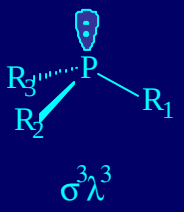
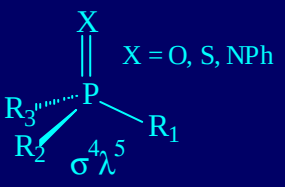
ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY
Ischia Porto (Napoli) Hotel Continental Terme
September 21-26, 2002

New P*(III) and P*(V) Chirogenic Ligands and Catalysts

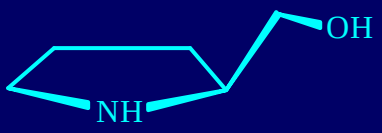


Pr. Gérard BUONO

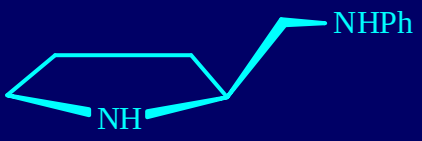
Université Aix-Marseille



Chiral Auxiliaries for the Synthesis of Oxaza and Diazaphospholidines

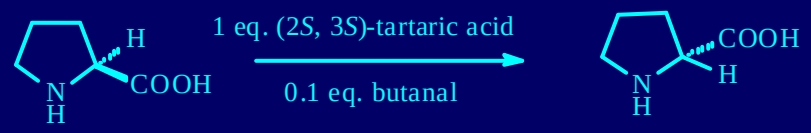


(*S*)-Prolinol



(*S*)-2-(anilinomethyl) pyrrolidine

Facile Production of (*R*)-Proline by Asymmetric Transformation of (*S*)-Proline



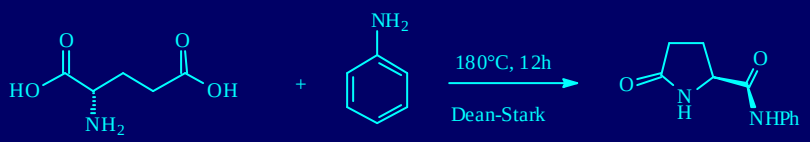
(*S*)-Proline

(*R*)-Proline

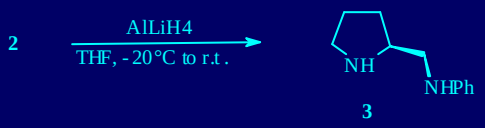
C.y: 85%
E.e: 100%

T. Shiraiwa et al. *Chem. Lett*. **1989**, *8*, 1413-1414

Obtention of the (*S*) and (*R*)-2-(Anilinomethyl)pyrrolidines



1 **2**

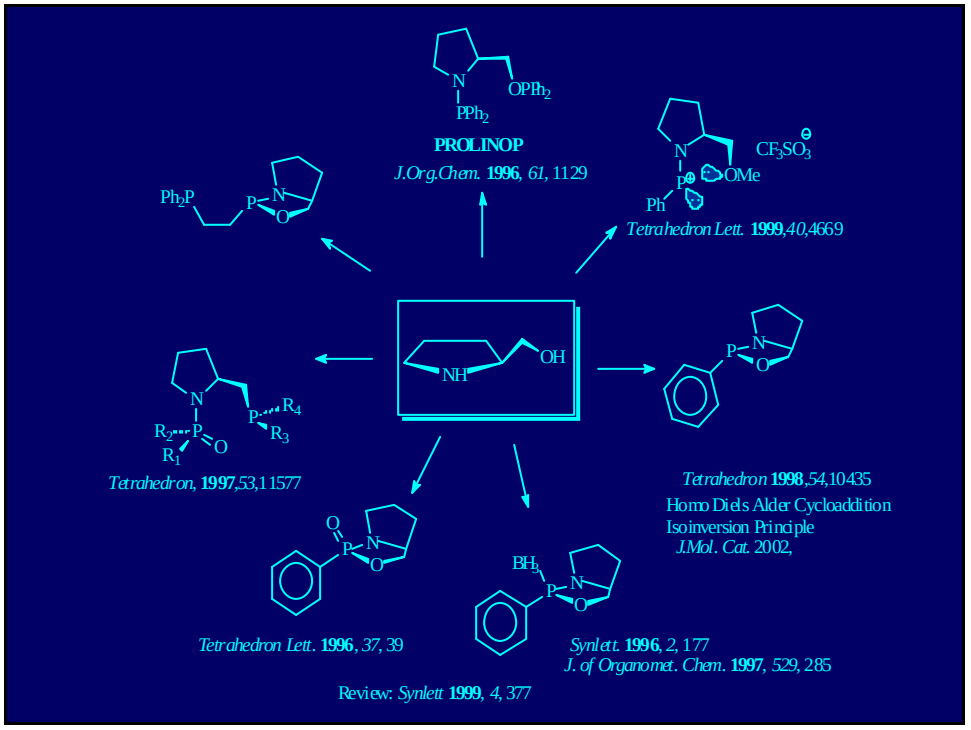


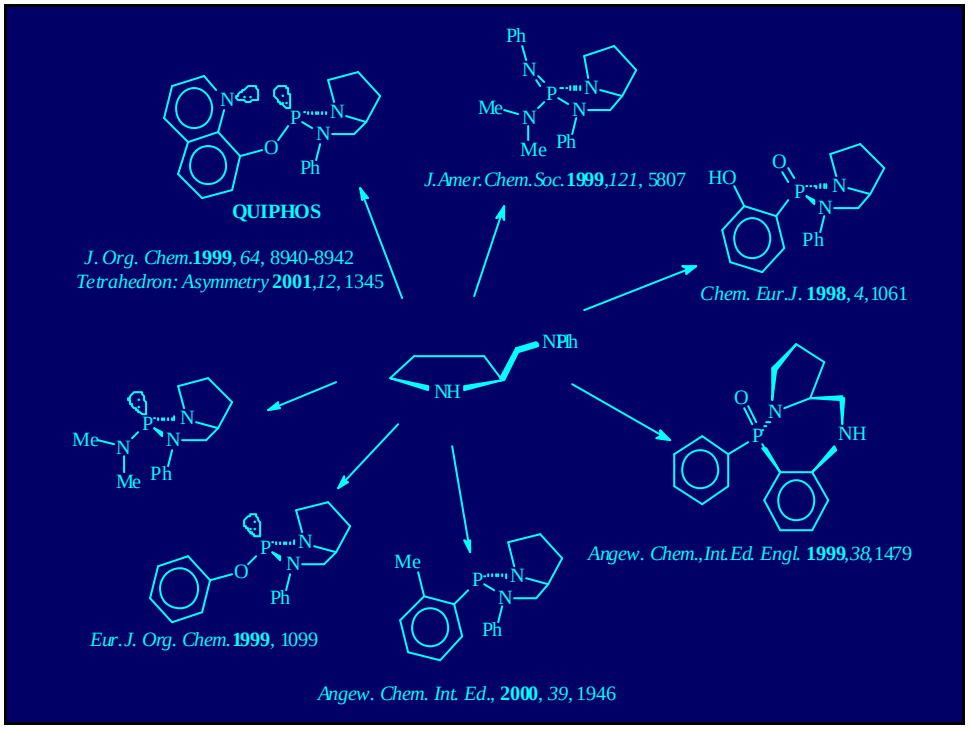
3

Chem.y. 92%

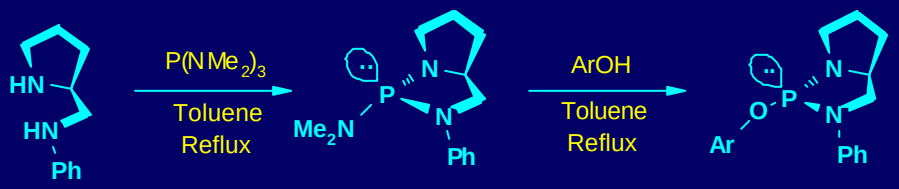
(±)-2-(Anilinomethyl)pyrolidine was effectively resolved into a pair of the enantiomers by fractional crystallisation of its mandelic acid salt.

