CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

CHIMIE PARIS
Ecole Nationale Supérieure de Chimie de Paris

EFFICIENT TECHNOLOGIES in ASYMMETRIC CATALYSIS for ORGANIC SYNTHESIS

IASOC -Ischia September,18-23, 2004

HOMOGENEOUS CATALYSIS
Palladium,Rhodium
Ruthenium,Nickel

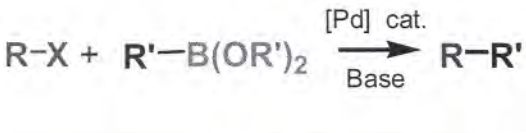
Synthetic Applications

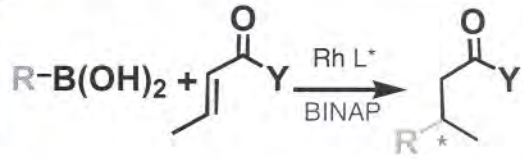
Marine Natural Products : Dolastatin 10,
SulfobacineA Fragrances: (+) Dihydrojasmonate

C-C :Rh
Conjugate Addition,
Carbometallation
Organoboron Compounds
C-H : Ru
Hydrogenation

ORGANO BORON REAGENTS

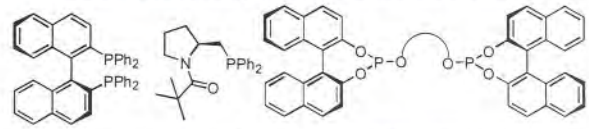
Cross Coupling Reactions (Pd) BORONIC ACIDS and ESTERS (Rh) Conjugate Addition Reactions



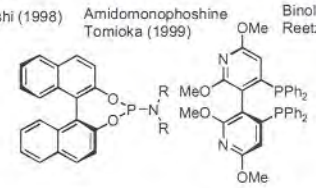


Among metal-mediated reactions ,the Pd-catalyzed cross-coupling between organoboron reagents and various electrophiles provides the most powerful and general methodology. The coupling offers several advantages :
- Mild reactions conditions
-Tolerance of a broad functionality
-Good regio and stereoselectivity
-Nontoxic reaction

Wide range of Michael acceptors,excellent ee.
Complementary with Cu-catalyzed addition.



Hayashi (1998) Amidomonophoshine Tomioka (1999) Binol based diphoshonites Reetz (2001)



Phosphoramidite Miyaura, Feringa (2003) bipyridine,P-Phos Chan (2003)

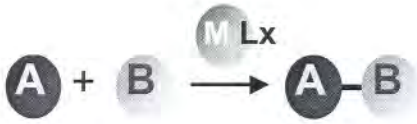
Books ***Tamao, K. Comprehensive Organic Synthesis; Pergamon : New York, 1991; Vol. 3, Chap. 2.Tsuji, J. Palladium Reagents and Catalysts; John Wiley/Sons : New York, 1995***

Les complexes du palladium en synthèse organique. Innovation et guide pratique.J.M.Campagne,D.Prim CNRS Editions ,2001-

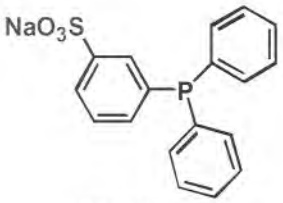
Handbook of organopalladium. Chemistry for organic syntheses (2vol) Ed. E. Negishi, J. Wiley N.Y., 2002

Reviews:Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457. T. Hayashi, Synlett 2001, 879. (b) T. Hayashi and K. Yamasaki, Chem. Rev. 2003, 103, 2829.

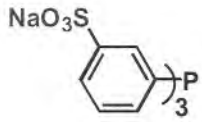
Organometallic catalysis in water



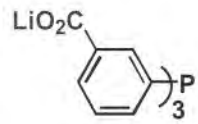
M = Pd, Rh, Ni...
L_x = chiral & non-chiral water-soluble ligands
"Green Chemistry"



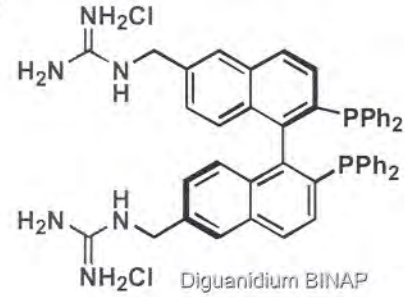
TPPMS
80g/l of water



TPPTS
1100g/l of water



TPPTC
1100g/l of water

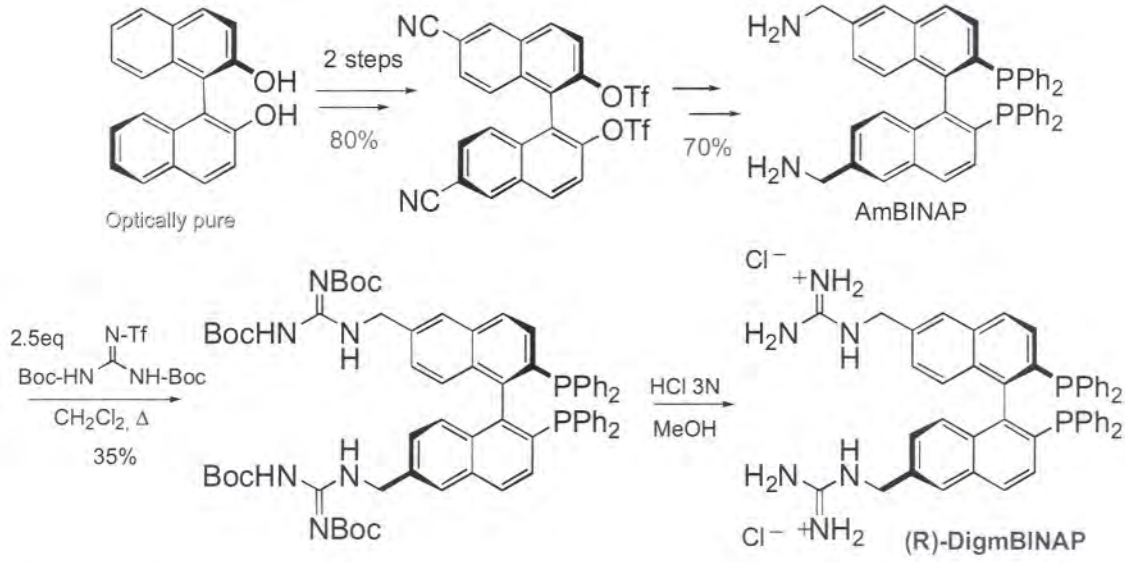


Diguanidium BINAP

TPPTS Emile Kuntz Homogeneous catalysis in water Chemtech September 1987,570
(Rh -TPPTS) 600 000t /year Production of Butanal
TPPMS A.L. Calsalnuovo et al J.Am.Chem.Soc. 112,4324,1990
Genêt, J.P. M.Savignac,E.Blart Synlett 1992, 715. J. Organomet. Chem. 1999, 305. IUPAC Monographs,Transition Metal Catalyzed Reactions, Murahashi, S.-I. and Davies S. G., Ed.; 1999, 55. Michelet, V.; Savignac, M.; Genêt, J.P. Electronic Encyclopedia of Reagents for Organic Synthesis, John Wiley & Sons, 2004, in press.

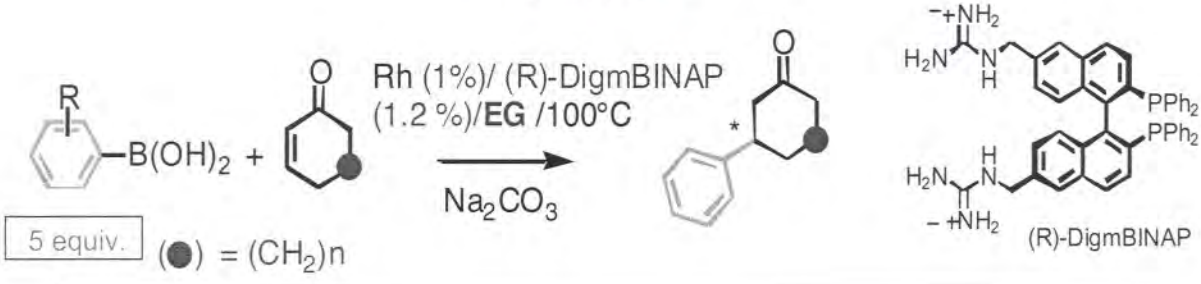
TPPTC Y.Michelet,R. Amengual,J.P.GenetyAdv. Synth. Catal. 2002, 344, 393. Ibid Tetrahedron Lett. 2002, 43, 5905.

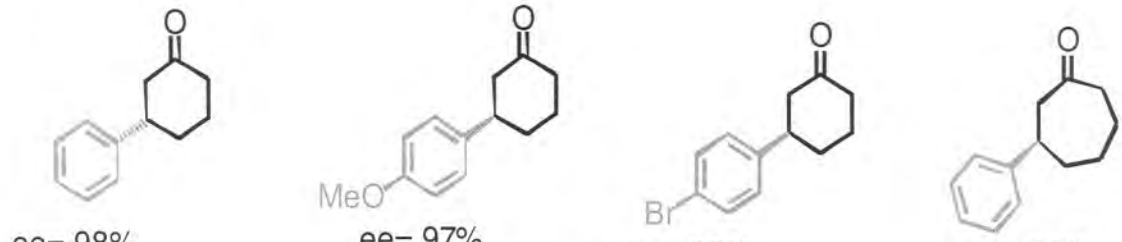
SYNTHESIS of 6,6'diamino-(R)-BINAP



For AmBINAP M.Lemaire et coll. French patent 9902510,Tet.Letters 643,2000
***For(R)- DigmBINAP** J.P.Genet,P.Guerreiro,V. Vidal.P.Dellis French patent 9915217, P. GueirreroV.Vidal,P.DellisJ.P.GenetTet. Lett. 3423,2001*

Rhodium Catalysed Enantioselective Addition of Organoboron Reagents to α,β-unsaturated Ketones





ee= 98%
100 % yld

ee= 97%
57% yld

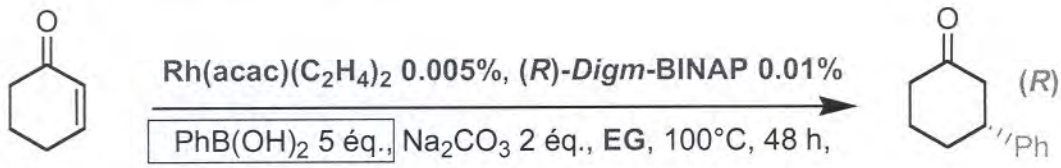
ee= 92%
99% yld

ee= 90%
50% yld

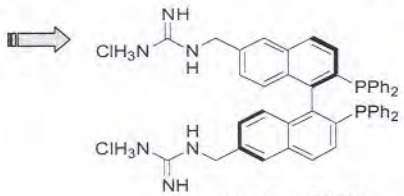
R.Amengual,V.Michelet,J.P.Genet Synlett 1791, 2002

ASYMMETRIC 1,4 ADDITION

Low catalytic loading

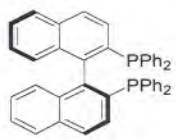


66%, 88% e.e.



(*R*)-*Digm*-BINAP

TON = 13200



(*S*)-BINAP

TON = 1000

The major advantage of this procedure : **(i) a very easy separation of the product from the catalyst, with no purification step.**

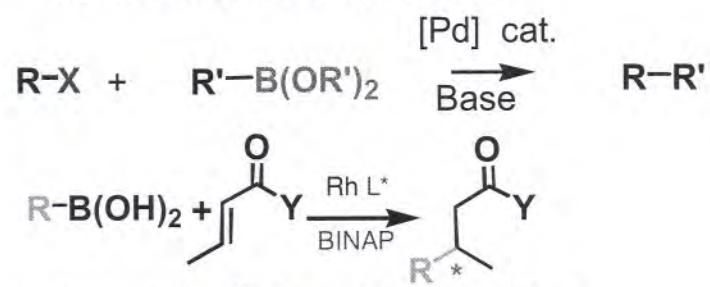
(ii)Low mole fraction of catalyst and ligand could be employed with still acceptable yield and ee.

Drawback: Large excess of reagent is necessary

ORGANO BORON REAGENTS

BORONIC ACIDS and ESTERS

$RB(OR)_2$



Complementary with Cu-catalyzed addition.

Drawbacks

-Large excess of reagent is necessary
-Boronic acids not always easily available (purification)
-Stability toward oxygen and water

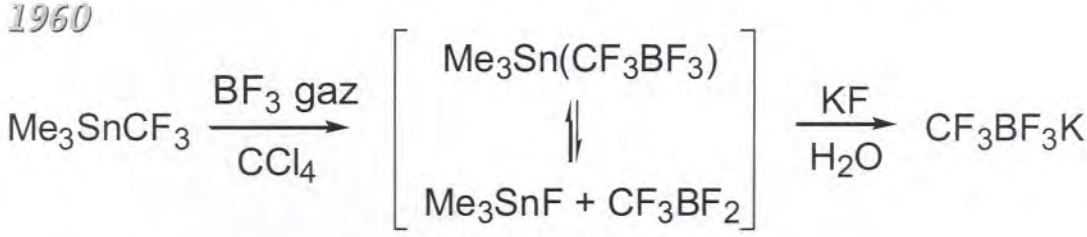
RBF_3K

POTASSIUM ORGANO TRIFLUROBORATES

S.Darses J.P.Genet J.L.Brayer,J.P.Demoute;Tet. Letters 1997,. S.Darses J.P.Genet G.Michaud,Tet. Letters 1998 ibid Eur J.Org.Chem.1999
Review :S.Darses,J.P.Genet Eur. J. Org. Chem. 2003, 4313

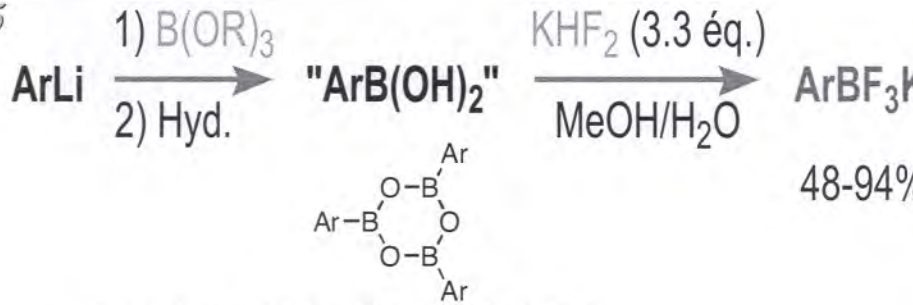
PREPARATION OF POTASSIUM ARYLTRIFLUOROBORATES

- *1960*



H. C. Clark, C. J. Willis, J. Am. Chem. Soc. 1960, 82, 1888-1891. - R. D. Chambers, H. C. Clark, C. J. Willis, Chem. Ind. (London) 1960, 76-77.
For a long time these reagents remained laboratory curiosities

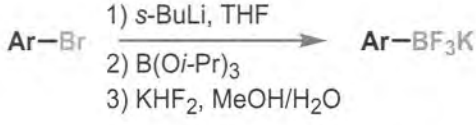
- *1995*

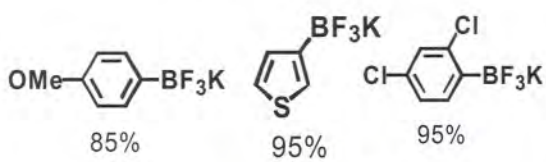


Vedejs, E et coll. J. Org. Chem. 1995, 60, 3020.

