From Racemic to Enantiorich Compounds: Recent Advances in Transition-metal Catalyzed Enantioconvergent Transformations

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Literature Review – 14 Dec 2017

University of Oxford

Content

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Question / Food Breaks

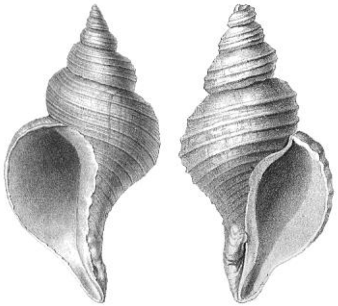
1. Introduction

Chirality, enantiorich molecules, and enantioselective preparations

Introduction: Concepts

Chirality

A chiral molecule is a type of molecule that has a non-superposable mirror image.

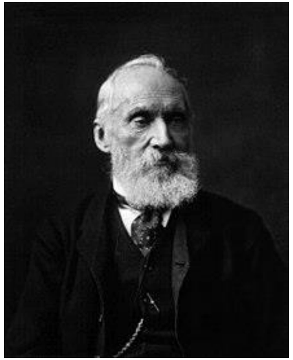


Enantiomer

Also known as an optical isomer, is one of two stereoisomers that are mirror images of each other that are non-superposable.

Enantioselective Preparation

Method for preparation of chemical compounds which aims to bias the synthesis in favour of producing one enantiomer over another enantiomer.

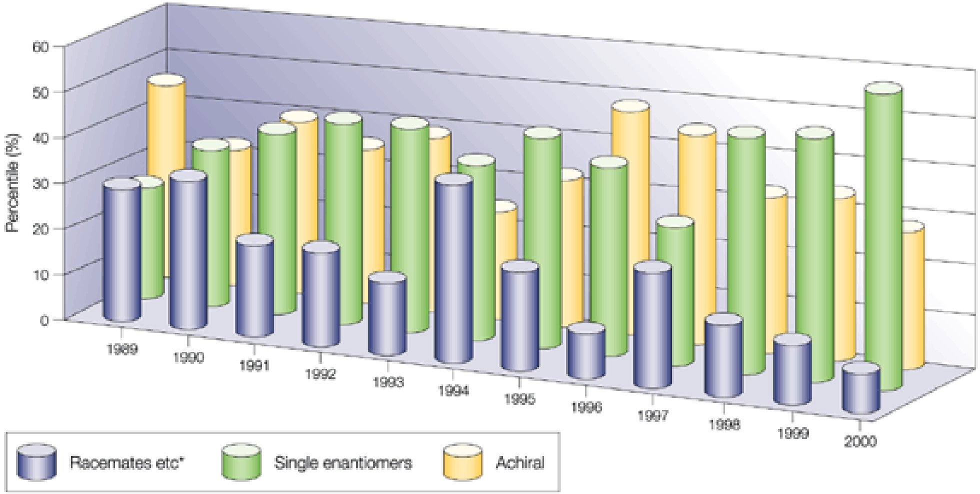


1893, Lord Kelvin, Oxford University Junior Scientific Club

‘I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.’

Introduction: Why are they important?

- Enantiorich compounds play a critical role in pharmaceuticals, agrochemicals, as well as everyday life;
- In 1987: 57% marketed drugs were chiral; 2% single enantiomers;
- In 2006: 80% drugs approved by FDA were chiral; 75% single enantiomers;
- The percentage of single enantiomer variant drugs doubled (40% to 80%) from 2000 to 2004;
- Small change in chemical structure leads to big change in bioactivity;

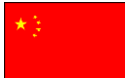


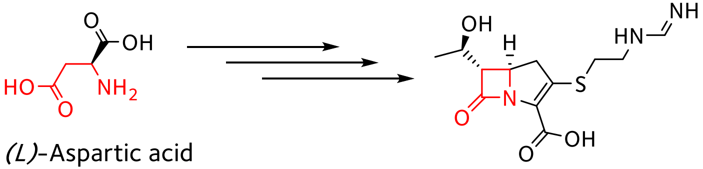
Challener C. A. *Overview of chirality. In: Chiral drugs.* 1st ed. Aldershot (England): Ashgate Publisher. **2001**; 3-14.
Drayer D. E. *The early history of stereochemistry. In: Drug stereochemistry. Analytical methods and pharmacology.* 2nd ed., Wainer IW, editor. New York: Marcel Dekker Publisher. **1993**; 1-24.
Lin G. Q. *Chiral Drugs: Chemistry and Biological Action.* John Wiley & Sons, Hoboken. **2011**. 472.

Introduction: Chiral pool synthesis

- *Chiral pool synthesis*: use of enantiopure, readily available natural products to obtain more complex structures;
- Especially helpful if the desired molecule bears a great resemblance to starting material;
- Limited by availability;
- Not all natural products are cheap;

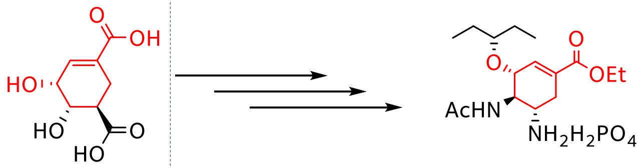

$150,000 per kg from Sigma-Aldrich


$1-25 per kg from Alibaba



(L)-Aspartic acid

Imipenem (Primaxin)
Antibiotic for treating multiple drug-resistant Gram-negative bacteria



Shikimic acid

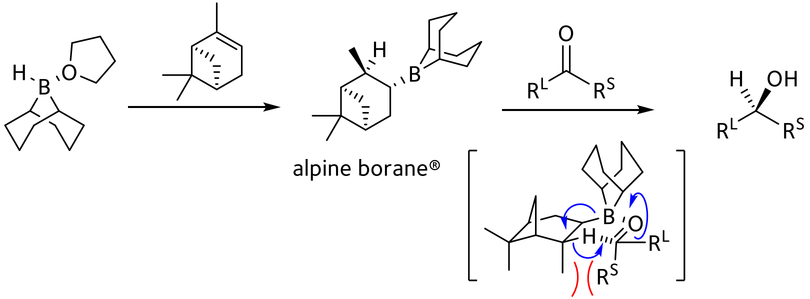
Oseltamivir (Tamiflu)
antiviral medication used to treat and prevent influenza A and influenza B (flu)

Guthikond *et. al. Pure & Appl. Chem.* **1987**, *59(3)*, 455.
Karpf *et. al. J. Org. Chem.* **2001**, *66(6)*, 2044.

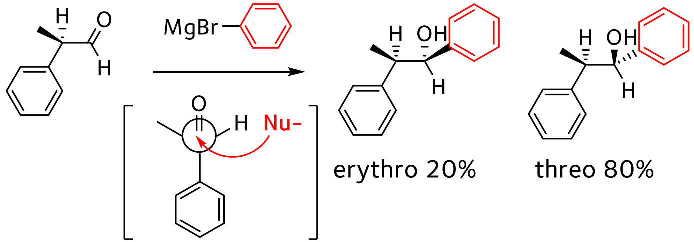
Introduction: Asymmetric synthesis

- *Asymmetric synthesis*: use of various techniques to prepare the desired compound in high enantiomeric excess.
- Techniques encompassed include the use of **chiral reagents**, **chiral catalysts**, and **asymmetric induction**.
- The use of enzymes (**biocatalysis**) may also produce the desired compound (limited by availability);

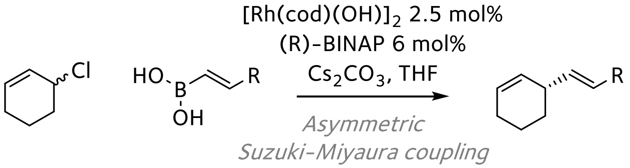
Chiral reagent



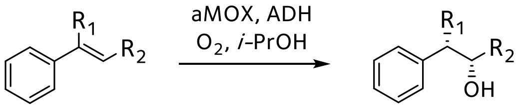
Asymmetric induction

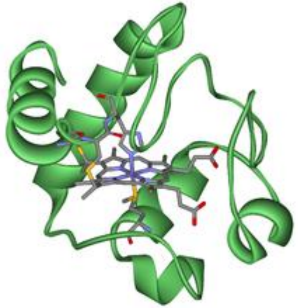


Chiral catalyst



Biocatalyst





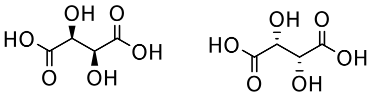
Midland *et. al. Org. Synth. Coll. Vol. 7*, 402.
Schafer *et. al. Nature Chem.* **2017**, *8*, 15762.

Cram *et. al. J. Am. Chem. Soc.* **1952**, *74(23)*, 5828.
Colombo *et. al. Clin. Microbiol. Rev.* **2011**, *24(4)*, 682.
Hammer *et al. Science* **2017**, *358*, 215.

Introduction: Chiral resolution

- *Chiral resolution*: a process for the separation of racemic compounds into their enantiomers;
- An important tool in the production of optically active drugs;
- Only 50% of a desired enantiomer is obtained;

Separation by tweezer

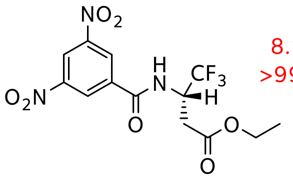


Spontaneous resolution: tartaric acid

Separation by column

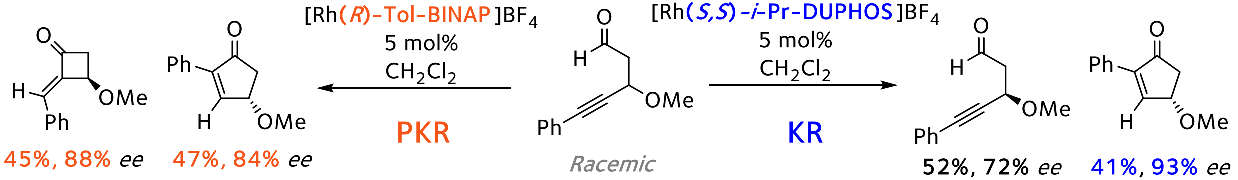
Chiral column: HPLC

hexane / EtOAc (5:1)
61% *ee* sample
8.1% *ee* (first fraction)
>99.9% *ee* (last fraction)



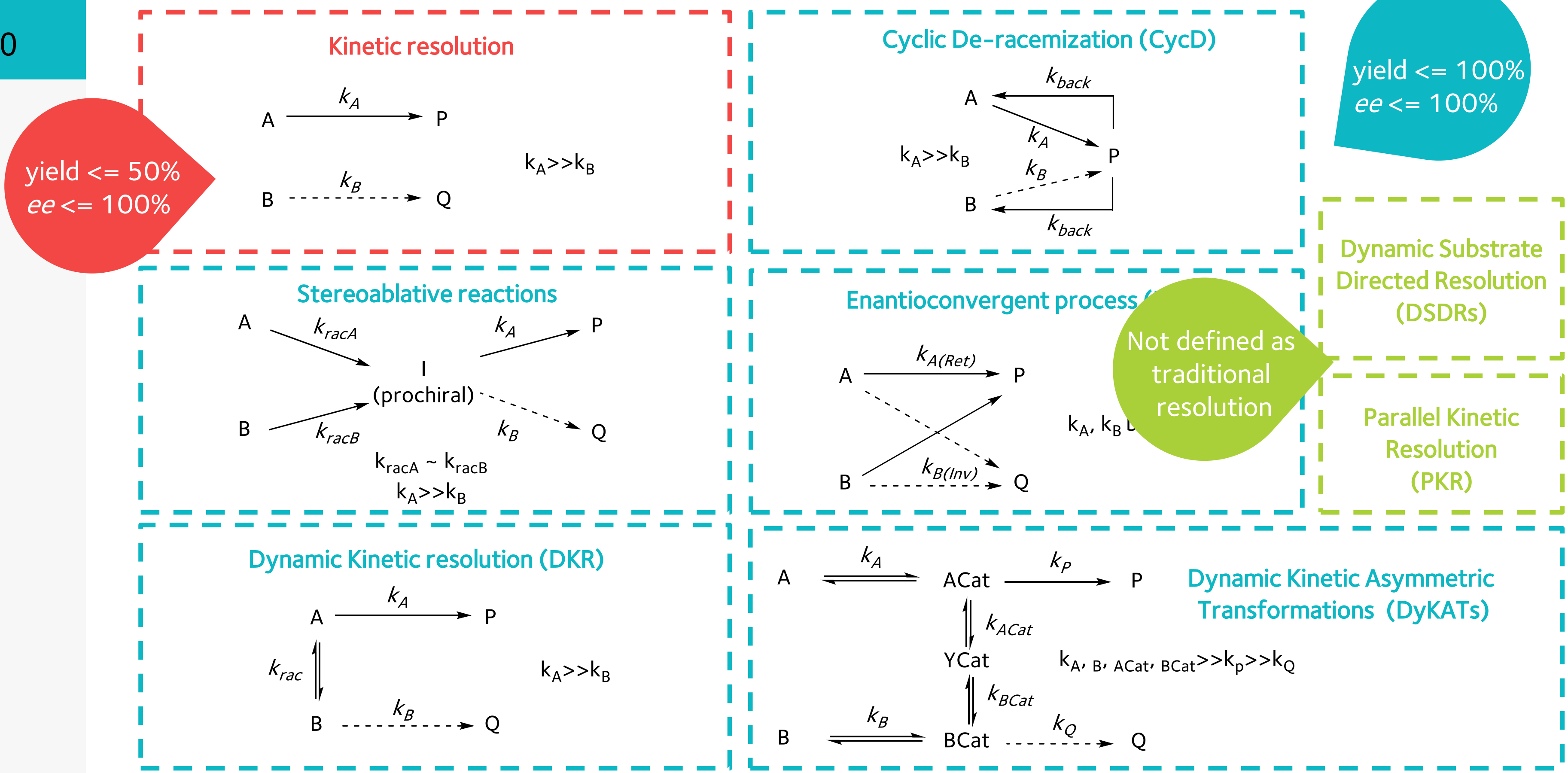
Achiral column: enantiomer self-disproportionation

Kinetic resolution (KR) / Parallel kinetic resolution (PKR)



Andrade-Gamboa *et. al. J. Chem. Educ.* **2007**, *84 (11)*, 1783.
Kauffman *et. al. J. Chem. Educ.* **1975**, *52*, 777.
Fujima *et. al. Org. Process Res. Dev.* **2006**, *10 (5)*, 905.
Cundy *et. al. J. Chromatogr.* **1983**, *281*, 17.
Soloshonok *et. al. Angew. Chem. Int. Ed.* **2006**, *45(5)*, 766.
Tanaka *et. al. J. Am. Chem. Soc.* **2009**, *131*, 444.