K. Saigo et *al*; *Bull. Chem. Soc. Jpn*, **1982**, 55, 2299-2300

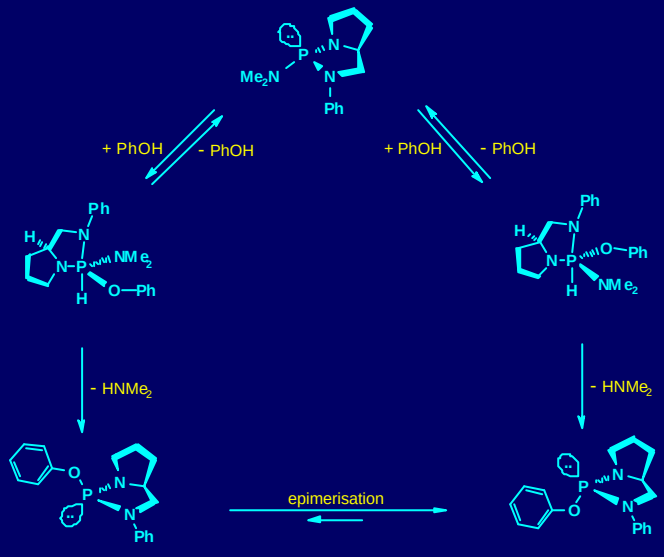

PROLINOP
J.Org.Chem. 1996, 61, 1129
Tetrahedron Lett. 1999,40,4669
Tetrahedron, 1997,53,11577
Tetrahedron 1998,54,10435
Homo Diels Alder Cycloaddition
Isoinversion Principle
J.Mol. Cat. 2002,
Tetrahedron Lett. 1996, 37, 39
Synlett. 1996, 2, 177
J. of Organomet. Chem. 1997, 529, 285
Review: Synlett 1999, 4, 377


QUIPHOS
J. Org. Chem.1999, 64, 8940-8942
Tetrahedron: Asymmetry 2001,12, 1345
J.Amer.Chem.Soc.1999,121, 5807
Chem. Eur.J. 1998, 4, 1061
Angew. Chem.,Int.Ed. Engl. 1999,38,1479
Eur.J. Org. Chem.1999, 1099
Angew. Chem. Int. Ed., 2000, 39, 1946

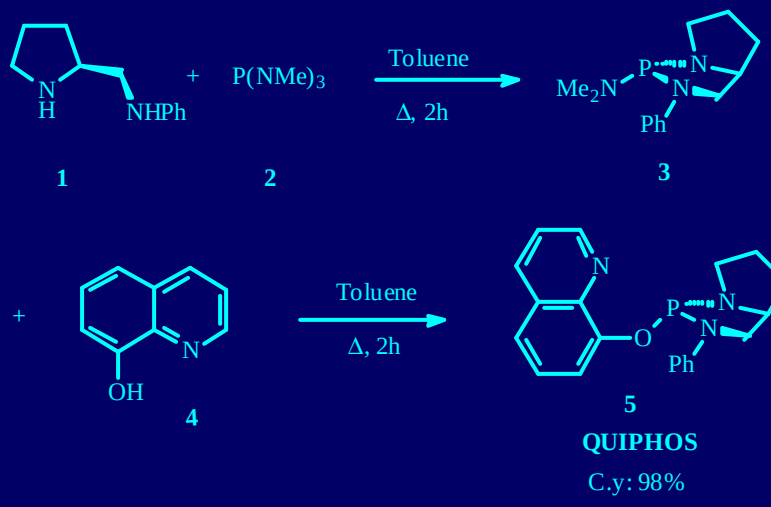
Synthesis Diastereoselective of Diazaphospholidine



Mechanism for the Diastereoselective Synthesis of Diazaphospholidine

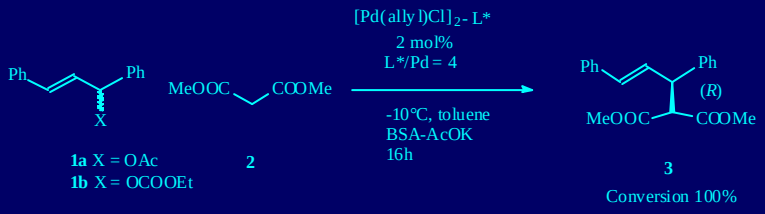


A Practical Method for the Large-Scale Synthesis of Diastereomerically Pure Ligand QUIPHOS



J. Org. Chem. **1999**, *64*, 8940-8942

Enantioselective Palladium Catalyzed Allylic Substitution with Chiral Pyridine-Phosphine Ligands



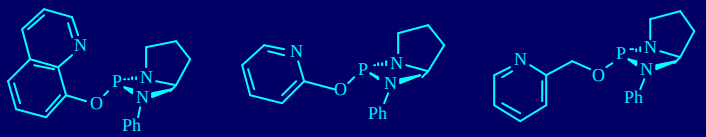
1a X = OAc
1b X = OCOOEt

2

3

Conversion 100%

Enantioselectivity (E.e %)



4 QUIPHOS

1a = 85%
1b = 87%

5

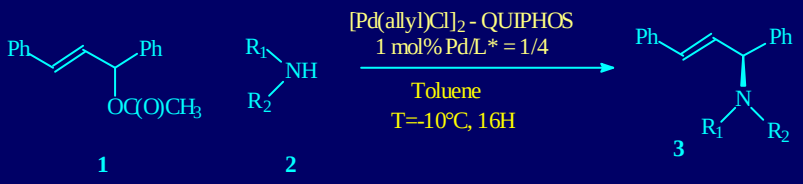
1a = 87%
1b = 83%

6

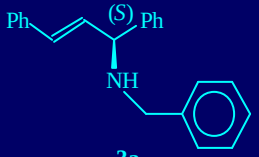
1a = 76%
1b = 78%

Tetrahedron Lett. **1997**,*34*, 5971-5974

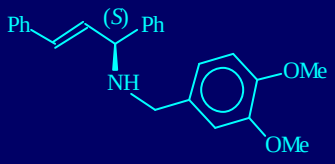
Allylic Amination catalyzed by Pd-QUIPHOS Complexes



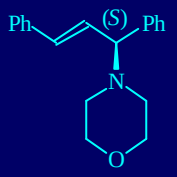
1 **2** **3**



3a
C.y.= 95%
E.e = 93%



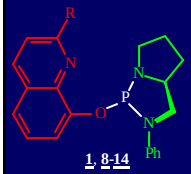
3b
C.y. = 97%
E.e. = 94%



3c
C.y. = 88%
E.e. = 88%

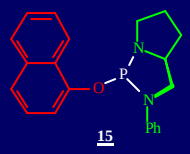
Synlett, **1998**,*1*, 49-50

QUIPHOS DERIVATIVES

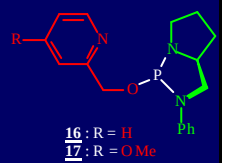


1, **8**-**14**

1 : R = H
8 : R = CN
9 : R = Me
10 : R = Ph
11 : R = *t*-Bu
12 : R = Ph
13 : R = Ph
14 : R =

