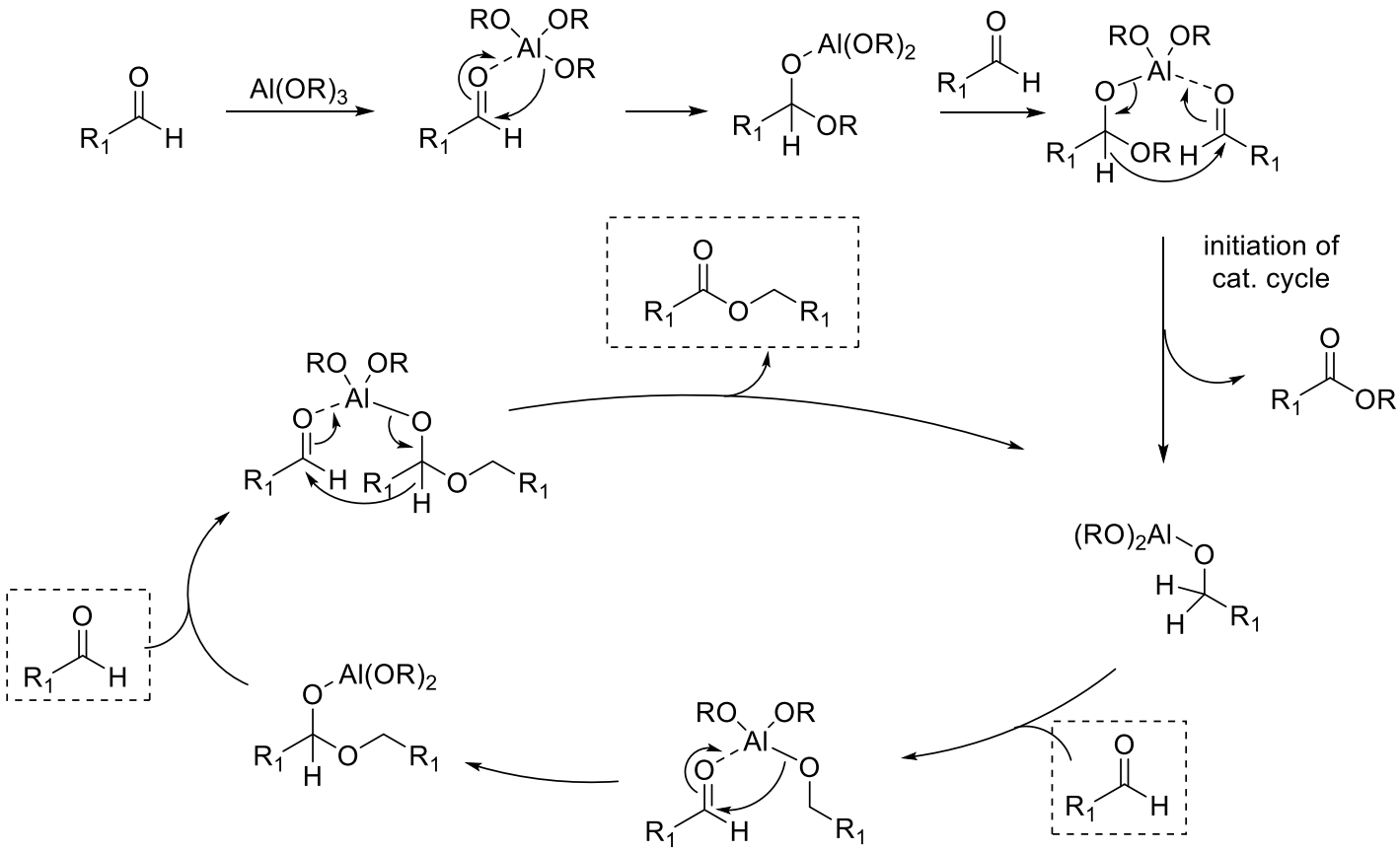
- Key mechanistic step is the transfer of hydride from a hemiacetal intermediate



Kürti, L. and Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, **2005**

Tishchenko Reaction Mechanism

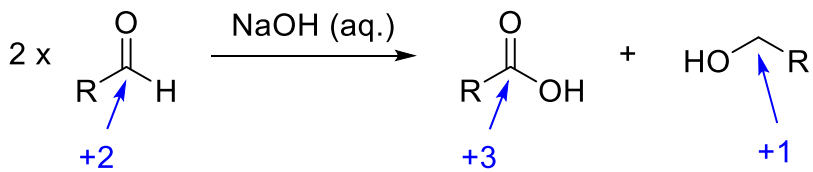
- Accepted mechanism:



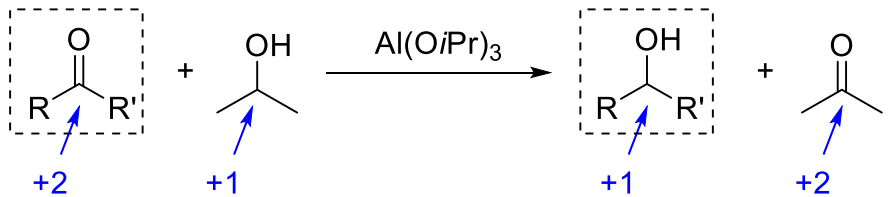
Kataja, A. O. and Koskinen, A. M. P. “The Tishchenko Reaction” in *Organic Reactions*, **2015**, 86(2), 107-409

Related Reactions

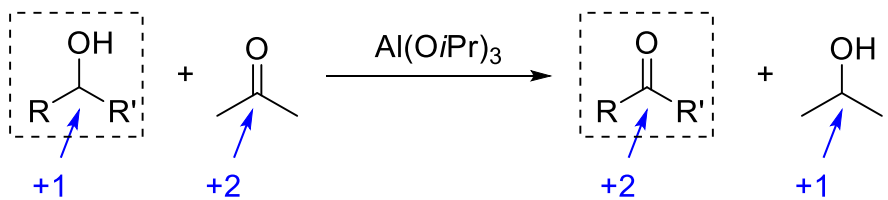
- Cannizzaro Reaction (1853)



- Meerwein-Ponndorf-Verley (MPV) Reduction (1925)



- Opperhauer Oxidation (1937)

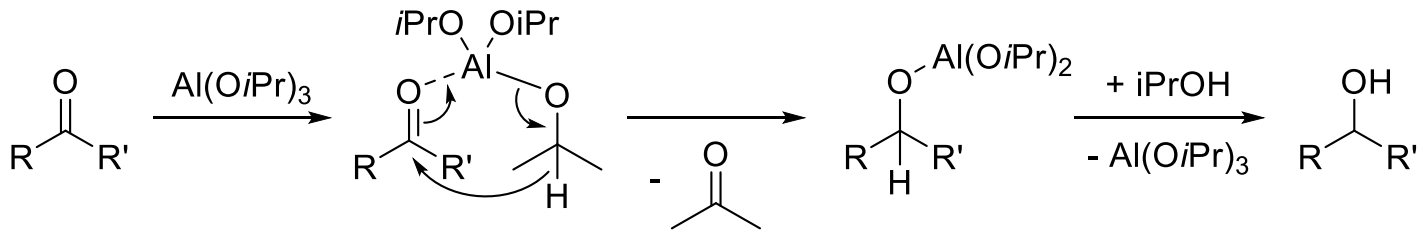


Kataja, A. O. and Koskinen, A. M. P. “The Tishchenko Reaction” in *Organic Reactions*, **2015**, 86(2), 107-409

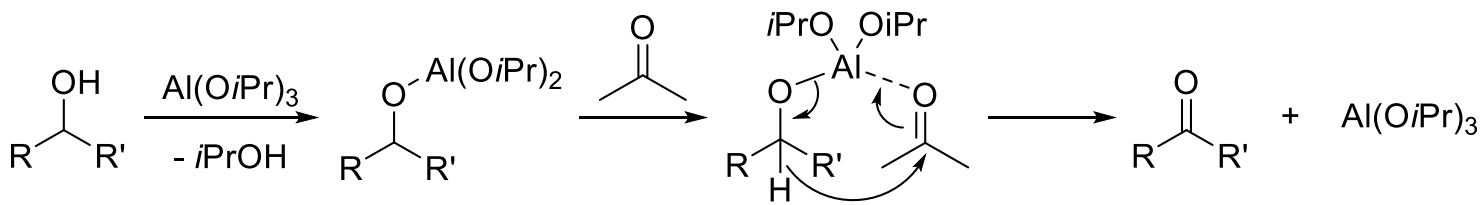
MPV Reduction/Oppenhauer Oxidation

- These reactions involve a 1,5-hydride transfer aided by an aluminum alkoxide catalyst

- Meerwien-Ponndorf-Verley Reduction:
  - isopropanol used as stoichiometric oxidant



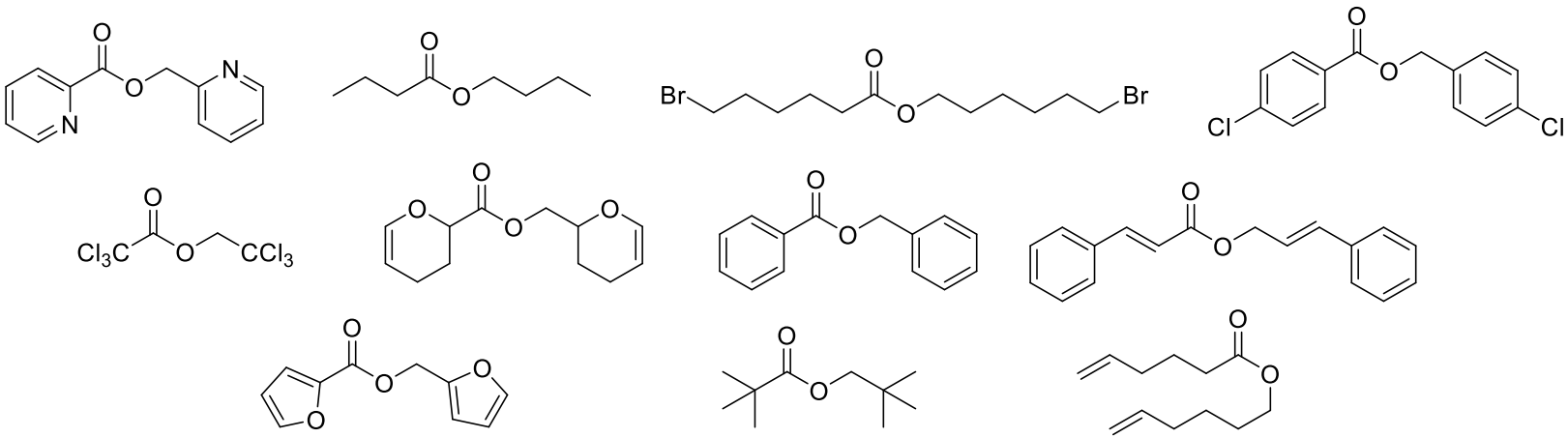
- Oppenhauer Oxidation:
  - acetone used as stoichiometric reductant



Kürti, L. and Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, **2005**

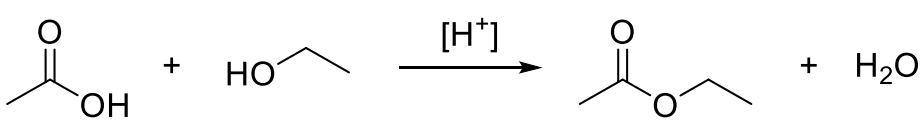
Tishchenko Reaction: Scope

- alkyl, aryl, heteroaryl aldehydes
- a plethora of catalysts/reaction conditions have been used successfully

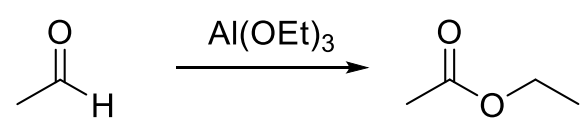


- one important industrial application: synthesis of ethyl acetate

USA:



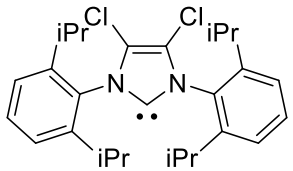
Germany/Japan:



Kataja, A. O. and Koskinen, A. M. P. “The Tishchenko Reaction” in *Organic Reactions*, **2015**, 86(2), 107-409

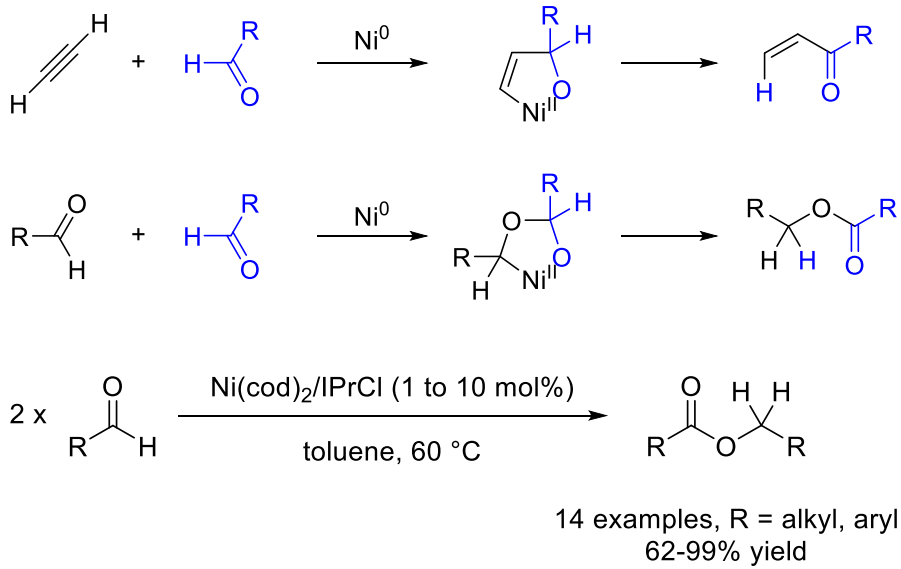
Weissermel, K.; Arpe, H.-J. *In Industrial Organic Chemistry*, 4th ed.; Wiley-VCH:Weinheim, 2003; p 189.

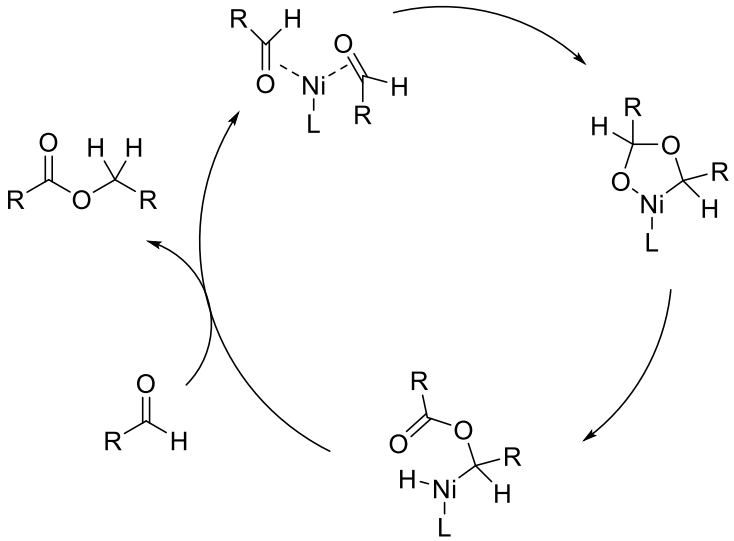
TM-Catalyzed Tishchenko Reaction



IPrCl ligand

- Ogoshi et al. (2010)
  - Tishchenko rxn can be viewed as a hydroacylation of an aldehyde



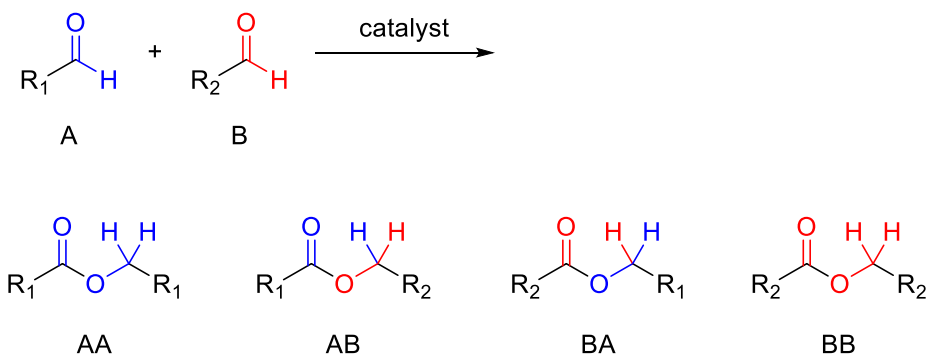


- Both aldehyde molecules are simultaneously bound to Ni (NMR)
- Rxn 0th order in aldehyde, primary KIE observed for aldehyde proton (k_H/k_D = 1.9)
- Suggests RDS is either β-hydride elimination or reductive elimination
- Notably, alkyl aldehydes required shorter reaction times than aryl aldehydes

Ogoshi, S. et al. *Chem. Commun*. **2010**, 46(19), 3354

Cross-Tishchenko Reaction

- Reaction between two different aldehydes to yield unsymmetrical esters
- Typically leads to statistical mixtures of products
  - Scattered literature reports of cross-Tishchenko with modest selectivities (up to 0.71)
  - These are typically achieved through careful matching of electronic/steric parameters of both partners, controlling rate of addition, etc.
  - Not general methods

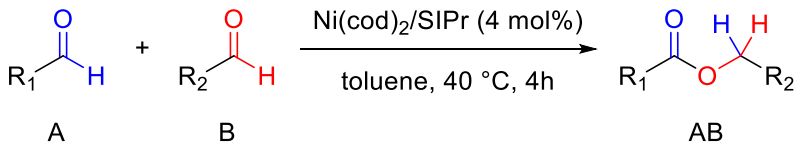


selectivity for AB = AB/(AA + AB + BA + BB)

Ogoshi, S. et al. *J. Am. Chem. Soc*. **2011**, 133(13), 4668

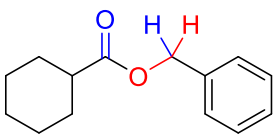
Ni-Catalyzed Cross Tishchenko

- Ogoshi et al. (2011)
  - General method for coupling alkyl and aryl aldehydes with predictable regioselectivity

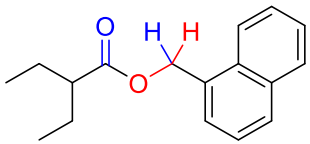


13 examples, **47-85%** yield
AB selectivity > 0.87
R_1 = alkyl (linear, branched, cyclohexyl)
R_2 = aryl (electron rich/neutral)

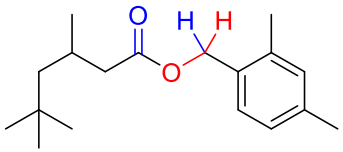
  - Scope is still small, and most examples use aldehydes lacking diverse functionality



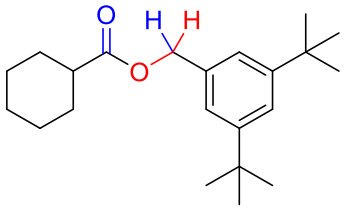
yield: 84%
selectivity: 0.94



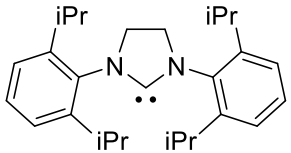
yield: 65%
selectivity: 0.93



yield: 66%
selectivity: 0.94



yield: 81%
selectivity: 0.89



SIPr ligand

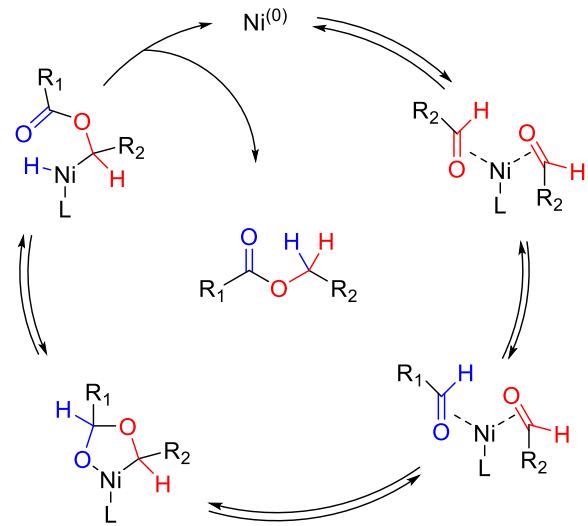
Ogoshi, S. et al. *J. Am. Chem. Soc.* **2011**, 133(13), 4668

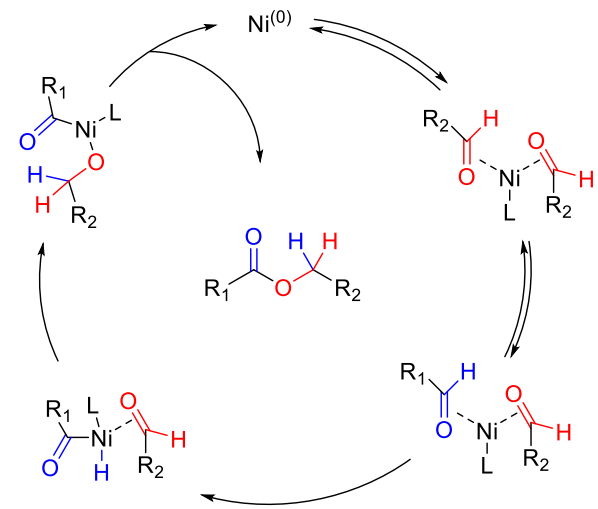
Ni-Catalyzed Cross Tishchenko

- Mechanistic studies
  - exchange of coordinating B with non-coordinating A occurs at r.t. (NMR)
  - zeroth-order in both aldehydes … coordination not RDS
  - first-order in catalyst
  - KIE studies:

Experiment	X	Y	k_N[a]	KIE(N)[b]	Selectivity
I	H	H	12.9(1)	–	0.94
II	H	D	10.9(1)	1.2	0.93
III	D	H	6.4(3)	2.0	0.83[c]
IV	D	D	6.7(1)	1.9	0.85[d]

- Path 1: KIE(III) and (IV) are consistent with BHE or red. elim. as the RDS, KIE(II) is consistent with red. elim. as the RDS
- Path 2: KIE(III) and (IV) are consistent with ox. addn. or insertion as the RDS, but KIE(II) is consistent with neither

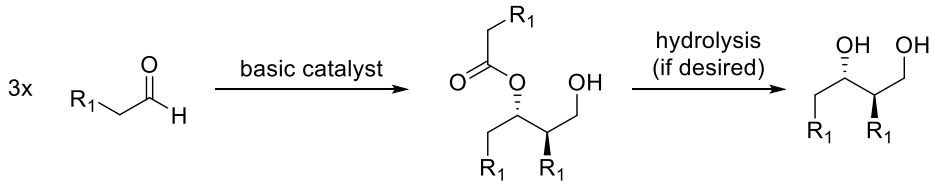




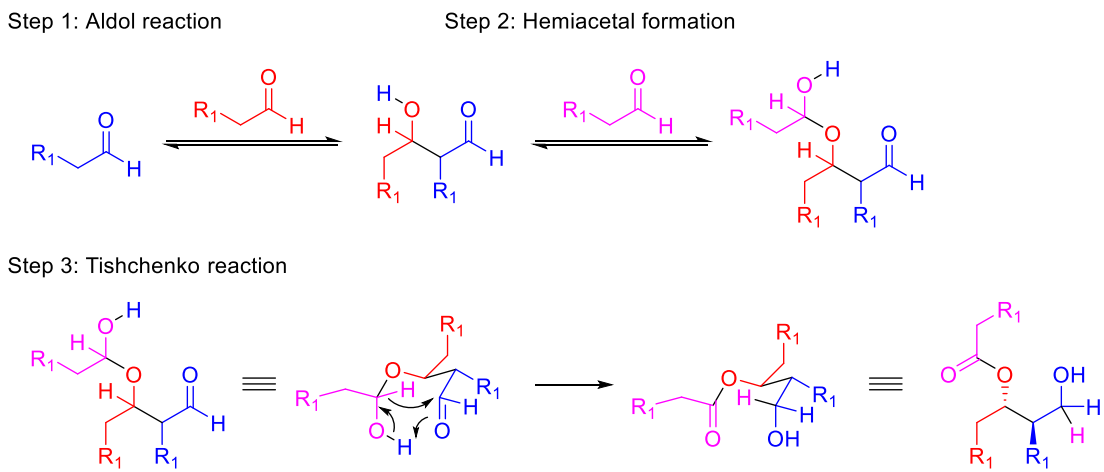
Ogoshi, S. et al. *J. Am. Chem. Soc.* **2011**, 133(13), 4668