OVERCOME THE LIMITATIONS



2.
Stereoablative reactions

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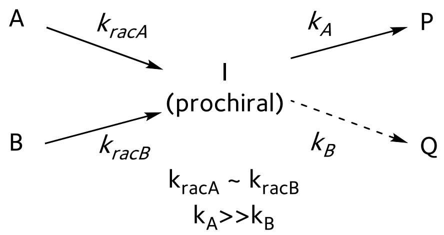
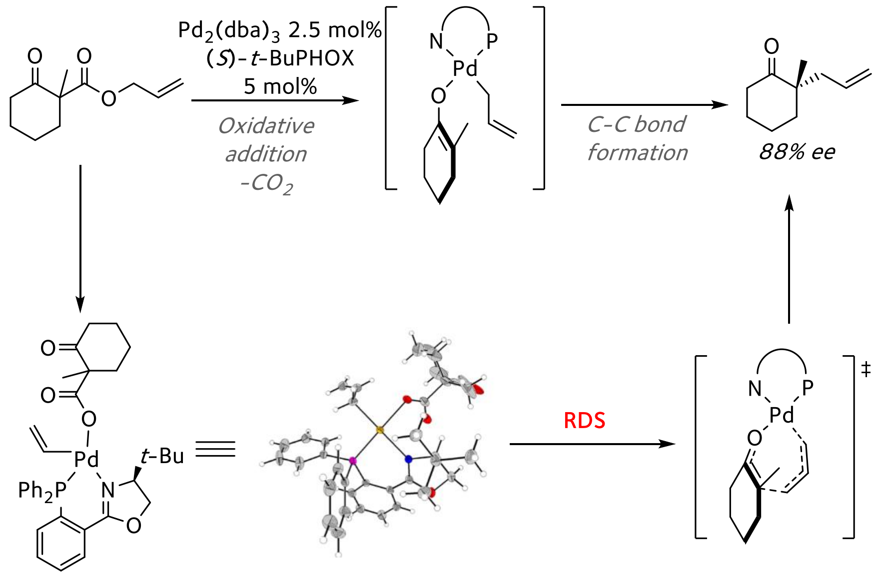
Stereoablative reactions

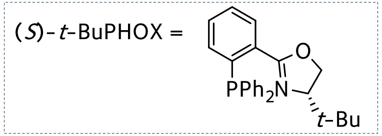
- A key reactive intermediate is formed *via* the **irreversible** destruction of a stereocenter;
- Identical or nearly identical rates of stereoablation ($k_{racA} \sim k_{racB}$);
- Substantially different rates of product formation ($k_A >> k_B$);
- No discernible dynamic or reversible nature to the process with respect to the organic stereogenicity;



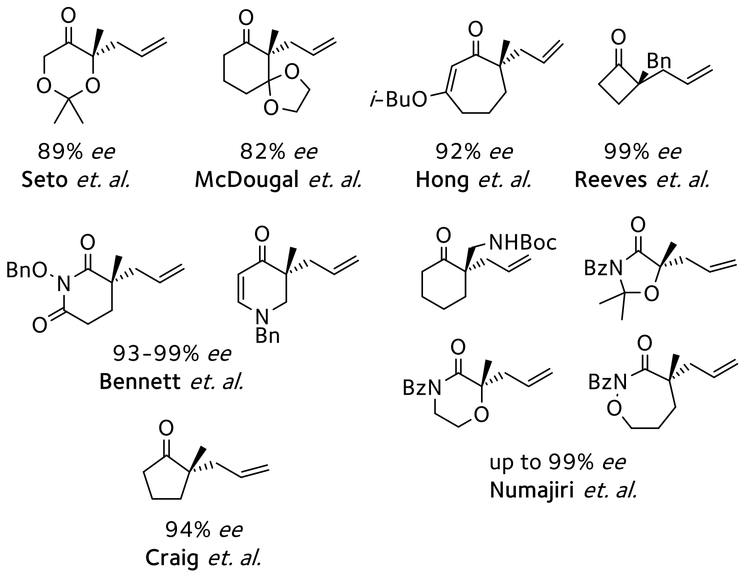
STEREOABLATIVE REACTIONS

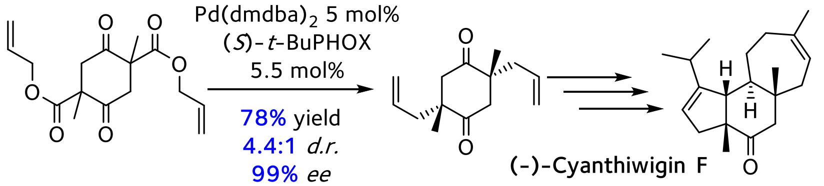
Allylic Alkylation





Substrate Scope

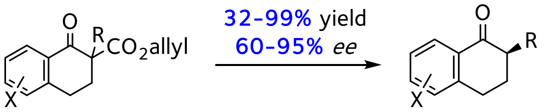


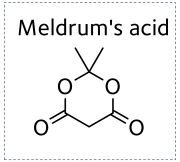


Trost *et al. Chem. Rev.* **1996**, *96*, 395.
Keith *et. al. J. Am. Chem. Soc.* **2007**, *129*, 11876.
Sherden *et. al. Angew. Chem. Int. Ed.* **2009**, *48*, 6840.
Enquist *et. al. Nature* **2008**, *453*, 1228.

Stereoablative reactions

Enantioselective Protonation





Condition A:
$Pd(OAc)_2$ 10 mol%
(*S*)-*t*-BuPHOX 12.5 mol%
HCO_2H, dioxane, 40 °C

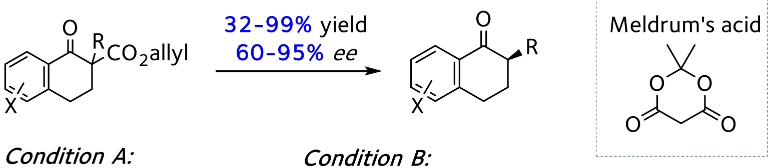
Condition B:
$Pd_2(dba)_3$ 5 mol%
(*S*)-*t*-BuPHOX 12.5 mol%
Meidrum's acid, dioxane, 40 °C

- substantial optimization was required for each substrate;
- enolates were not always protonated from the same face;
- Very limited mechanistic studies;

Mohr *et. al. J. Am. Chem. Soc.* **2006**, *128*, 11348.
Marinescu *et. al. Org. Lett.* **2008**, *10*, 1039.
Zhang *et. al. J. Am. Chem. Soc.* **2016**, *138*, 8084.

STEREOABLATIVE REACTIONS

Enantioselective Protonation



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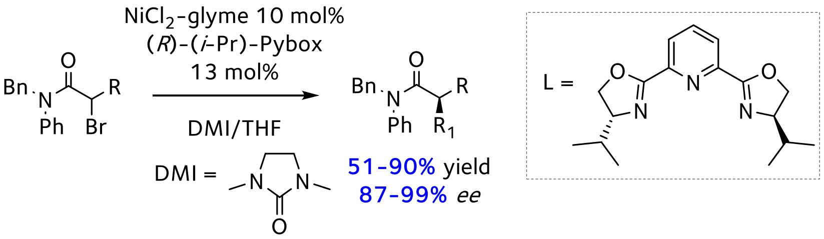
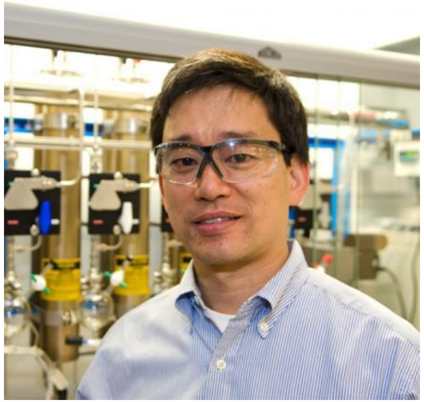
Cross-coupling Reactions



Mohr *et. al. J. Am. Chem. Soc.* **2006**, *128*, 11348.
Marinescu *et. al. Org. Lett.* **2008**, *10*, 1039.
Zhang *et. al. J. Am. Chem. Soc.* **2016**, *138*, 8084.

Fischer *et. al. J. Am. Chem. Soc.* **2005**, *127*, 4594.

Stereoablative reactions



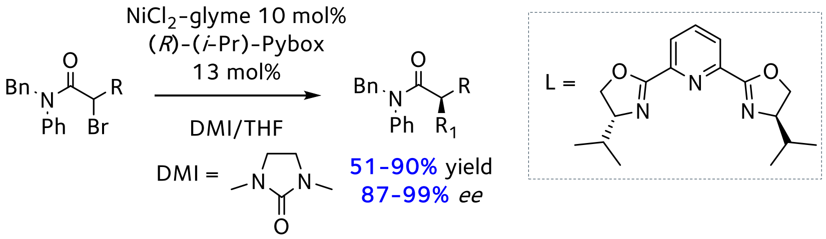
Gregory C. Fu

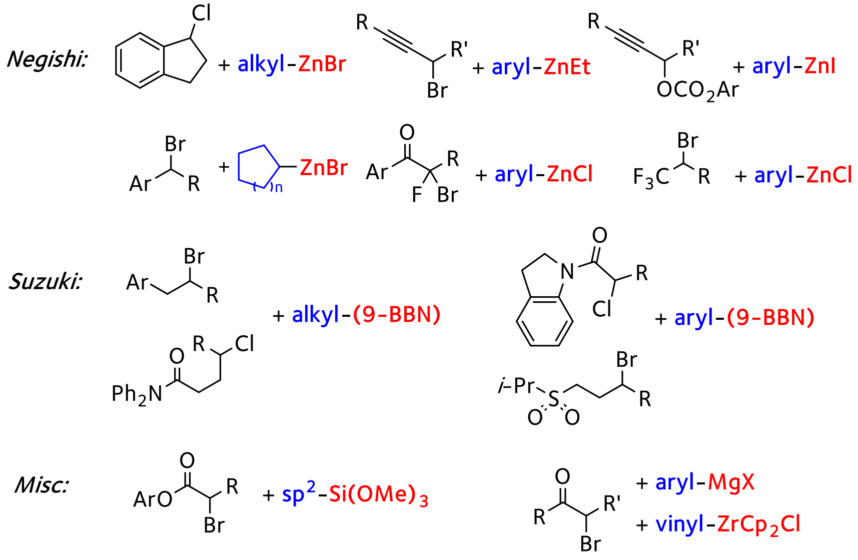
2012 – present Altair Professor of Chemistry, Caltech
1999 – 2012 Professor of Chemistry, MIT

Selected publication (35 in total from 2005 - 2017)

Negishi: (a) Do *et. al. J. Am. Chem. Soc.* **2013**, *135*, 16288; (b) Liang *et. al. J. Am. Chem. Soc.* **2014**, *136*, 5520; (c) Liang *et. al. J. Am. Chem. Soc.* **2015**, *137*, 9523.
Suzuki: (a) Saito *et. al. J. Am. Chem. Soc.* **2008**, *130*, 6694; (b) Lundin *et. al. J. Am. Chem. Soc.* **2010**, *132*, 11027; Wilsily *et. al. J. Am. Chem. Soc.* **2012**, *134*, 5794.
Hiyama: Dai *et. al. J. Am. Chem. Soc.* **2008**, *130*, 3302.
Kumada: Lou *et. al. J. Am. Chem. Soc.* **2010**, *132*, 1264.
Zirconium-Negishi: Lou *et. al. J. Am. Chem. Soc.* **2010**, *132*, 5010.

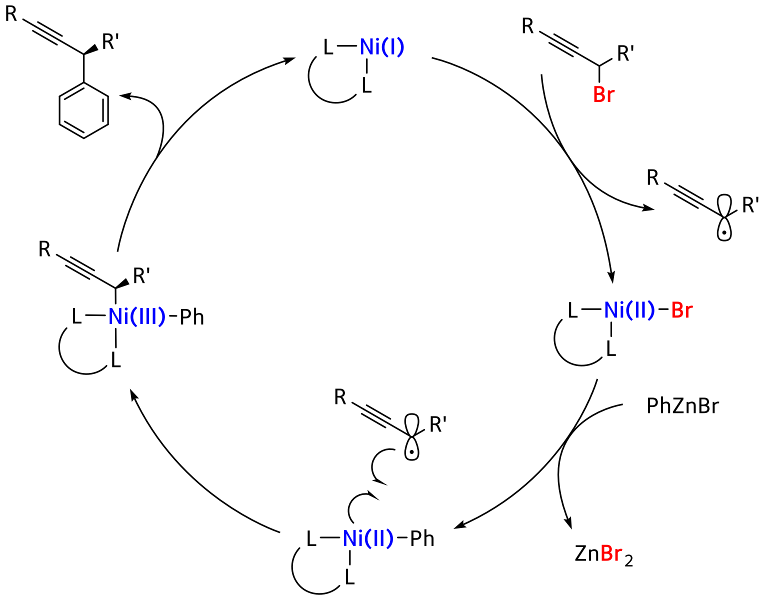
Cross-coupling Reactions





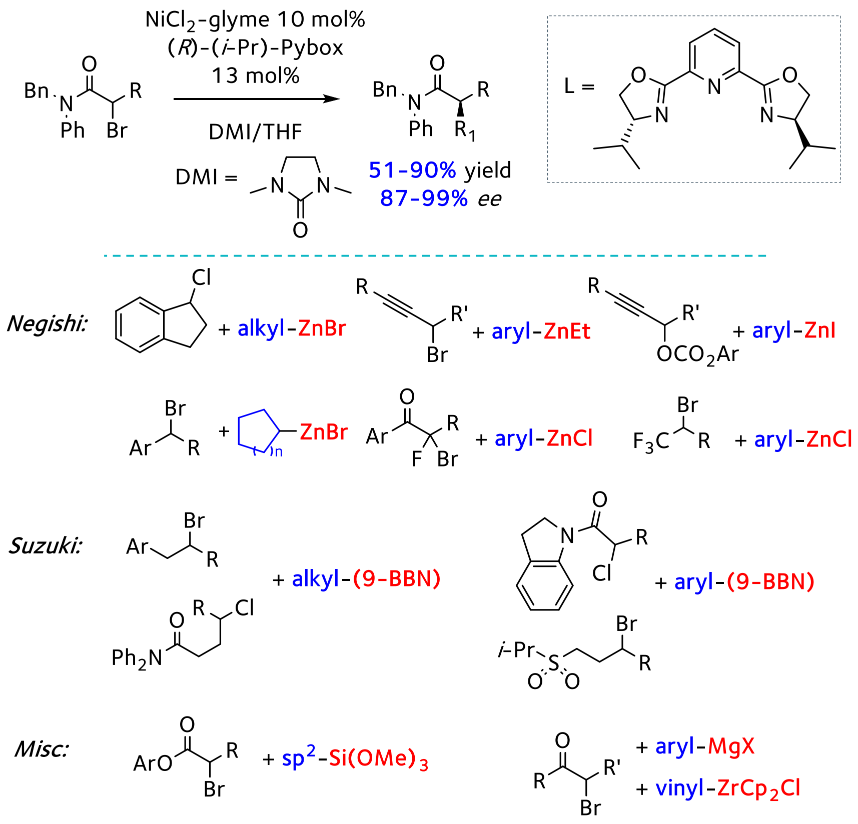
Fischer *et. al. J. Am. Chem. Soc.* **2005**, *127*, 4594.

Stereoablative reactions



Schley *et. al. J. Am. Chem. Soc.* **2014**, *136,* 16588.