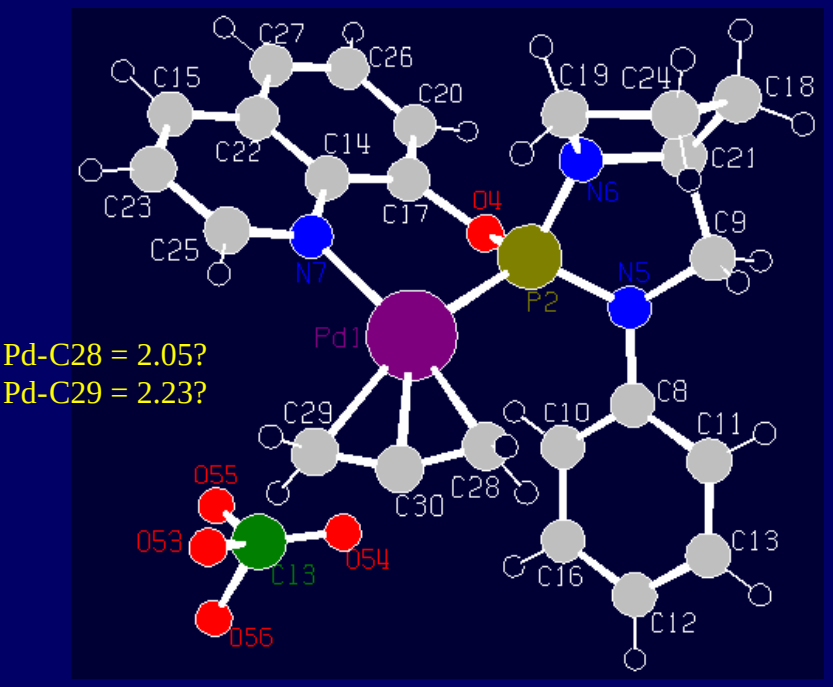


15



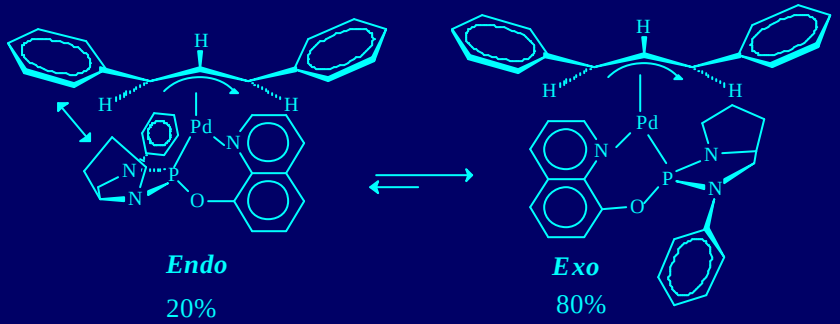
16 : R = H
17 : R = O Me

Entrée	Ligand	Nu = $(CO_2Me)_2CH_2$, BSA		Nu = $BnNH_2$	
		conv. (%)	ee (%)	conv. (%)	ee (%)
1	**1 (QUIPHOS)**	100	85 (*R*)	95	93 (*S*)
2	**8**	95	74 (*R*)	15	60 (*S*)
3	**9**	100	42 (*R*)	60	38 (*S*)
4	**10**	100	64 (*R*)	100	72 (*S*)
5	**11**	100	41 (*R*)	100	59 (*S*)
6	**12**	75	41 (*R*)	100	76 (*S*)
7	**13**	75	36 (*R*)	83	78 (*S*)
8	**14**	93	48 (*R*)	100	50 (*S*)
9	**15**	0	-	-	-
10	**16**	100	78 (*R*)	95	93 (*S*)
11	**17**	-	-	100	88 (*S*)



Pd-C28 = 2.05?
Pd-C29 = 2.23?

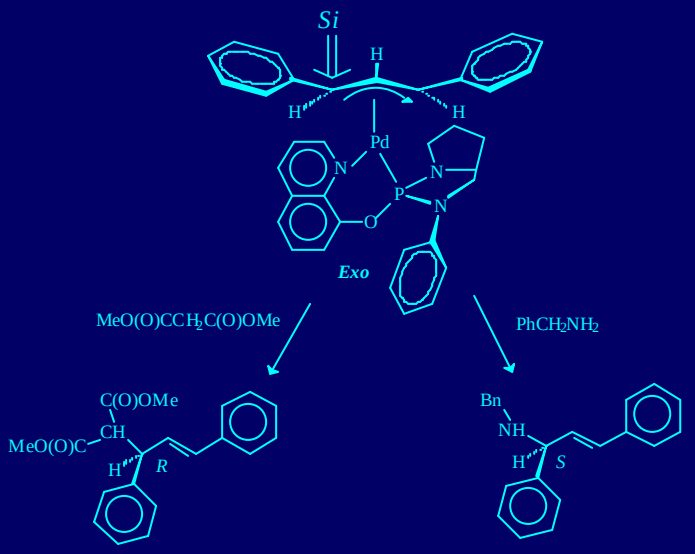
Pd-π-Allyl Complexes Containing QUIPHOS Ligand



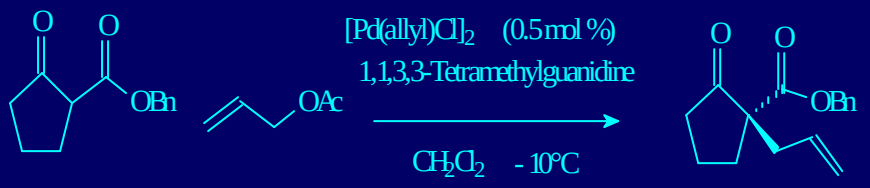
Endo
20%

Exo
80%

Preferential Attack on the exo Pd-π–cationic QUIPHOS Complex

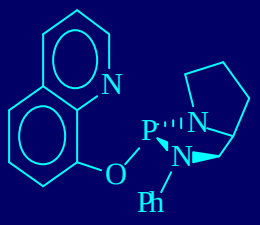


Enantioselective Formation of Quaternary Centers



1 **2** **3**

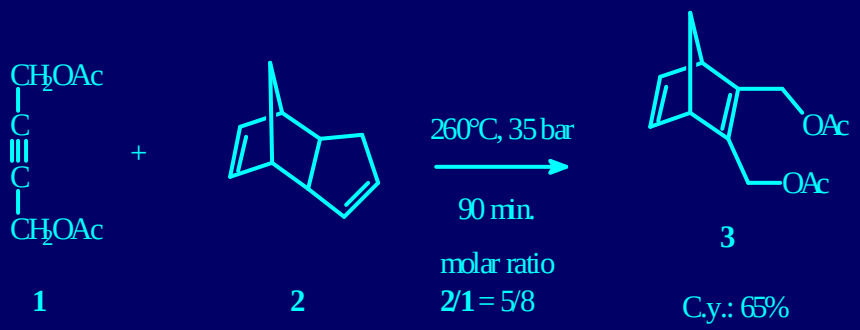
QUIPHOS (1.2 mol%)