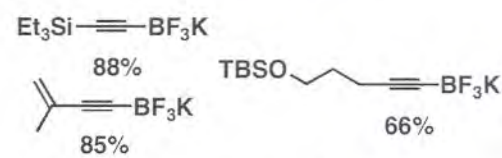
PREPARATION OF POTASSIUM ORGANOTRIFLUOROBORATES

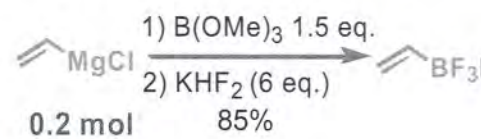
In situ PREPARATION of ARYL(K)TRIFLUOROBORATES

- 

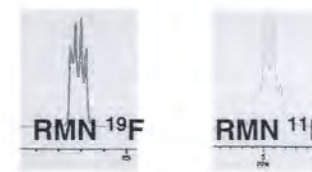


ALKENYL / ALKYNYL (K) TRIFLUOROBORATES





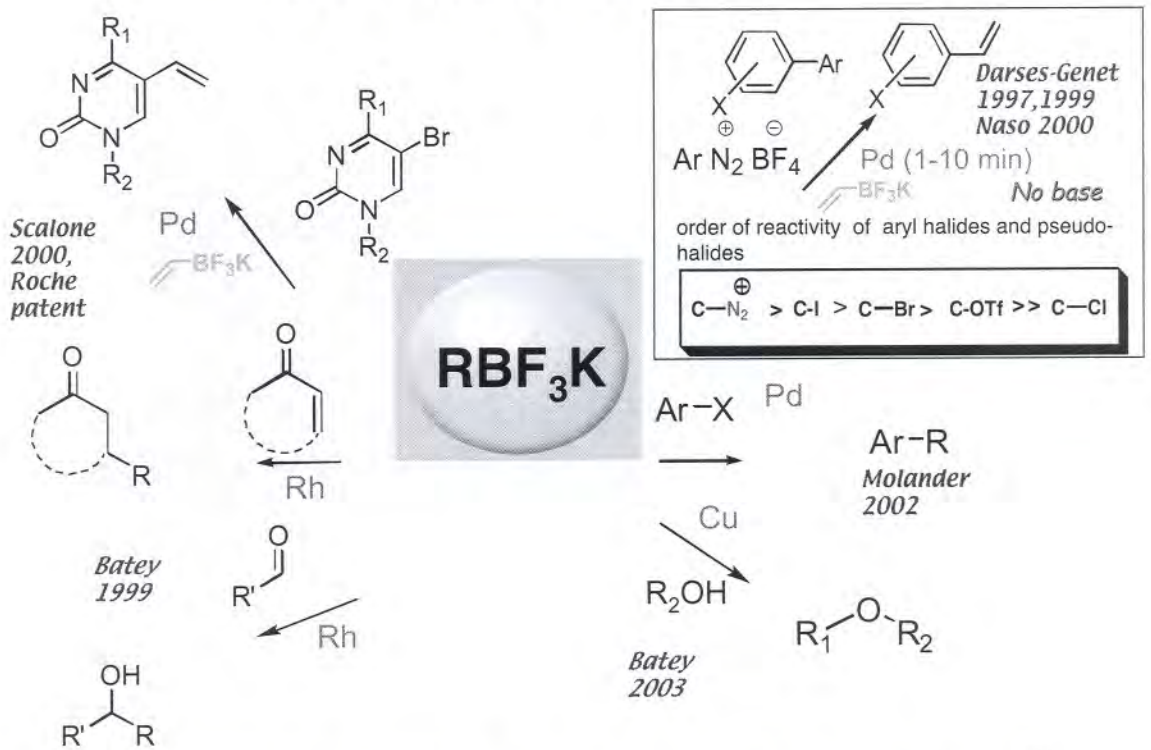
Commercially available
Highly Stable towards water and oxygen
(no degradation after several years !!!!)
Easy to prepare
Chemoselectivity:R_3Si,Halogens,CHO,OCOR



S.Darses J.P.Genet J.L.Brayer,J.P.Demoute;Tet. Letters 1997,. S.Darses J.P.Genet ,G.Michaud,Tet. Letters 1998 ibid Eur J.Org.Chem.1999

Review :S.Darses,J.P.Genet Eur. J. Org. Chem. 2003, 4313

POTASSIUM (ORGANO)TRIFLUROBORATES in TRANSITION METAL CATALYZED REACTIONS

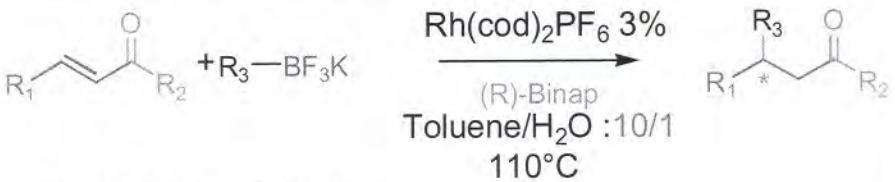


S.Darses J.L.Brayer,J.P.Demoute;Tet. Letters 1997,. S.Darses J.P.Genet G.Michaud,Tet. Letters 1998 [11]
ibid Eur J.Org.Chem.1999; ***Review :S.Darses,J.P.Genet Eur. J. Org. Chem. 2003, 4313***

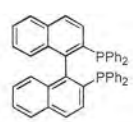
RBF_3K

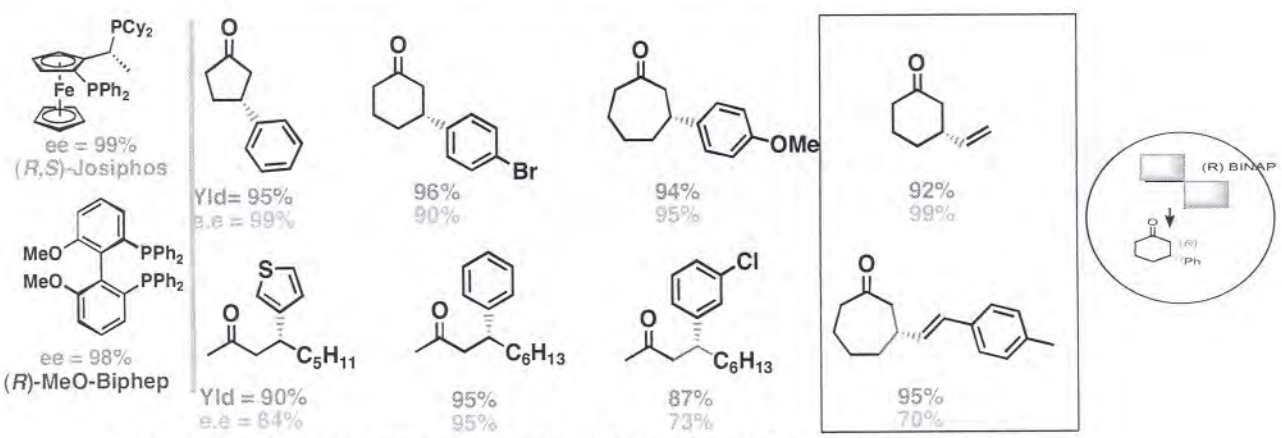
ASYMMETRIC 1,4 -ADDITIONS with ENONES

Rh



- Reaction time 1h-2h
- Temperature below 100°C Racemic product

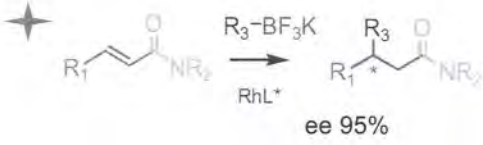




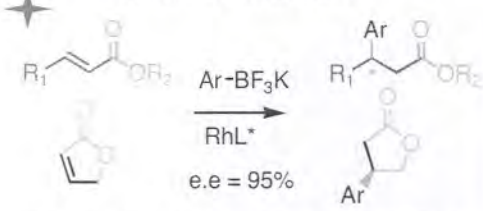
Potassium organotrifluoroborate as versatile reagents for catalytic enantioselective conjugate addition to enones. *Less equivalents of RBF_3K compared to $RB(OH)_2$ and faster reaction 1h vs 3h with $PhB(OH)_2$* [12]

M. Pucheault, S. Darses and J.-P. Genêt Tetrahedon Letters 43, 6155, 2002; Eur. J. Org. Chem., 3552, 2002

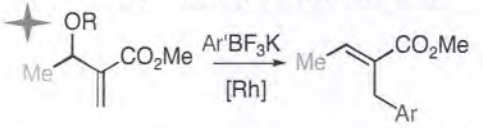
POTASSIUM (ORGANO)TRIFLUROBORATES in TRANSITION METAL CATALYZED REACTIONS



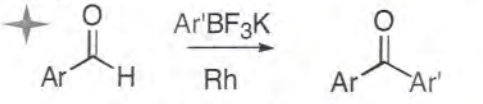
M.Pucheault, V.Michaut, S.Darses, J.P.Genet, Tetrahedron Letters, 2004



M. Pucheault ,L. Navarre, S.Darses unpublished



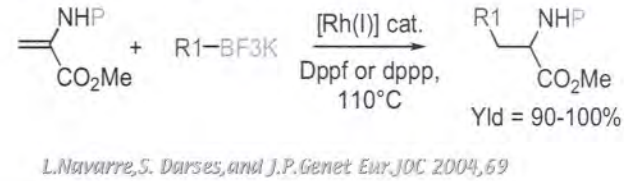
L.Navarre, S.Darses, J.P.Genet, Chem.Commun. 2004, 1108.



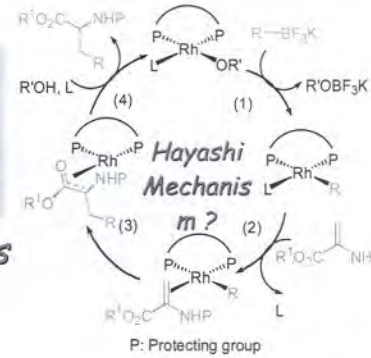
M.Pucheault, S.Darses, J.P.Genet, submitted

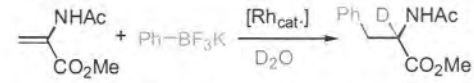
RBF_3K

New reactions



L.Navarre,S. Darses,and J.P.Genet Eur.JOC 2004,69





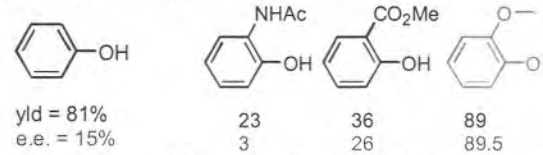
TANDEM 1,4 ADDITION / ENANTIOSELECTIVE PROTONATION ?

One example :$PhB(OH)_2$ Reetz Org Lett 2001 ee 72%

RBF_3K

TANDEM 1,4 ADDITION / ENANTIOSELECTIVE PROTONATION

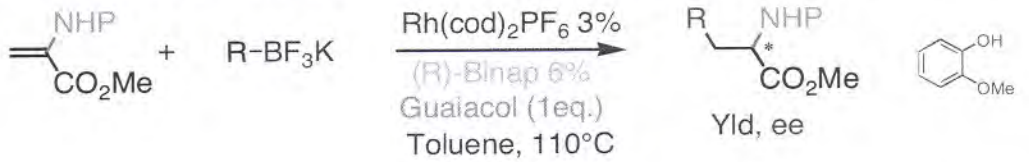
- water → Disappointing results were obtained using water as protonating agent enantiomeric excesses were usually below 28% whatever the chiral ligand
- Acids → carboxylic acids or sulfonic acids were not suitable, resulting in a blocking of the catalytic cycle no Michael addition product was observed
- Phenols →

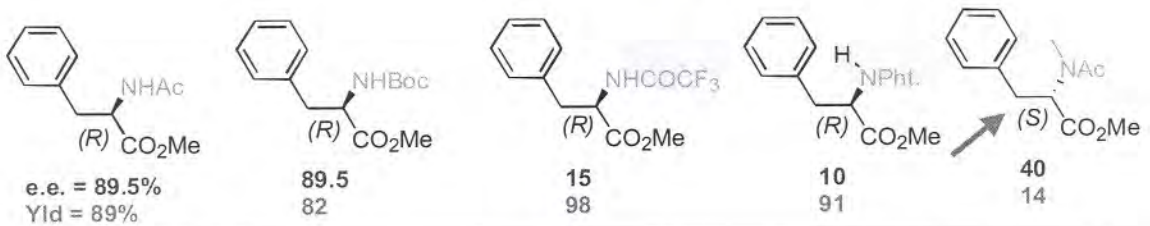


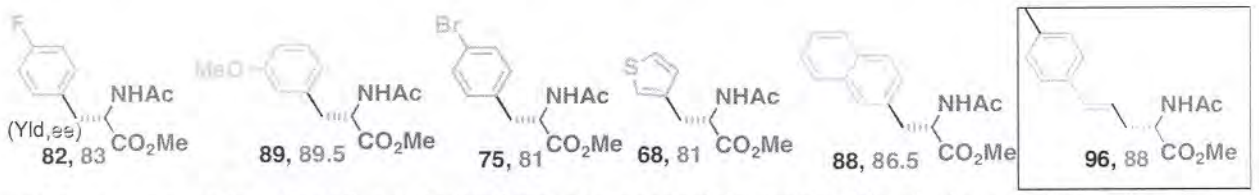
When better complexing ortho substituents such as carbomethoxy or acetamido groups were used significant decrease in enantioselectivity was observed.