Aldol-Tishchenko Reaction

- Simplest example is a trimerization of an enolizable aldehyde
  - Typical catalysts: NaOAc, K_2CO_3, KOH/MeOH, alkali metal alkoxides, alkaline earth metal alkoxides
  - Aluminum alkoxides will not give A-T product (too selective for classical Tishchenko … less basic)



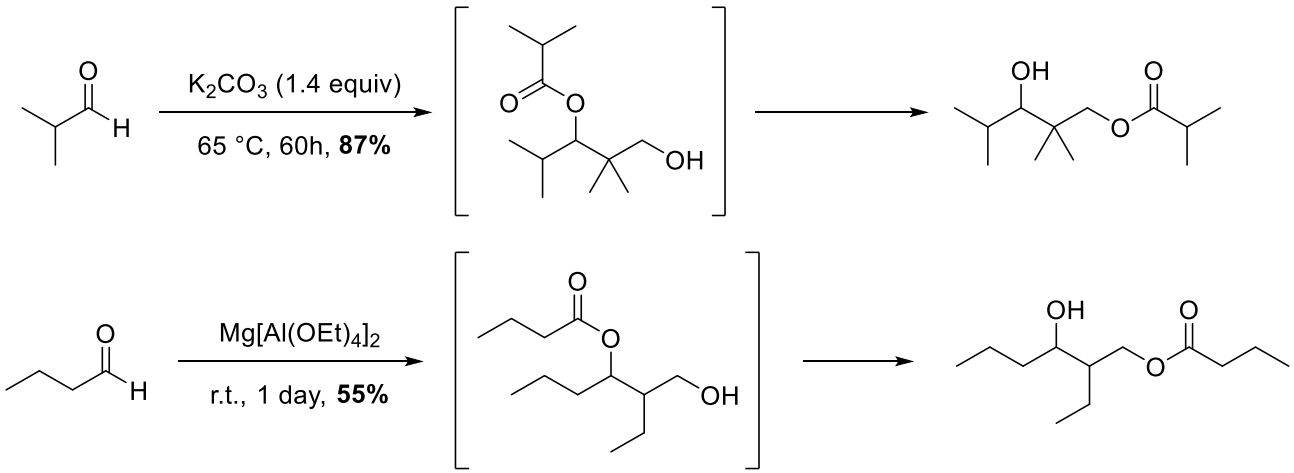
  - Mechanism consists of aldol reaction, hemiacetal formation, and hydride transfer



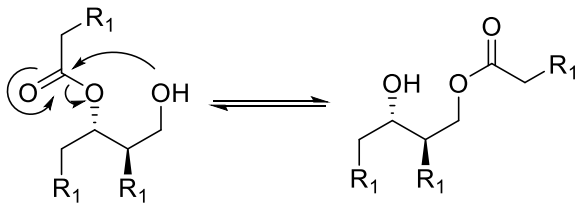
Kataja, A. O. and Koskinen, A. M. P. "The Tishchenko Reaction" in *Organic Reactions*, **2015**, 86(2), 107-409

A-T Reaction: Ester Migration

- Trimerization examples:



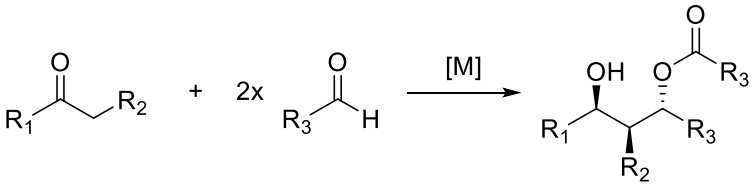
- 1,3-ester migration is commonly observed under thermodynamic control
  - secondary ester to primary ester



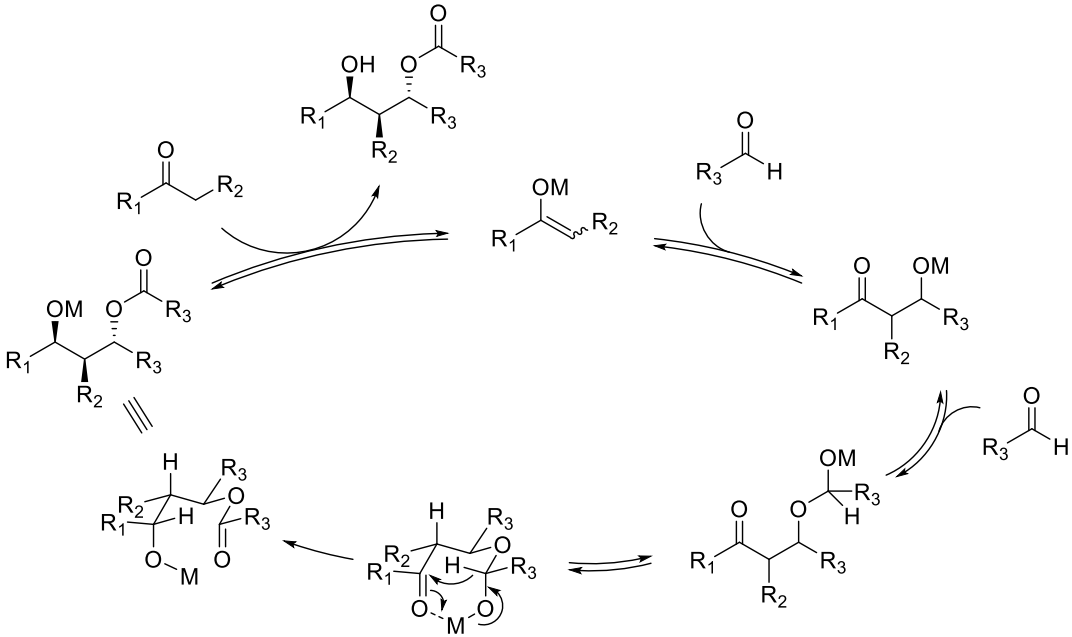
Kirchbaum, F. M. A. *Monatsh. Chem*. **1904**, 25, 249
Kulpinski, M. S.; Nord, F. F. *J. Org. Chem*. **1943**, 8, 256.

A-T Reaction: Ketone-Derived Enolates

- Catalysts are those generally used for enolate generation
  - LDA, LiTMP, LiHMDS, Na/Mg alkoxides
  - Many transition metal catalysts
  - Often paired with Reformatsky reaction

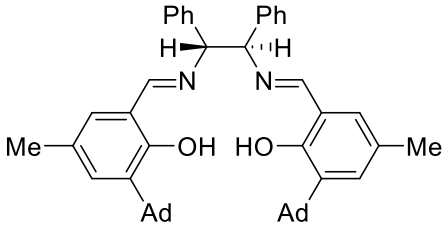


- Accepted mechanism:
  - Major diastereomer arises from the TS in which all substituents are equatorial

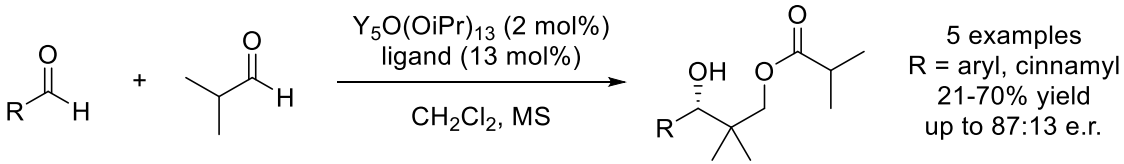


Kataja, A. O. and Koskinen, A. M. P. “The Tishchenko Reaction” in *Organic Reactions*, **2015**, 86(2), 107-409

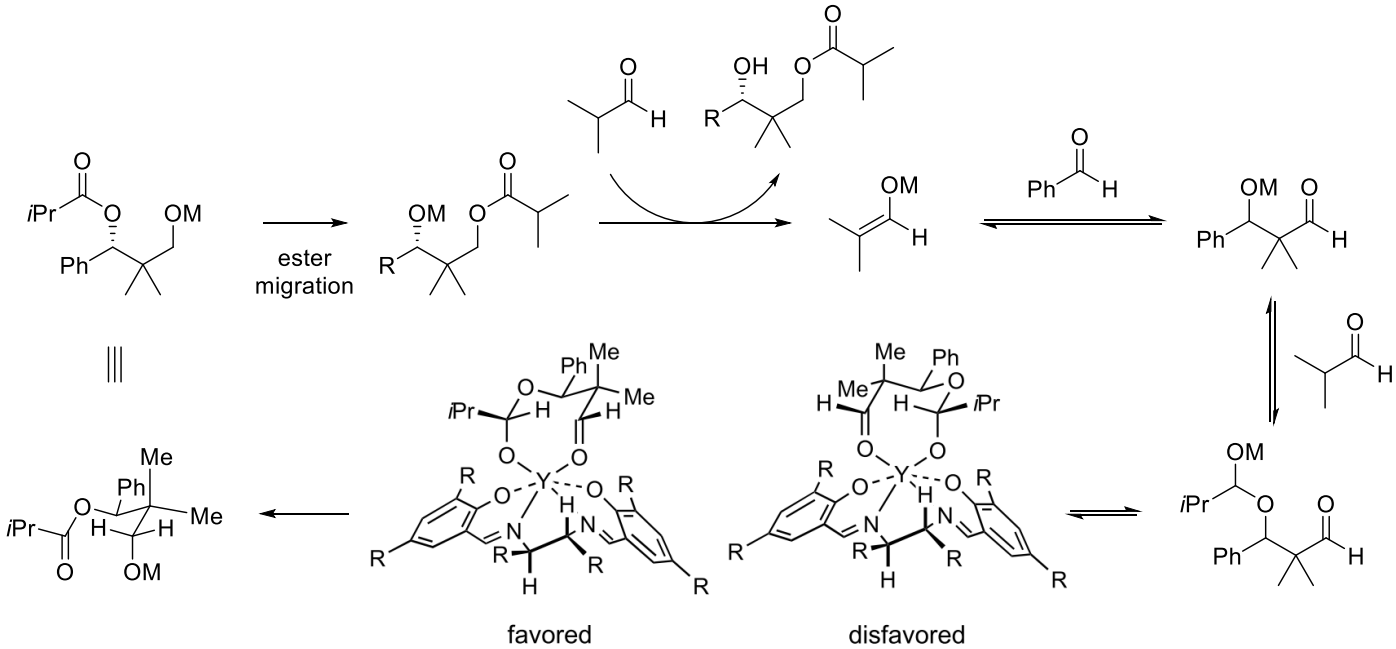
Enantioselective A-T Reaction



- Morken (2001)



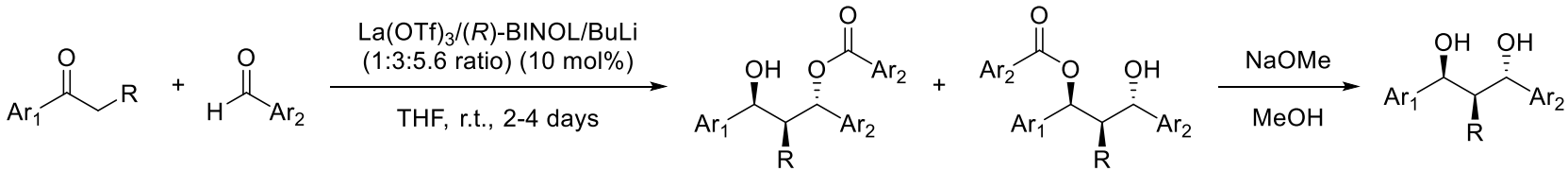
  - Employs a Yttrium complex and Salen ligand
  - Enantiodetermining step is hydride transfer in Y-bound TS (Tishchenko reduction)