Cross-coupling Reactions



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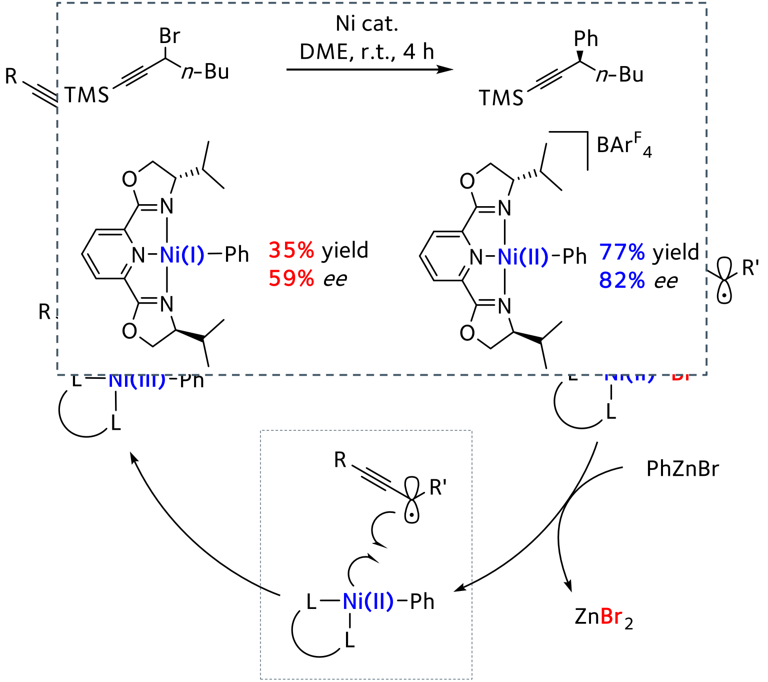
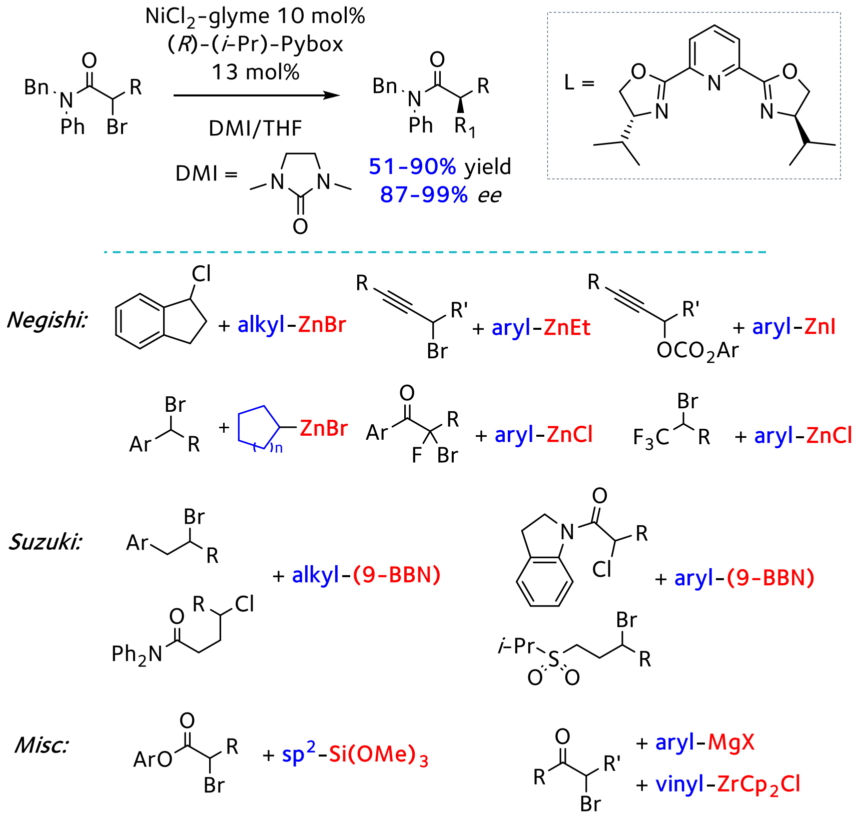
Stereoablative reactions



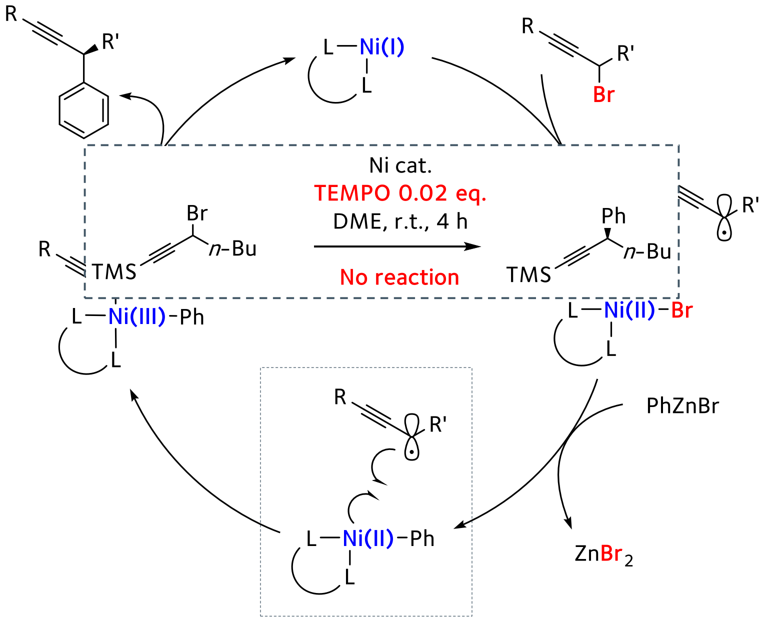
Schley et. al. J. Am. Chem. Soc. **2014**, *136*, 16588.

Cross-coupling Reactions



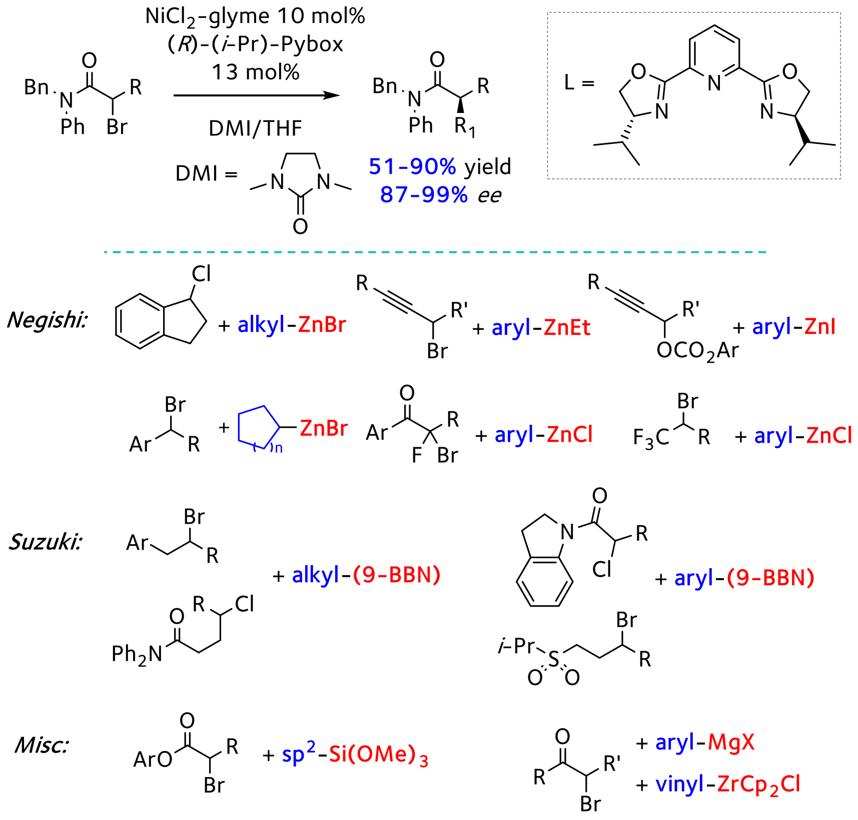
Fischer et. al. J. Am. Chem. Soc. **2005**, *127*, 4594.

STEREOABLATIVE REACTIONS



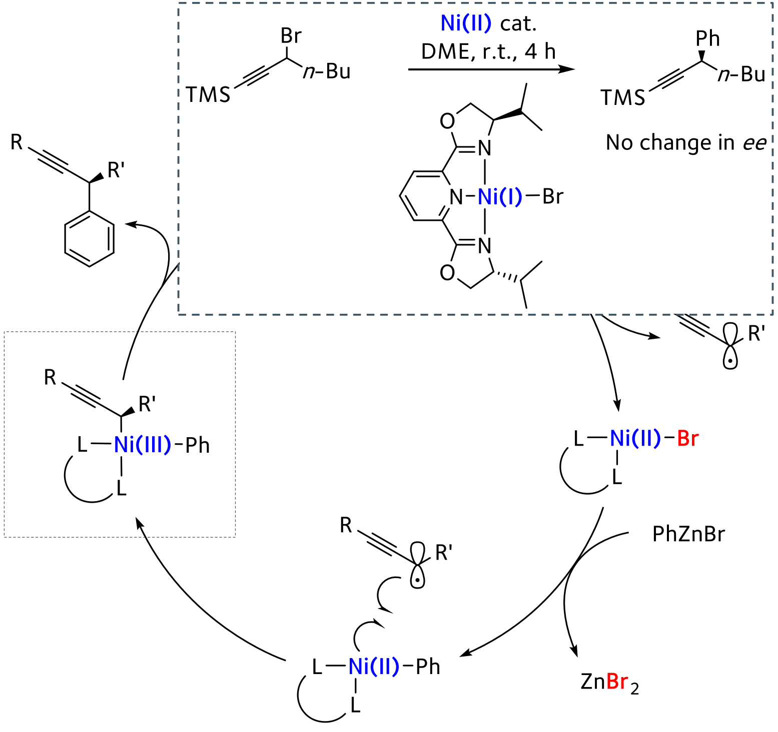
Schley *et. al. J. Am. Chem. Soc.* **2014**, *136*, 16588.

Cross-coupling Reactions



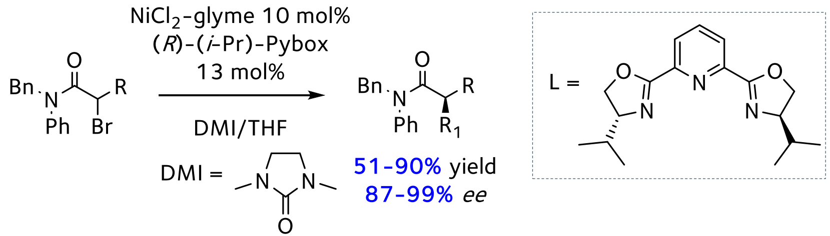
Fischer *et. al. J. Am. Chem. Soc.* **2005**, *127*, 4594.

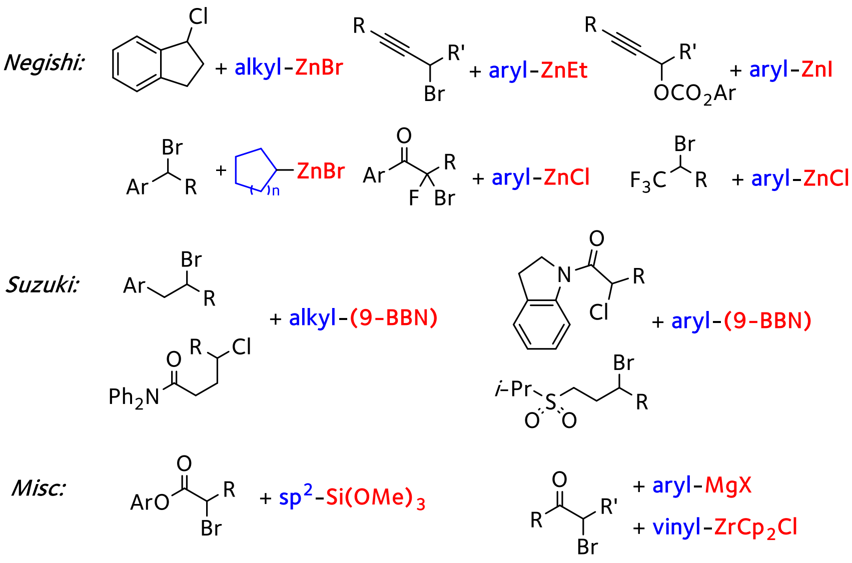
Stereoablative reactions



Schley *et. al. J. Am. Chem. Soc.* **2014**, *136*, 16588.

Cross-coupling Reactions

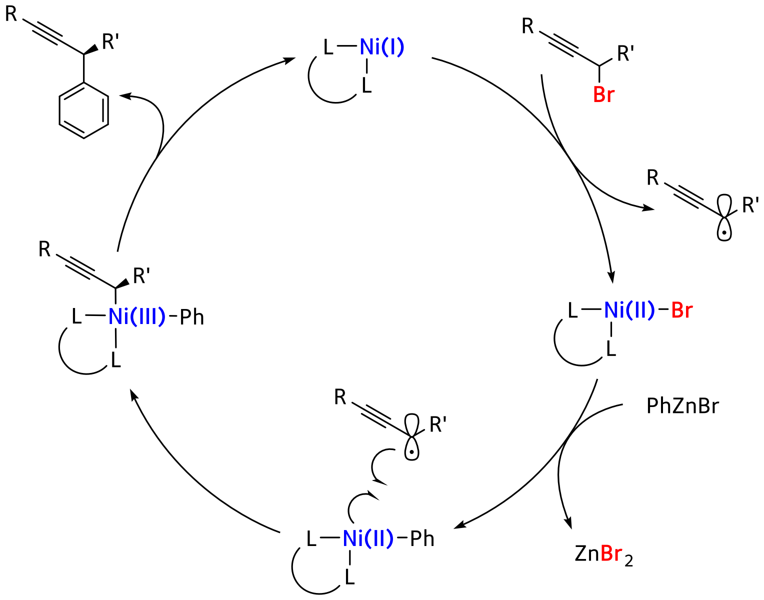




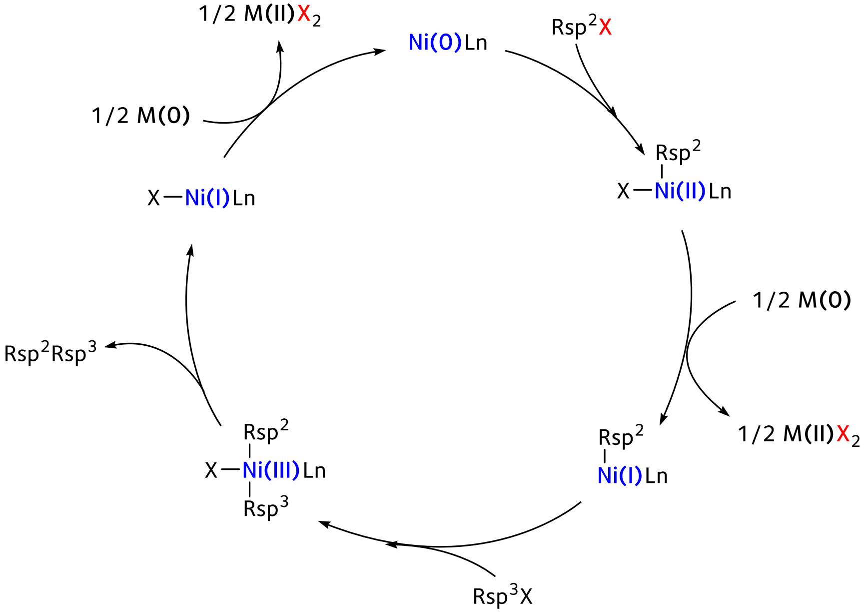
Fischer *et. al. J. Am. Chem. Soc.* **2005**, *127*, 4594.

Stereoablative reactions

Traditional Cross-coupling Reactions



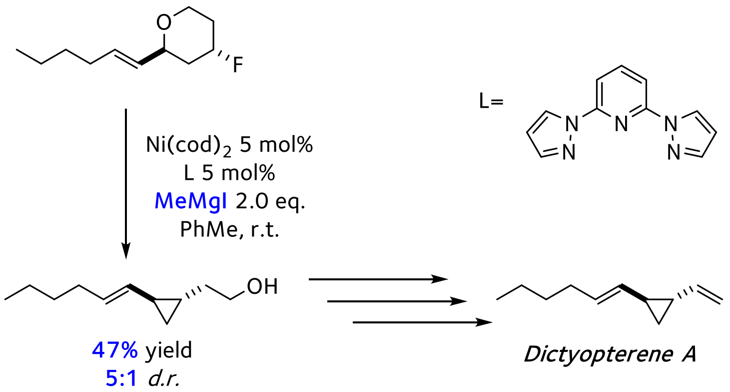
Cross-Electrophile Couplings

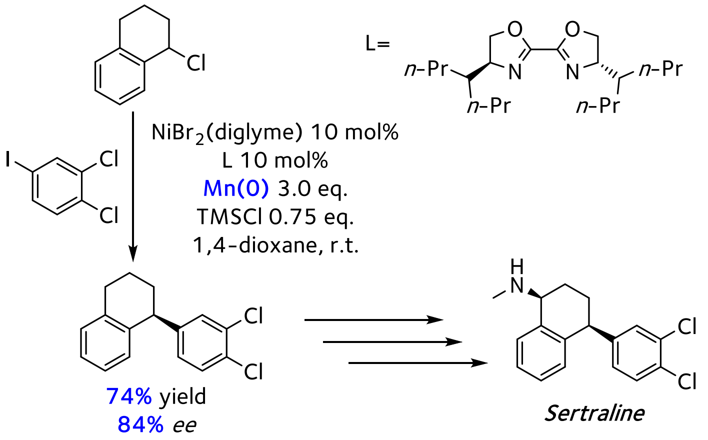


Schley *et. al. J. Am. Chem. Soc.* **2014**, *136,* 16588.