RBF$_3$K

TANDEM 1,4 Addition/ENANTIOSELECTIVE PROTONATION





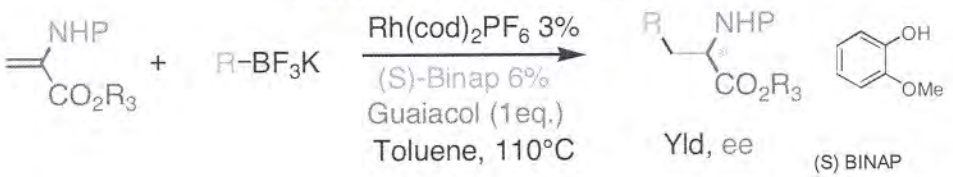


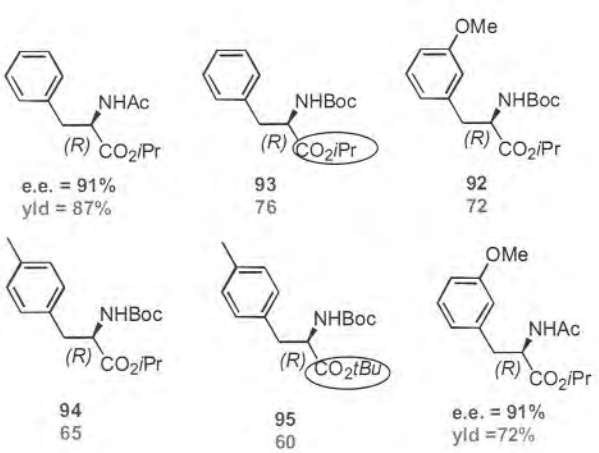
Heterocyclic or functionalized derivatives are accessible using this strategy.Using potassium alkenyltrifluoroborates alkenyl substituted alanines derivatives are efficiently produced with good e.e. and yields This represents an interesting feature of this carbometallation since these products are not easily accessible even using efficient asymmetric hydrogenation processes.

L.. Navarre, S.Darses,J P Genet Angew.Chem.Int Ed 2004,43,719

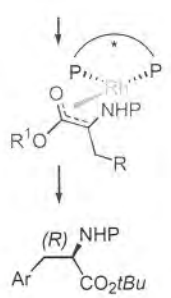
RBF$_3$K

TANDEM 1,4 Addition/ENANTIOSELECTIVE PROTONATION





(S) BINAP



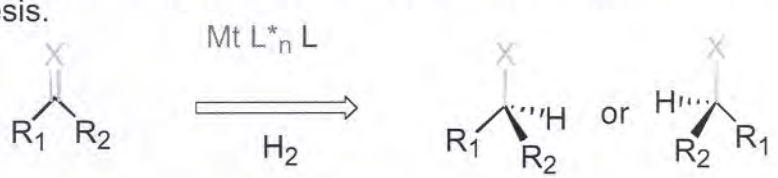
Mechanism ?

Using potassium organotrifluoroborates with more hindered esters substituted alanines derivatives are efficiently produced with e.e up 95%(iPr and t-Bu esters).

L.. Navarre, R. Martinez,S.Darses unpublished

ASYMMETRIC HYDROGENATION the ORGANOMETALLIC STRATEGY

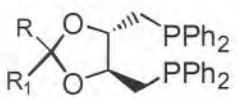
A broad variety of pharmaceuticals, fragrances, agrochemicals contain a stereogenic center. Very often this center is tertiary, thus the enantioselective catalytic hydrogenation of C=X double bonds constitutes a powerful tool in organic synthesis.



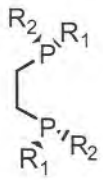
Mt = Rh,Ir,Ru

L* coordinated to the metal contains the chiral information.The catalyst also often contains a secondary ligand ,L,spectator?.

Historical Chiral ligands for modified Rh(I) catalysts



DIOP(Kagan)

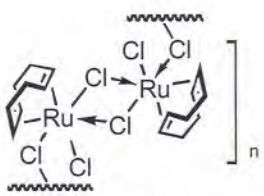


DIPAMP type(Knowles)

CHIRAL Ru(II) CATALYSTS

1975 *James, R.R.; Wang, D.; Voigt, R.F. X-ray crystal structure of trans-chlorohydridobis (diop) ruthenium(II) J. Chem. Soc. Chem. Commun. 1975, 574.*

1985

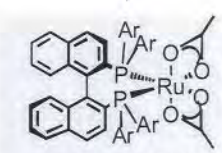


Starting material
for the preparation of ruthenium (II)

Toluene reflux
+ NEt_3

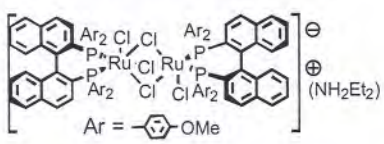
IKARIYA/SABURI
(1985)
$[RuCl_2(Binap)]_2(NEt_3)$
Binuclear Complex
(very good catalyst)

tBuOH,16h ,AcONa



Fluka Price 1989

Takaya, H.; Mashima, K.
Organometallics 1996



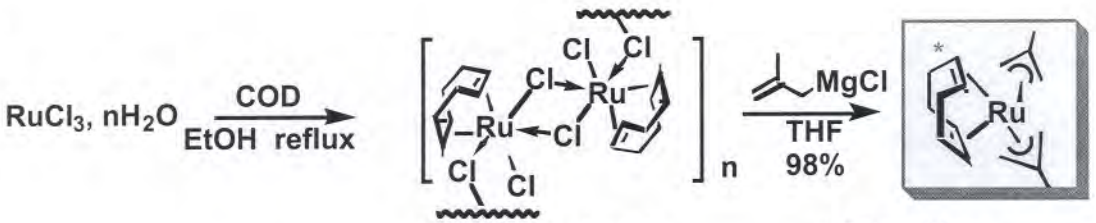
NOYORI (1986)

Highly efficient Catalysts : Allylic Alcohols, α,β unsaturated acids, Keto groups

A common limitation of these procedures was the harsh reaction conditions : long reaction times, high temperature non comptatible with Chiral Phosphines having a Chiral Phosphorus Atom

GENERAL METHODS FOR THE PREPARATION OF CHIRAL Ru(II) CATALYSTS

The method was based on the easy availability of mononuclear ruthenium complex



Starting material for the preparation of ruthenium (II)

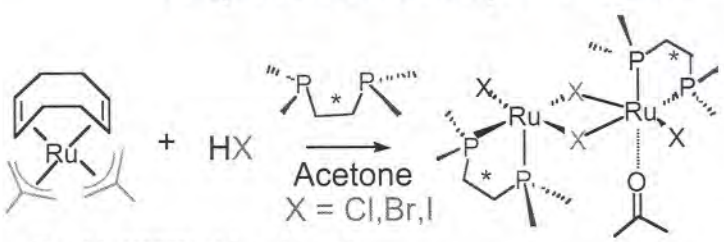
* Cristalline
* Stable
* Easy to handle
* Commercially available

Preparations (Arran Chemical Company ,Ireland);Batches up to 500g with high purity M.Bulliard,B.Laboue,J.Lastenet,S.Roussiasse Organic Process Research and Development 2001,5,438

* Commercially available from Acros

Genet, J.-P.; Mallart, S.; Pinel, C.; Jugé, S.; Laffitte, J.A.Tetrahedron : Asymmetry1991, 2, 43-46.;Tetrahedron : Asymmetry.1991, 2, 555-567.;Genet, J.P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Caño de andrade, C.; Laffitte, J.A.Tetrahedron : Asymmetry.1994, 5, 675-690.: Reviews : a) J.P. Genet inReduction Organic Synthesis, Am. Chem. Soc. Symposium Series 64,Abdel F. Magid, Ed., Chapter 2, 31, (1996) ; b) J.P. Genet, V. Ratovelomanana-Vidal, J. Organomet. Chem, 163, (1998).

In situ SYNTHETIC ROUTE to Ru(II) CHIRAL bis(PHOSPHINE) CATALYSTS



$Ru_2X_4(P^*P)_2(Acetone)$

$[RuX(P^*P)]_2(\mu\text{-}X)_2$

‖

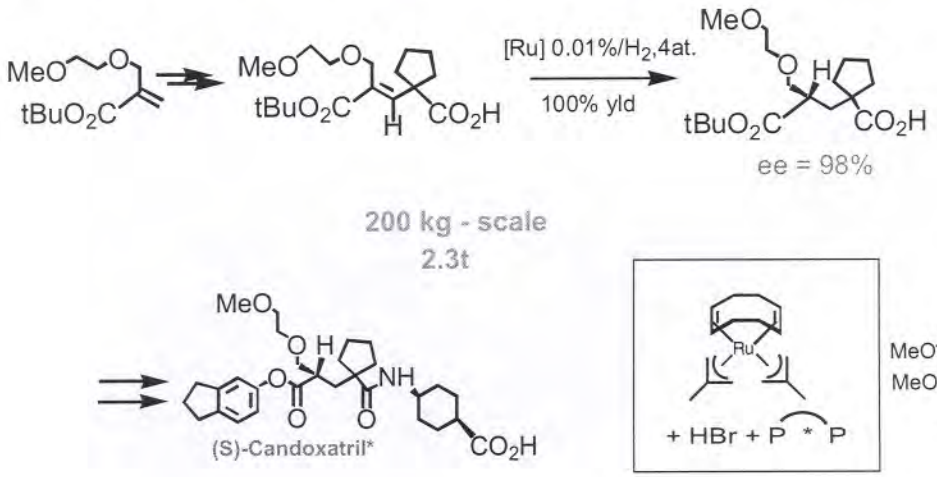
in situ $Ru((P^*P)X_2)$

* The method does not require multistep synthesis
* Complexes can be used as crude catalysts
* Very convenient for a rapid screening of chiral ligands ***at RT***
* Highly efficient for prochiral Keto groups and olefins

Reviews: J.P. Genet Account Chem.Res. 2003 908, J.P. Genet in Reduction Organic Synthesis, Am. Chem. Soc. Symposium Series 641, Abdel F. Magid, Ed., Chapter 2, 31, (1996) ; b) J.P. Genet, V. Ratovelomanana-Vidal, J. Organomet. Chem., 163, (1998).

Others Laboratories:M.J. Burk, T.G.P. Harper, C.S. Kalberg J. Am. Chem. Soc., 117, 4423, (1995) V. Blandin, J.F. Carpentier, A. Mortreux Tetrahedron: Asymmetry, 9, 2765, (1998) Tetrahedron: asymmetry, Vol. 8, 17, 2881, (1997) Tetrahedron Letters, 40, 4551, (1999);F. Robin, F. Mercier, Louis Ricard, F. Mathey, M. Spagnol Chem. Eur. J., 3, 8, (1997);P.J. Pye, K. Rossen, R.A. Reamer, R.P. Volante, P.J. Reider Tetrahedron Letters, 39, 4441, (1998);T. Yamano, N. Taya, M. Kawada, T. Huang, T. Imamoto Tetrahedron Letters, 40, 2577, (1999);T.Shiori,N.Irako Tetrahedron Letters, 5793, (1999);R. ter Halle, B. Colasson, E. Schulz, M. Spagnol, M. Lemaire Tetrahedron Letters, 41, 643, (2000) Tetrahedron Letters, 42, 663, (2000)

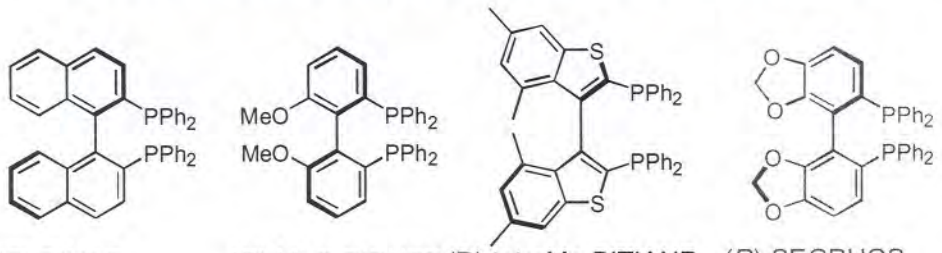
*Large Scale Synthesis of (S)-Candoxatril*An inhibitor of Neutral Endopeptidase for treatment of Congestive Heart Failure*



Bulliard, M.; Laboue, B.; Lastanet, J.; Roussiasse, S. Org. Proc. Dev. 2001, 5, 438.
J.P. Genet,V.Vidal et coll Tetrahedron Asymmetry 1994

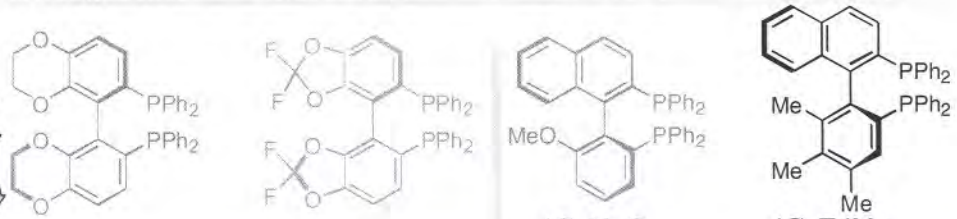
PPG-SIPSY used this procedure(Ru-MeOBiphep) to prepare tons of a key chiral succinate intermediate by asymmetric hydrogenation of a tri substituted olefin. The succinate was then transformed for clinical trials to Candoxatril a cardiovascular drug developed by Pfizer in the mid 1990's. *Pfizer, Drug Discoveries Oct.1997*