Cy: 75%
Ee: 95%

Tetrahedron: Asymmetry **2000**, *11*, 3585

Synthesis of a prochiral bicyclic compound

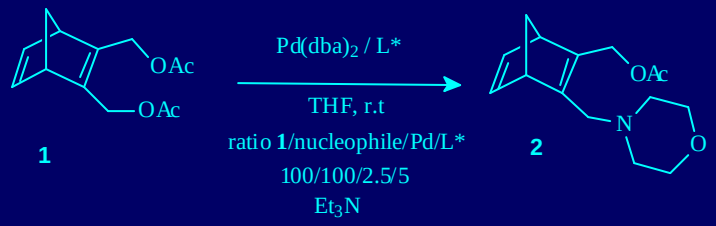


1 **2** **3**

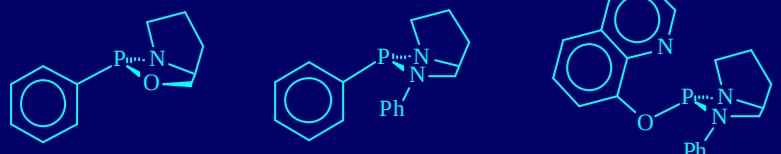
C.y.: 65%

J. Org. Chem. **1995**, *60*, 852-855

Pd(0) Catalyzed Asymmetric Amination of a Prochiral Bicyclic Allylic Diacetate



1 **2**



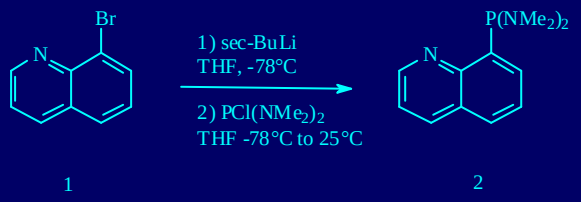
C.y = 88%
E.e = 74%

C.y = 74%
E.e = 51%

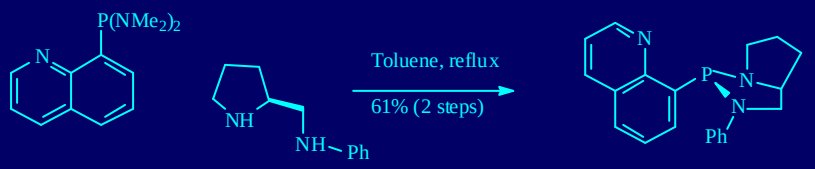
C.y = 93%
E.e = 89%

Tetrahedron **1998**, *54*, 10435

Diastereoselective Synthesis of QUIPHOS-PN5



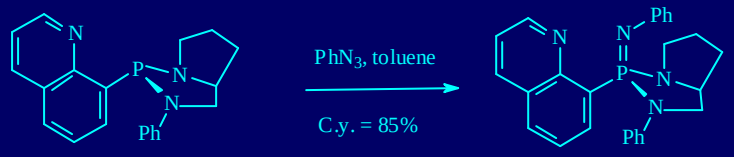
1 2



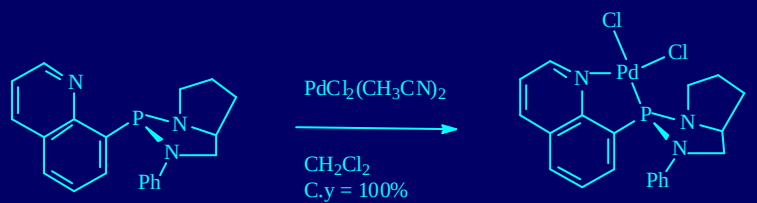
2 3 4 **QUIPHOS-PN5**

Tetrahedron Lett. **2002**, *43*, 4025-4028

Applications of QUIPHOS-PN5



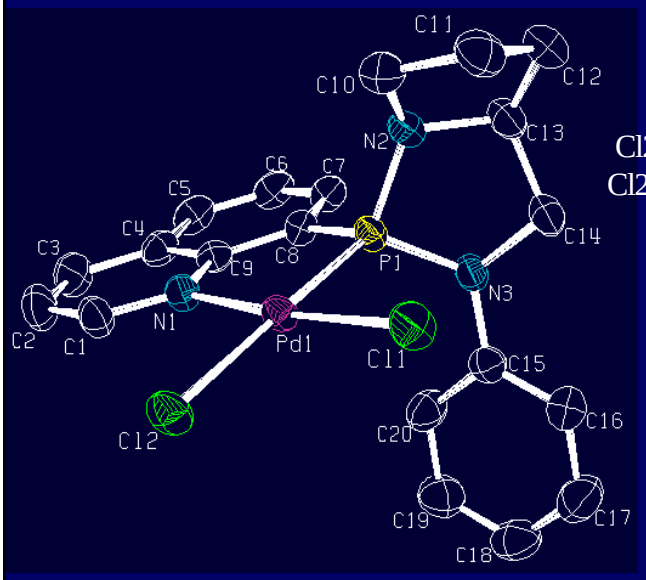
4 5



4 6

Tetrahedron Lett. **2002**, *43*, 4025-4028

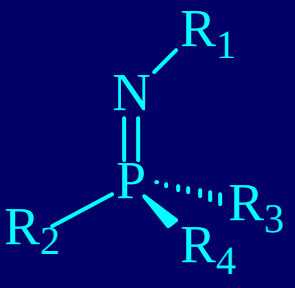
[$PdCl_2$(**QUIPHOS-PN5**)]



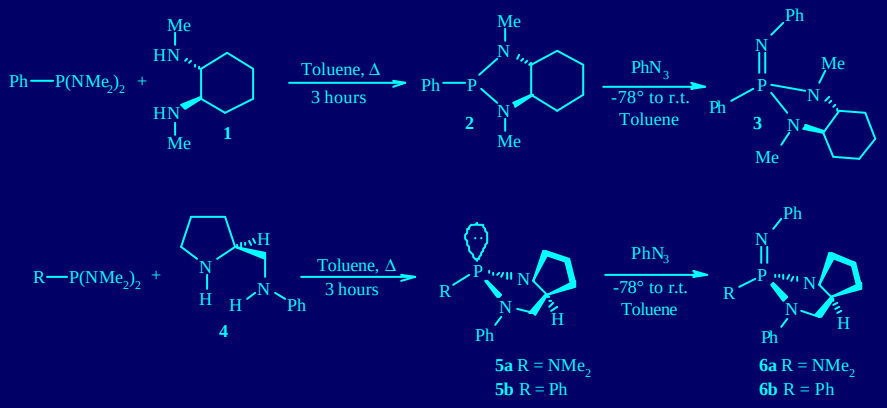
Cl2-Pd1-Cl1-P1 = 178,6°
Cl2-Pd1-Cl1-N1 = -177,8°

Pd1-Cl1 = 2,30 Å
Pd1-Cl2 = 2,40 Å

CHIRAL IMINOPHOSPHORANE

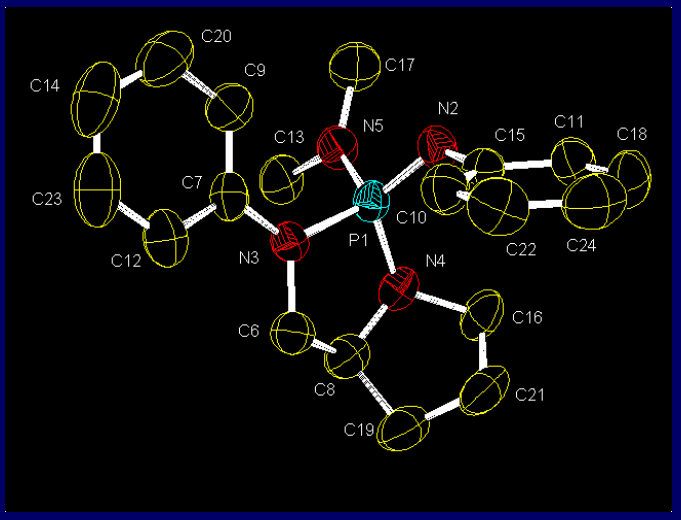


First Iminodiazaphospholidines with a Stereogenic Phosphorus Center



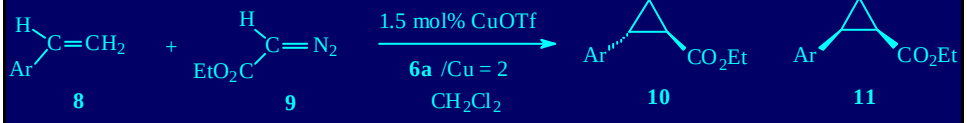
J. Am. Chem. Soc. **1999**, *121*, 5807-5808