Lucas *et. al. Nature Rev. Chem.* **2017**, *asap.*

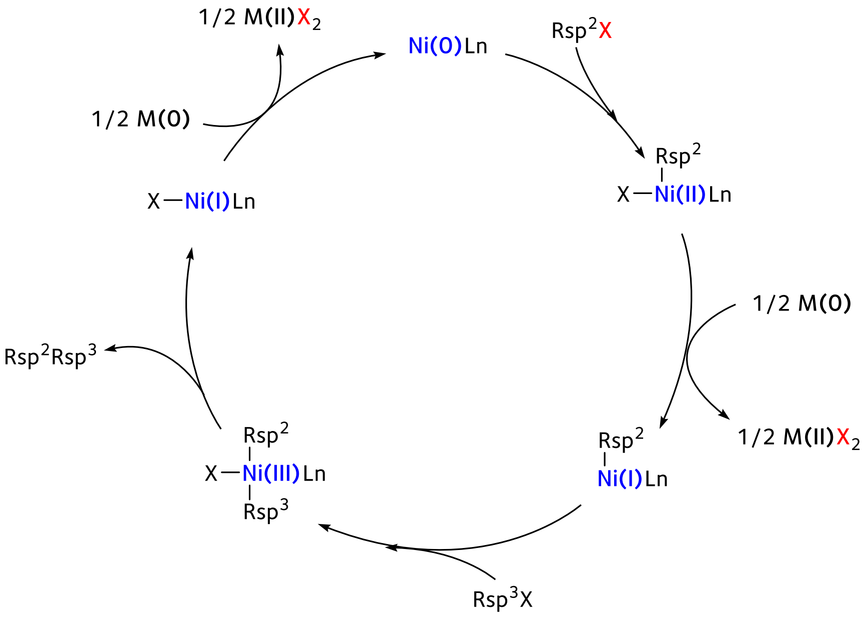
STEREOABLATIVE REACTIONS





Erickson *et. al. J. Am. Chem. Soc.* **2016**, *138,* 14006.
Poremba *et. al. J. Am. Chem. Soc.* **2017**, *139*, 5684

Cross-Electrophile Couplings



Lucas *et. al. Nature Rev. Chem.* **2017**, *asap.*

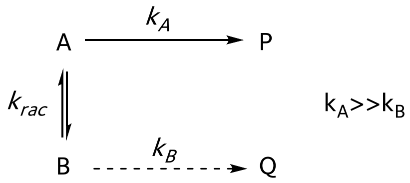
Any Questions?

”

3. Dynamic Kinetic Resolution

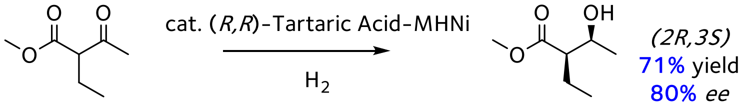
Dynamic Kinetic Resolution (DKR)

- Involve **reversible** racemization prior to the selective reaction of one enantiomer with the chiral catalyst;
- Interconversion of enantiomers must be rapid and independent of the catalyst (fast k_{rac});
- One enantiomer of substrate with the chiral catalyst must occur with a significantly higher rate than that of the other enantiomer ($k_A >> k_B$);
- The equilibrium between A and B shifts according to Le Châtelier's principle as reaction proceeds;

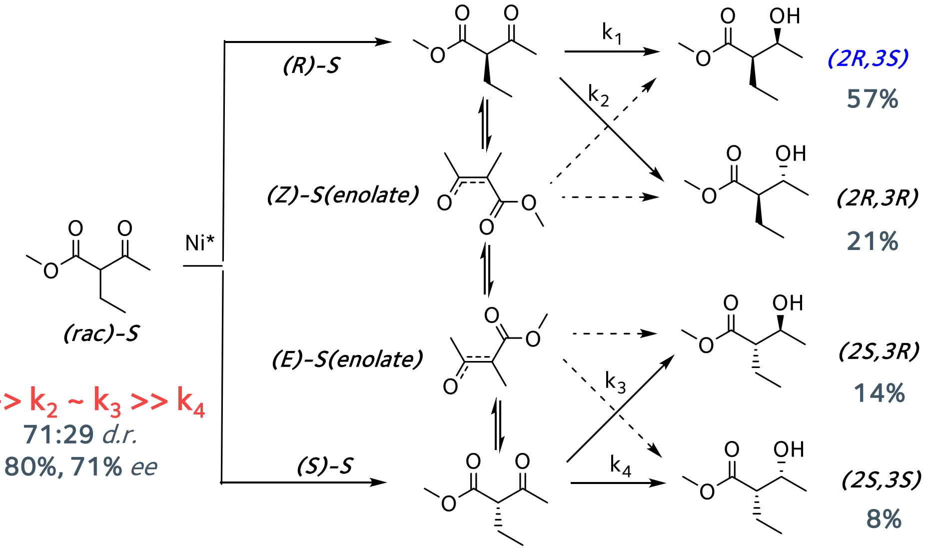


Dynamic Kinetic Resolution (DKR)

Asymmetric Hydrogenation



MHNI = Modified activated nickle prepared by hydrogenlysis of nickle oxide



$k_1 >> k_2 \sim k_3 >> k_4$

71:29 *d.r.*

80%, 71% *ee*

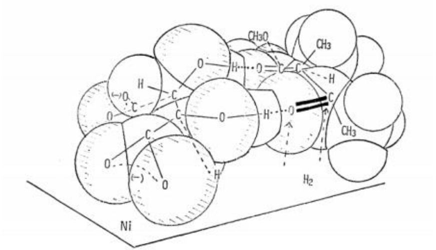


Fig. 1. Schematic representation of the complex between I(keto form) and (*R*,*R*)-tartaric acid on the MNi catalyst. The complex gives (2*S*,3*R*)-III by the at-

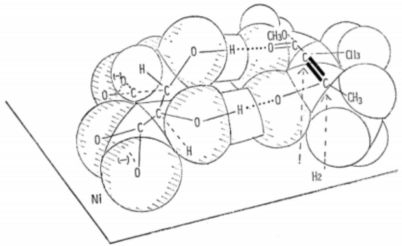
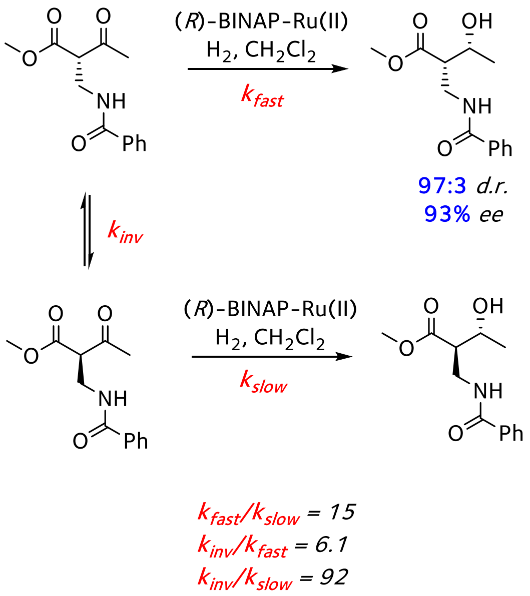


Fig. 2. Schematic representation of the complex between I(enolate) and (*R*,*R*)-tartaric acid on the MNi catalyst. The complex gives (2*S*,3*R*)-III by the attack of hydrogen from the catalyst-side (*si*-face attack).

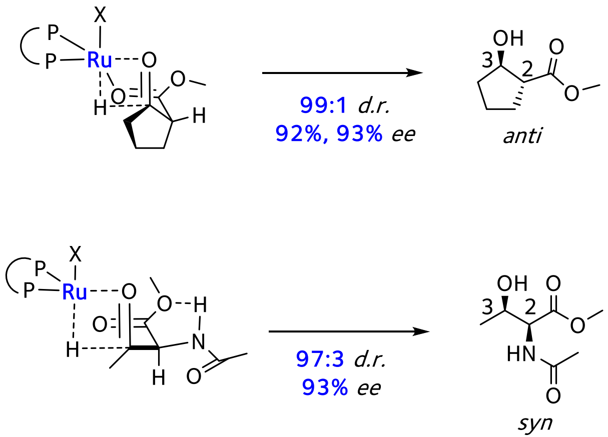
Tai *et. al. Bull. Chem. Soc. Jpn.* **1979**, *52*, 1468.

Dynamic Kinetic Resolution (DKR)

Asymmetric Hydrogenation (Noyori Reduction)



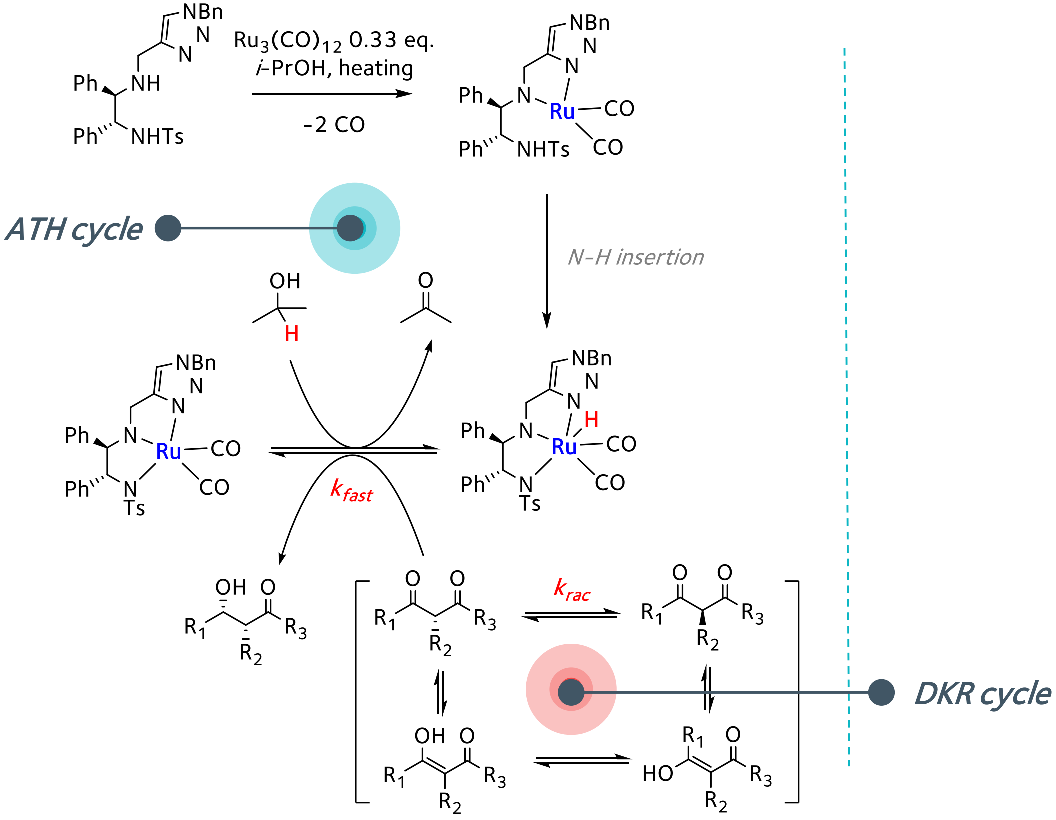
'The absolute configuration at C-3 is governed by the handedness of the BINAP ligand while the C-2 configuration is dependent on substrate structures.'



Noyori *et. al. Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.
Noyori *et. al. J. Am. Chem. Soc.* **1989**, *111*, 9135.
Noyori *et. al. Org. Lett.* **1999**, *1*, 1119.

Dynamic Kinetic Resolution (DKR)

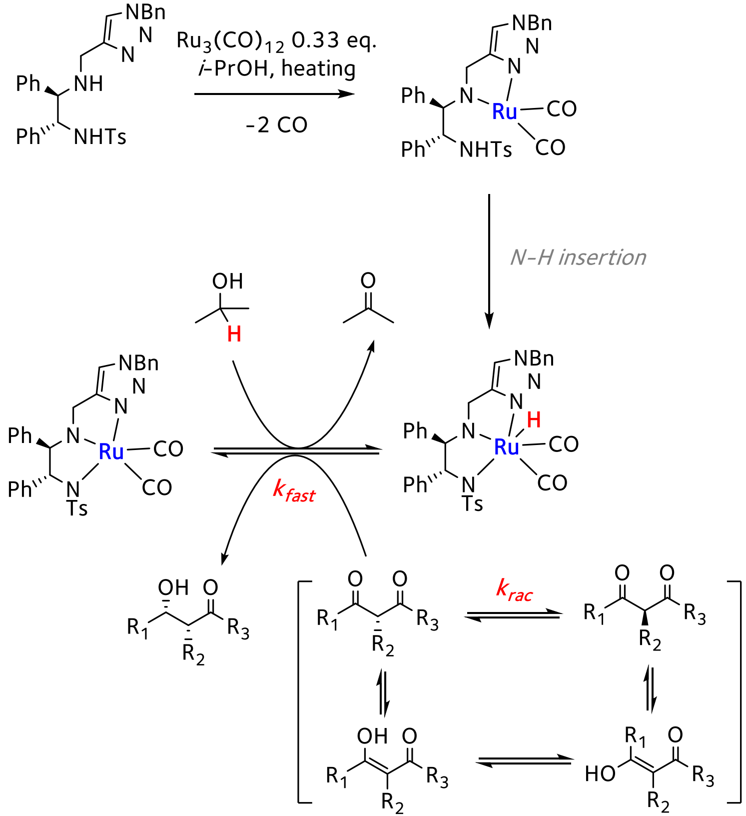
Asymmetric Transfer Hydrogenation (ATH)

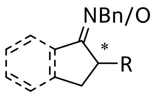
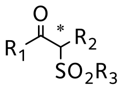
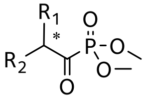
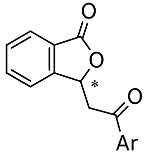
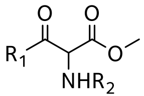


Wang *et. al. Chem. Rev.* **2015**, *115*, 6621.

Dynamic Kinetic Resolution (DKR)

Asymmetric Transfer Hydrogenation (ATH)

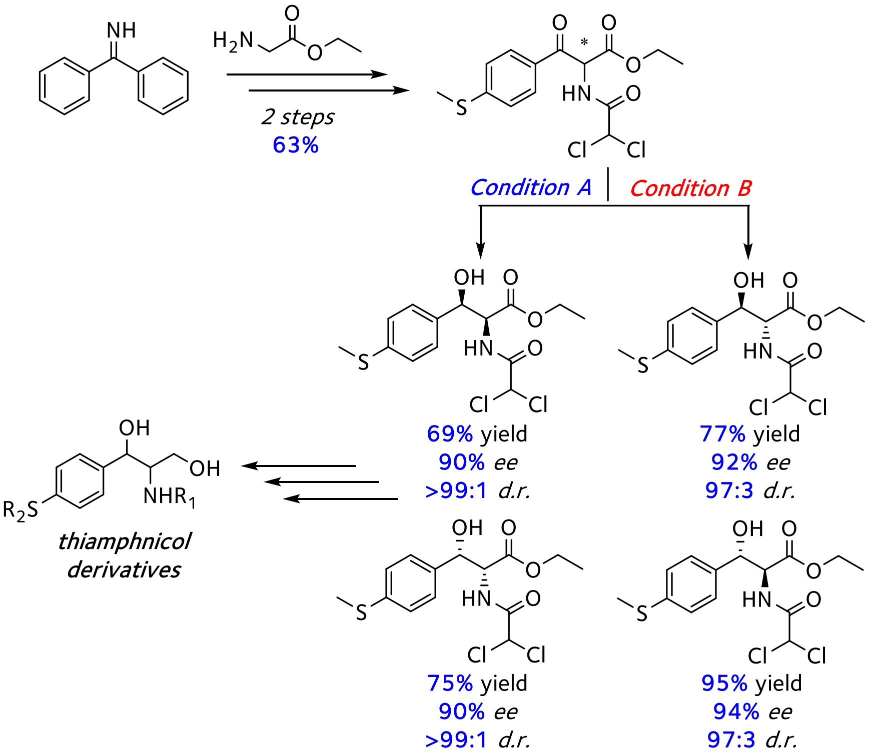


Substrate	Condition	Result	Ref.
	[RuCl(p-cymene)L*] 0.2-2.5 mol% HCO_2H-NEt_3(5:2)	22-98% yield 45-99% *ee* 75:51-99:1 *d.r.*	Ros *et. al.* **2006**
		73-96% yield 18-99% *ee* 67:33-99:1 *d.r.*	Ding *et. al.* **2009**
		84-94% yield >99% *ee* 80:20-95:5 *d.r.*	Corbett *et. al.* **2013**
		90-99% yield 99% *ee* 69:31-90:10 *d.r.*	Cheng *et. al.* **2015**
	$[RuCl_2(C_6H_6)]_2L^*$ 10 mol% HCO_2Na-H_2O	68-85% yield 78-96% ee 87:13-96:4 d.r.	Seashore-Ludlow *et. al.* **2012**

Wang *et. al. Chem. Rev.* **2015**, *115*, 6621.

