Dynamic Kinetic Resolution via Coupled Ruthenium and Enzyme Catalysis

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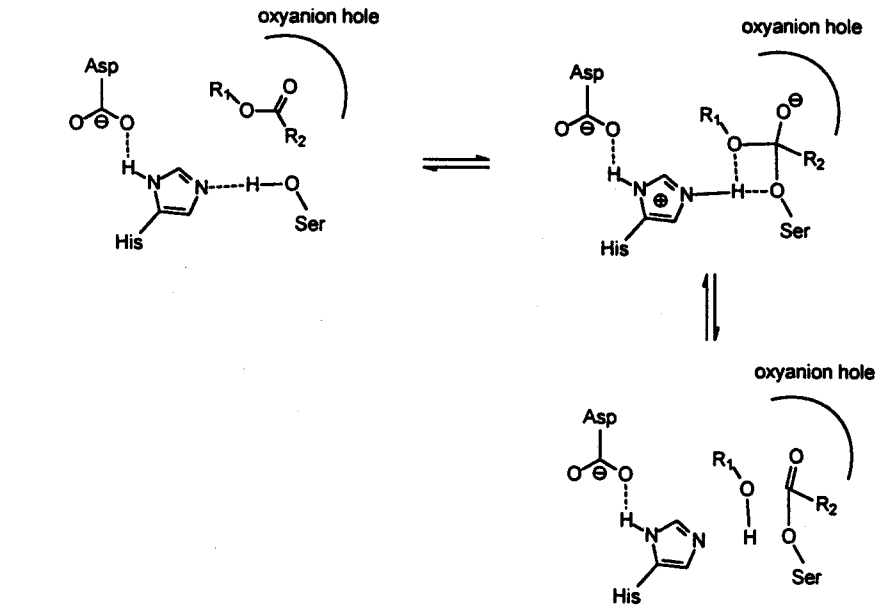
- Introduction to enzyme catalysis
- Dynamic kinetic resolution of secondary monoalcohols
- Dynamic kinetic resolution of secondary diols
- Dynamic kinetic resolution of other substrates

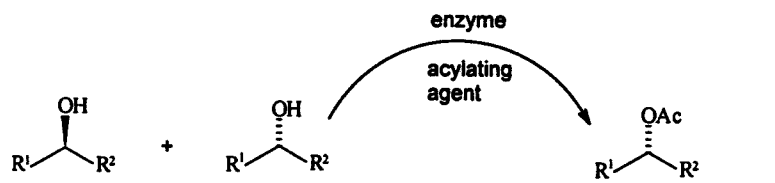
Classification of enzymes

1. Oxidoreductases
2. Transferases
3. Hydrolases *lipases, esterases*
4. Lyases
5. Isomerases
6. Ligases

The mechanism of hydrolases e.g. lipases - "the catalytic triade"

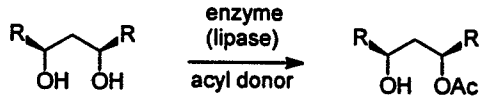


Kinetic Resolution of Alcohols

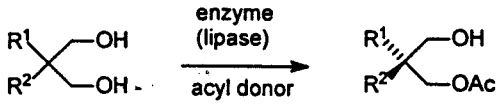


Desymmetrizations

The meso trick:



Prochiral substrates:

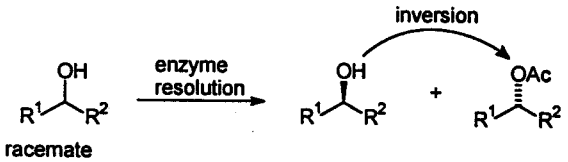


Deracemization

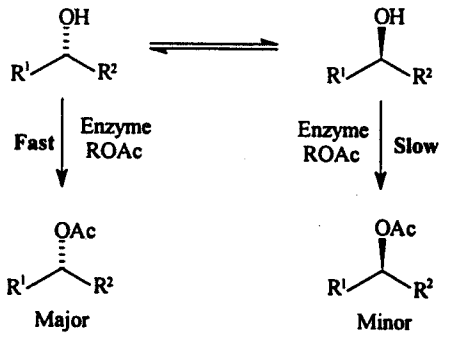
- Stereoinversion
- Dynamic kinetic resolution

Stereoinversion

The non-reacting isomer is inverted (e.g. Mitsunobu reaction)

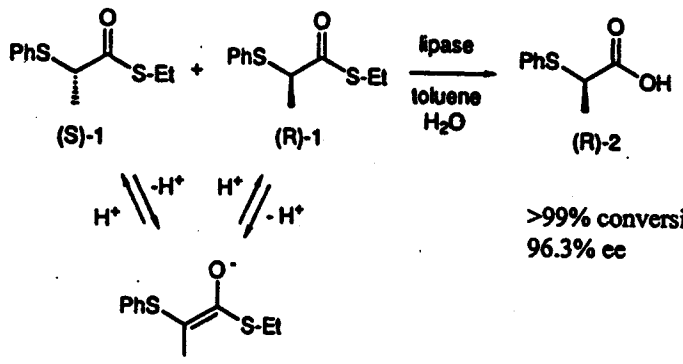


Dynamic Kinetic Resolution



With this principle 100% of the racemate can be used.