ATROPISOMERIC DIPHOSPHINES



(*R*)-BINAP Takasago 1980 | (*R*)-MeO-BIPHEP Roche 1991 | (R)-tetraMe-BITIANP Sannicolo 1994 | (*R*)-SEGPHOS Takasago 2002

20Kg/scale : Commercially Available, STREM

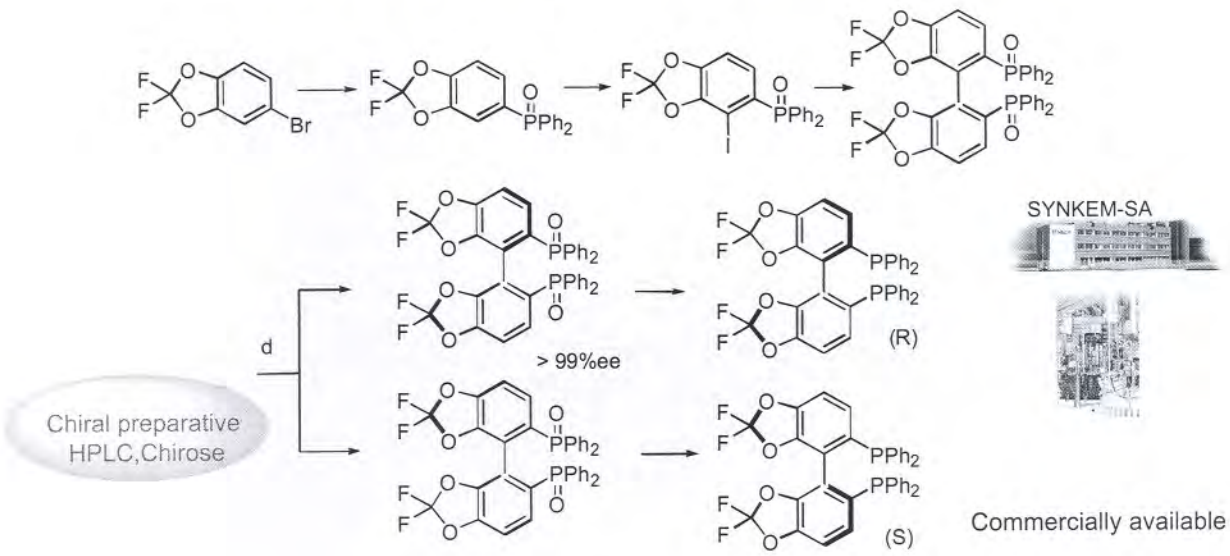


(*R*)-SYNPHOS® | (*R*)-DIFLUORPHOS® | (*S*)-MeO-NaPhePHOS | (*S*)-TriMe-NaPhePHOS

2001 SYNKEM-SA *2001 PPG-SIPSY*

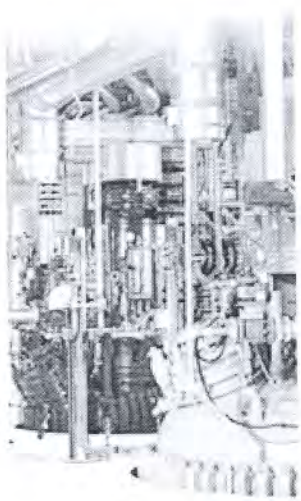
Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.P.; Champion, N.; Dellis, P. Patent SYKEM-SA FR2830254, 2001 ; WO03029259, 2003 ;; Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.P.; Champion, N.; Dellis, SYNPHOS®, Tetrahedron Lett. 2003, 44, 823 ; ibid Eur. J. Org. 2003, 1931 ; Org. Proc. R & D, 2003, 7, 399. Chan et al Tetrahedron Lett 2002 S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion, P. Dellis, Angew.Chem.Int Ed 2004,320 22
G.Michaud, M. Bulliard, J.P.Genêt, A. Marinetti Chemistry Eur. JOC. 15,,3327,2002; J.Madec, G.Michaud, J.P.Genet, A.Marinetti, Tetrahedron: Asymmetry, 2004, 2253

Synthesis of DIFLUORPHOS ligand



a) Mg, THF then $ClP(O)Ph_2$, 66%; b) LDA, THF, -78°C, 2 h then I_2, -78°C to rt, 87%; c) Cu, DMF, 130°C, 69%; d) Chiral preparative HPLC, 90% e) $HSiCl_3$, Bu_3N, xylene, 140°C, quantitative.

S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion, P. Dellis, Angew.Chem.Int. Ed 2004,320, Proceeding of National Academy of Sciences, Special Feature Issue on Asymmetric Catalysis, 2004, 101, 16, 5799.

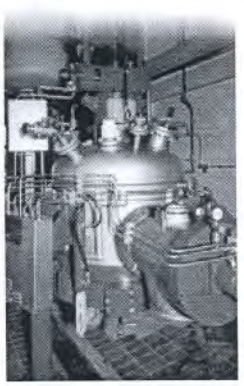


(*R*)-(+)SYNPHOS

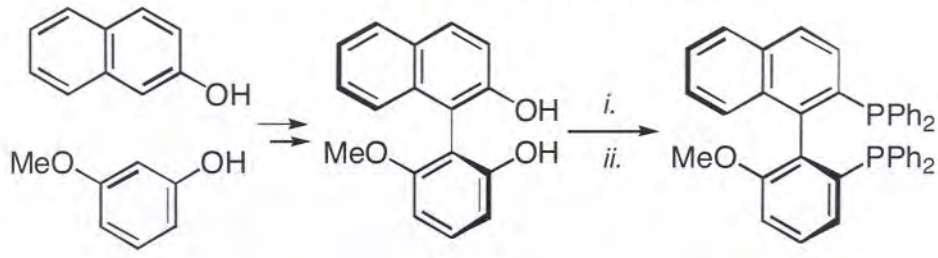
(R) DIFLURPHOS

(*S*)-(-)SYNPHOS

(S) DIFLURPHOS



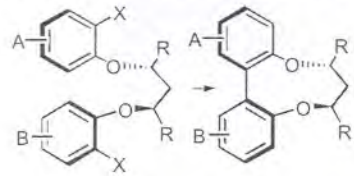
Synthesis of Unsymmetrical Atropisomeric Diphosphine
A New Biaryl Diphosphine

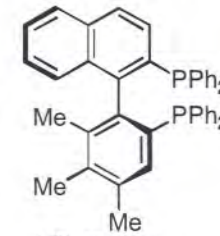


(*R*)- (*S*)-
MeO-NaPhePHOS
NaphtylPhenylphosphine

i. Tf_2O, pyridine, CH_2Cl_2, rt., 12 h.: 70% yield ; *ii.* $HPPh_2$, $NiCl_2$(ddpe), DABCO, DMF, 100°C, 3 days: 60% yield

The aryl-aryl bond was formed by applying Lipshutz's method *(Angew.Chem.Int. Ed 1994,5567)*





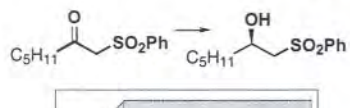
Highly modular ligands

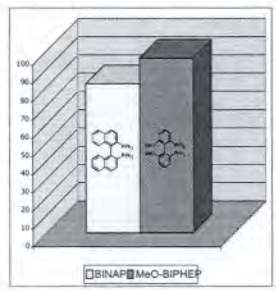
(*S*)-TriMe-NaPhePHOS

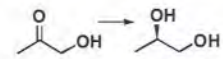
G.Michaud, M. Bulliard, J.P.Genët, A. Marinetti Chemistry Eur. JOC. 15,,3327,2002; J.Madec, G.Michaud, J.P.Genet, A.Marinetti, Tetrahedron: Asymmetry, 2004, 2253

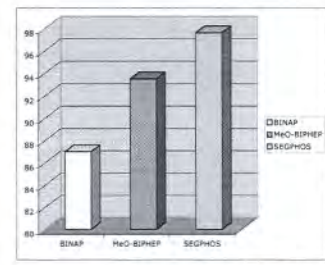
25

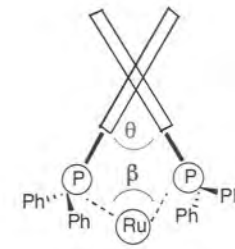
The dihedral angle θ a key steric parameter in Ru-mediated asymmetric hydrogenation







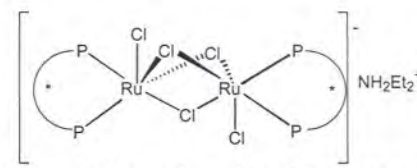




θ :Dihedral angle
β :chelation angle
or "bite angle"

J.P.Genet ,V. Vidal et al Tet.Lett., 39, 3473,1998,; Tetrahedron Lett., 1997, 38, 2951. Tetrahedron Lett., 1998,39, 3473. Tetrahedron: Asymmetry, 1999, 10, 1369.J. Organomet. Chem. 2000, 603, 128.

Saito and coll. Adv. Synth. Catal. 2001, 343;

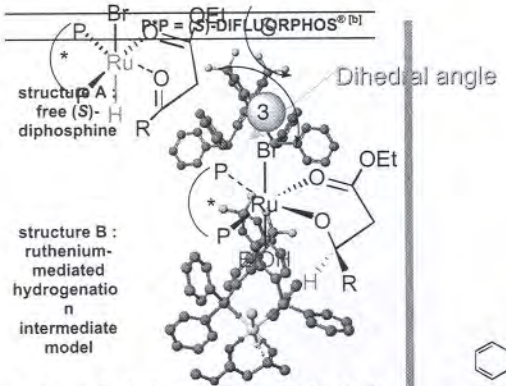


The steric effects play a crucial role.The steric consideration is based on the dihedral angle in the biaryl backbone. A narow **dihedral** angle directly related to the bite angle angle is a key to obtain good enantioselectivities in asymmetric hydrogenation. Molecular mechanics calculation (MM2) using CAChe program proved to be the tool of choice for a rapid and easy quantification of the dihedral angle of the biaryl backbone.

26

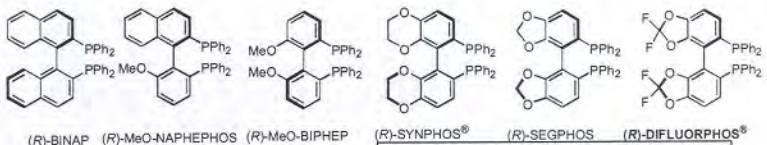
Free Ligands 87° BINAP 87° MeO-BIPHEPX.Tunaphos Zhang J.Org. Chem.6223,2000

Steric Profiles of Atropisomeric Diphosphanes

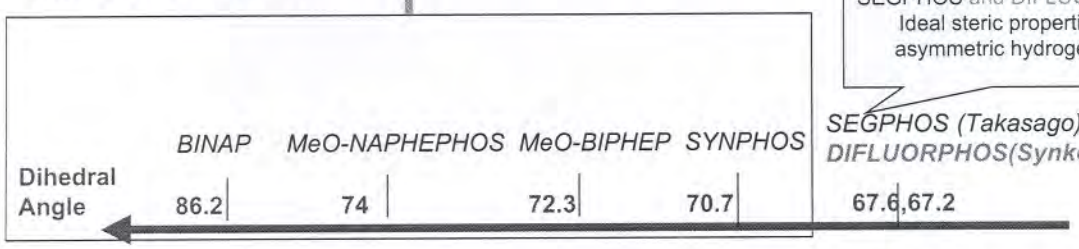


Diphosphine ligand	Dihedral angle, θ /°	
	structure A (free diphosphine)	structure B (Ru complex)
BINAP	86.2	79.5
MeO-NAPHEPHOS	74	77.2
MeO-BIPHEP	72.3	75.7
SYNPHOS®	70.7	75.4
SEGPHOS	67.2	73.3
DIFLUORPHOS®	67.6	73.3

Daley, C. J. A.; Bergens, S. H. J. Am. Chem. Soc. 2002, 124, 3680
Stereo-Determining ,(Stability-Controlled Mechanism)

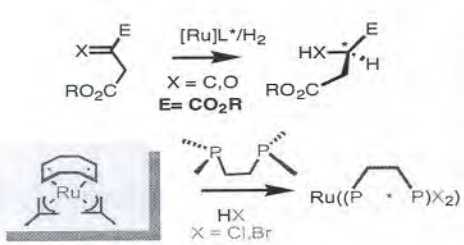


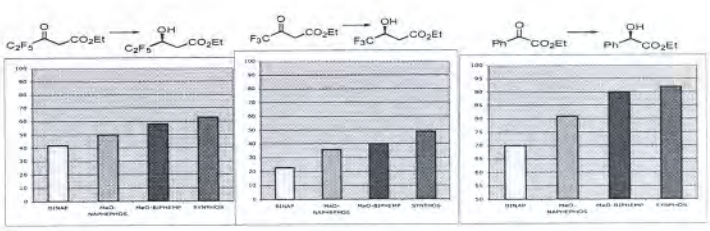
SEGPHOS and DIFLUORPHOS : Ideal steric properties for asymmetric hydrogenation

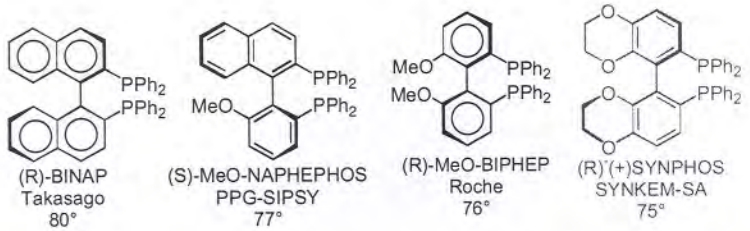


S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion, P. Dellis, Eur. J. Org. Chem. 2003, 1931. Ibid Angew.Chem.Int 2004,43,320, Proceeding of National Academy of Sciences, Special Feature Issue on Asymmetric Catalysis, 2004, 101, 16, 5799.