Dynamic Kinetic Resolution (DKR)

Asymmetric Transfer Hydrogenation (ATH)



Condition A

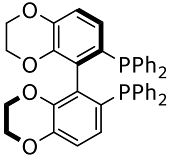
[Ru(cod)(n^3-methylallyl)$_2$]**L***

aq. HBr, H_2 (120 bar)

CH_2Cl_2/EtOH (95:5)

S/C = 33, 50 °C, 48 h

L* =



Condition B

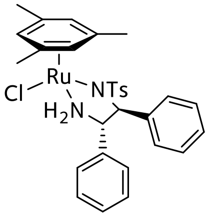
Ru cat.

HCO_2H/Et_3N (5:2)

Et_2O

S/C = 100, 50 °C. 1.5-3 h

Ru cat. =

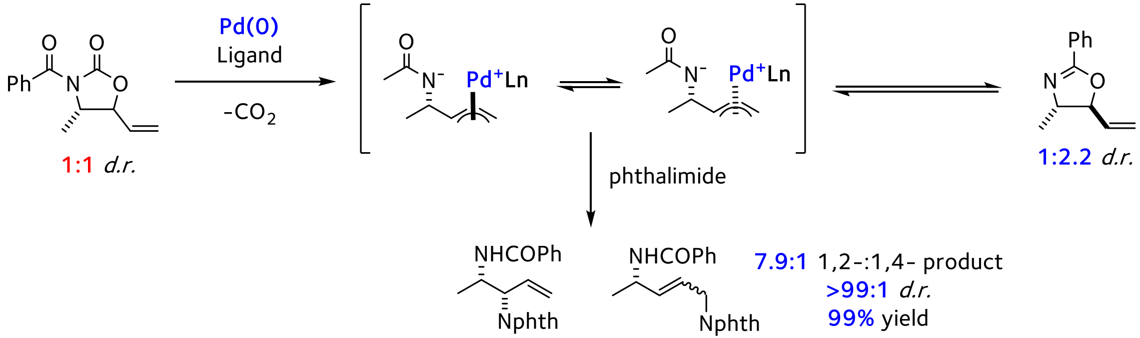


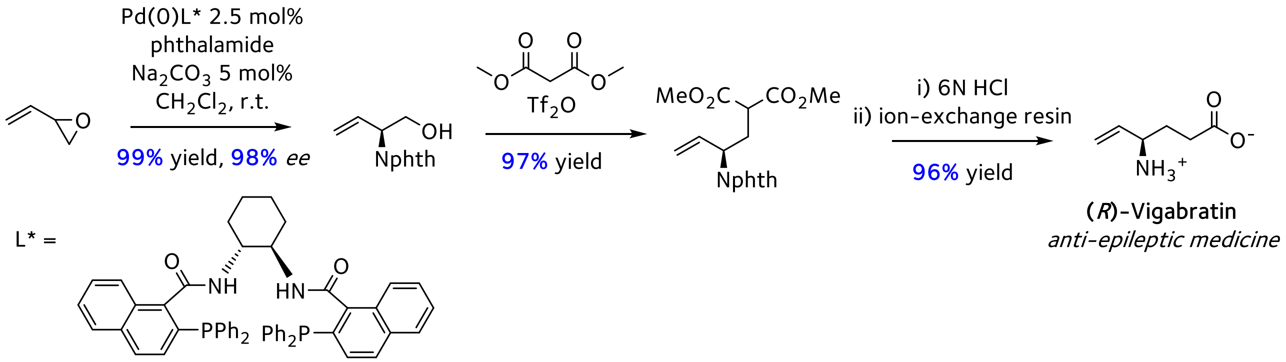
Echeverria *et. al. Synthesis* **2016**, *48,* 2523.

Perez *et. al. Eur. J. Org. Chem.* **2015**, 5949.

Dynamic Kinetic Resolution (DKR)

π-Allyl Palladium Catalysis



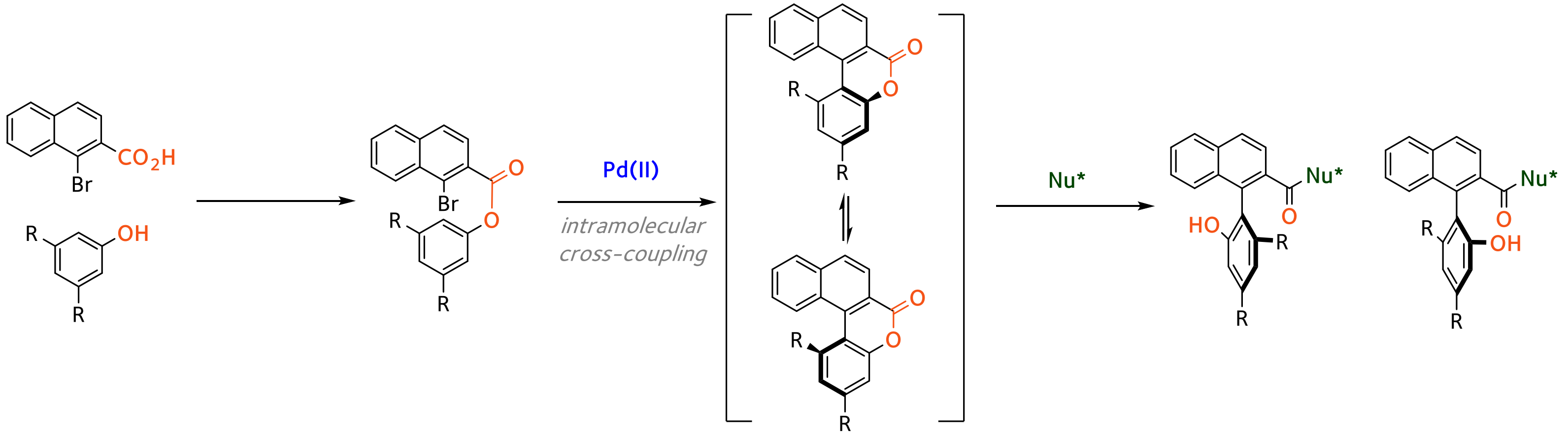


Cook *et. al. Angew. Chem. Int. Ed.* **1999**, *38(1/2)*, 110.
Trost *et. al. J. Am. Chem. Soc.* **2000**, *122 (25)*, 5968.

Dynamic Kinetic Resolution (DKR)

π-Allyl Palladium Catalysis: Atroposelective Reactions

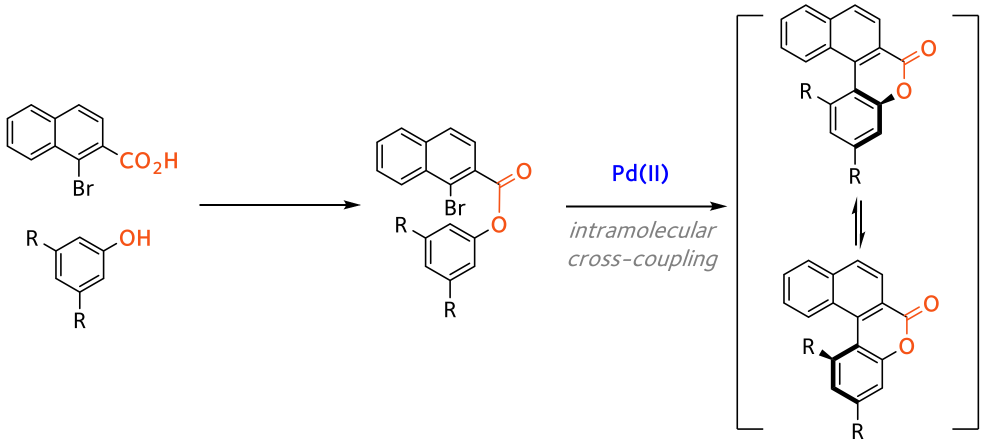
- The '**Lactone Concept**': Bringmann *et. al.*, 2002;
- Intramolecular cross-coupling followed by asymmetric ring cleavage;
- Configurationally unstable lactone intermediate;



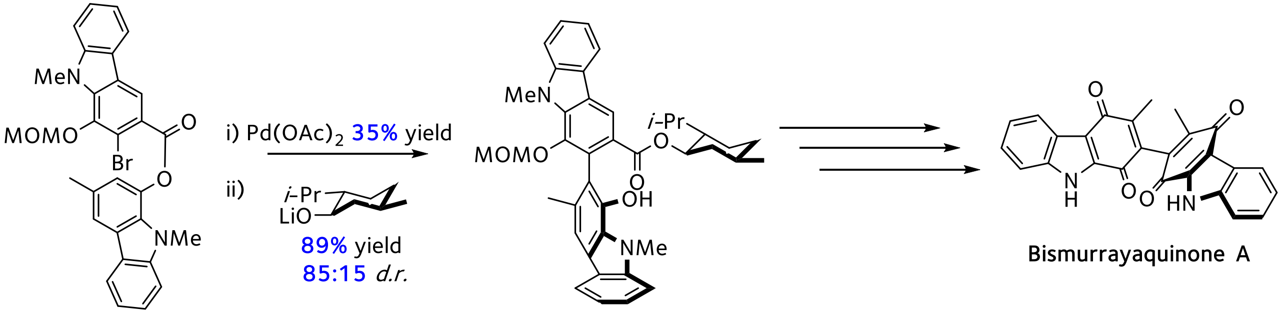
Bringmann *et. al. J. Organomet. Chem.* **2002**, *661*, 31.

Dynamic Kinetic Resolution (DKR)

π-Allyl Palladium Catalysis: Atroposelective Reactions



R	$t_{1/2}$ (r.t.)
H	<< 1 ms
OMe	ca. 1 ms
Me	ca. 1 s
Et	ca. 1 min
i-Pr	ca. 30 min
t-Bu	>2 d



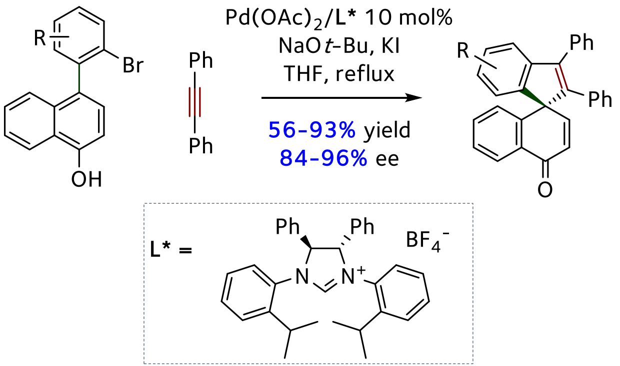
Bismurrayaquinone A

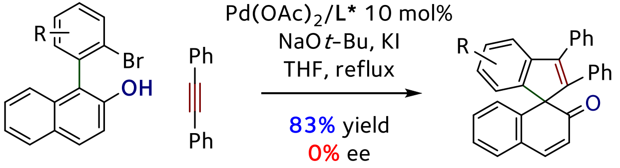
Bringmann *et. al. J. Organomet. Chem.* **2002**, *661*, 31.

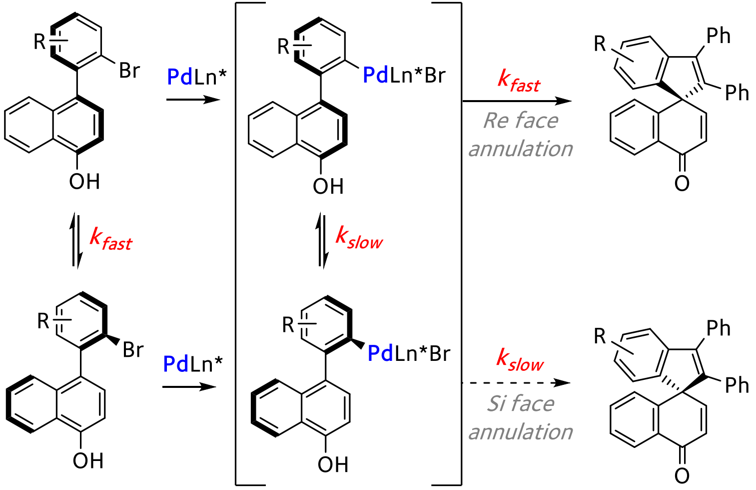
Dynamic Kinetic Resolution (DKR)

π-Allyl Palladium Catalysis: Other Reactions

Dearomative Spirocyclization *via* DKR





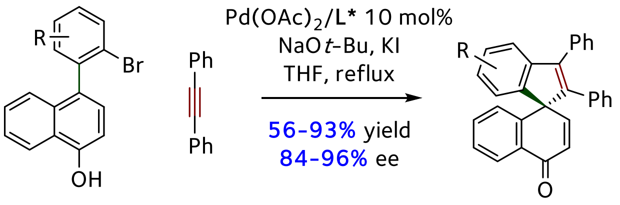


Yang *et. al. J. Am. Chem. Soc.* **2015**, *137*, 4876.

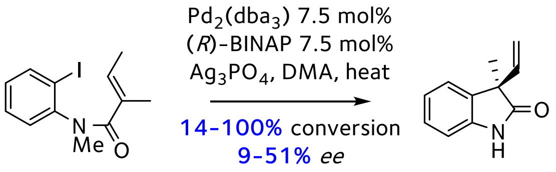
Dynamic Kinetic Resolution (DKR)

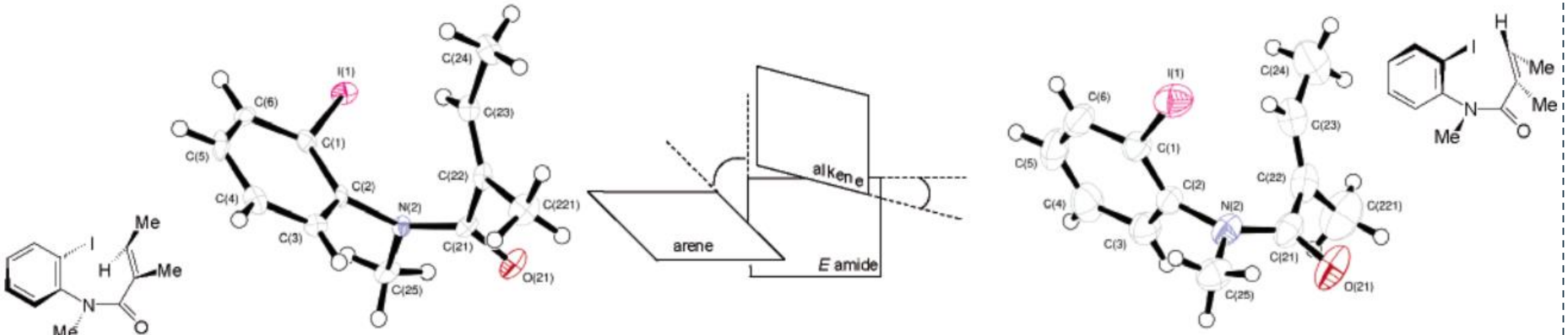
π-Allyl Palladium Catalysis: Other Reactions

Dearomative Spirocyclization *via* DKR



Asymmetric Heck Cyclization





5 **6** **7**

Yang *et. al. J. Am. Chem. Soc.* **2015**, *137*, 4876.
Trost *et. al. J. Am. Chem. Soc.* **2005**, *127*, 14186.
McDermott *et. al. Org. Lett.* **2006**, *8*, 2917.
Hosoi *et. al. Tetrahedron* **2015**, *71*, 2317.