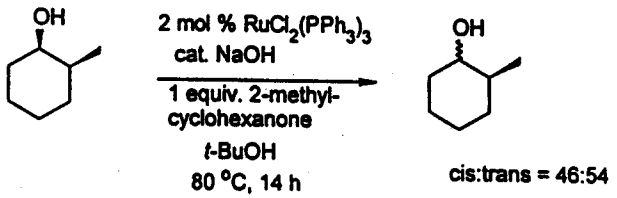
Example of Dynamic Kinetic resolution



>99% conversion
96.3% ee

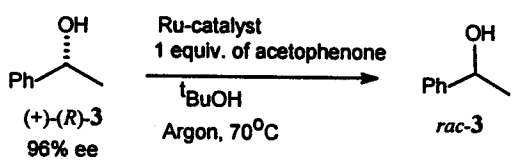
D. S. Tan, M. M. Günther, D. G. Drueckhammer, *J. Am. Chem. Soc.* **1995**, *117*, 9093
P. J. Um, D.G. Drueckhammer, *J. Am. Chem. Soc.* **1998**, *120*, 5605

Isomerization of alcohols



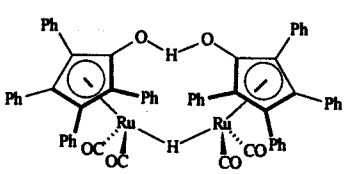
Ruthenium-catalyzed racemization of (+)-(*R*)-**3**

Reaction conditions: 2 mol% of **1**, 10 mol% of NaOH, 4h
or 2 mol% of **2**, 45h



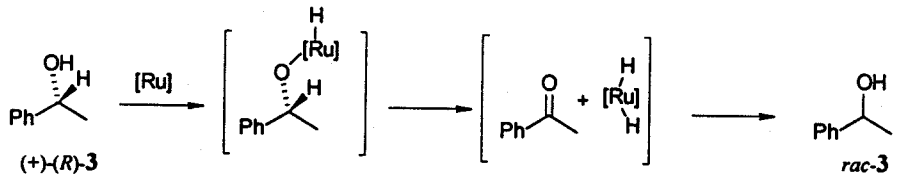
$(PPh_3)_3RuCl_2$

1



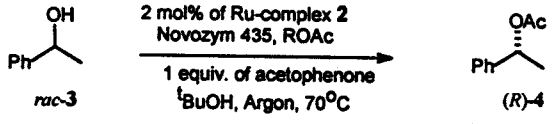
2

Racemization via dehydrogenation re-addition

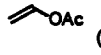
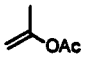
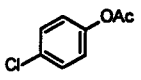
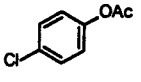


(+)-(*R*)-**3** *rac*-**3**

Dynamic Enzymatic Resoution of Alcohols (Novozym 435: *Candida antarctica* component B lipase)

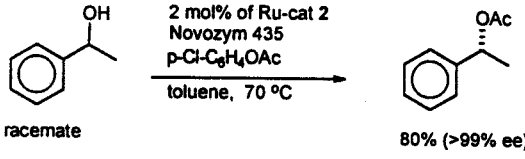


rac-**3** (*R*)-**4**

ROAc (equiv.)	Time (h)	% conv. to (*R*)-4	% ee of (*R*)-4
 (5.5)	17	50	>99.5
 (5)	24	72	>99.5
 (3)	70	88	>99.5
 (3)	87	100 92% isol. yield of (*R*)-4	>99.5

A. L. E. Larsson, B. A. Persson, J. E. Bäckvall, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1211

Also without additionof corresonding ketone (in toluene)

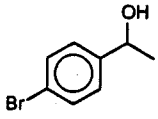


racemate

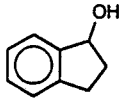
80% (>99% ee)

Novozym 435 = *Candida Antarctica* Lipase

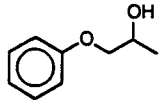
Other substrates



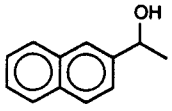
78% (>99% ee)



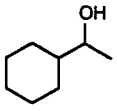
77% (>99% ee)



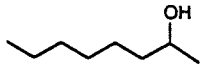
88% (>99% ee)



79% (>99% ee)



79% (>99% ee)



80% (>99% ee)