CORRELATION θ /e.e



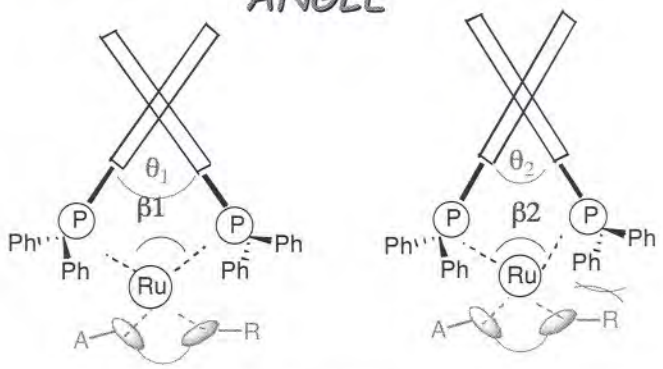




the enantioselectivities in the hydrogenation of the selected substrates are influenced remarkably by the dihedral angle of the ligand.. **It can be seen the highest ee values were always obtained with SYNPHOS ligand which has the lowest dihedral angle.**

S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.P. Genet, N. Champion, P. Dellis, Tetrahedron Letters, 2003, 44,823;Eur. J. Org. Chem., 2003,1931,G.Michaud,J.Madec,A.Marinetti unpublished

STERIC CONSIDERATIONS based on the DIHEDRAL ANGLE



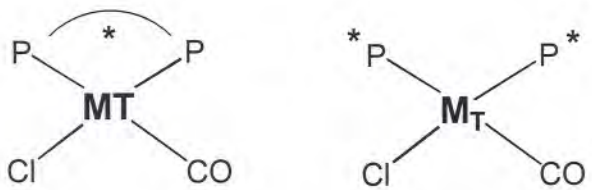
θ :Dihedral angle
β :chelation angle
or "bite angle"

Steric Effects A small dihedral angle which controls directly the asymmetric special environment around the metal enhances interactions between the steric bulk of the diphenylphosphino group and the the substituents of the substrate giving better enantioselectivities

Electronic Effects : are also known to dramatically influence the selectivity and the present model does not consider electronic properties of the complex

ELECTRONIC EFFECTS

Electronic donor-acceptor properties of diphosphines can be conveniently evaluated by measuring the carbonyl stretching frequency of [RhCl(P*P))CO] complexes by infra-red spectroscopy.



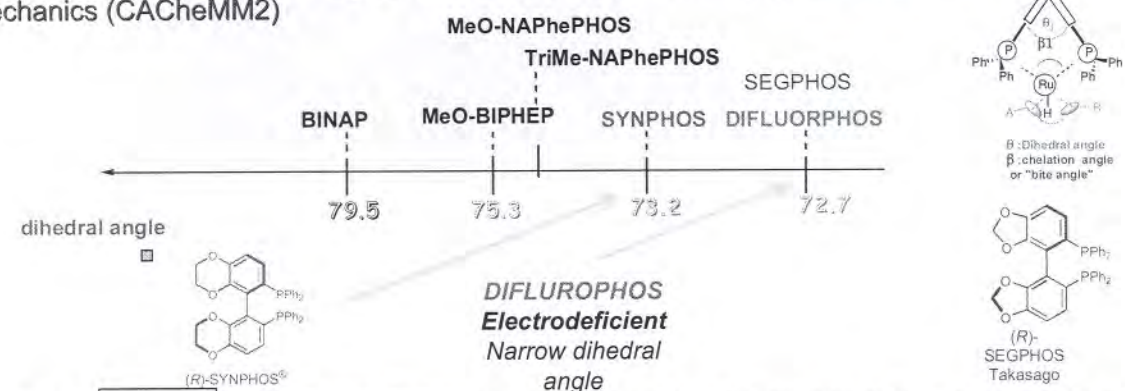
The higher the carbonyl stretching frequency of the CO ,the higher the p-acidity of the ligand

Allen,Taylor, J.Chem.Soc. Dalton Trans 1982 ,51, Suarez,A Mendez-Rojas,Pizano,A Organometallics 2002,21,4611

Steric and Stereoelectronic Profiles of Atropisomeric Ligands

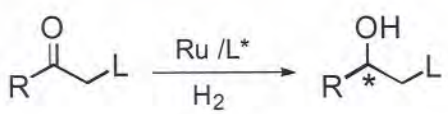
- Evaluation of the Electron donor-acceptor properties of these ligands have been investigated by studying the carbonyl streching frequencies of RhCl(Diphosphane)CO complexes

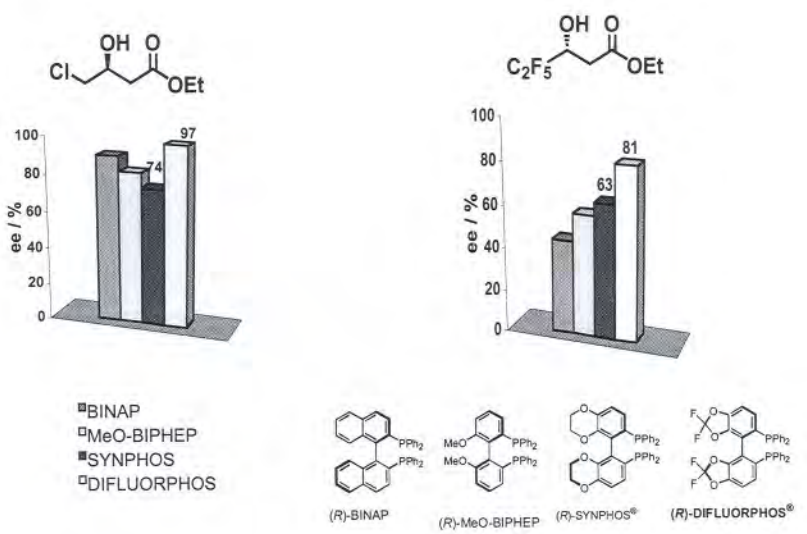
- Evaluation of dihedral angles of (P*P)RuHBr(substrate) by molecular mechanics (CACheMM2)



S.Duprat de Paule, S.Jeulin, V.Vidal, J.-P.Genet, N.Champion, P.Dellis, Angew.Chem.Int Ed. 2003,43,320 ; Proceeding of National Academy of Sciences, Special Feature Issue on Asymmetric Catalysis, 2004, 101, 16, 5799. J.Madec, G.Michaud, J.P.Genet, A.Marinetti, Tetrahedron: Asymmetry, 2004, in press MeO- and triMMe NAPhePHOS)Saito and coll. Adv. Synth. Catal. 2001, 343 (Segphos).

Ru(II)-catalyzed hydrogenation using DIFLUORPHOS ligand



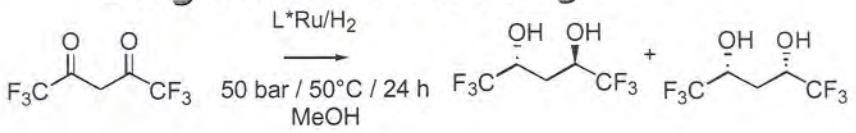


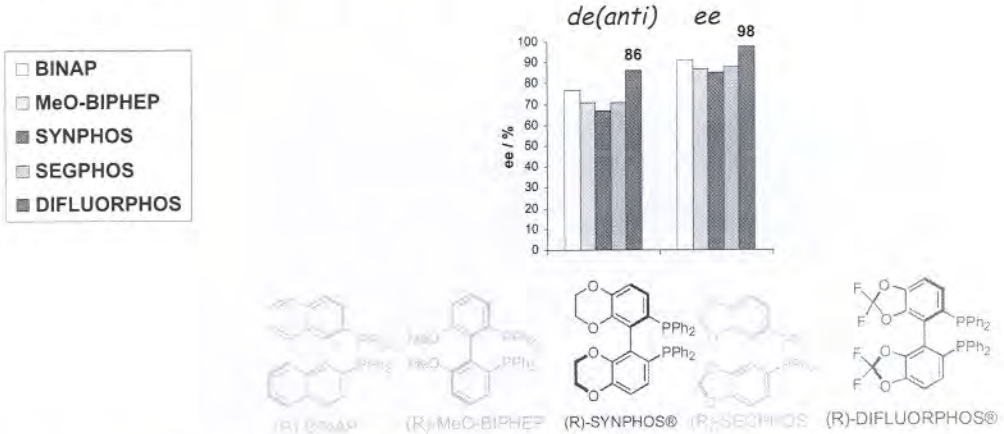
S. Jeulin, S. Duprat de Paule, V. Vidal, J.P. Genet, N. Champion, P. Dellis, Angew.Chem.Int Ed 2004,320, ;ibid Proc. Nat. Acad. Sciences, 2004, 5799

Ru(II)-catalyzed hydrogenation of Fluorinated Compounds using DIFLUORPHOS ligand

products :

conditions :

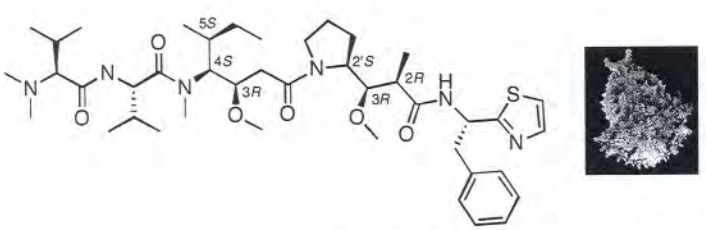




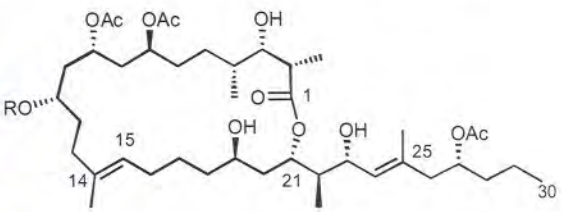
The superiority of Diflurophos on its non fluorinated analogue is due to the atypical combination a narrow dihedral angle and a stronger π-acidity giving the best ee's on fluorinated β-functionnalized ketones.

S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion, P. Dellis, Angew.Chem.Int Ed 2003,43,320 ; Proceeding of National Academy of Sciences, Special Feature Issue on Asymmetric Catalysis, 2004, 101, 16, 5799.

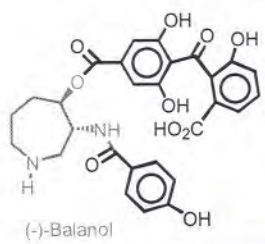
Dolastatin 10



Dolabelide



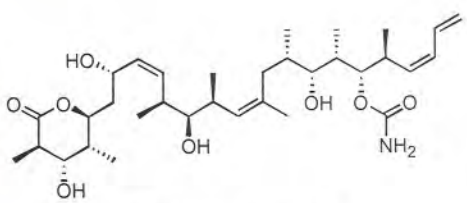
Marine natural products from *Dolabella auricularia*



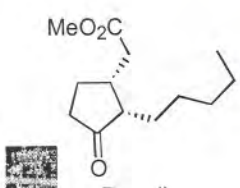
(-)-Balanol

Genet et coll Eur.J.Org.Chem. 3903,2000

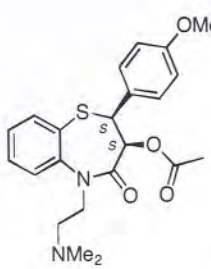
SYNTHESES using ASYMMETRIC HYDROGENATION



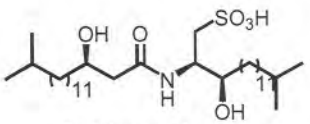
(+)-Discodermolide



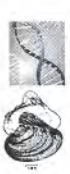
Paradisone



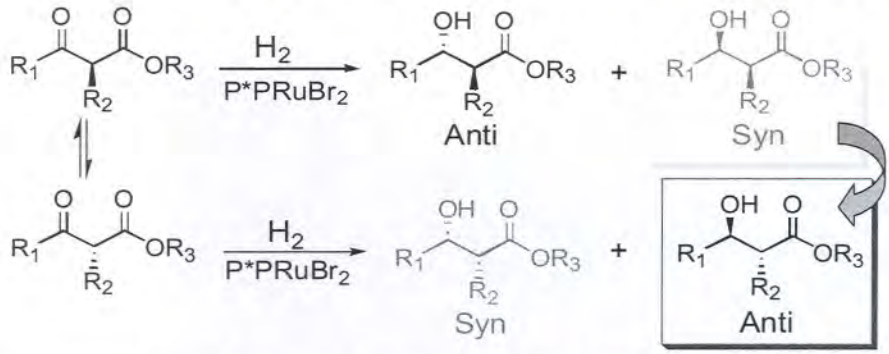
diltiazem



Sulfobacine A



Dynamic Kinetic Resolution (DKR)



The nature of R_2 is regulating the selectivity

Dynamic Kinetic Resolution associated to Ru-catalyzed hydrogenation is a powerful tool to control the stereochemistry of two adjacent stereogenic centers from a racemic starting material in one single operation .The product (*syn or anti*) is produced with a chemical yield up to 100% and high ee.

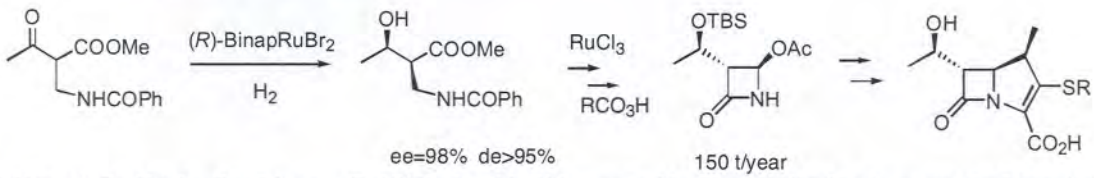
Early papers: ***Noyori, R.; Ikida, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H.. J. Am. Chem. Soc. 1989, 111, 9134 ;***

Genet, J.-P.; Mallart, S.; Juge, S. French Patent 8911159, 1989. ;Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. Tetrahedron: Asymmetry 1991, 2, 555-567; Reviews:V.Vidal, J.P. Genet Can. J. Chem., 78, 846, 2000; J.P. Genet Acc.Chem.Res. 2003,36,908

Reviews: (b) Noyori, R.; Tokunaga, M.; Kitamura, M. Bull. Chem. Soc. Jpn. 1995, 68, 36-55. Ratovelomanana-Vidal, V.; Genet, J.-P. Can. J. Chem. 2000, 78, 846-851 , Pelissier Tetrahedron 2003, 59, 8291. Pelissier Tetrahedron 2003, 59, 8291.