Morken, J. P. et al. *Angew. Chem. Int. Ed*. **2001**, 40(3), 601

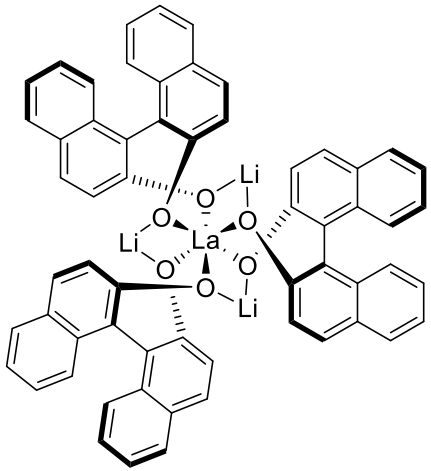
Enantioselective A-T Reaction

- Shibasaki (2004)
  - First broadly applicable approach using $LaLi_3(BINOL)_3$ complexes



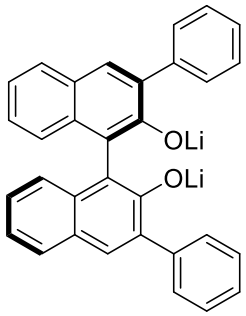
17 examples, **85-95% ee**, **60-96% yield**
Ar_1 = electron-poor, R = alkyl
Ar_2 = electron-rich/poor, heteroaryl

- Consistent with previous studies on the A-T reaction, any isolated aldol byproducts displayed no enantiomeric/diastereomeric enrichment
- The hydride transfer (Tishchenko step) is the stereodetermining step



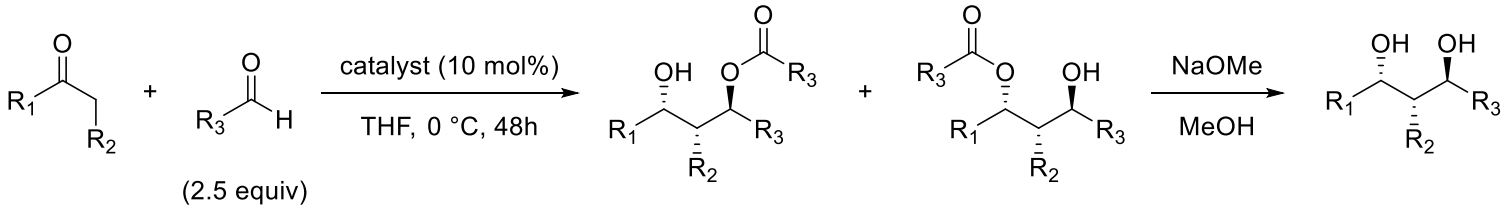
Shibasaki, M. et al. *J. Am. Chem. Soc*. **2004**, 126(25), 7782

Enantioselective A-T Reaction



catalyst

- Nakajima (2011)
  - Enantioselective A-T reaction catalyzed by chiral Li-binaphtholate
  - Catalyst easily prepared in situ from *n*-BuLi and corresponding BINOL



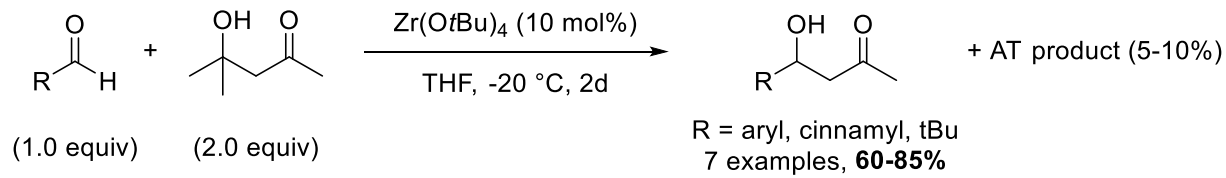
9 examples, **61-91%** yield, **> 85% ee**

R_1 = alkyl/alkenyl, R_2 = alkyl, R_2 = aryl/cinnamyl

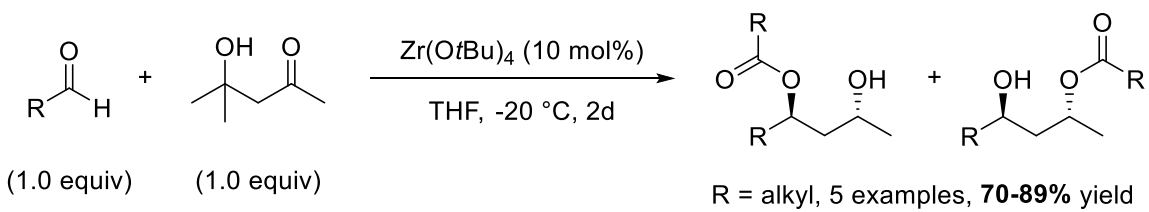
Nakajima, M. et al. *Org. Lett*. **2011**, 13(7), 1579

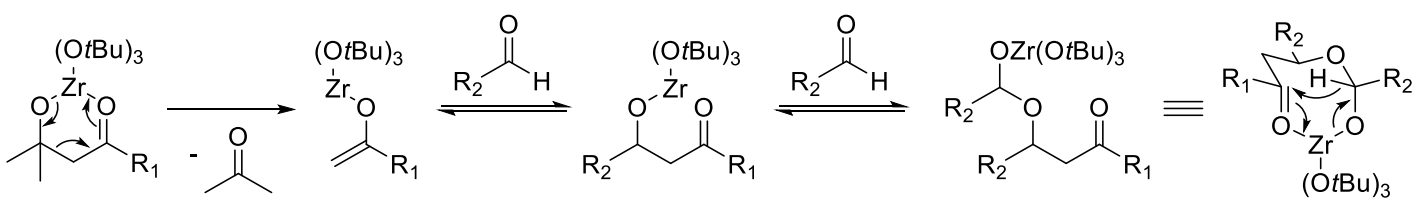
A-T Reaction Modifications

- Diacetone alcohol can serve as a precursor for the aldol-Tishchenko reaction
  - Under Lewis acid catalysis, desired products are formed via retro-aldol-aldol-Tishchenko (RAAT) process
  - Aryl aldehydes stop at acetone aldol adduct



  - Alkyl aldehydes afford the RAAT product in good yield
  - Substantial amounts of ester migration product observed in most cases
  - *Anti*-1,3-diol is formed predominantly in all cases (> 97:3 d.r.)

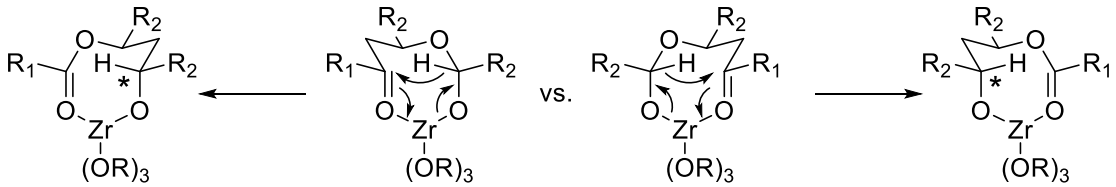




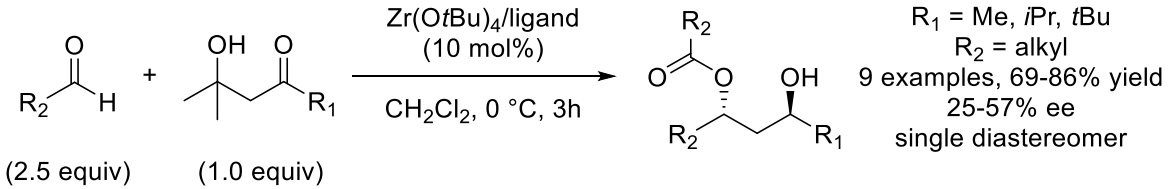
Schneider, C. et al. *Chem. Commun*. **2001**, 13, 1218

Enantioselective Variants

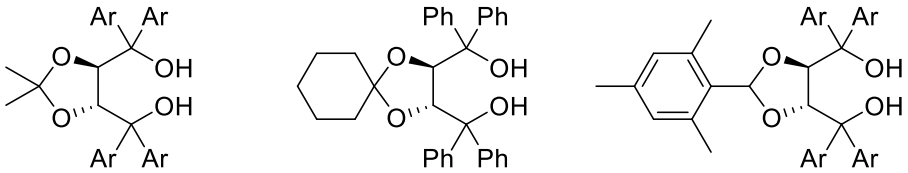
- Chiral environment around Zr leads to diastereomeric TS



  - chiral Zr-TADDOLates were used with reasonable success
  - additionally, ester migration was significantly suppressed



  - ligands screened:

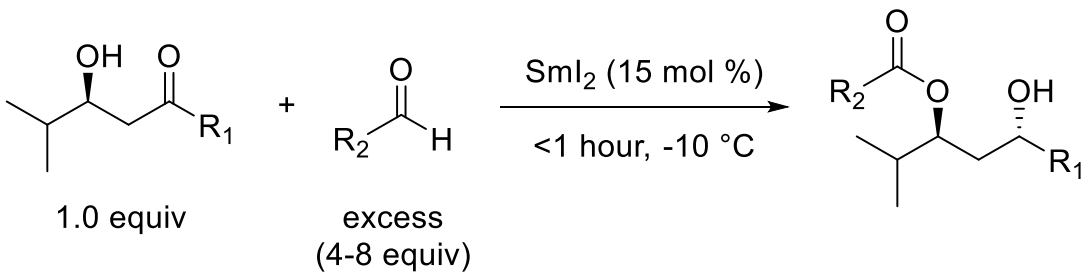


Ar = Ph, 1-naphthyl, 3,5-Me_2-Ph

Schneider, C. et al. *Synlett*. **2003**, 6, 837

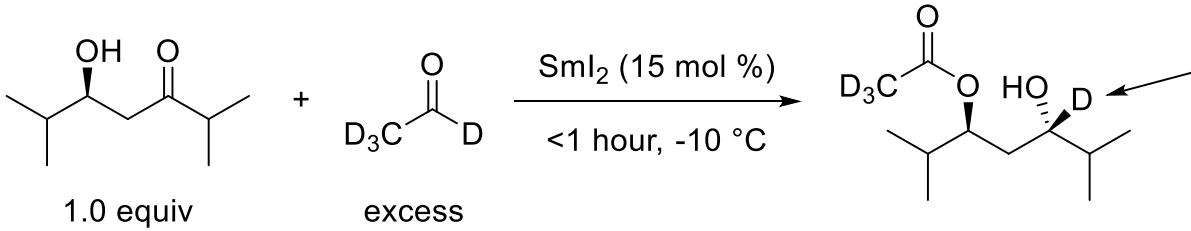
Evans-Tishchenko Reaction

- Seminal publication (Evans and Hoveyda, 1990)
- Method for diastereoselective reduction of β-hydroxy ketones to *anti*-1,3-diols

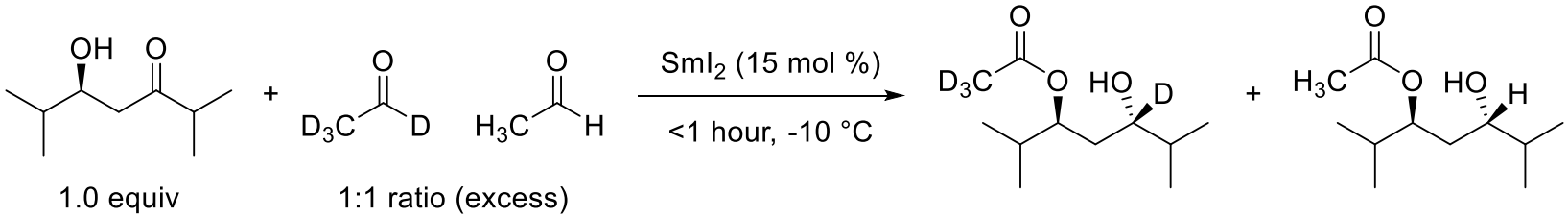


5 examples
R_1 = alkyl; R_2 = alkyl, Ph
85-99% yield, >99:1 d.r.