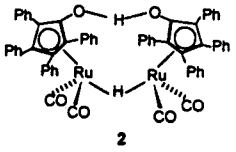
B.A. Persson, A.L.E. Larsson, M. Le Ray, J.E. Bäckvall, *J. Am. Chem. Soc.* 1999, *121*, 1645

Dynamic Kinetic Resolution of Isomeric Diols

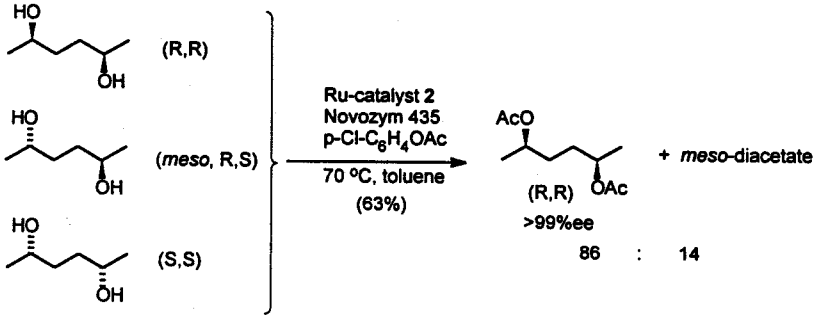
Racemate : *Meso* ≈ 1:1

(RR : RS : SS = 1 : 2: 1)

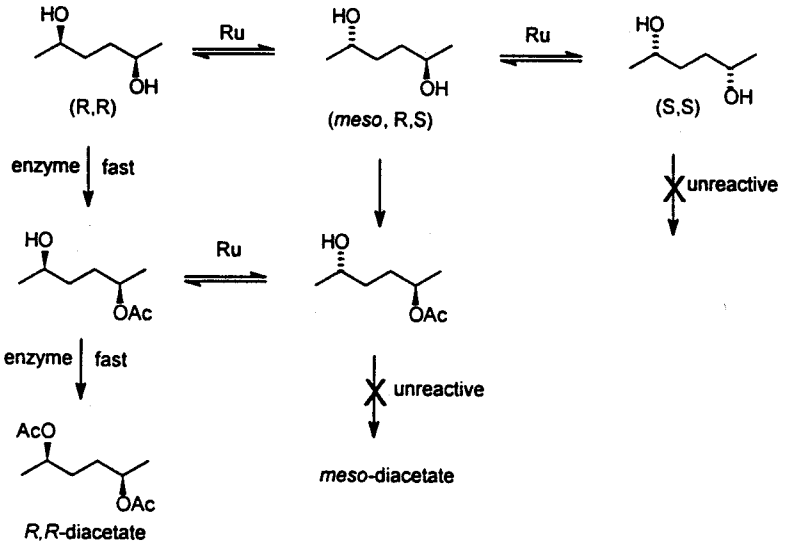
Ru-catalyst:

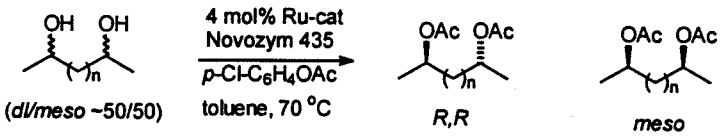


2



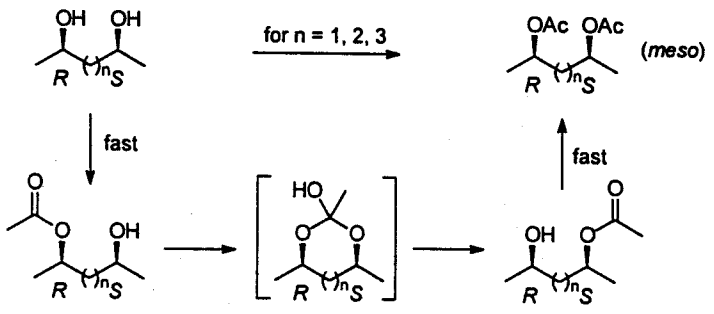
Dynamic kinetic resolution involving two stereocenters



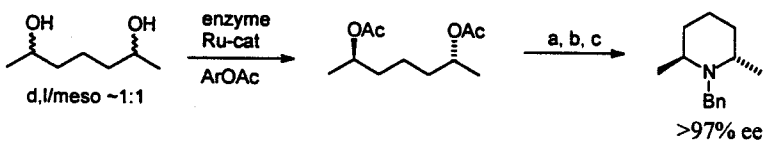


	Yield of diacetate	*R,R/meso*	%ee (of *R,R*)
n = 1	90%	38/62	>99
n = 2	63%	86/14	>99
n = 3	63%	90/10	>99

Formation of *meso*-compound by intramolecular acyl transfer



Application to enantioselective synthesis of C_2-symmetric 2,6-substituted piperidine