Dynamic Kinetic Resolution SYN Selectivity

✦ Synthesis of acetoxy azetidinone

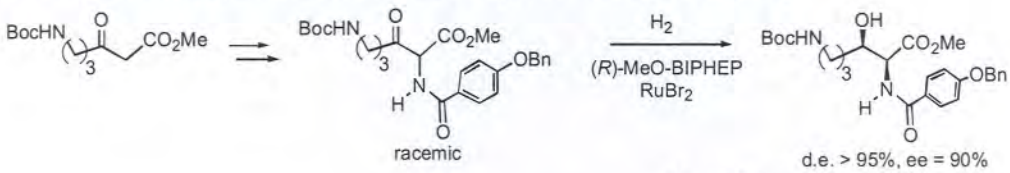


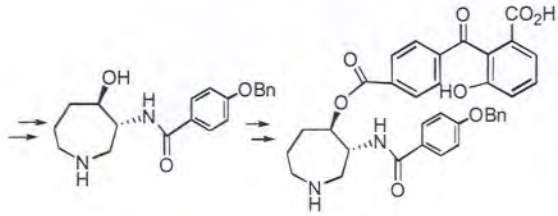
ee=98% de>95%

150 t/year

(a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H., J. Am. Chem. Soc. 1989, 111, 9134 ; (b) Murahashi, E.I.; Nakota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S., J. Am. Chem. Soc. 1990, 112, 7820

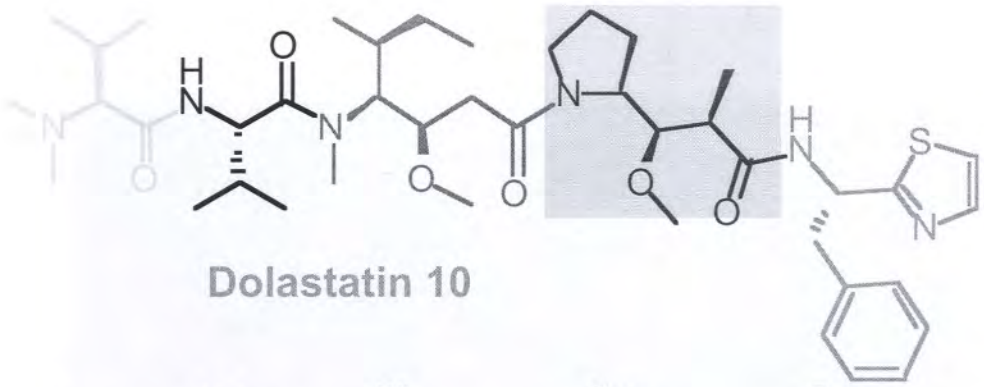
✦ Synthesis of the azepane core of Balanol (protein kinase inhibitor)





7 steps shortest synthesis of Balanol core

Phansavath, P.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.P., Eur. J. Org. Chem. 2000, 3903



Dolastatin 10

Dov — dolavaline

Val — valine

Dil — dolaisoleucine

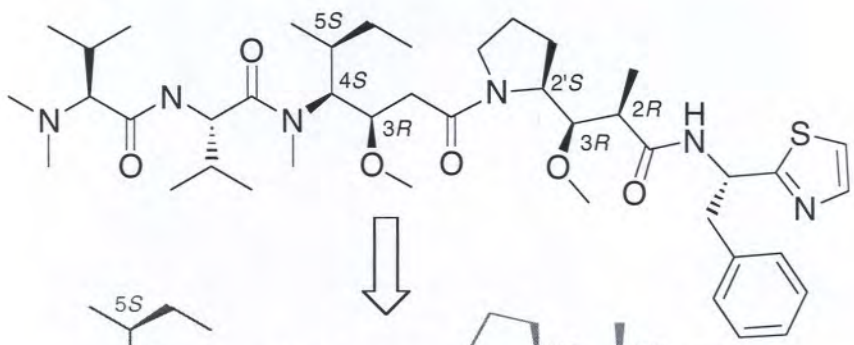
Dap — dolaproline

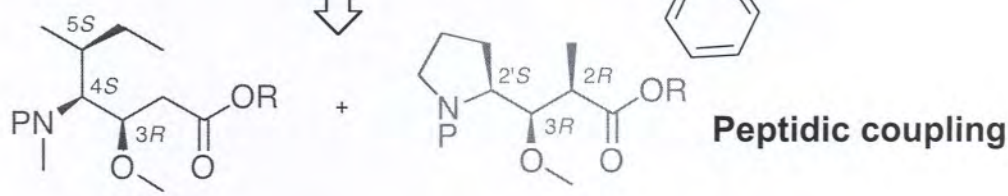
Doe — dolaphenine

Isolated from the Indian Ocean sea hare *Dolabella auricularia*
ED_{50} = 4,6 x 10^{-5} mg/mL against PS leukemia, is currently under clinical investigation
As new cancer agent phase II
1000 kg of sea hare *Dolabella auricularia* *< 30 mg of isolated material* .

Pettit, G.R.; Kamano, Y.; Herald, C.L.; Tuinman, A.A.; Boettner, F.E.; Kizu, H.; Schmidt, J.M.; Baczynskyj, L.; Tomer, K.B.; Bontems, R.J. J. Am. Chem. Soc., 1987, 109, 6883.Syntheses Pettit (1989) ***mainly based on aldol condensation of N-protected (S)-prolinal with various propionyl enolates.***

RETROSYNTHETIC ANALYSIS



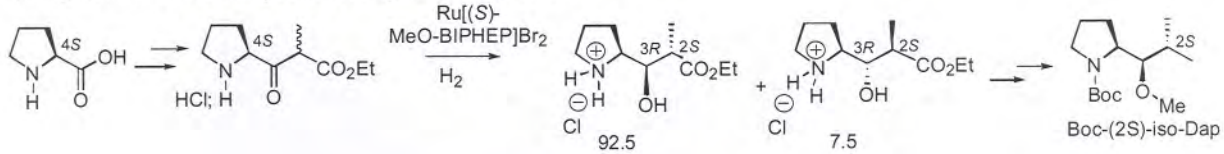


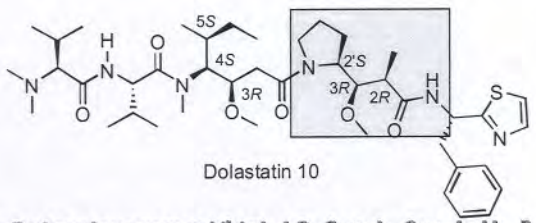
Peptidic coupling

Asymmetric Hydrogenation

Dynamic Kinetic Resolution ANTI Selectivity

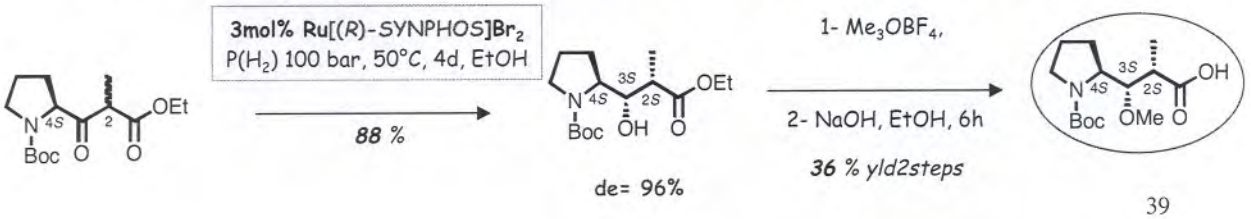
✦ Synthesis of Boc-(2*S*,3*R*,3*S*)-isodaloproine





D. Lavergne, C. Mordant, V. Ratovelomanana-Vidal, J.P. Genet, Org. Lett., 3, 12, 1909, 2001

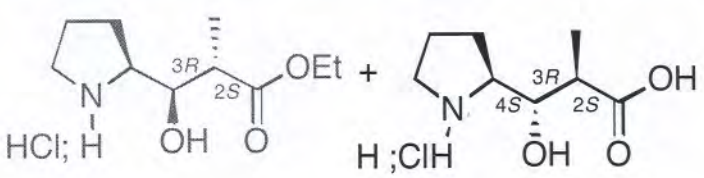
Dynamic Kinetic Resolution SYN Selectivity

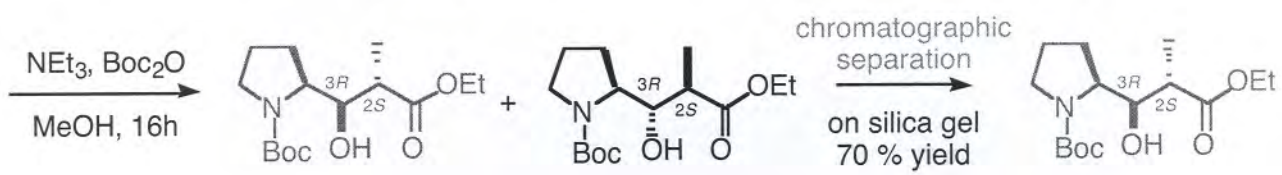


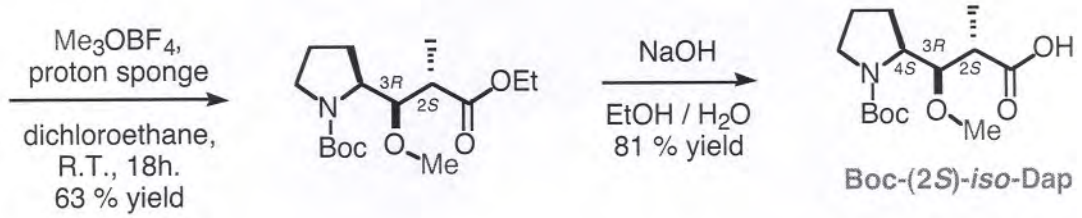
39

C.Mordant,V.Vidal,J.P.Genet,D.Lavergne,,Symposium-in-print "Catalytic Tools Enabling Total Synthesis", 2004, in press

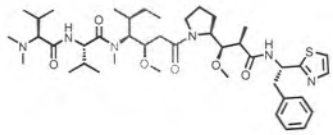
SYNTHESIS of Boc-(2S)-*iso*-DOLAPROINE



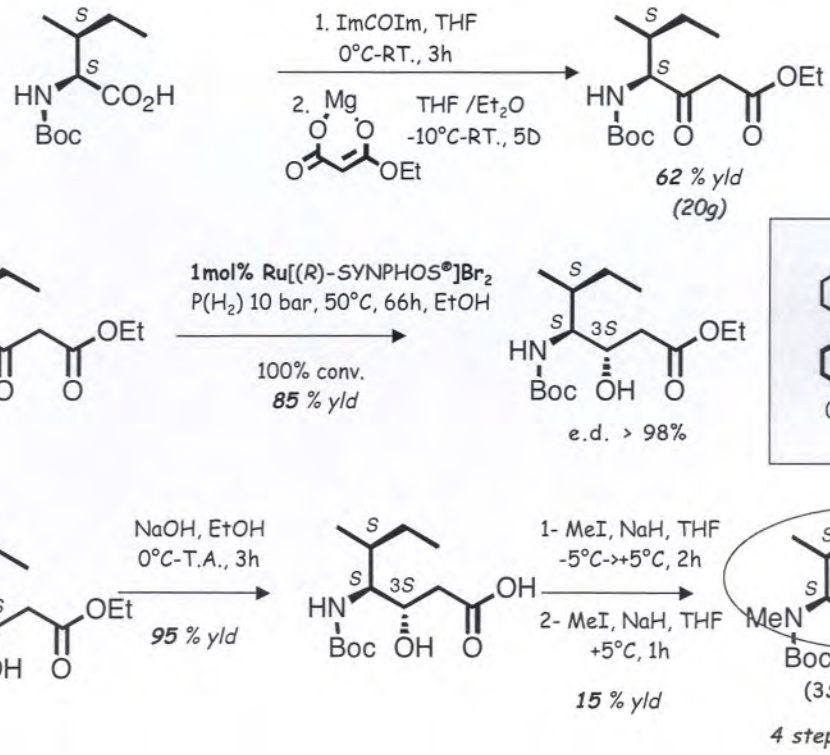




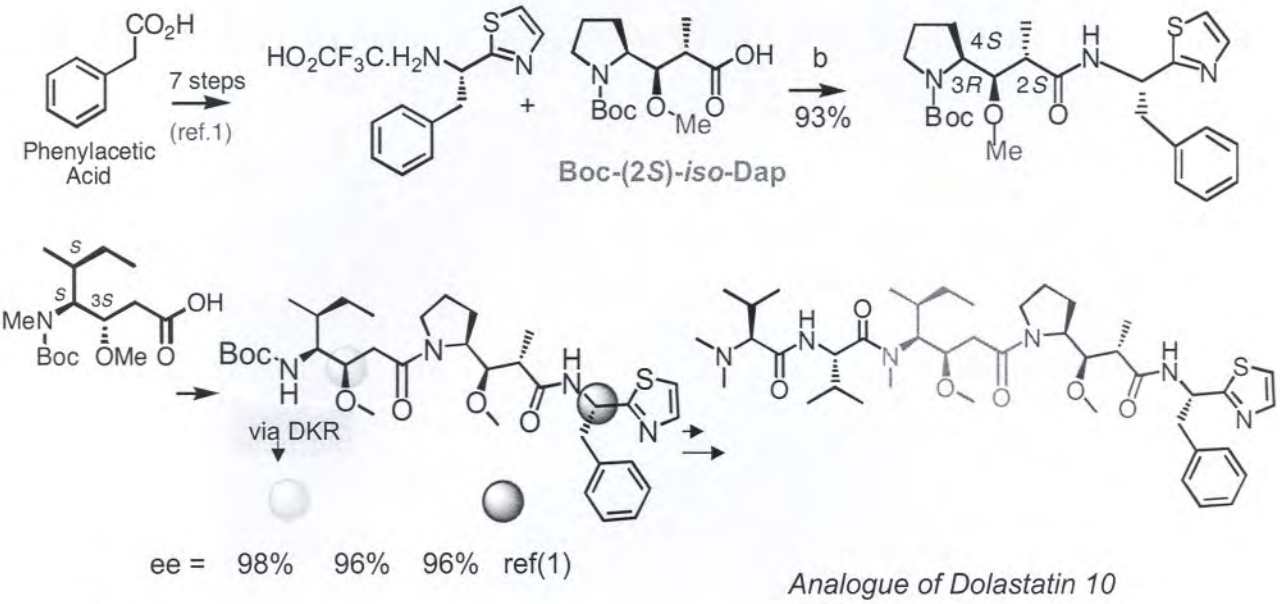
Damien Lavergne, Céline Mordant, Virginie Ratovelomanana-Vidal Organic Letters 1909, 2001



iso-Dolaisoleucine Unit



TOWARD SYNTHESIS of DOLASTATINE 10 ANALOGUE



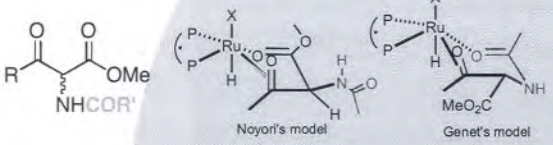
a)TFA,CH_2Cl_2,2h ;
b)(EtO)2P(O)CN/NEt_3,2h,0°C,24h RT