- Deuterium-labeling studies:



100% deuterium incorporation

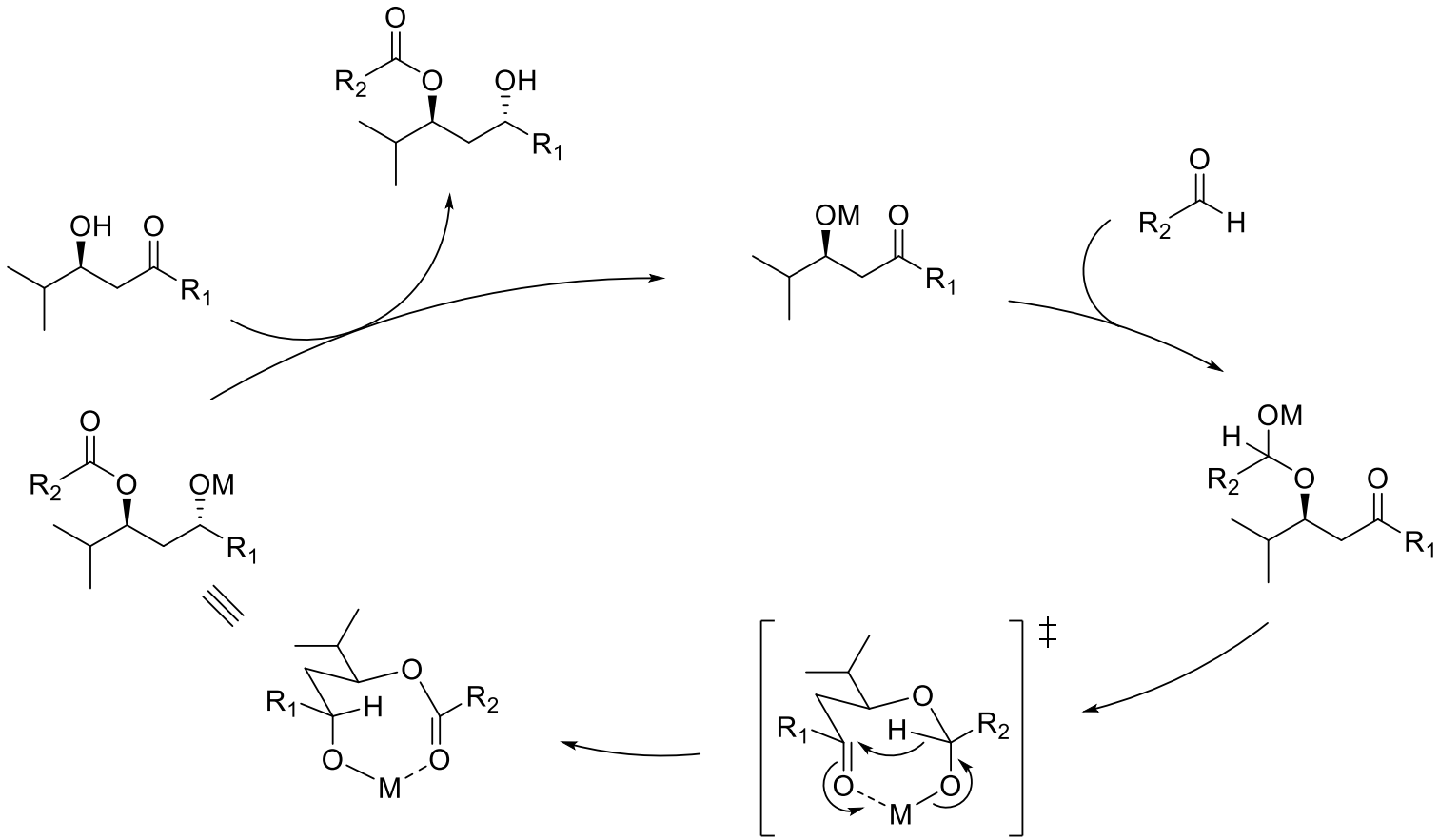


1:1 product ratio (k_H/k_D = 1)

Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, 112, 17, 6447

Evans-Tishchenko Reaction Mechanism

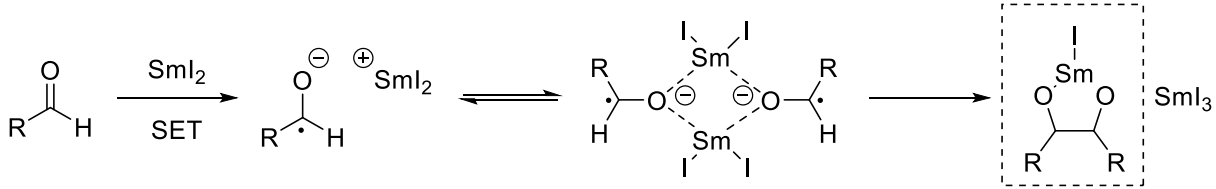
- High level of diastereoselectivity results from chair-like TS for intramolecular hydride delivery



Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, 112, 17, 6447

Catalytically Active Species

- Active species is believed to be the samarium-pinacolate



- First proposed/tested by Evans in the seminal publication

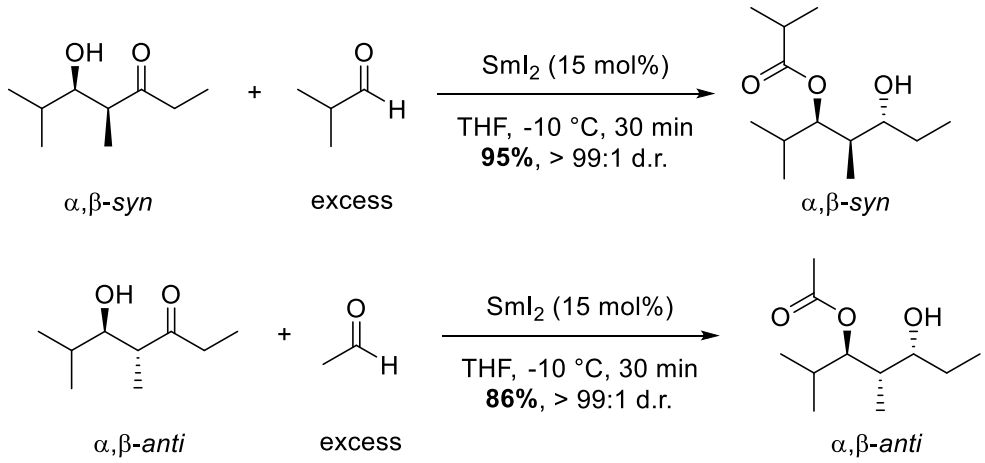
> Our studies indicate that the active samarium catalyst may well be some Sm(III) entity. Upon addition of SmI_2 to the mixture of β-hydroxy ketone and excess aldehyde, the blue color of Sm(II) is quickly replaced by the yellow-orange hue of Sm(III), resulting from the Sm(II)-mediated aldehyde pinacol reduction.[15]

  - Pre-stirred mixtures of 1:1 benzaldehyde and samarium iodide are equally effective as SmI_2 alone
  - SmI_3 is an inferior catalyst, and $SmCl_3$ and $Sm(acac)_3$ show no activity

Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, 112, 17, 6447
Organic Synthesis Using Samarium Diiodide: A Practical Guide; Procter, D. J.; Flowers, R. A.; Skrydstrup, T., Eds.; RSC: Cambridge, **2010**

Effect of α-substitution

- Evans and Hoveyda (1990)
  - stereochemistry of α-position is preserved

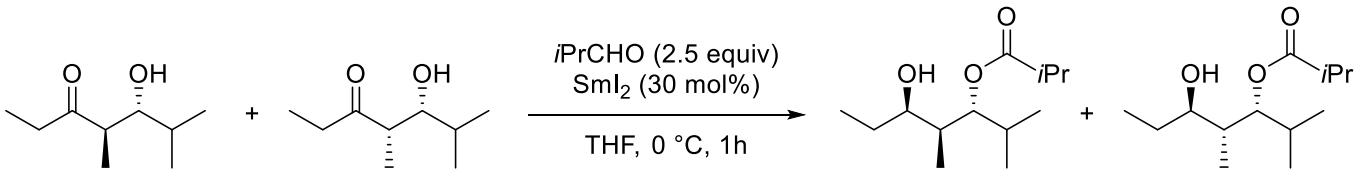


The reductions of both syn and anti α-methyl β-hydroxy ketones follow the same stereochemical course with equally high levels of asymmetric induction. In analogy with our earlier studies on the reduction of the same substrates with triacetoxyborohydride,[2b] asymmetric induction from the distal hydroxy stereocenter dominates any bias induced by the α-methyl-bearing center

Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, 112, 17, 6447

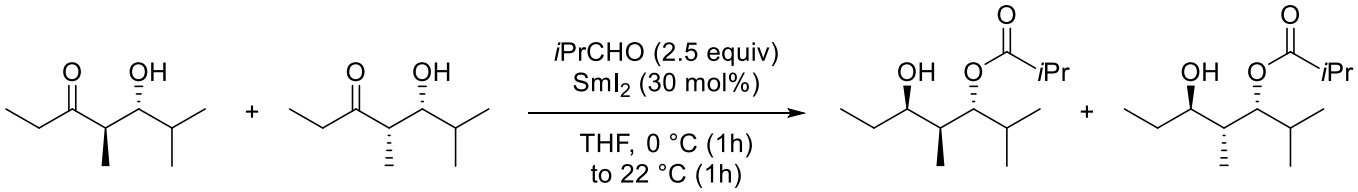
… but wait!

- α-epimerization is observed upon slight modification of the rxn conditions/substrate



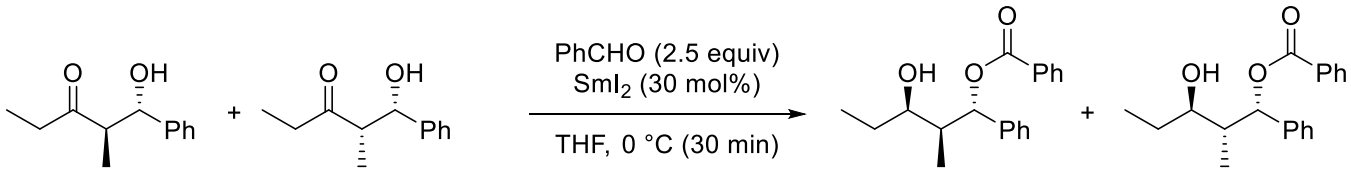
64 (α,β-*anti*) : 36 (α,β-*syn*)

76 (α,β-*anti*) : 24 (α,β-*syn*)



64 (α,β-*anti*) : 36 (α,β-*syn*)

82 (α,β-*anti*) : 18 (α,β-*syn*)