Any Questions?

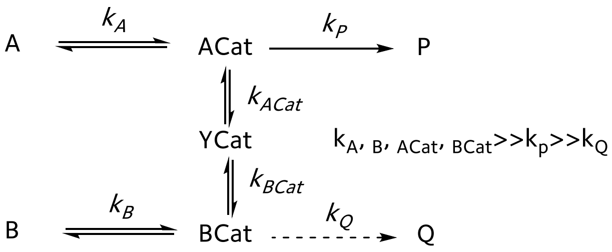
”

4.
Dynamic Kinetic Asymmetric Transformation

Dynamic Kinetic Asymmetric Transformation (DyKAT)

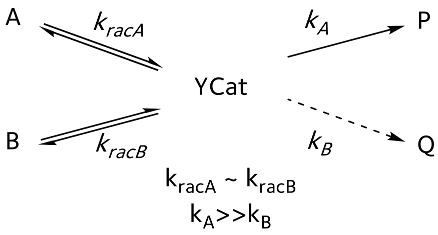
Type I DyKAT

- Binding of both enantiomers to provide a mixture of **diastereomeric** substrate–catalyst pairs (ACat, BCat);
- Rapid equilibration through a prochiral intermediate;
- Resemble DKRs in that $k_{Cat} >> k_P >> k_Q$
- $k_{ACat} \neq k_{BCat}$



Type II DyKAT

- Bear similarity to stereoablative transformations in that $k_{racA} \sim k_{racB} >> k_A >> k_B$
- The loss of chirality is both **reversible** and **catalyst-mediated;**

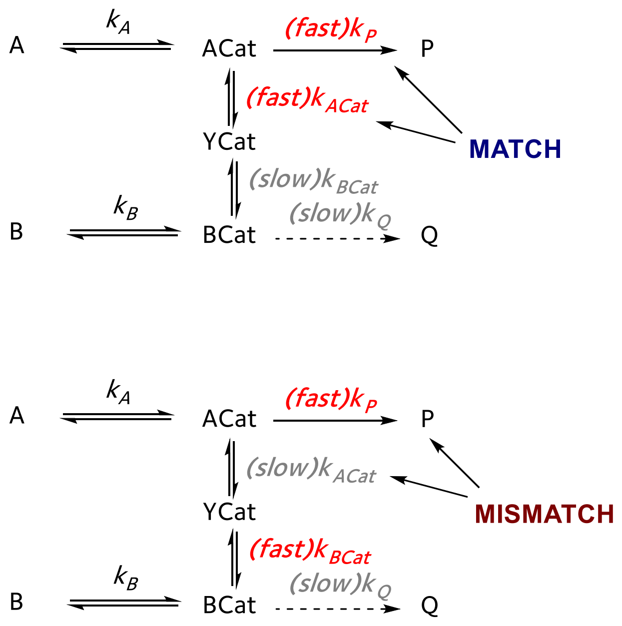


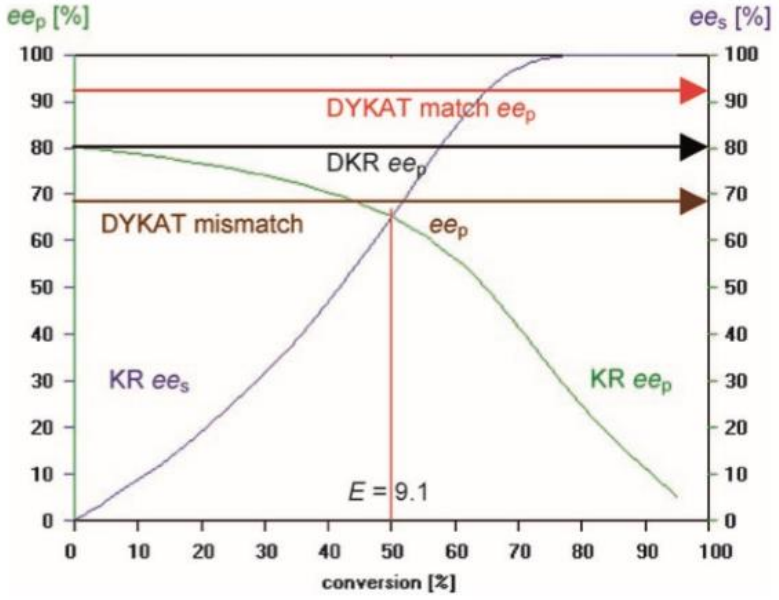
Barry M. Trost, 2000:

A dynamic kinetic asymmetric transformation has a potential advantage over a resolution (kinetic or dynamic kinetic)— fewer synthetic steps. If the act of converting a racemic mixture into a single enamatiomeric series is combined with one of the structural transformations, the dynamic resolution is not an additional step in the synthesis and thereby saves a step.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

Type I DyKAT: Matched vs. Mismatched

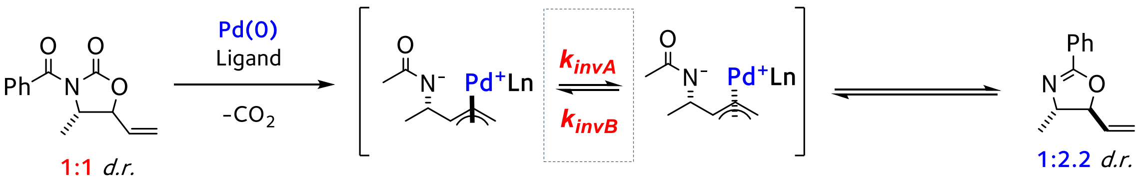




Trost *et. al. J. Am. Chem. Soc.* **2000**, *122*, 5968.
Ostrovskii *et. al. Vestsi Nats. Akad. Navuk Belarusi, Ser. Biyal. Navuk* **1994**, 60.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

There is no strict definition!



DKR:
Interconversion between enantiomers
$k_{racA} = k_{racB}$

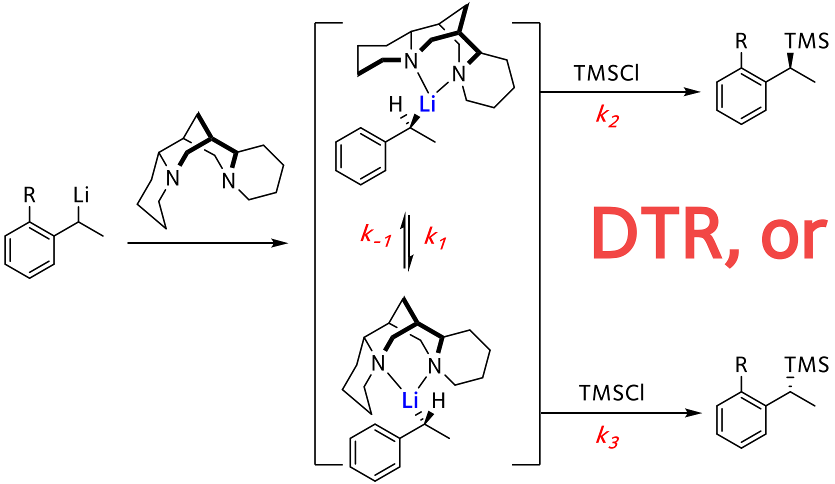
DyKAT:
Interconversion between diastereomers
$k_{invA} \neq k_{ivB}$

DKR, or DyKAT?

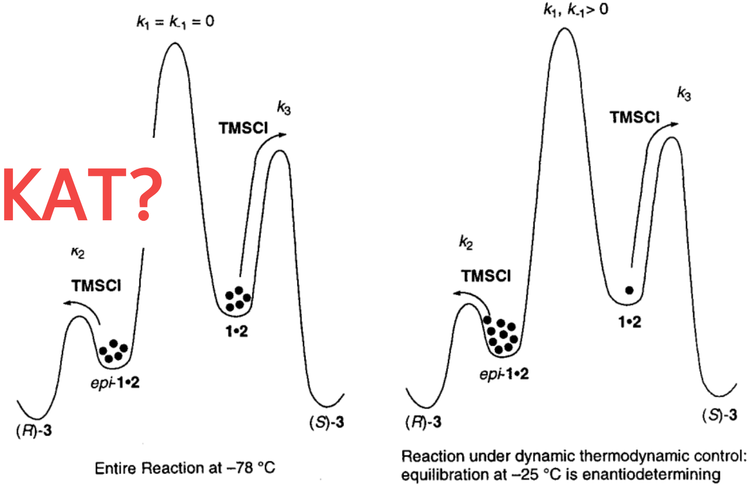
Cook *et. al. Angew. Chem. Int. Ed.* **1999**, *38(1/2)*, 110.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

There is no strict definition!



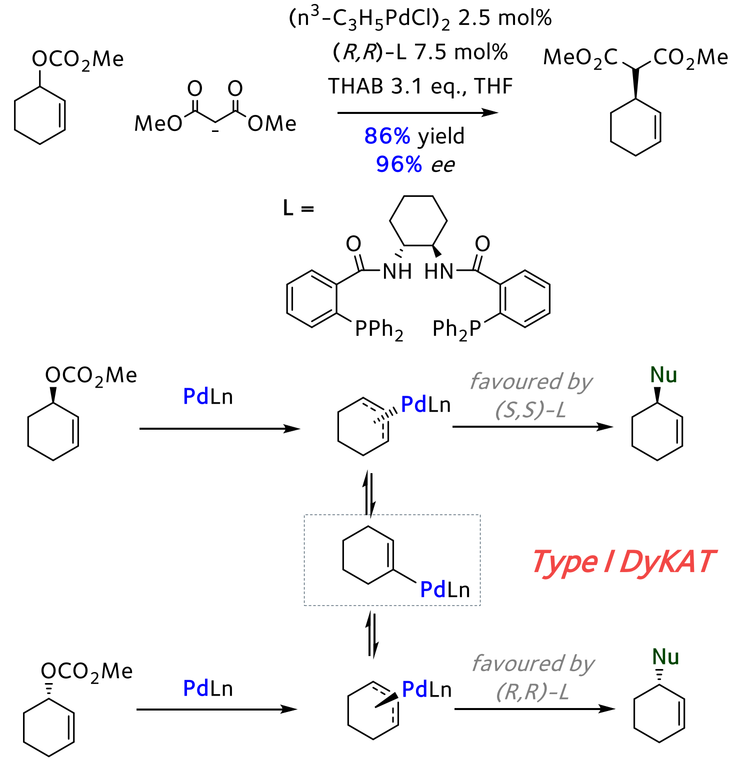
DTR, or DyKAT?

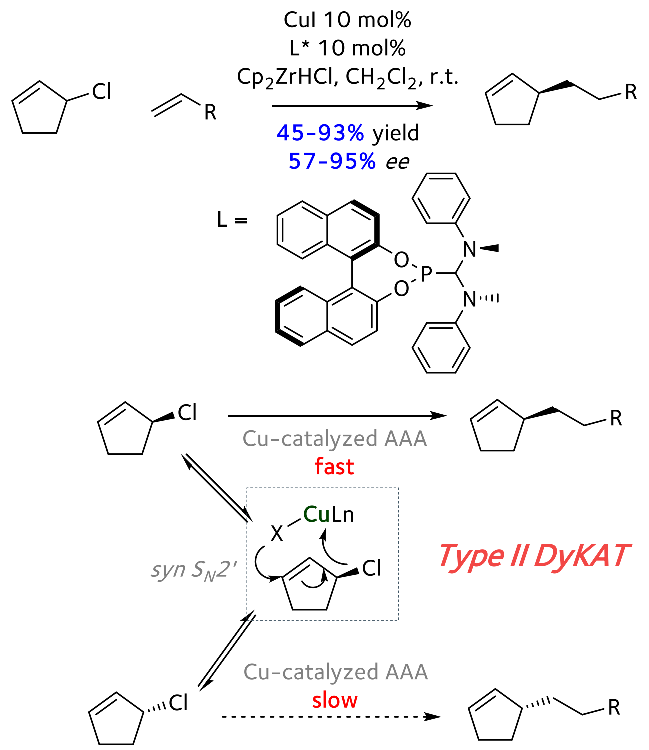


Beak *et. al. Acc. Chem. Res.* **2000**, *33,* 715.
Park *et. al. Org. Lett.* **2006**, *8(13)*, 2667.
Lee *et. al. Acc. Chem. Res.* **2009**, *42(2)*, 224.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

Type I DyKAT vs. Type II DyKAT: Asymmetric Allylic Alkylation (AAA)



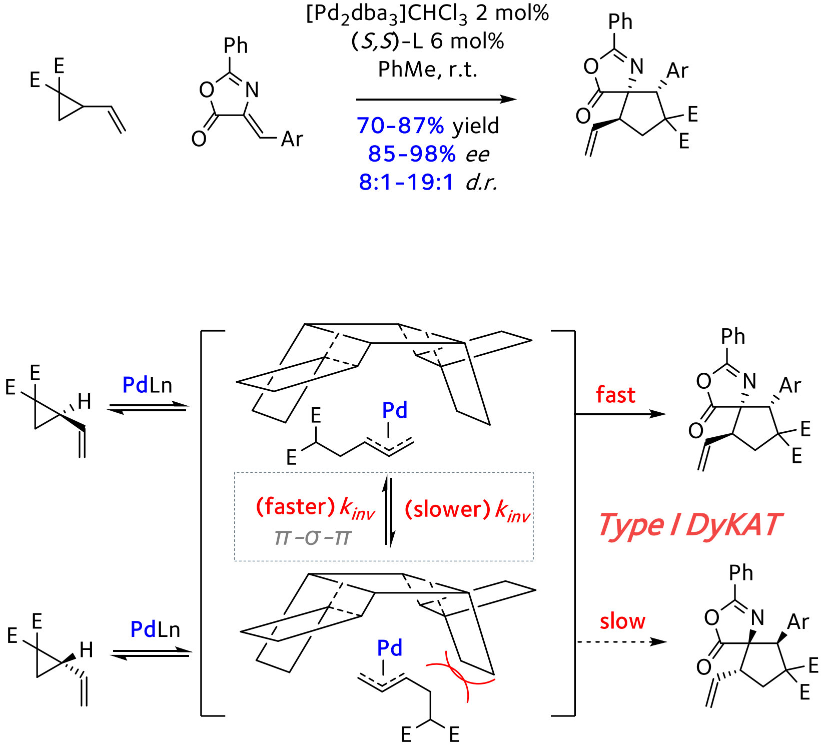


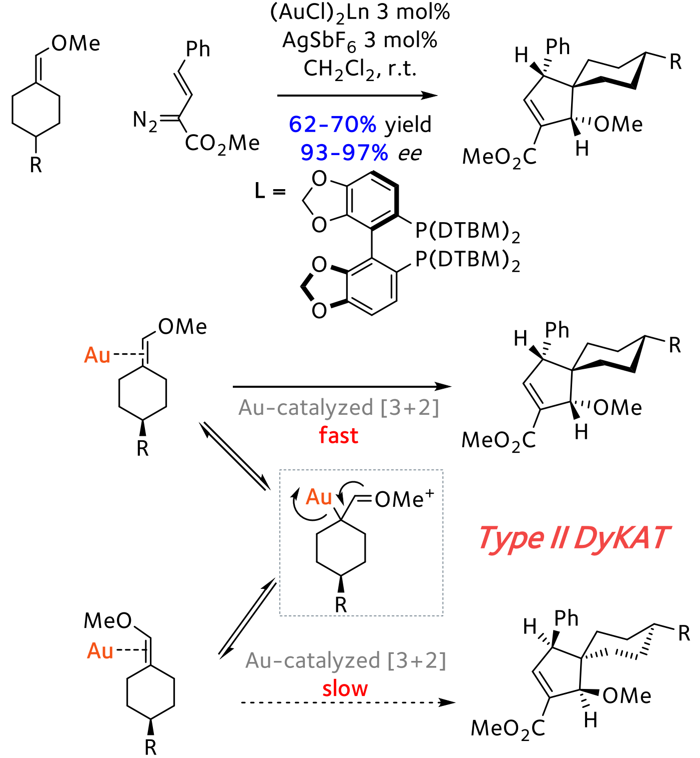
Trost *et. al. J. Am. Chem. Soc.* **2009**, *131*, 12056.
Trost *et. al. J. Am. Chem. Soc.* **1999**, *121*, 3543