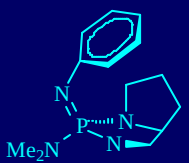
Structure of Iminophosphorane



J. Am. Chem. Soc. **1999**, *121*, 5807-5808

Catalytic Asymmetric Cyclopropanation of Olefins by Ethyl Diazoacetate





6a

1*R*, 2*R*

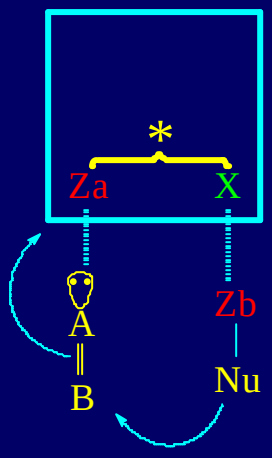
1*R*, 2*S*

Ar = Ph
T -20°C; C.y. = 80% 98% 2%
E.e = **94%** **90%**

Ar = 1-Napht.
T -78°C; C.y. = 76% 100%
E.e = **95%**

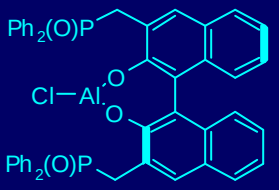
J. Am. Chem. Soc. **1999**, *121*, 5807-5808

Asymmetric Two-Center Catalysis

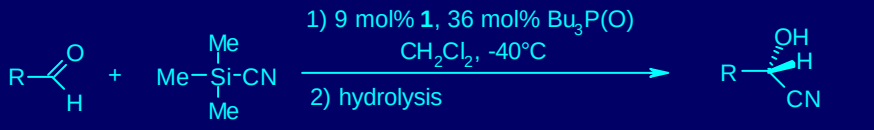


H. Steinhagen, G. Helmchen, *Angew. Chem. Int. Ed. Engl*. **1996,** *35*, 2339

Enantioselective Catalyzed Trimethylcyanation of Aldehydes Catalyst 1



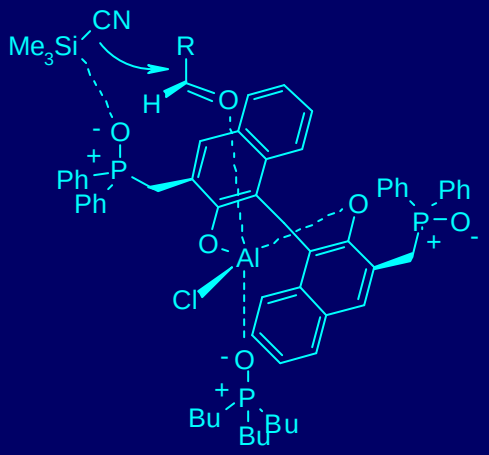
1



C.y. = 85-100 %
E.e = 80-99 %

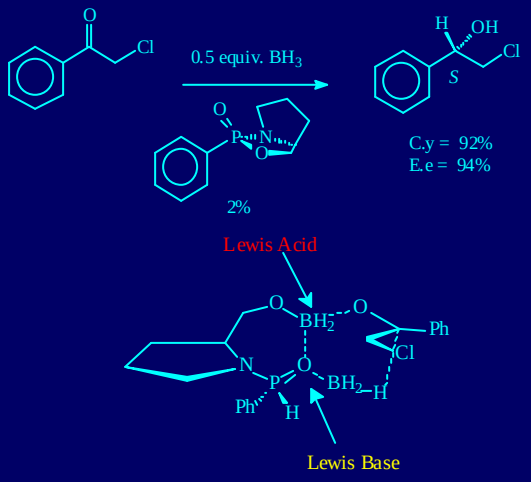
Shibasaki M. et al. *J. Am. Chem. Soc*. **1999**, *121*, 2641

Working Model for the Addition of TMSCN to adehydes catalyzed by Chiral Lewis Acid-Lewis Base Complexes



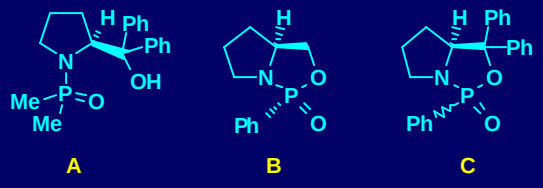
Shibasaki M. et al. *J. Am. Chem. Soc*. **1999**, *121*, 2641

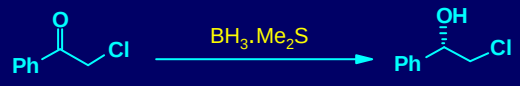
Enantioselective Reduction of the Ketones Catalyzed by Chiral Aryloxazaphospholidine Oxide



Tetrahedron Lett. **1996**, *37*, *39* and *Synlett*, **1999**, *4*, 377-388

Enantioselective Reduction of Ketones with Borane Activated by Phosphine Oxides

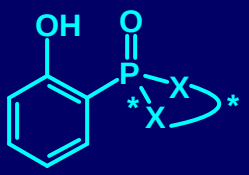




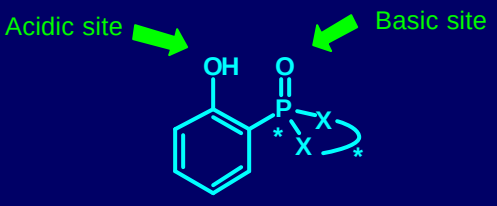
A: ee : 92%
B: ee : 94%
C: ee : 97%

Synlett **1999**, *4*, 377-388 and Topics in Current Chemistry, 220 , 2002

New Chiral
o-Hydroxyarylphosphine Oxides
Synthesis and Applications in
Asymmetric Catalysis

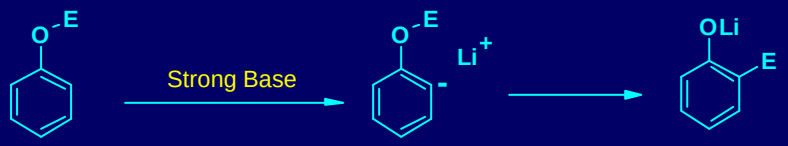


Chiral *o*-Hydroxyarylphosphine Oxides



?

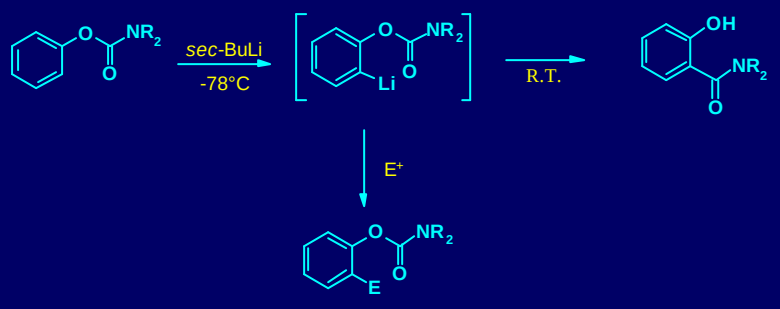
Aromatic Anionic [1,3] Rearrangement



E : carbonyl or phosphoryl group

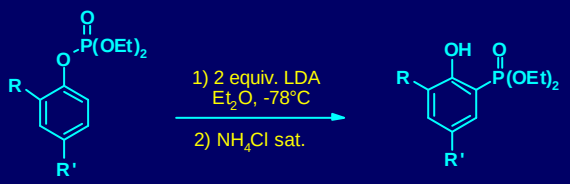
➡ Preparation of *ortho*-substituted phenols

Rearrangement of Arylcarbamates to Salicylamides



V. Snieckus *Chem. Rev.* **1990**, *48*, 879-933

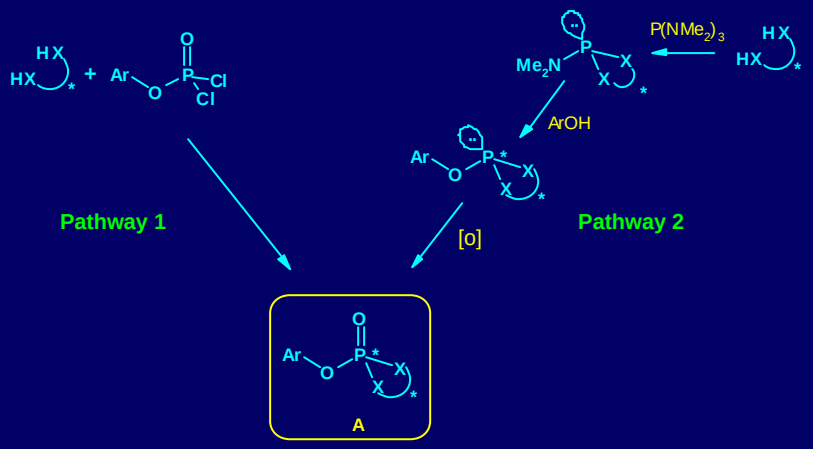
Rearrangement of Arylphosphates to *o*-Hydroxyarylphosphonates