Ref 1 :Irako, N.; Hamada, Y.; Shiori, T. Tetrahedron **1992**, *48, 7251*

C.Mordant,R.Touati ,V.Vidal,S. Reymond unpublished

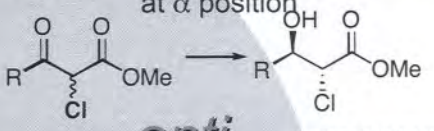
Dynamic Kinetic Resolution (DKR) Acyclic Substrates

Chelating group of ruthenium at α position



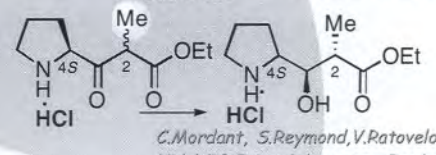
syn

Non-chelating group of ruthenium at α position



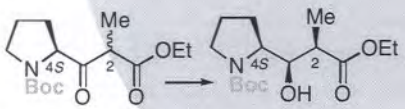
anti

Synthesis 2003,2405

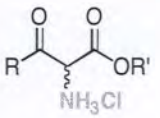


C.Mordant, S.Reymond,V.Ratovelomanana-Vidal,J.P.Genet,D.Lavergne,Org.Lett 2001,

Non-chelating group at α of ester* group - substituent at γ position



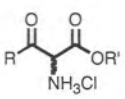
C.Mordant,V.Vidal,J.P.Genet,D.Lavergne,,Symposium-in-print "Catalytic Tools Enabling Total Synthesis", 2004, in press



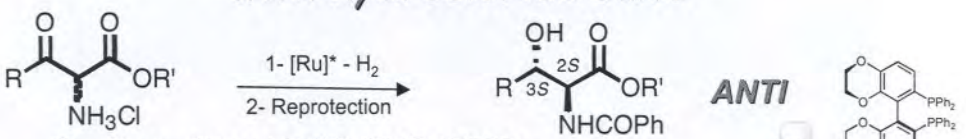
anti amino-acids and alcohols

anti ?

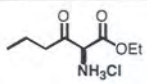
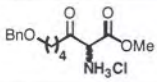
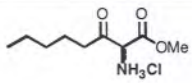
The nature of group at the α position of the ester and remote functional groups are regulating the selectivity

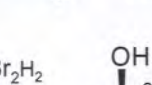


Synthesis of anti α-amino-ß-hydroxyesters via DKR with hydrocloride salts



Conditions : 2% mol Ru[(*S*)-SYNPHOS®]Br_2
CH_2Cl_2 + ε R'OH
$P(H_2)$ 12 bar, 50°C, 24h
100% conv.

Substrate	Yield (%)	e.d. anti (%)	e.e. (%)
	90	86	92 (2*S*,3*S*)
	94	92	92 (2*S*,3*S*)
	85	93	93 (2*S*,3*S*)

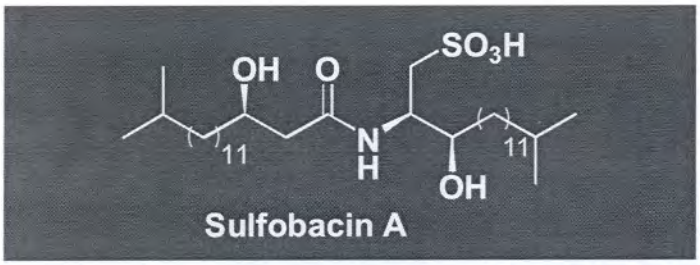
Substrate	Yield (%)	e.d. anti (%)	e.e. (%)
	83	96	96 (2*S*,3*S*)
	90	99	97 (2*S*,3*S*)

Determination by HPLC

excellents e.d. et e.e.

C.Mordant, P.Dünkelmann, V.Ratovelomanana-Vidal, J.-P.Genet Chem.Com. 2004, 1296 ; ibid Eur.JOC 2004 , 3017.

K. Makino, T. Goto, Y. Hiroki, Y. Hamada Angew. Chem. Int. ed. 2004, 43, 882 Binap Ru 100 at, 50°C, 48 h.



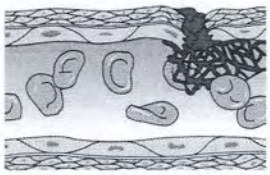
Sulfobacin A

Marine bivalve *Cristaria plicata* (Ishikary Bay - Japan)

Soil Sample
(Iriomote Iland - Japan)

Antithrombotic activity[1] (inhibition of the binding of von Willebrand Factor to the glycoprotein GPIb/IX)

J. Antibiotics **1995**, *48*, 924-936



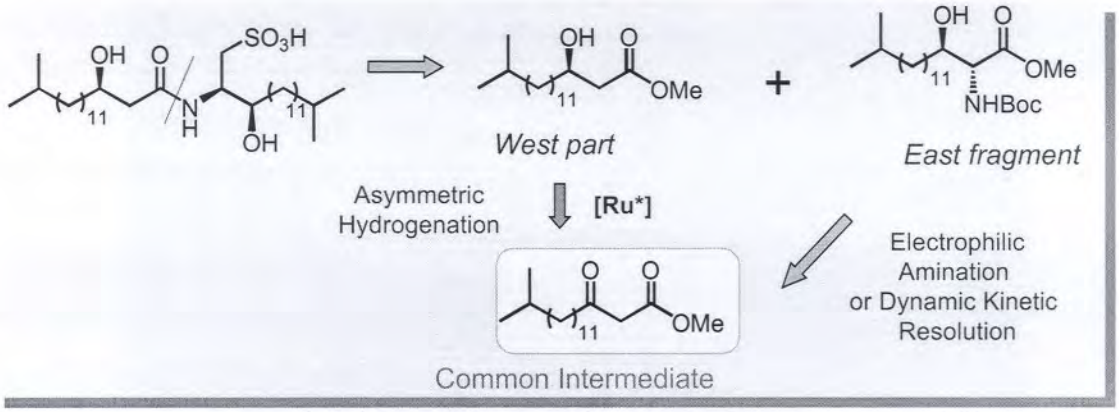
Inhibitor activity against DNA polymerase α

Tetrahedron **1995**, *51*, 10487-10490

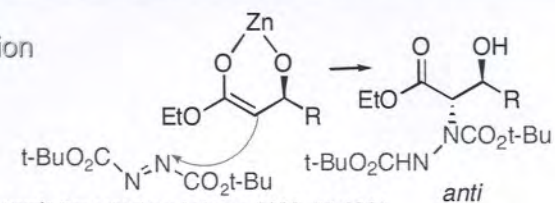
2 total syntheses were published in 1998 by Shioiri (21 steps) and by Mori (24 steps). They are based on a coupling reaction between *west* and *east* fragments, the latter is synthesized from the "chiral pool".

Sulfobacin A

Our synthetic approach relies on a common intermediate for the synthesis of the two fragments and is entirely based on stereoselective reactions. The common intermediate would be prepared using catalytic asymmetric hydrogenation.



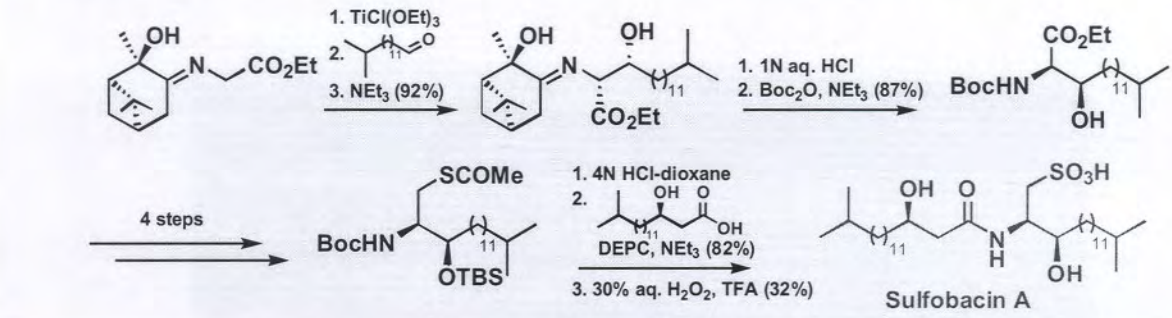
Electrophilic Amination



O.Labeeuw, P. Phansavath and J-P. Genêt Tetrahedron Letters 2003 ,44,6383
Greck,C.Lavergne,D.,Genêt, JP., Modern Amination Methods, Wiley-VCH, Ricci, A., Ed., 2000, 65-102

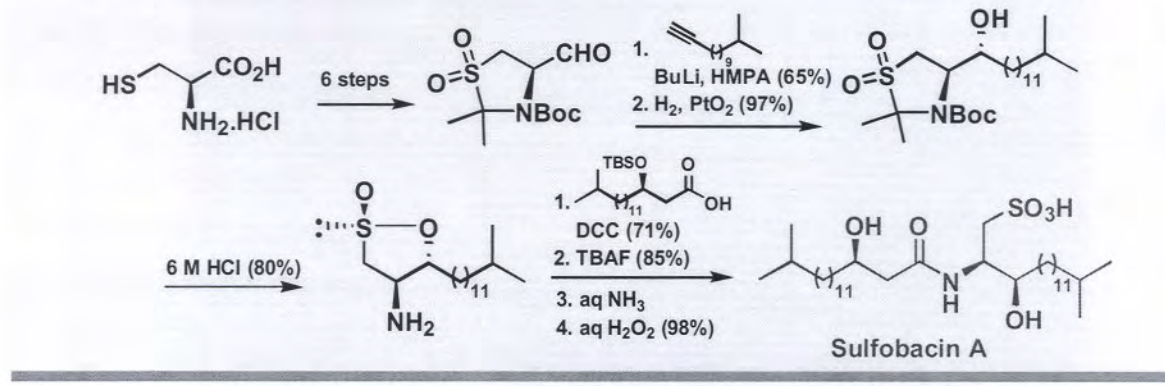
Shioiri 21 steps

Irako, N.; Shioiri, T. Tetrahedron Lett. 1998, 39, 5793-5796.
Shioiri, T.; Irako, N. Tetrahedron 2000, 56, 9129-9142.

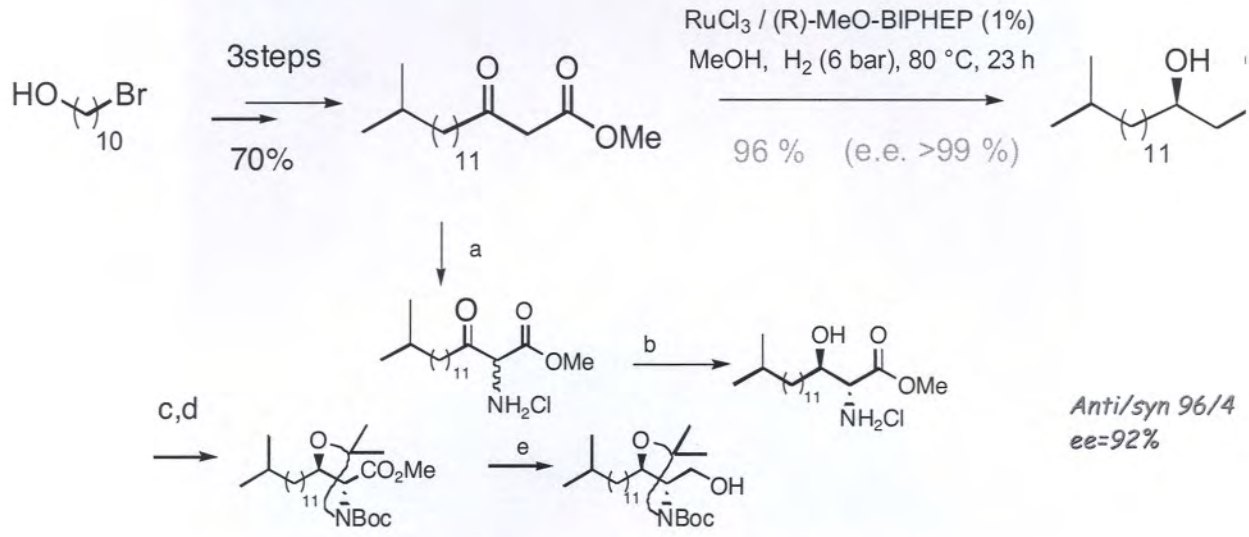


Mori 24 steps

Mori, K. et al.Tetrahedron Lett. 1998, 39, 6931-6934.
Mori, K. et al J. Chem. Soc., Perkin Trans. 1 1999, 2467-2477.