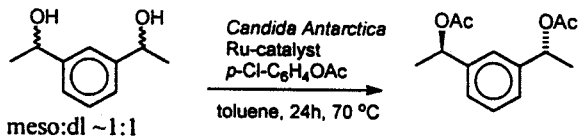


d,l/meso ~1:1

>97% ee

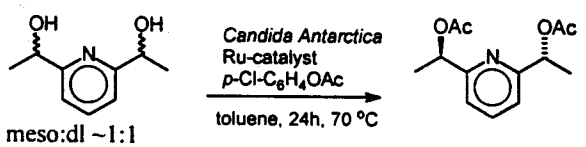
a) K_2CO_3, MeOH-H_2O, rt., 16 h, 82%; b) MsCl, NEt_3, CH_2Cl_2, -15°C , 72%
c) $BnNH_2$, rt, 74%.

Preparation of enantiomerically pure diol derivatives from meso/dl mixtures



meso:dl ~1:1

76% (>99%ee)



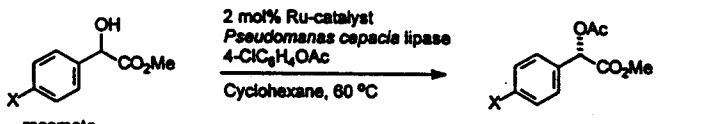
meso:dl ~1:1

78% (>99%ee)

No meso diacetate formed

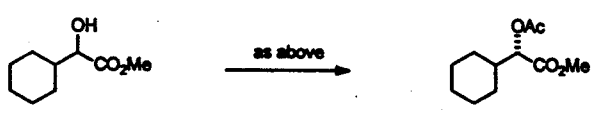
B. A. Persson, F. F. Huerta, and J. E. Bäckvall, *J. Org. Chem.* 1999, *64*, 5237

Dynamic kinetic resolution of hydroxy acids



racemate
X= H, OMe, Br

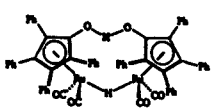
X = H; 80% (94% ee)
X = OMe; 76% (94% ee)
X = Br; 69% (98%ee)



racemate

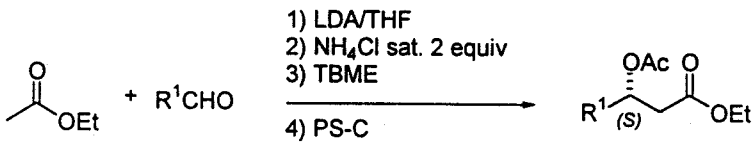
80% (98% ee)

Ru-catalyst:



F. F. Huerta, Y. R. S. Laxmi, J. E. Bäckvall, *Organic Lett.* **2000**, *2*, 1037

One Pot Asymmetric Aldol Adducts via Dynamic Kinetic Resolution



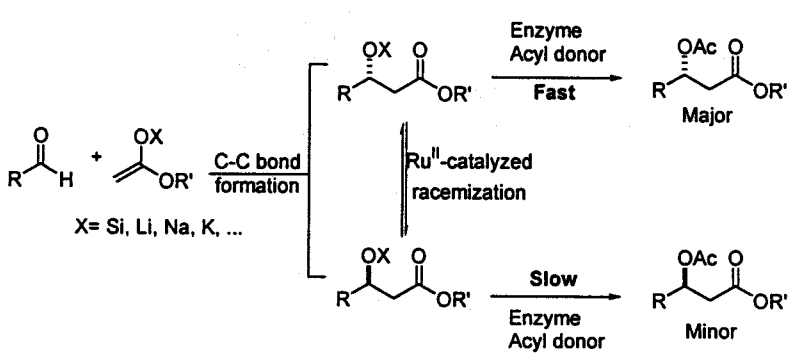
R^1	yield	
Ph	73%	95% ee
*p*MeO-Ph	69%	99% ee
$PhCH_2$	75%	96% ee
Cy	71%	70% ee

PS-C = lipase of Pseudomonas Species type C

F. Huerta, unpublished results

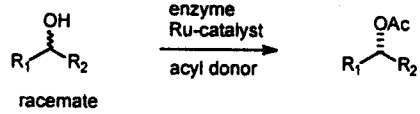
One Pot Asymmetric Aldol Adducts via Dynamic Kinetic Resolution

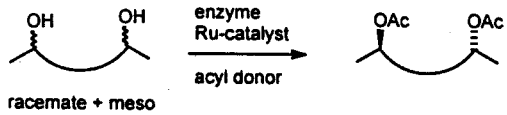
Mechanism:



Conclusions

Efficient deracemization of alcohols

A: 

B: 

C: α- and β-hydroxy esters (racemate) —enzyme, Ru-catalyst, acyl donor→ α- and β-acetoxy esters (enantiomericaly pure)

Enantiomerically pure products obtained with efficient use of all the starting material

Acknowledgements

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Santosh Laxmi
Mikaël Le Ray
Anders Persson
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