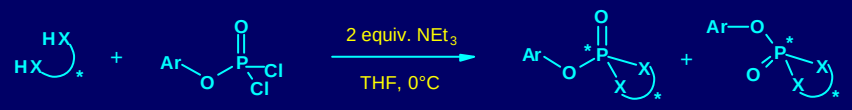
R	R'	Yield (%)
H	H	93
Me	H	87
H	MeO	93

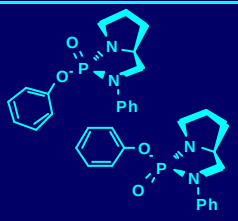
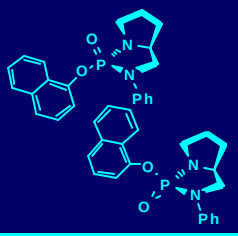
L. S. Melvin *Tetrahedron Lett*. **1981**, *22*, 3375-3376

Pathway for the Synthesis of Precursors

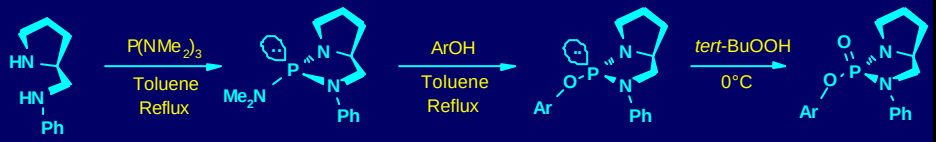


Synthesis of Precursors by Pathway 1

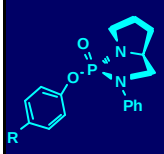
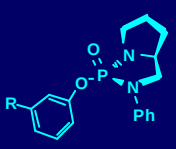
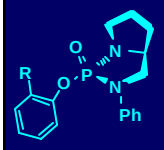
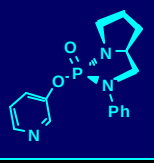


Precursors	Yield (%)	Diastereoisomeric Ratio	Precursors	Yield (%)	Diastereoisomeric Ratio
	69	80/20		91	50/50
	78	75/25		76	60/40

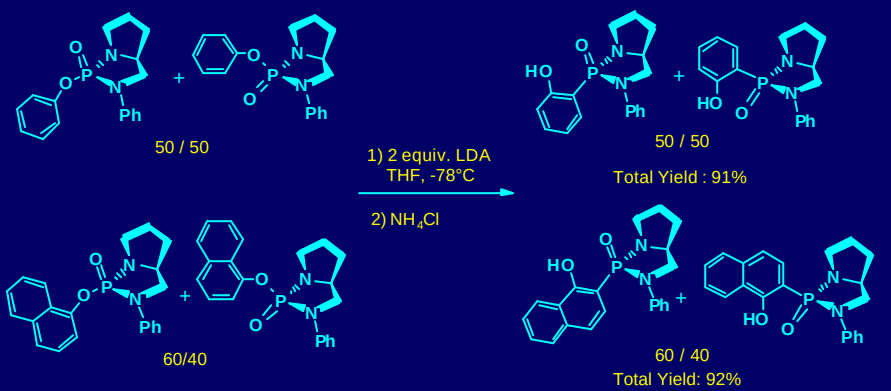
Synthesis of Precursors by the Diastereoselective Pathway 2



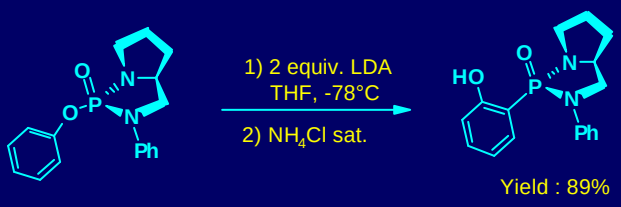
Synthesis of Precursors by the Diastereoselective Pathway 2

Precursors	R	Yield (%)	Diastereoisomeric Ratio	Precursors	R	Yield (%)	Diastereoisomeric Ratio
	H	87	100/0		MeO	75	100/0
	MeO	84	95/5		Cl	70	100/0
	Cl	81	100/0		F	75	100/0
	F	83	95/5		*tert*-Bu	63	100/0
	Ph	70	95/5			77	94/6
	Me	55	100/0				
	*tert*-Bu	63	100/0			62	100/0

Synthesis of Chiral *ortho*-Hydroxyarylphosphines Oxides



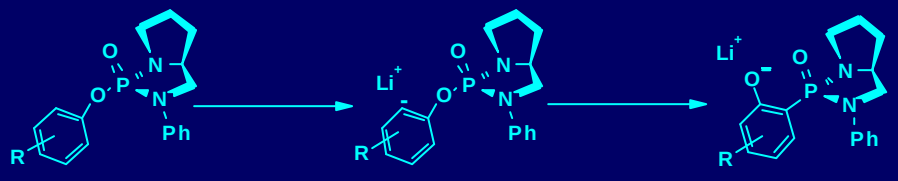
Synthesis of Chiral *ortho*-Hydroxyarylphosphines Oxides



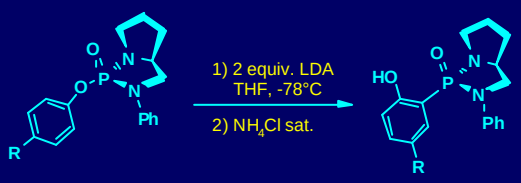
Yield : 89%

Chem. Eur. J. **1998**, *4*, 1061

Regioselectivity of the Anionic [1,3] Rearrangement



Example of Precursors with a Substituent on the *para* Position



R : OMe Yield : 86%

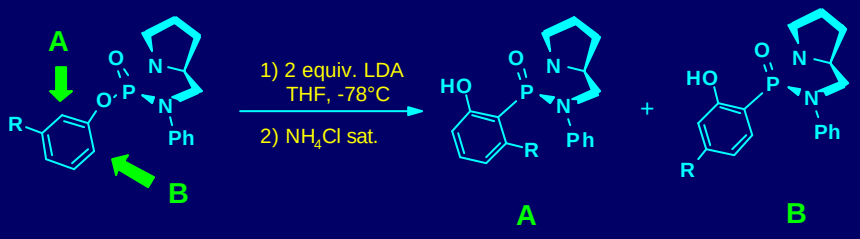
R : Cl Yield : 76%

R : F Yield : 77%

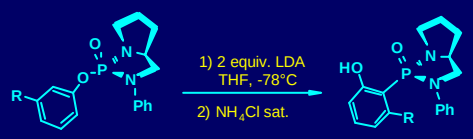
Totally Regioselectivity

Eur. J. Org. Chem. **1999**, 1099

Example of Precursors with an Unsymmetrical Aromatic Ring

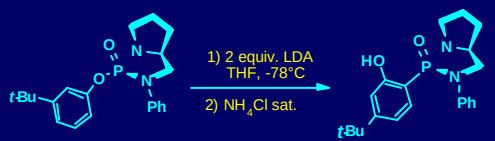


Example of Precursors with a Substituent on the *meta* Position



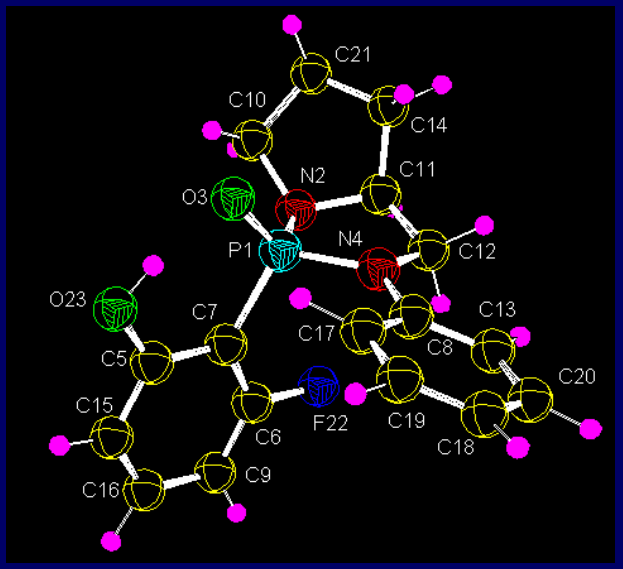
R : OMe Yield: 72%
R : Cl Yield: 92%
R : F Yield: 85%