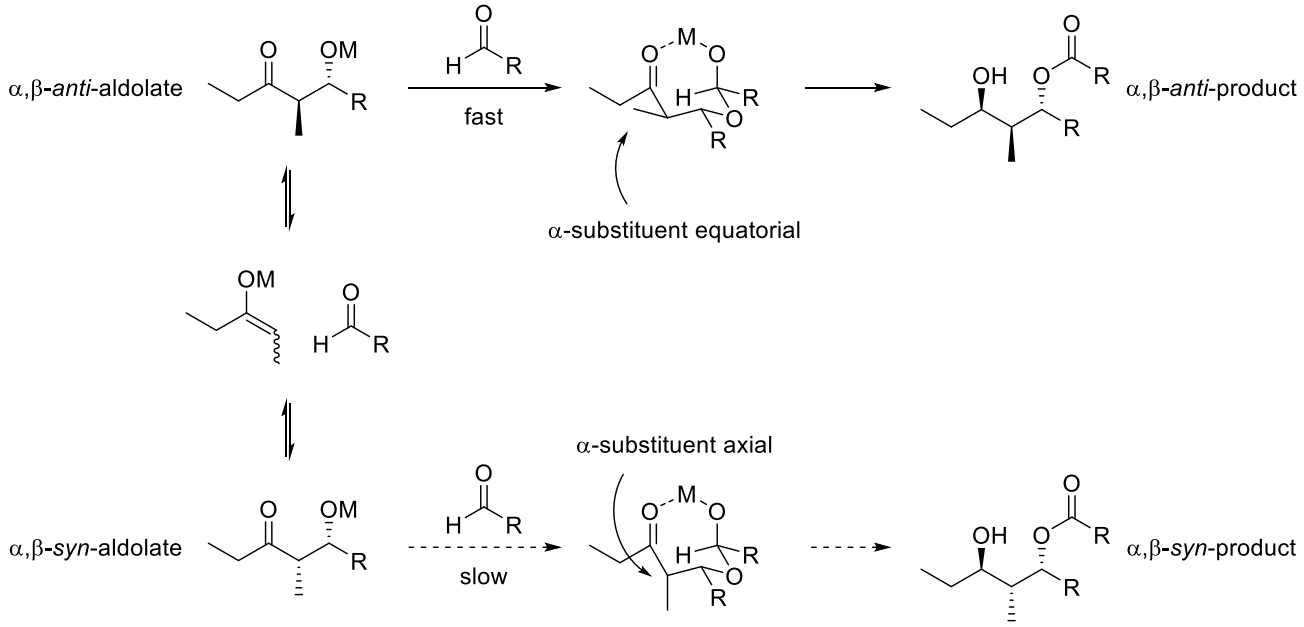
50 (α,β-*anti*) : 50 (α,β-*syn*)

100 (α,β-*anti*) : 0 (α,β-*syn*)

Fang, J.-M. et al. *J. Org. Chem*. **1999**, 64(3), 843

Justification

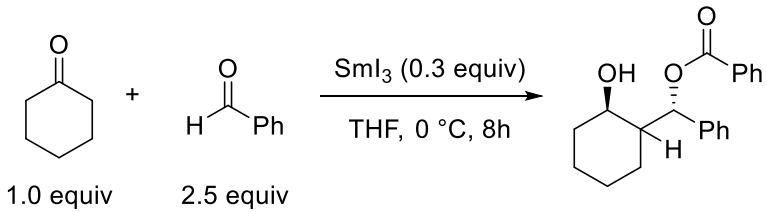
- RAAT (Retro-Aldol-Aldol-Tishchenko)
  - syn/anti aldolate equilibration under thermodynamic control
  - hydride transfer is faster for *anti*-intermediate (α-substituent equatorial in TS)
  - commonly observed side reaction for Evans-Tishchenko



Fang, J.-M. et al. *J. Org. Chem*. **1999**, 64(3), 843

Group Problem

- The reaction of cyclic ketones with benzaldehyde in the presence of SmI_3 also gives exclusively one diastereomer.
  - This is a general result regardless of the exact catalyst used.

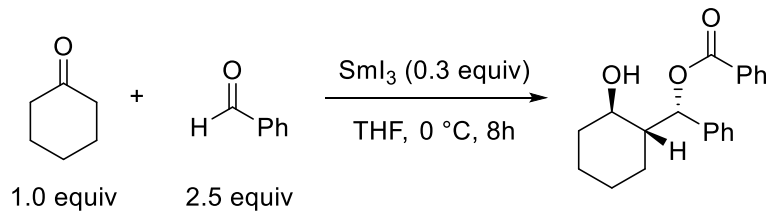


- What is the configuration of the α-position? Defend your answer.

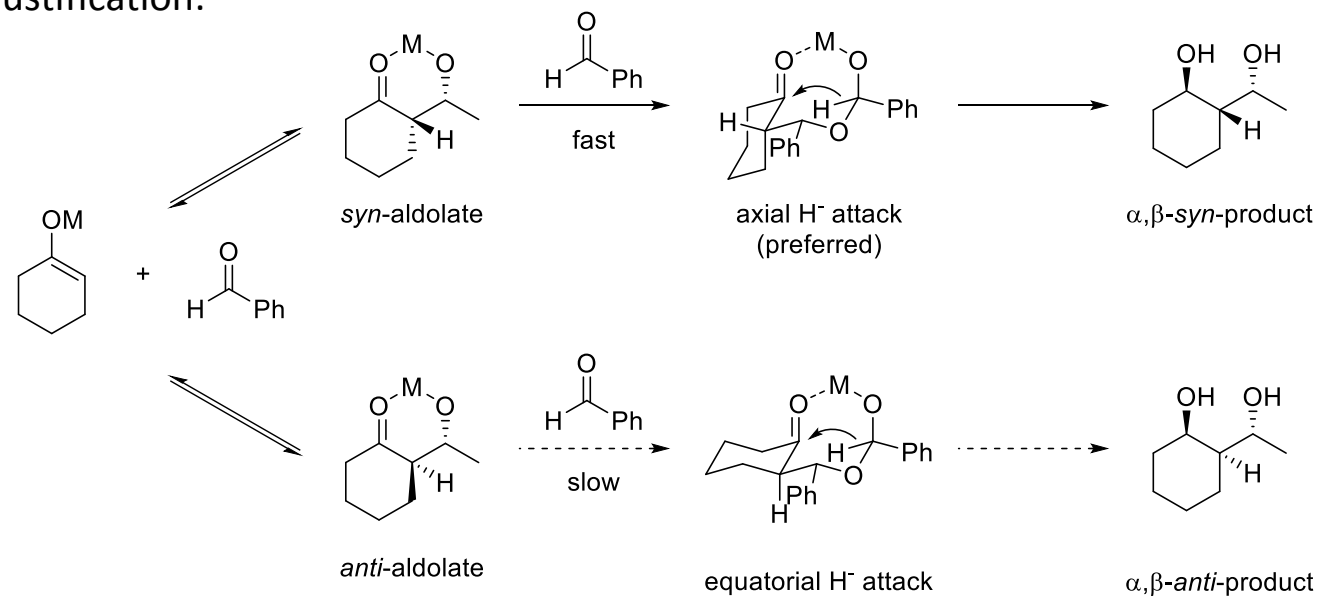
Fang, J.-M. et al. *J. Org. Chem*. **1999**, 64(3), 843

Group Problem: Solution

- 1,2-*syn*-1,3-*anti* (different from before!)



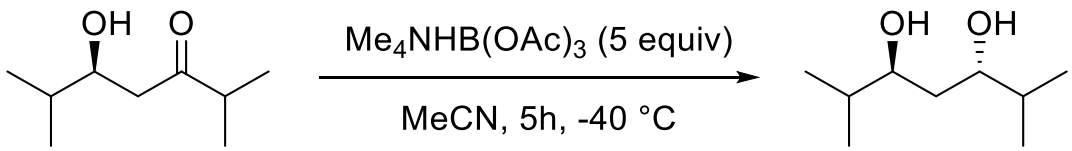
- Justification:



Fang, J.-M. et al. *J. Org. Chem*. **1999**, 64(3), 843

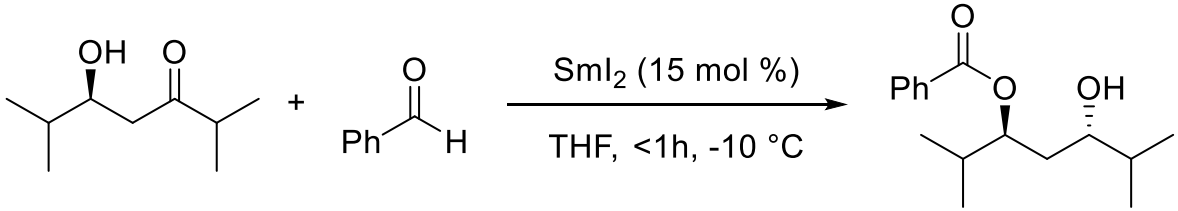
Application: 1,3-*anti*-reduction

- Several methods exist for diastereoselective 1,3-reduction
- Evans et al. (1988):
  - Intramolecular hydride delivery leads to high *anti*-selectivity



86% yield, 96:4 d.r.

- Evans et al. (1990):



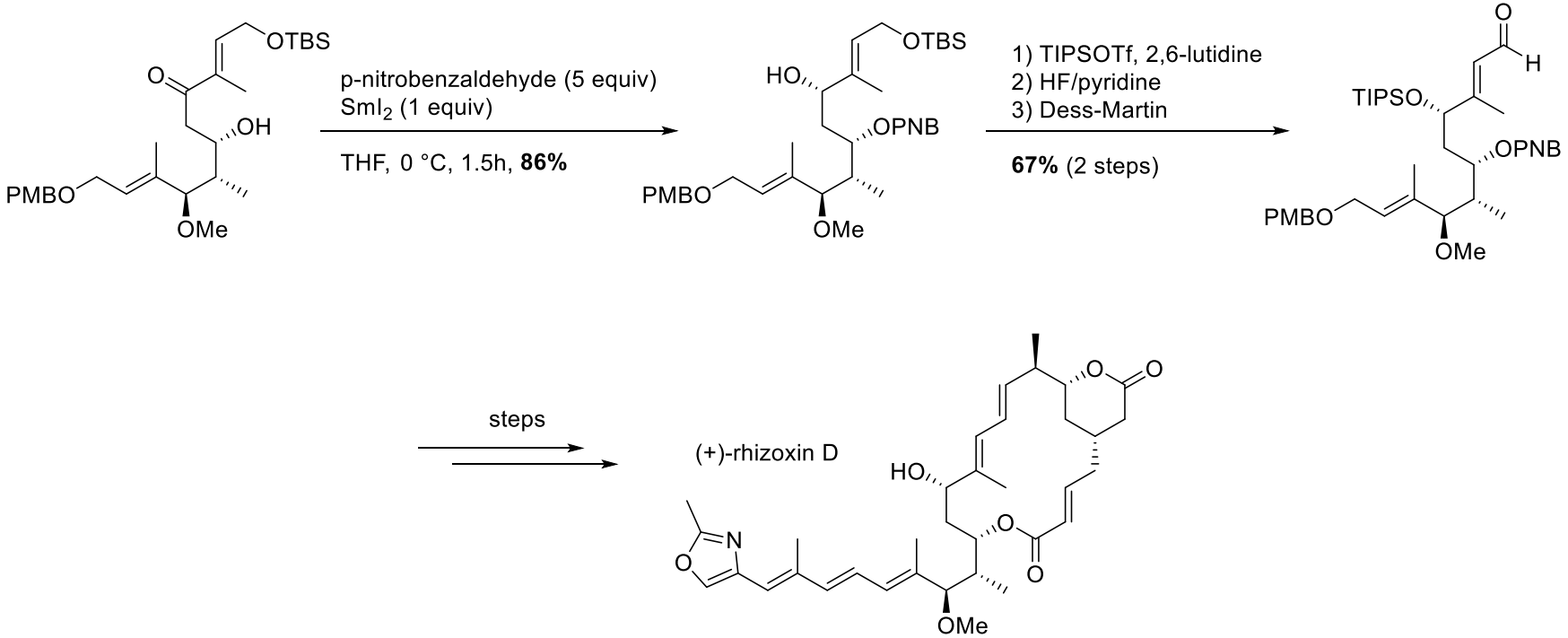
99% yield, >99:1 d.r.

- Key advantage in the second case: hydroxyl groups are differentiated after the reduction!