You *et. al. Nature* **2015**, *517*, 351.
Sidera *et. al. Chem. Commun.* **2015**, *51*, 5044.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

Type I DyKAT vs. Type II DyKAT: [3+2] Cycloaddition



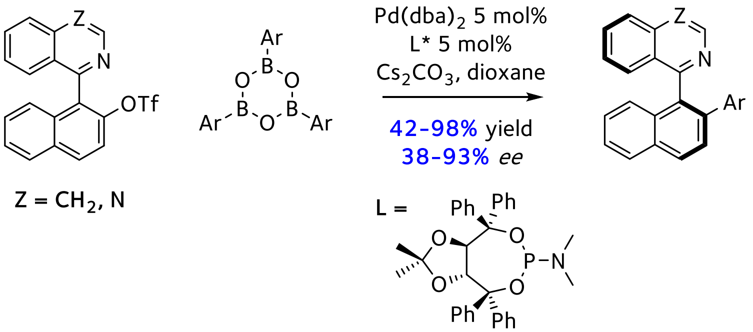


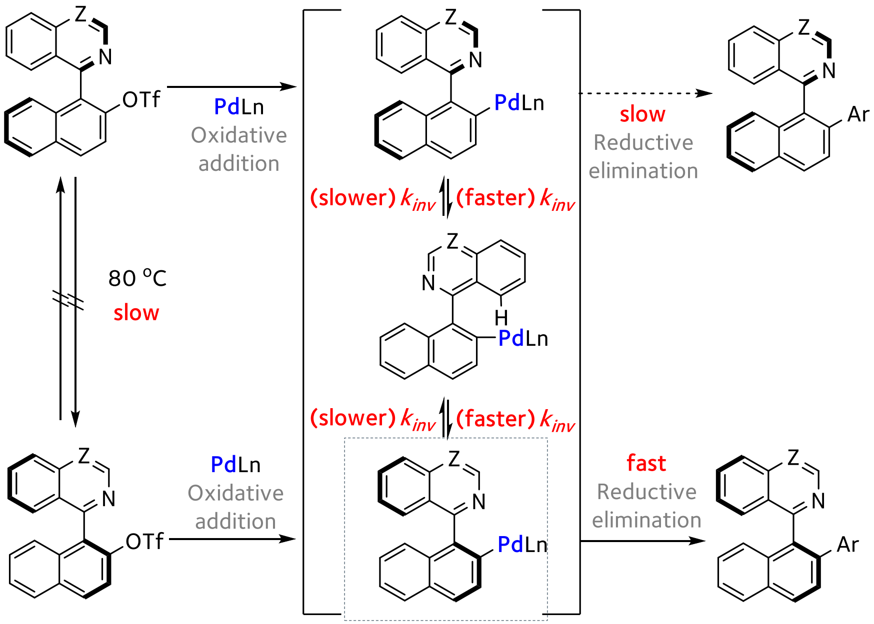
Trost *et. al. Angew. Chem., Int. Ed.* **2011**, *50*, 6167.

Briones *et. al. J. Am. Chem. Soc.* **2013**, *135*, 13314.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

Type I DyKAT vs. Type II DyKAT: Suzuki–Miyaura Coupling Reaction





Favoured intermediate

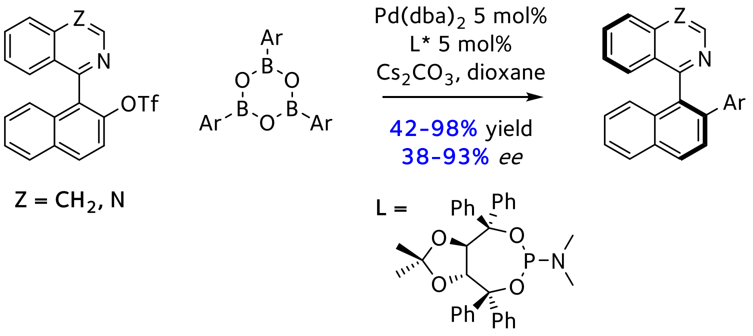
Type I DyKAT

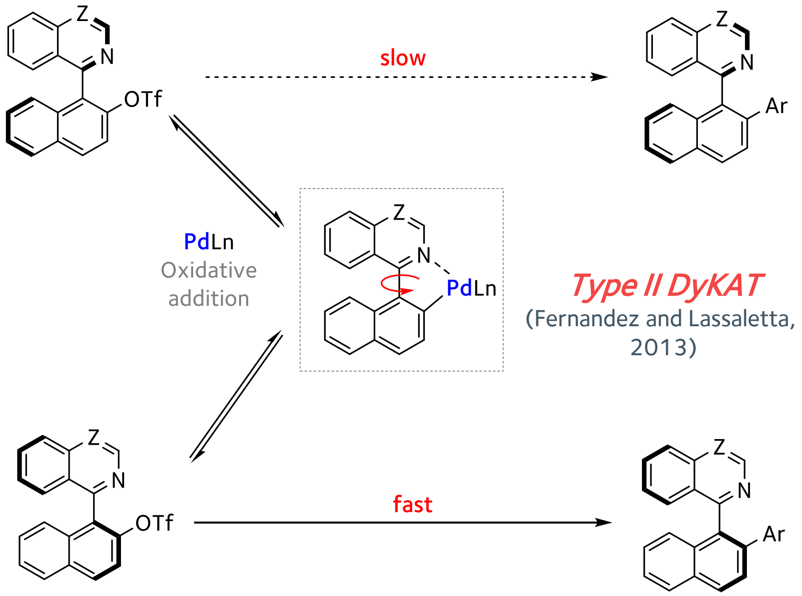
(Stoltz and Virgil, 2013)

Ros *et. al. J. Am. Chem. Soc.* **2013**, *135*, 15730.
Wencel-Delord *et. al. Chem. Soc. Rev.* **2015**, *44*, 3418.
Bringmann *et. al. Angew. Chem. Int. Ed.* **2005**, *44*, 5384.
Bhat *et. al. J. Am. Chem. Soc.* **2013**, *135*, 16829.

Dynamic Kinetic Asymmetric Transformation (DyKAT)

Type I DyKAT vs. Type II DyKAT: Suzuki–Miyaura Coupling Reaction





Ros *et. al. J. Am. Chem. Soc.* **2013**, *135*, 15730.
Wencel-Delord *et. al. Chem. Soc. Rev.* **2015**, *44*, 3418.
Bringmann *et. al. Angew. Chem. Int. Ed.* **2005**, *44*, 5384.
Bhat *et. al. J. Am. Chem. Soc.* **2013**, *135*, 16829.

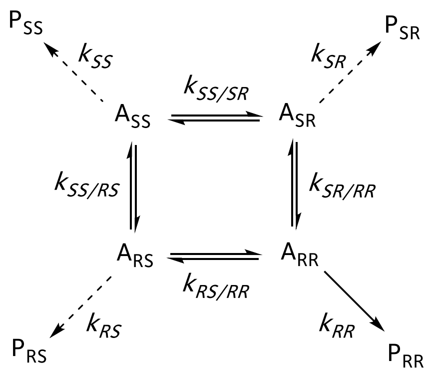
Any Questions?

5.
Miscellaneous Reactions

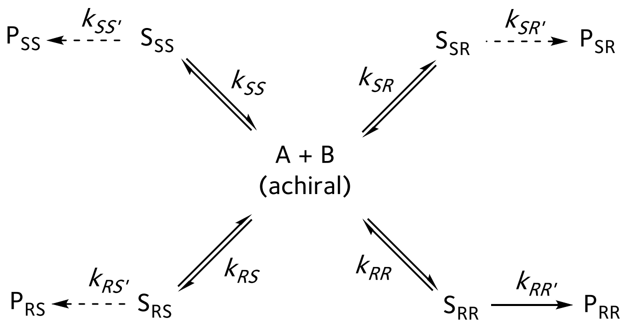
Miscellaneous Reactions

Type III DyKAT | **Type IV DyKAT**

- De-epimerization of diastereomers *via* rapid equilibration through a prochiral intermediate;
- Overall resolution of enantiomers (type I and II) *versus* the resolution of diastereomers (type III and IV);



$k_{SS/SR}, k_{SR/RR}, k_{RS/RR}, k_{SS/RS} >> k_{RR} >> k_{SS}, k_{SR}, k_{RS}$



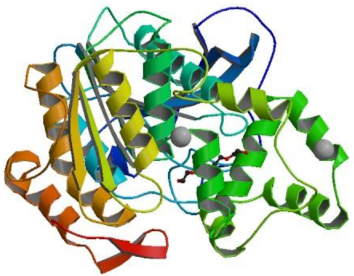
$k_{RR}, k_{SS}, k_{SR}, k_{RS} >> k_{RR'} >> k_{SS'}, k_{SR'}, k_{RS'}$

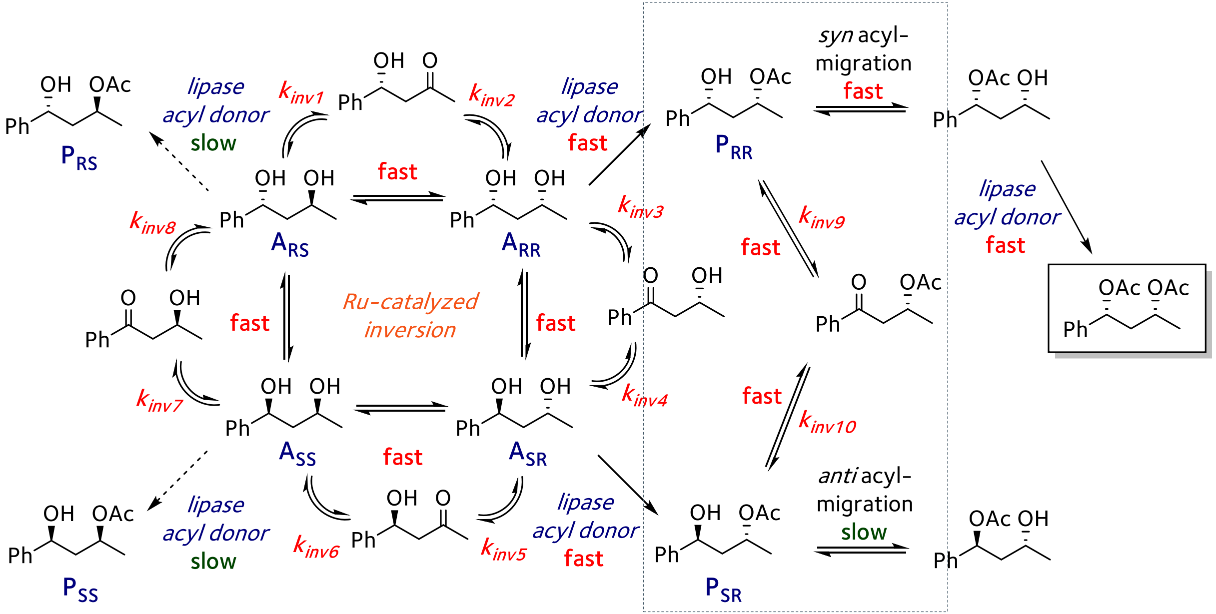
Miscellaneous Reactions

Type III DyKAT: 1,3-Diacetate Synthesis

Type III, or Matched-Matched-Type I?

CALB = *Candida antarctica lipase B*



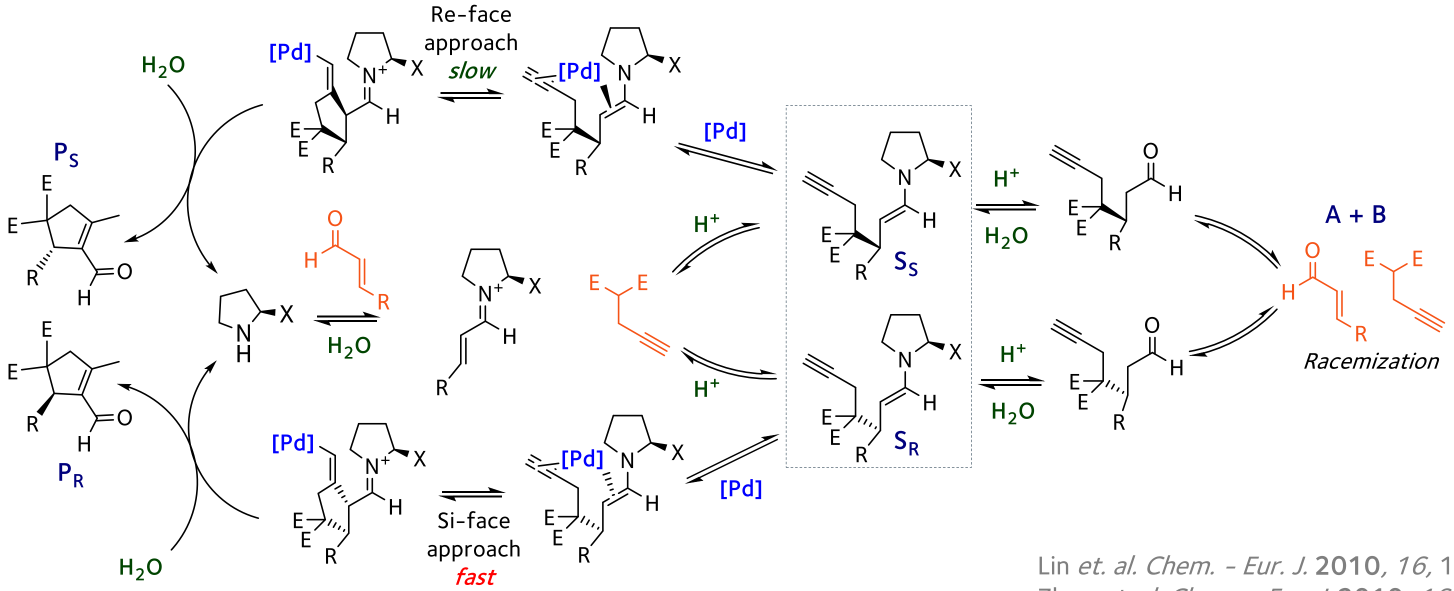


Edin *et. al. Proc. Natl. Acad. Sci. USA.* ***2004***, *101*, 5761.
Steinreiber *et. al. Chem. Eur. J.* **2008**, *14*, 8060.

Miscellaneous Reactions

Type IV DyKAT: Enantioselective DHF Synthesis

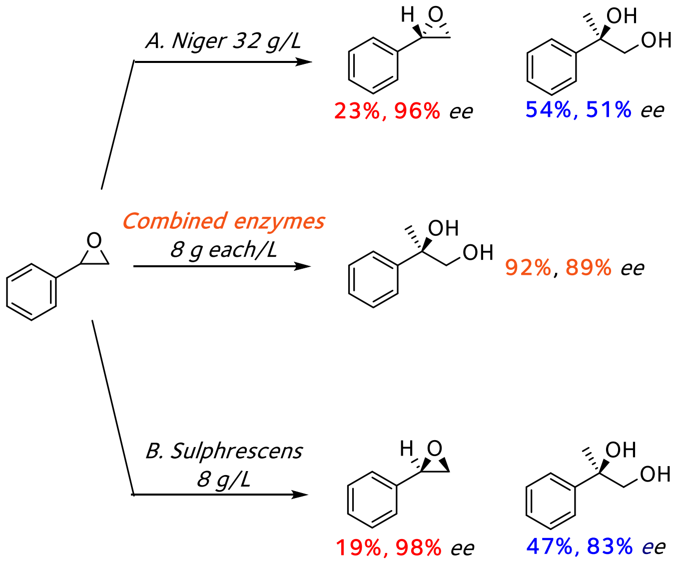
Type IV, or Type II?