Totally Regioselective

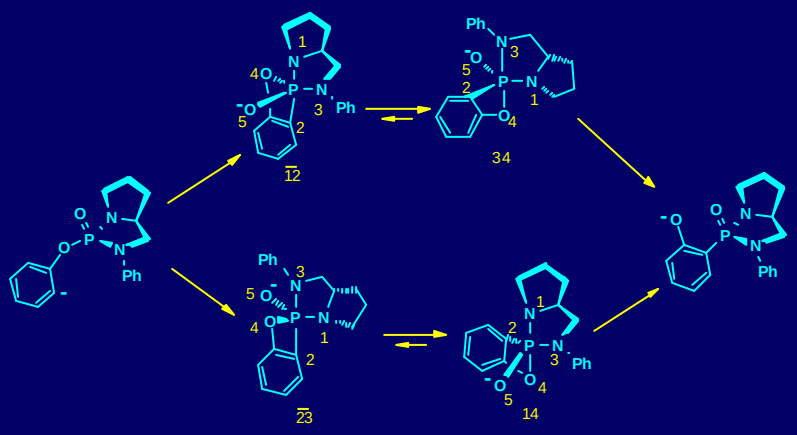


Yield: 84%

Eur. J. Org. Chem. **1999**, 1099

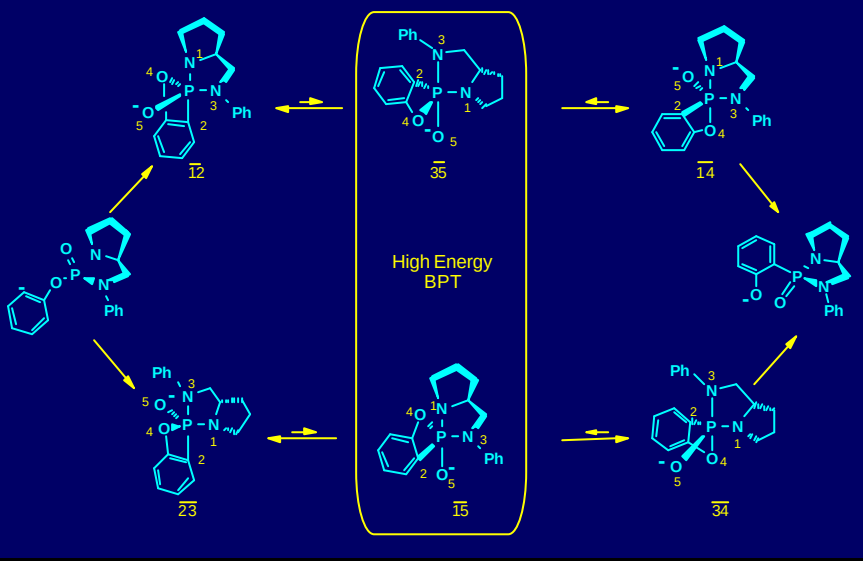


Possible Mechanism for the Stereospecific Anionic [1,3] Rearrangement.

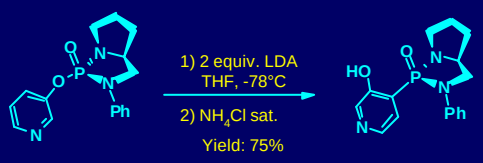


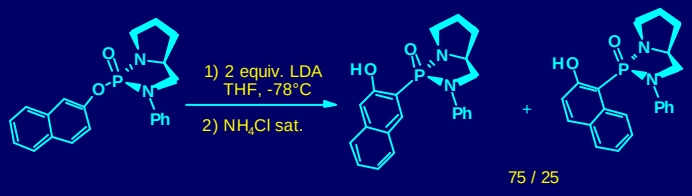
Chem. Eur. J. **1998**, *4*, 1061

Possible Mechanism for the Stereospecific Anionic [1,3] Rearrangement

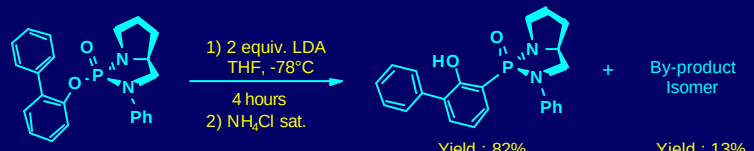


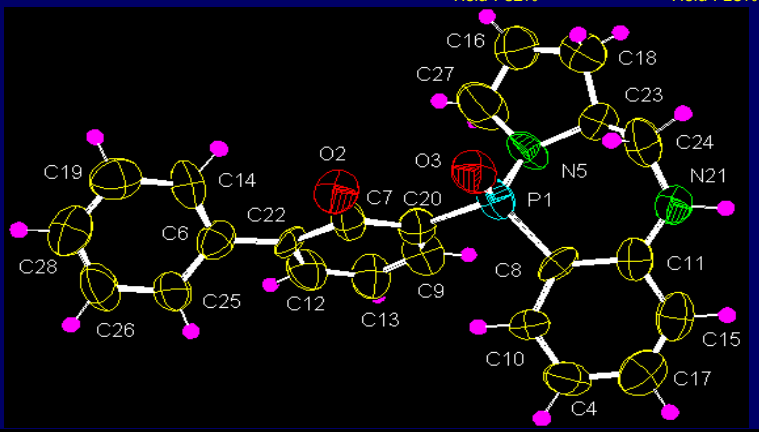
Other Example of Precursors with an Unsymmetrical Aromatic Ring