Evans, D. A. et al. *J. Am. Chem. Soc*. **1988**, 110(11), 3560
Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, 112(17), 6447

(+)-rhizoxin D

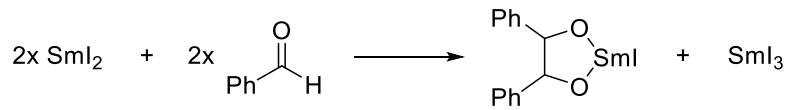
- Evans-Tishchenko rxn used to install PNB-protected *anti*-diol

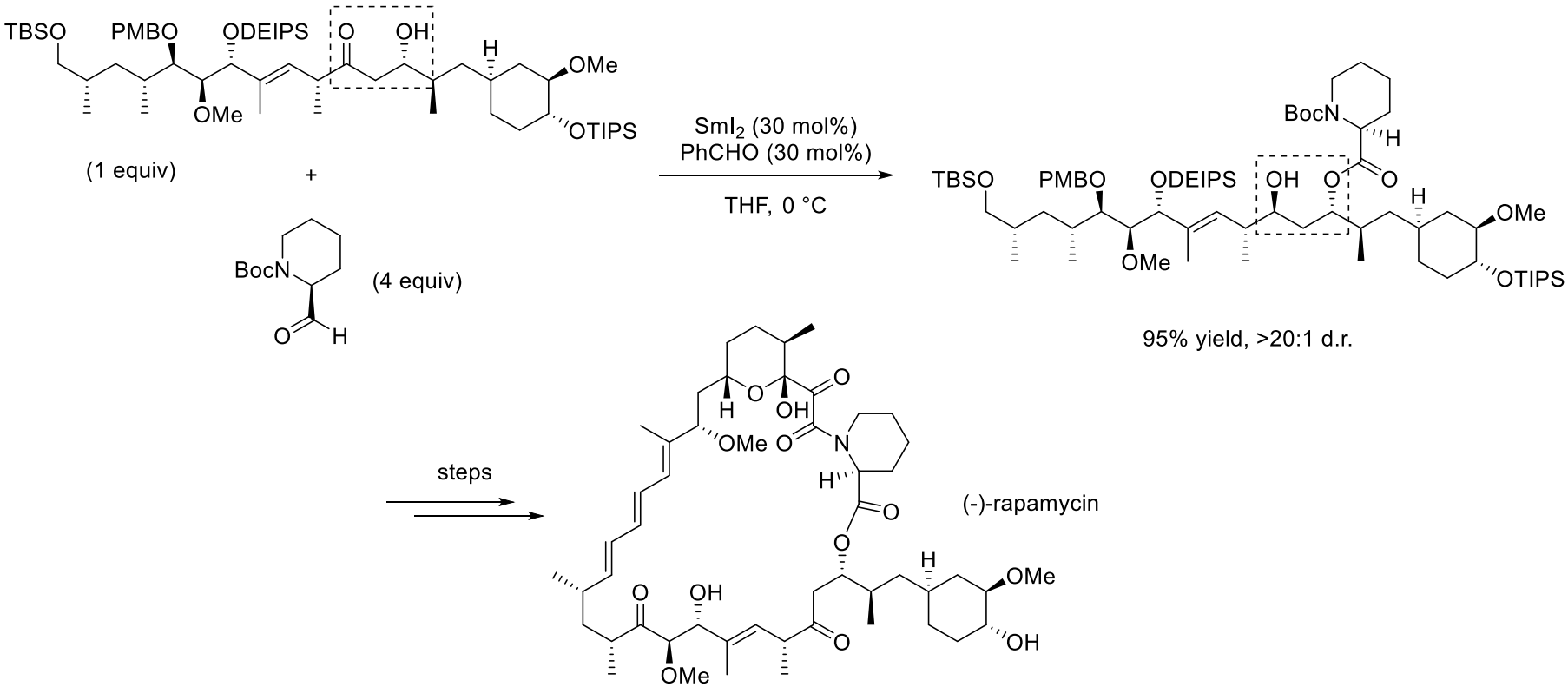


Burke, S. D. et al. *Org. Lett*. **2004**, 6(9), 1445

Application: Fragment Coupling

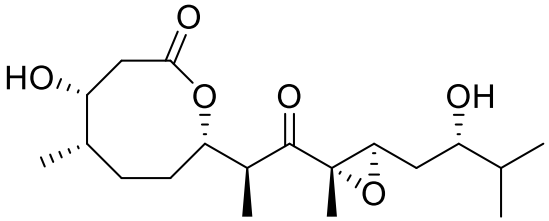
- Schreiber et al. (1993)





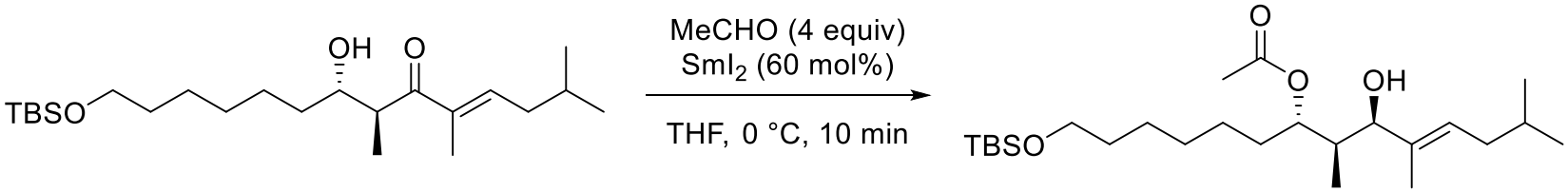
Schreiber, S. L. et al. *J. Am. Chem. Soc*. **1993**, 115(17), 7906

Octalactin A



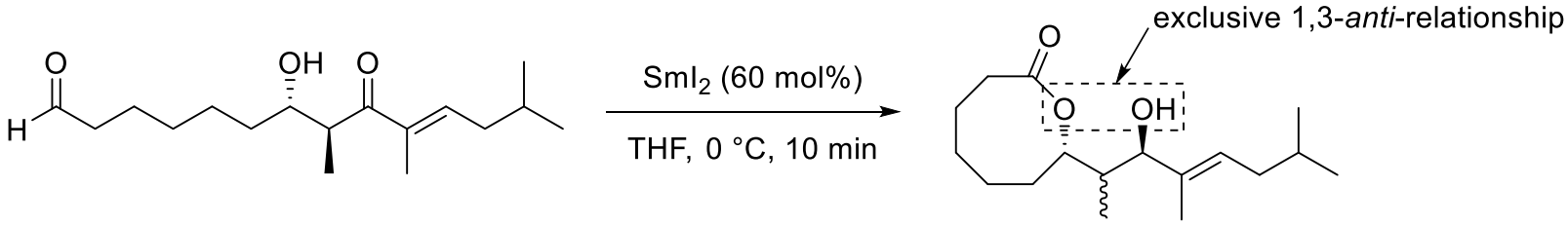
octalactin A

- First (and only) reported attempt to employ the E-T rxn for macrolactonization
- Test system provided good results:



70% yield, single diastereomer

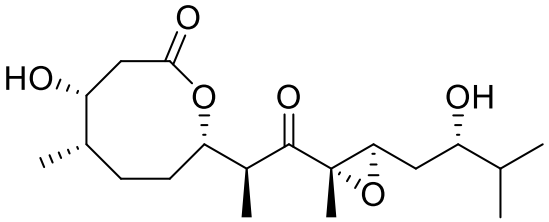
- However, rxn of model intramolecular system led to epimerization of the methyl-bearing α-stereocenter



30% yield, 1:1 d.r.

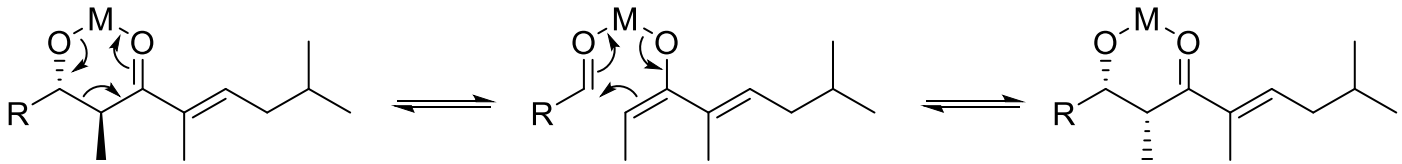
Hulme, A. N. et al. *Tetrahedron* **1997**, 38(47), 8245

Octalactin A

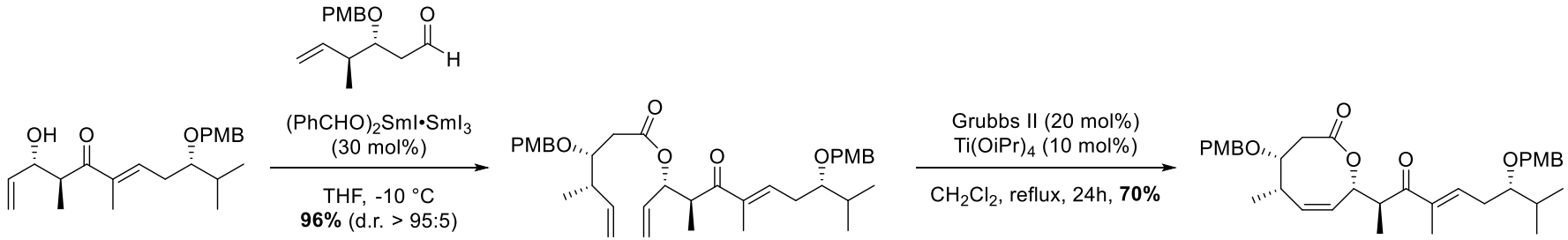


octalactin A

- At longer rxn time required for closure of 8-membered ring, retro aldol/aldol process outcompetes Evans-Tishchenko



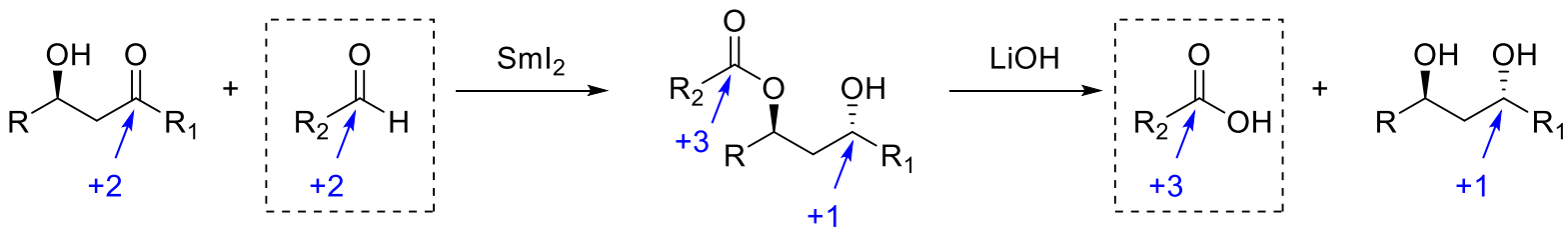
- Solution: couple fragment containing terminal olefin, and subsequent RCM
- Allowed access to fully-functionalized core in 8 LLS



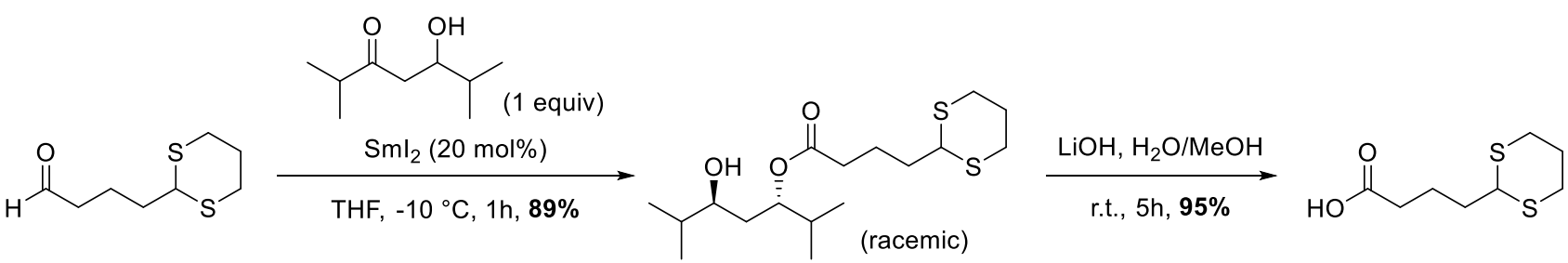
Hulme, A. N. et al. *Tetrahedron* **1997**, 38(47), 8245
Hulme, A. N. et al. *Org. Lett*. **2007**, 9(4), 631