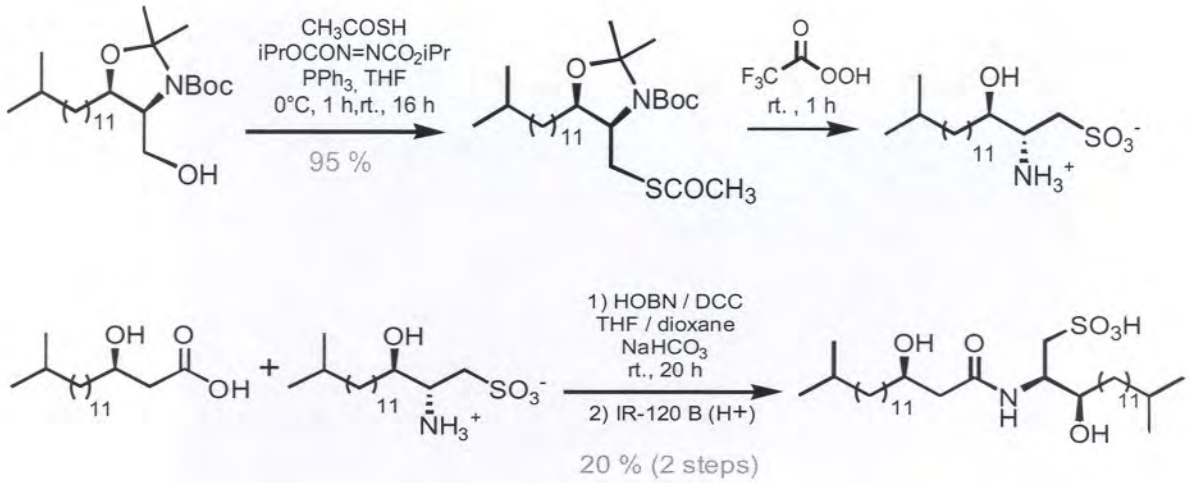


Synthesis of Sulfobacin A



(a) BuNO ether then H_2SO_4 98%,Pd/C,H_2 (1 atm),HCl; b Ru-(R-SYNPHOS H_2,12 bar 50°C,30h;c) Boc_2O, $NaHCO_3$, (d) $Me_2C(OMe)_2$, $Et_2O.BF_3$, CH_2Cl_2, rt, 1 h, 93%; (e)$Ca(BH_4)_2$, THF, EtOH, –15°C to rt, 22 h, 94%;

Sulfobacin A via DKR



Sulfobacin A

Sulfobacin A synthesized in 14 steps, (Shioiri : 21 steps and Mori : 24 steps)

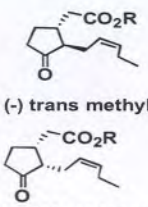
Ffexible synthesis : easy access to analogues

49

O.Labeeuw, P. Phansavath Tetrahedron:Asymmetry 2004, 15, 1899

Jasmonates

(jasminium grandiflorum)

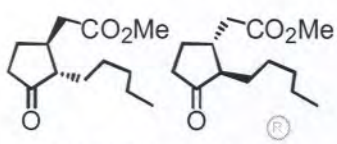


R = Me (-) trans methyl jasmonate

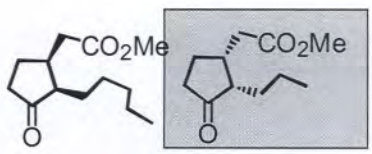
R = H ; (+) cis jasmonic acid
R = Me; (+) cis methyl jasmonate

Jasmin sambac

isolated from jasmine absolute,annual production 12t



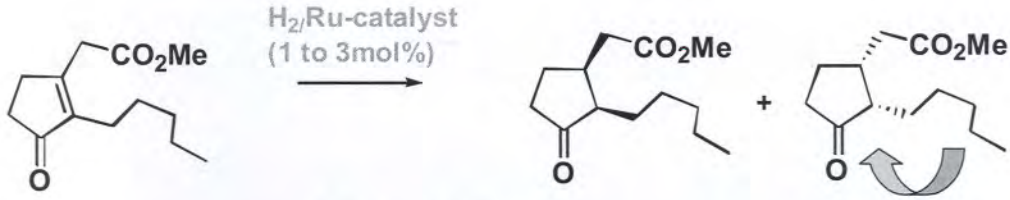
Hedione (racemic)



The olfactive properties of all four stereoisomers have been investigated. Evaluation by perfumers have established that (+) *cis* is the only stereoisomer that has the fragrance, its odor is caracteristic and intense.The presence of the other three stereoisomers affects the performance of the perfume in which the mixture is used.*V.Rautestrauch,J.J.Riedhauser (Firmenich)EP 715615*

50

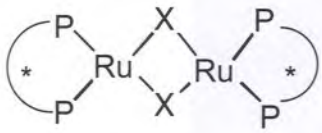
Synthesis of Cis-Dihydrojasmonates



Highly substituted olefin

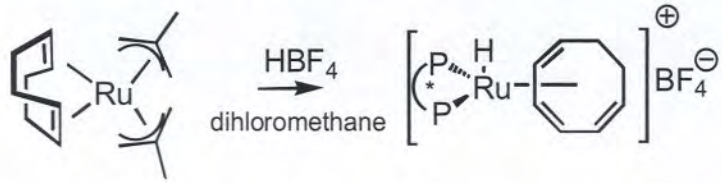
Epimerisation leads to the useless trans dihydrojasmonate

Ru-catalyst

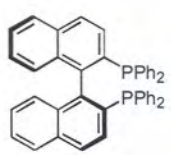


No reaction even high pressure 120 bar ,50°C several days

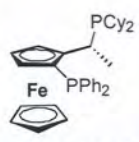
PREPARATION of Ru-HYDRIDE CATALYST and IDENTIFICATION of (Ru(R,R-MeDuPHOS)(H)η6-COT)BF_4



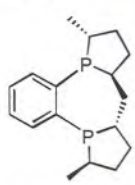
This transformation requires a weakly coordinating reaction medium such as CH_2Cl_2



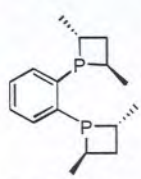
(*S*)-BINAP



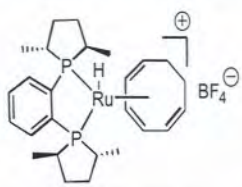
(*R,S*)-JOSIPHOS



(*R,R*)-Me-DuPHOS



(*R,R*)-Me-CnrPHOS



65%
isolated
Bright
yellow
Cristalline

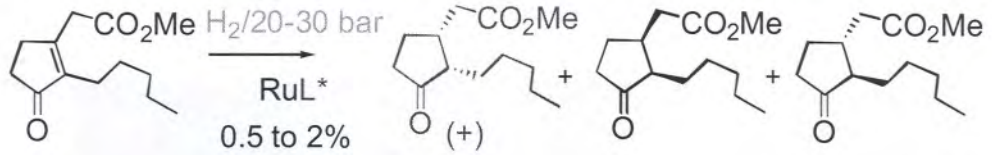
Precatalyst stable several months at -25°C glove bag

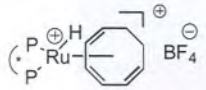
Indentity of the precatalyst was acertained from multinuclear

one and two dimentional NMR spectroscopy ,Mass spectroscopy

and X- Ray diffraction

Synthesis of (+) Cis-Dihydrojasmonate





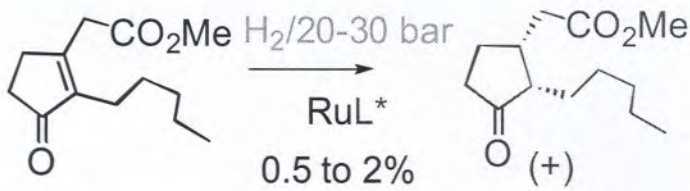
L*

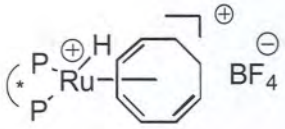
L*	(+) cis	ee %	trans
(*R*)-BINAP	80	40	20
(*R*,*R*)-Et-DuPHOS	93	40	7
(*S*,*S*)-iPr-DuPHOS	97	46	3

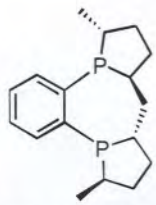
Electron-rich C2 Symmetric Phospholanes

J.Y. LENOIR, ENSCP 1994 -1995; V.RAUTENSTRAUCH,K.P.M.VANHESSCHE,J.Y. LENOIR,J.P.GENET ; E. Patent 0 810 903 B1/ WO97/18894/PCT/IB96/01263V.RAUTENSTRAUCH,K.P.M.VANHESSCHE,E.BRAZI,J.WILES;S.H. BERGENSJ.Y. LENOIR,J.P.GENET Angew. Chem. Int Ed. 39,11,1992,2000

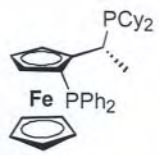
Industrial Synthesis of (+) Cis-Dihydrojasmonate







(*R*,*R*)-Me-DuPHOS



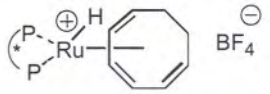
(*R*,*S*)-JOSIPHOS

Optimization :Solvents /reactions conditions
Cis / Trans > 99:1 , ee up to 90%
Since 1998 Firmenich: large scale production under the trade name of Paradisone®
First discovery ,1995,in our group of the catalyst

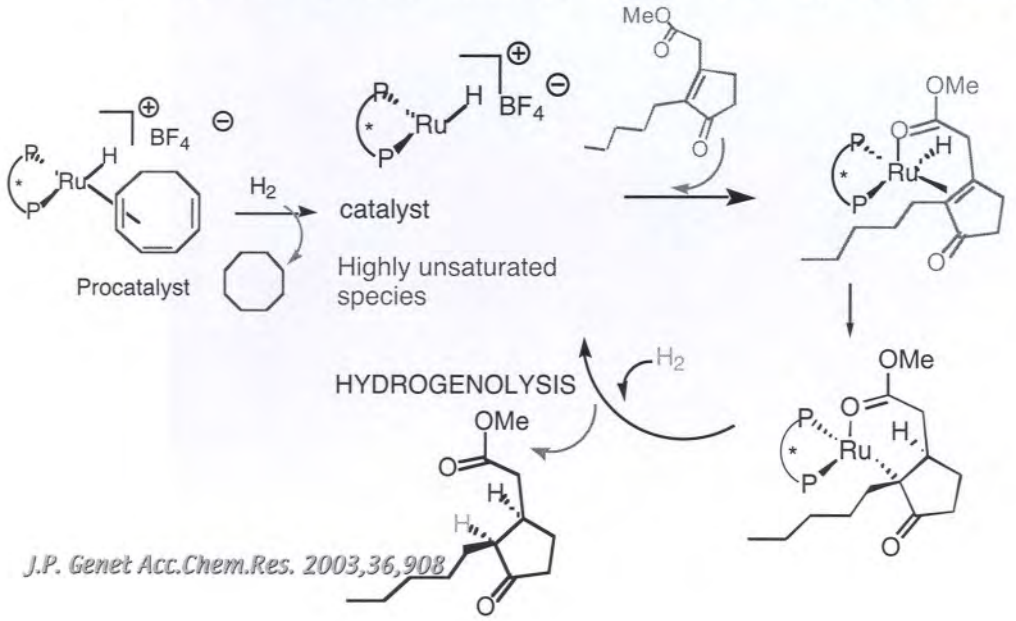
J.Y. LENOIR, ENSCP 1994 -1995; V.RAUTENSTRAUCH,K.P.M.VANHESSCHE,J.Y. LENOIR,J.P.GENET ; E. Patent 0 810 903 B1/ WO 97/18894 /PCT/IB96/01263V.RAUTENSTRAUCH,K.P.M.VANHESSCHE,E.BRAZI,J.WILES;S.H. BERGENSJ.Y. LENOIR,J.P.GENETAngew. Chem.Int Ed. 39,11,1992,2000

Recent use of this Procedure for challenging substrates

Dupau P,C.Bruneau,P.Dixneuf Adv.Synth.Catal.2001 ,343
W.Tang,S.Wu,X.Zhang J.Am.Chem.Soc. 9570,2003.

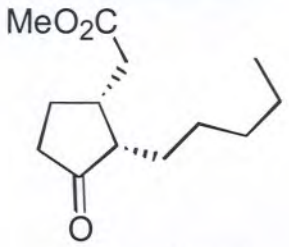


MECHANISM of HYDROGENATION of TETRASUBSTITUTED CYCLOPENTENONE with (R,R)DUPHOS Ru(II) CATALYST



J.P. Genet Acc.Chem.Res. 2003,36,908

Dolce Vita
(Christian Dior)



Paradisone
Genet-Firmenich 1995-2000

Eau de Dolce Vita
(Christian Dior)

Romance
(Ralph Lauren)

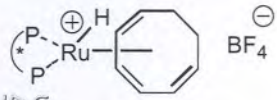
CONCLUSIONS

NEW PERSPECTIVES in ORGANOBORON CHEMISTRY

RBF_3K
Highly Stable

Ru USEFUL TECHNOLOGY IN FINE ORGANIC SYNTHESIS (DKR)

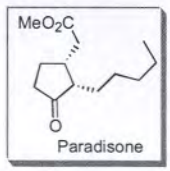
NEW GENERATION of Ru-CATALYSTS
NEW EFFICIENT ATROPISOMERIC LIGANDS



Dupau P,C.Bruneau,P.Dixneuf Adv.Synth.Catal.2001 ,343W.Tang,S.Wu,X.Zhang J.Am.Chem.Soc. 9570,2003

INDUSTRIAL APPLICATION

Second largest production (Firmenich) since 1999
First discovery of the catalyst in our laboratory 1995



ACKNOWLEDGEMENTS

ELF ATOCHEM

FIRMENICH S.A.

PPG-SIPSY

RHODIA ORGANIC DIVISION

ROCHE (Dr. Schmidt,Dr.M.SCALONE)

SYNKEM (Dr P. DELLIS ,Dr.N.CHAMPION)

ZENEKA PHARMA FRANCE

Dr. Saito (Takasago) genereous gift Of acetoxy azetidinone

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Prof. S. BERGENS (University of ALBERTA, Canada

Prof. C. BONINI (University of POTENZA, ITALY)

Dr J.Y Lenoir (Paradisone)

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- *(SYNPHOS,DIFLUORPHOS)*
- ***Céline Mordant** (DKR,Diltiazem)*
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- ***Olivier Labeeuw** (Sulfobacin A)*
- ***Nicolas Desroy** (Dolabelide)*
- ***Rémi Le Roux** (Dolabelide)*

Rh

- *Dr Sylvain Darses (MC)*
- ***Mathieu Pucheault** (1,4 addition ...ones,amides)*
- ***Laure Navarre** (1,4 addition Aminoacrylates)*
- ***Valérie Michaut***
- ***Rémi Martinez***

RBF_3K