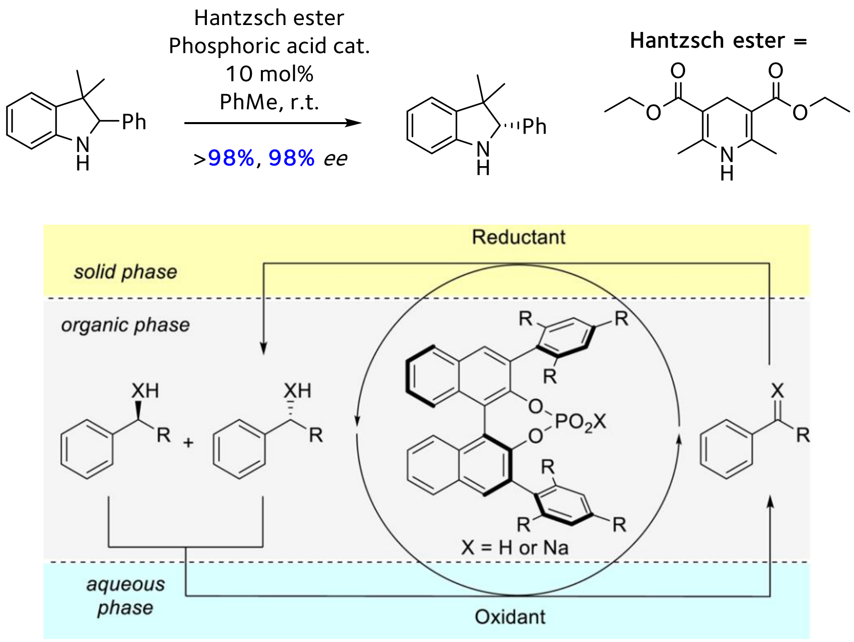
Lin *et. al. Chem. – Eur. J.* **2010**, *16*, 13930.
Zhao *et. al. Chem. – Eur. J.* **2010**, *16*, 1585.
Afewerki *et. al. ACS Catal.* **2015**, *5*, 126.

Miscellaneous Reactions

Undefined Enantioconvergent Process (ECP)



Cyclic De-racemization (CycD)

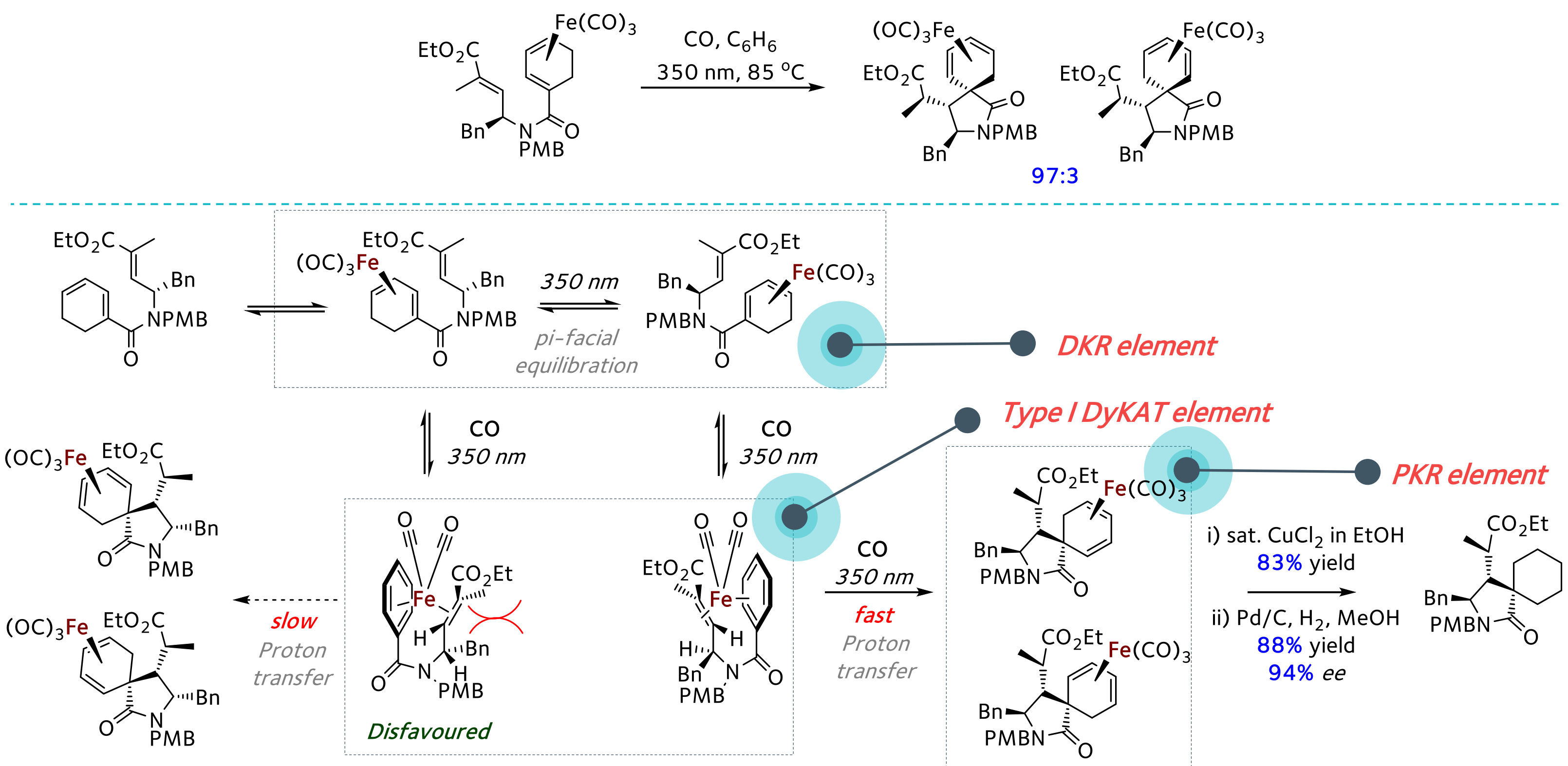


Pedragosa-Moreau *et. al. J. Org. Chem.* **1993**, *58*, 5533.

Toste *et al. J. Am. Chem.Soc.* **2013**, *135*, 14090.

Miscellaneous Reactions

Dynamic Substrate Directed Resolution (DSDRs)
Enantioselective Lactam Synthesis



Pearson *et. al. J. Org. Chem.* **2007**, *72*, 2547.

References: Useful Reviews

Enantioconvergent Reactions
Bhat *et. al. Chem. Rev.* **2017**, *117*, 4528.
Wencel-Delord *Synthesis* **2016**, *48*, 2981

Racemization Techniques
Ahn *Coord. Chem. Rev.* **2008**, *252*, 647.

Stereoablative Reactions
Pellissier *Tetrahedron* **2003**, *59*, 8291.

PKR Reactions
Dehli *Chem. Soc. Rev.* **2002**, *31*, 365.

DKR Reactions
Huerta *Chem. Soc. Rev.* **2001**, *30*, 321.
Quasdorf *Nature* **2014**, *516*, 181.

DyKAT Reactions
Faber *Chem. Eur. J.* **2001**, *7*, 5004.
Steinreiber *et. al. Chem. Eur. J.* **2008**, *14*, 8060.

Cross-coupling Reactions
Lucas *Nat. Rev. Chem.* **2017**, *1, 65.*
Everson *J. Org. Chem.* **2014**, *79*, 4793.
Gensch *Chem. Soc. Rev.* **2016**, *45*, 2900.

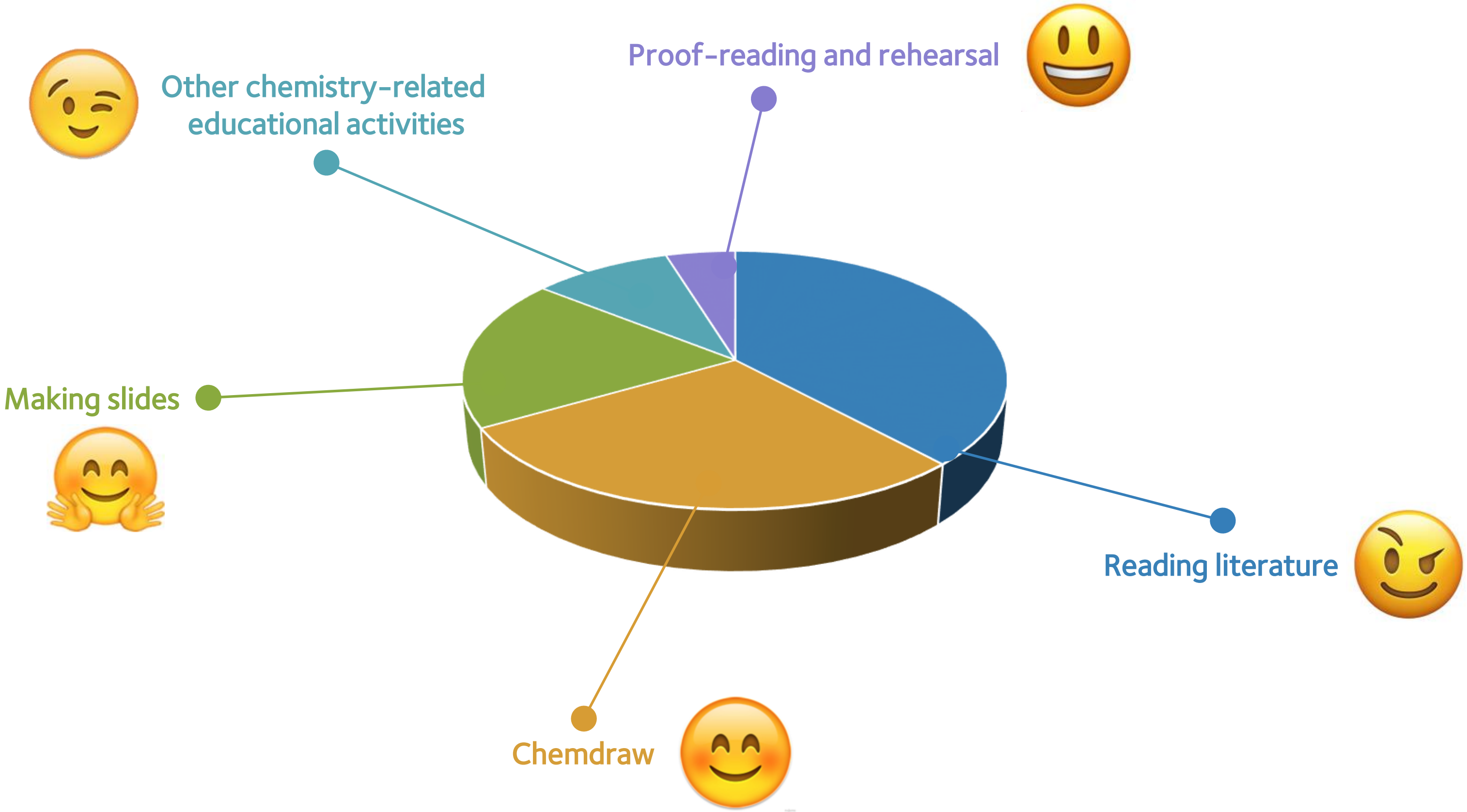
Atroposelective Reactions
Bringmann *Synthesis* **1999**, *1999(4)*. 525.
Bringmann *Chem. Rev.* **2011**, *111*, 563.
Baudoin *Eur. J. Org. Chem.* **2005**, 2005, 4223.
Kozlowski *Chem. Soc. Rev.* **2009**, *38*, 3193.
Wencel-Delord *Chem. Soc. Rev.* **2015**, 341.

DTR Reactions
Beak *et. al. Acc. Chem. Res.* **2000**, *33*, 715.
Lee *et. al. Acc. Chem. Res.* **2009**, *42(2)*, 224.

ATH Reactions
Echeverri *Synthesis* **2016**, *48*, 2523.
Wang *Chem. Rev.* **2015**, *115*, 6621.

AAA Reactions
Butt *Chem. Soc. Rev.* **2015**, *44*, 7929.

What I thought a literature review was like...



What it is really like…

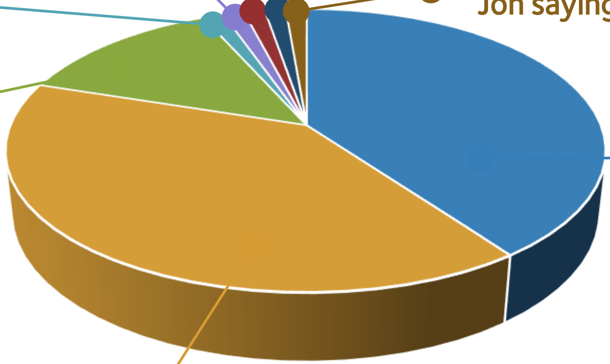
Fiddling with color and font size for hours
~~Making slides~~

Deleting slides

WHY DID I DELETE THEM?!?!

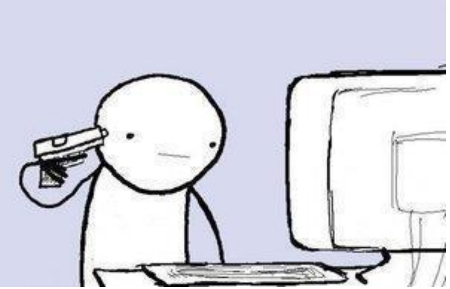
Facebook and Twitter
Other ~~chemistry-related educational activities~~
with guilt

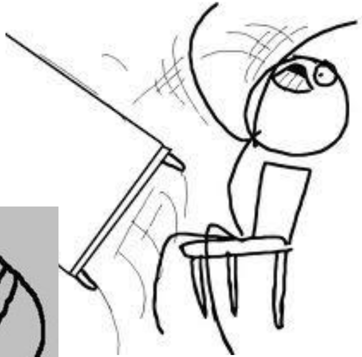
Crying at home;
Decided to go to lab for one day and heard Jon saying ‘I need your space why do you come back?’



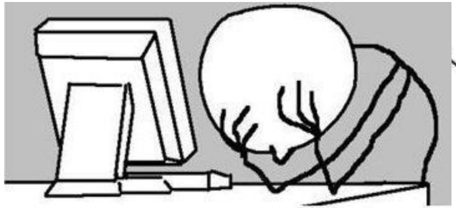
Moaning and panicking about presentation day

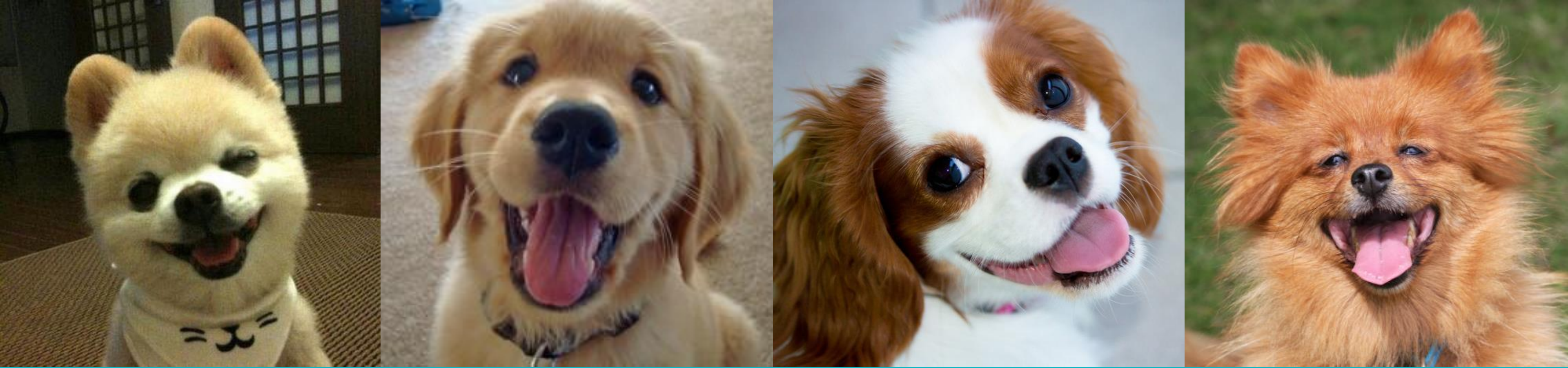
Organizing papers instead reading them





‘Chemdraw has stopped working’





Thanks for your attention!