Application: FGI

- Typically, the aldehyde is used in excess and is of little value
- However, these roles can be reversed
- Following basic hydrolysis, this is a mild method for oxidation of aldehydes to acids



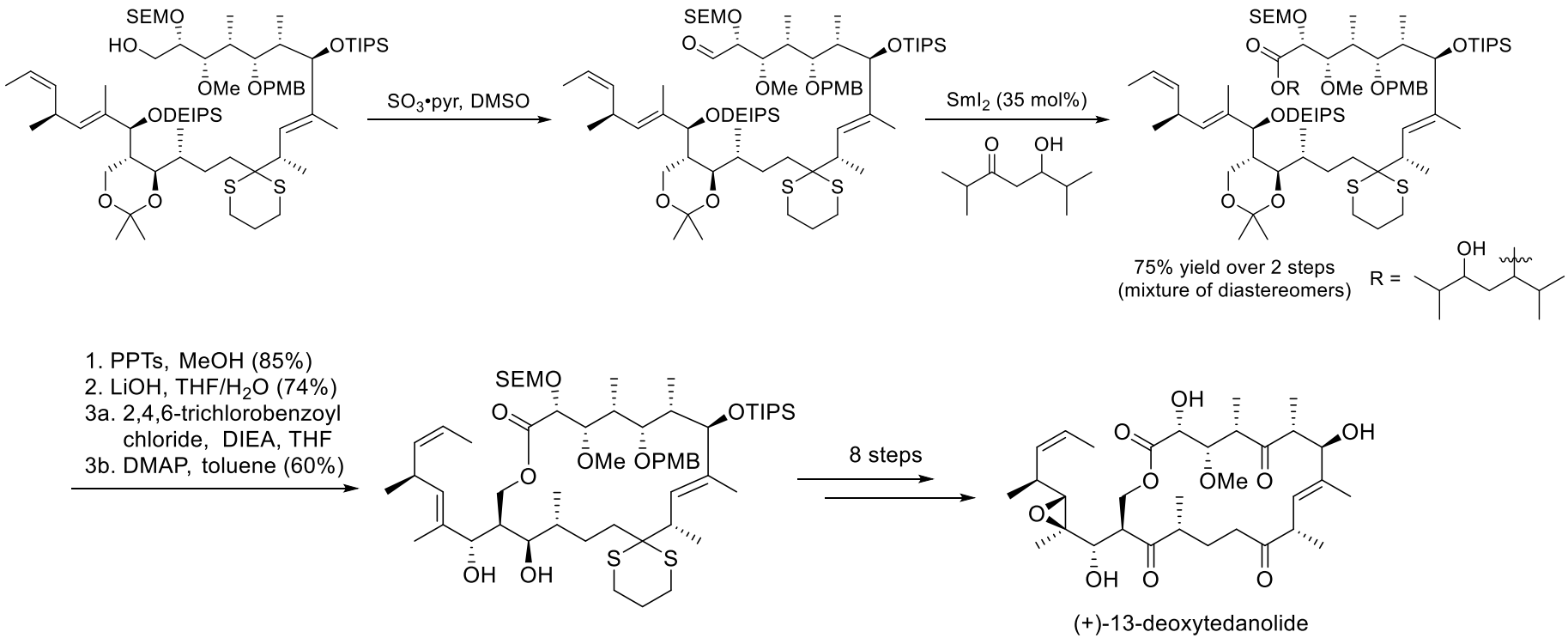
- This methodology can be used for aldehyde oxidation in the presence of dithianes



Smith, A. B.; Kozlowski, M. C. et al. *Org. Lett*. **2002**, 4(25), 4539

(+)-13-deoxytedanolide

- First total synthesis utilizes a Parikh-Doering oxidation followed by an Evans-Tishchenko reaction to oxidize a primary alcohol to a carboxylic acid (75% yield over 2 steps)



Smith, A. B. et al. *J. Am. Chem. Soc*. **2003**, 125, 2, 350

E-T Reaction in Total Synthesis

- Benefits:
  - High diastereoselectivity
  - Reasonable FG tolerance, amenable to late-stage synthesis
  - Generally short reaction times
  - To quote *Organic Reactions*:

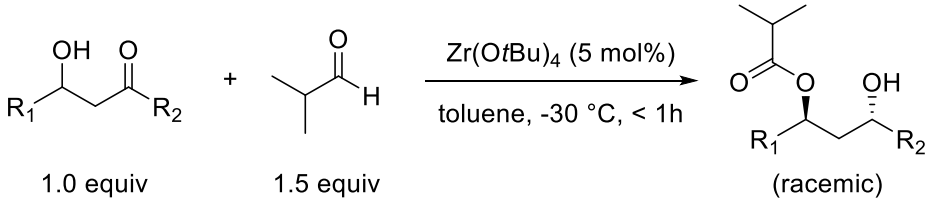
> been recently reviewed.[303] The Evans–Tishchenko method has proven to be quite generally applicable, with only a few reported cases where it does not work. On the

- Disadvantages:
  - Often requires somewhat high loadings of SmI_2 (even as high as 1 equivalent)
  - Samarium = $$$ (and other metals tend to give worse diastereoselectivity)
  - Typically requires large excess of aldehyde
  - Poor atom economy, particularly when used as an aldehyde oxidation protocol

Kataja, A. O. and Koskinen, A. M. P. "The Tishchenko Reaction" in *Organic Reactions*, **2015**, 86(2), 107-409

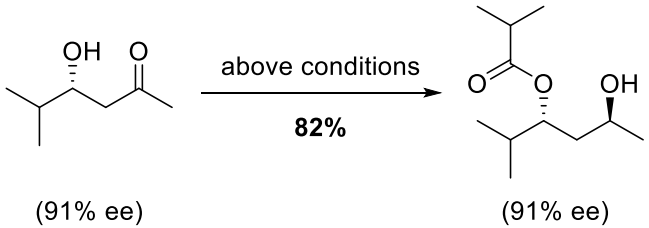
Other Metals

- Zirconium compounds can also serve as effective catalysts for the Evans-Tishchenko reaction
  - allows reactions to be run in toluene
  - other Lewis acid catalysts were tested: $Hf(O\mathit{t}Bu)_4$ (comparable), $Y(OiPr)_3$, $Zr(O\mathit{i}Pr)_4$, $Ti(O\mathit{i}Pr)_4$ (inferior)



10 examples, 61-90% yield
> 99:1 d.r.
R_1 = alkyl, Ph, alkenyl
R_2 = Ph, alkyl

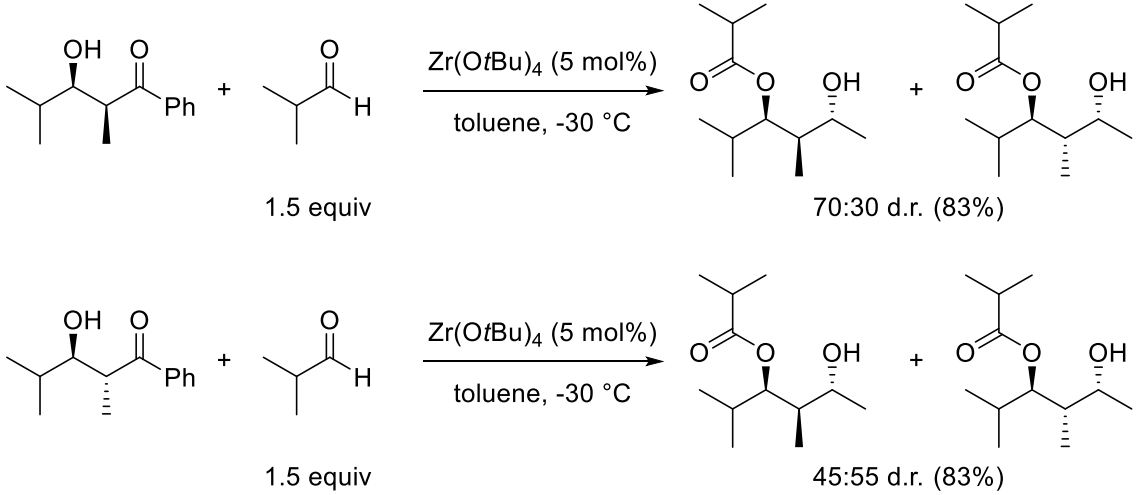
  - could be used on enriched material with no erosion in product e.r.



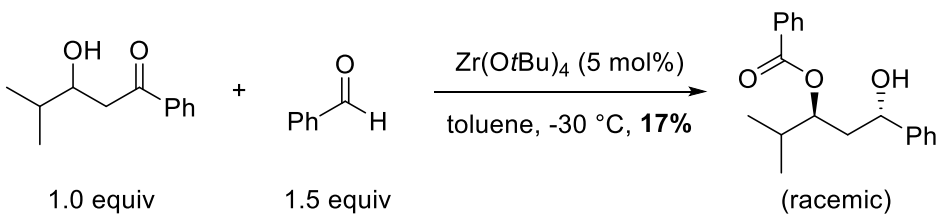
Schneider, C. et al. *Synlett*. **2005**, 1, 91

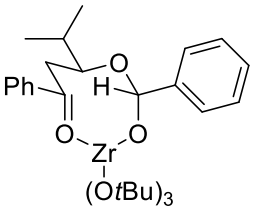
Zr-Catalyzed Reaction

- Also suffers from RAAT
  - α-substitution leads to a mixture of diastereomers



  - aryl aldehydes (e.g. benzaldehyde) result in low yields

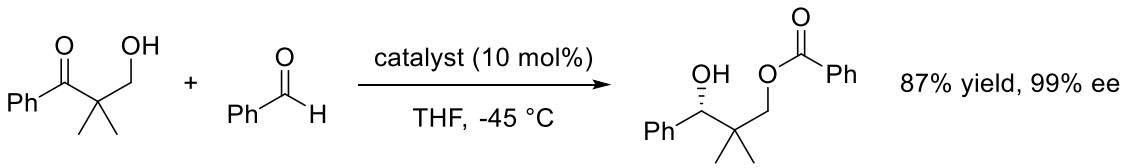


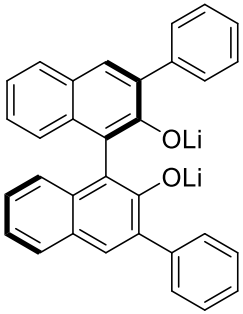


Schneider, C. et al. *Synlett*. **2005**, 1, 91

Enantioselective Variant

- Nakajima (2011)
  - Starting with achiral β-hydroxy ketones, enriched 1,3-diols may be obtained





catalyst

  - Some other scattered literature reports of enantioselective Evans-Tishchenko reactions, but they are really referring to Aldol-Tishchenko or RAAT reactions

Nakajima, M. et al. *Org. Lett*. **2011**, 13(7), 1579

Concluding Remarks

- Tishchenko Reaction
  - Reliable preparation of symmetrical esters with 100% atom economy
  - Current state-of-the-art for cross Tishchenko reaction employs Ni catalysis

- Aldol Tishchenko/Evans-Tishchenko Reactions
  - Reliable preparation of 1,3-*anti*-hydroxyl motifs
  - Highly diastereoselective
  - Enantioselective variants known
  - Mild conditions suitable for natural product synthesis

- Future Directions
  - Further generalization of cross-Tishchenko reactions
  - Further exploration of other metals for Aldol-Tishchenko/Evans-Tishchenko reactions

Key References

- Kataja, A. O. and Koskinen, A. M. P. “The Tishchenko Reaction” in *Organic Reactions*, **2015**, 86(2), 107-409

- Ralston, K. J. and Hulme, A. N. “The Evans-Tishchenko Reaction: Scope and Applications” in *Synthesis* **2012**, 44(15), 2310-2324

- All other references are cited on the slides in which they appear.