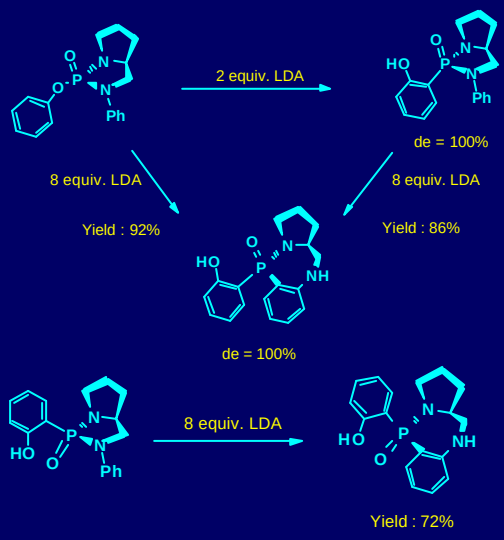


Discovery of a New Anionic [1,3] Rearrangement



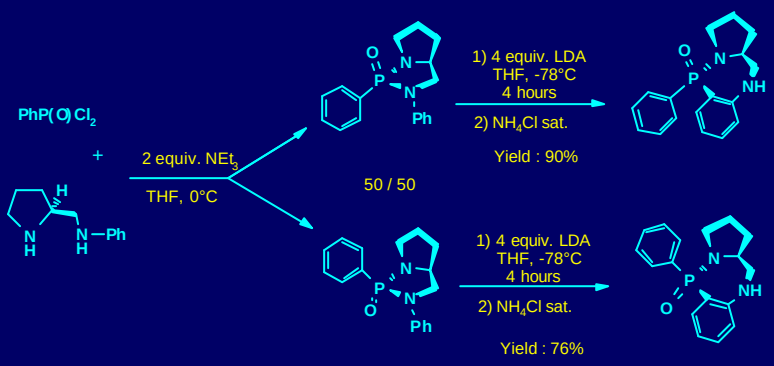


Double Stereospecific Anionic [1,3] Rearrangement



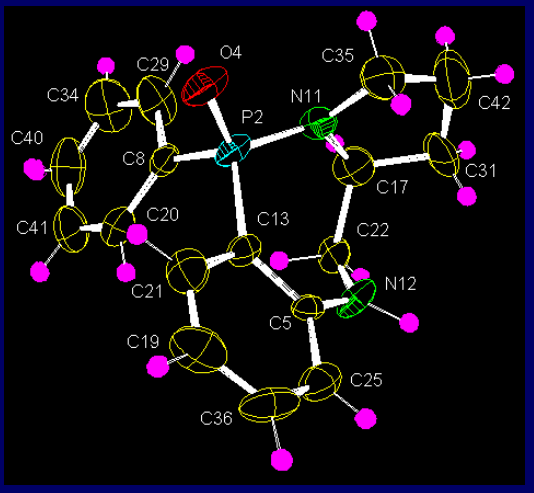
Legrand *et al*. *Angew. Chem.Int. Ed.* **1999**, *38*, 1479

Stereospecific P-N to P-Csp^2 Anionic [1,3] Rearrangement



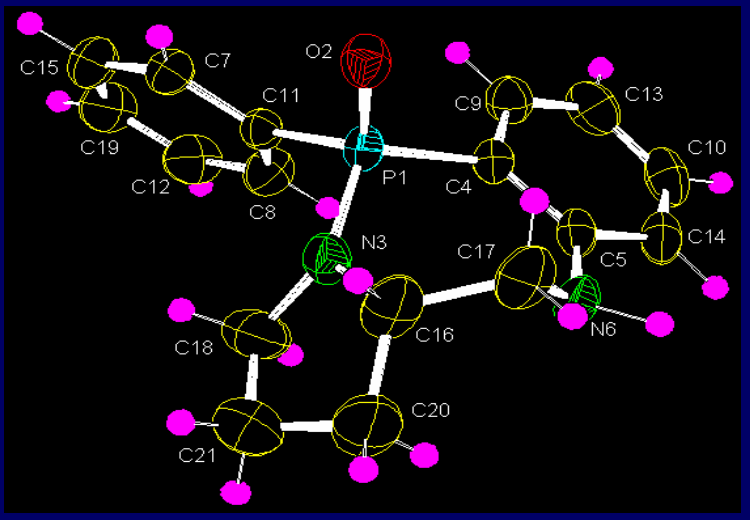
Legrand *et al. Angew. Chem.Int. Ed.* **1999**, *38*, 1479

Stereospecific P-N to P-Csp^2 Anionic [1,3] Rearrangement



Angewdt. Chem. Int. Ed. **1999**, *38*, 1479-1482

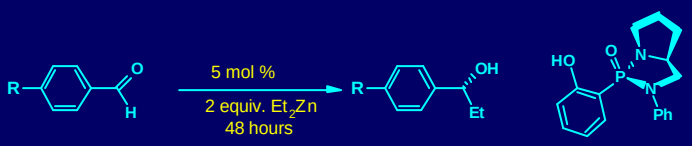
Stereospecific P-N to P-Csp^2 Anionic [1,3] Rearrangement



Applications in Asymmetric Catalysis

- Enantioselective Addition of Et_2Zn to Aromatic Aldehydes
- Enantioselective Addition of TMSCN to Aromatic Aldehydes

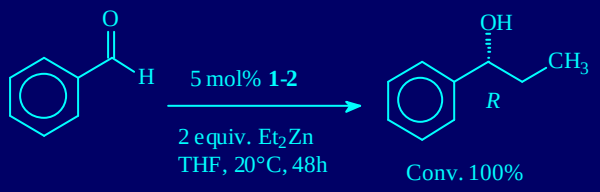
Enantioselective Addition of Et_2Zn to *para* Substituted Aldehydes

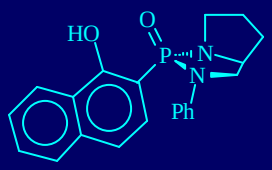


R	Yield (%)	E.e. (%)	Conf.
H	98	75	*R*
NMe_2	98	71	*R*
Cl	84	86	*R*
CN	**91**	**99**	***R***

Tetrahedron Lett. **1998**, *39*, 2961
Tetrahedron Lett. **1998**, *39*, 9419

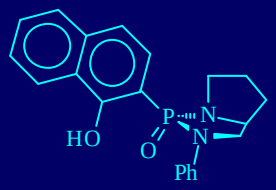
Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by Chiral *o*-Hydroxyphosphonamides





S_P-**1**

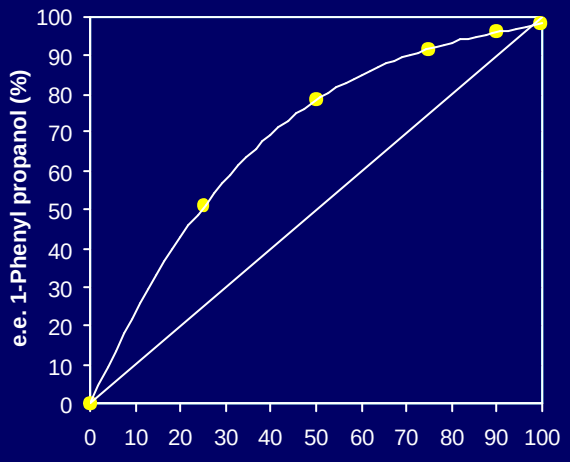
S_P-1 E.e: 98%
R_P-2 E.e: 92%



R_p-**2**

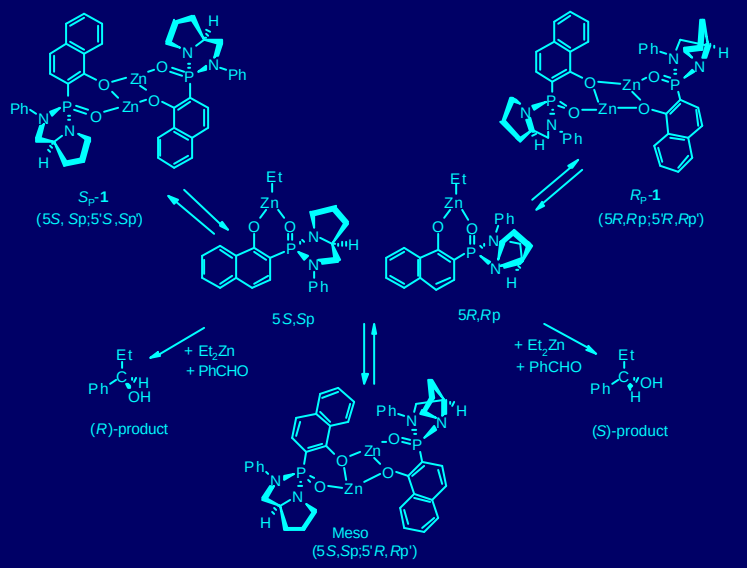
Tetrahedron Lett. **1998**, *39*, 9419-9422

Positive non-linear effect in the addition of diethylzinc to aromatic aldehydes catalyzed by chiral *o*-hydroxyaryldizaphosphonamides

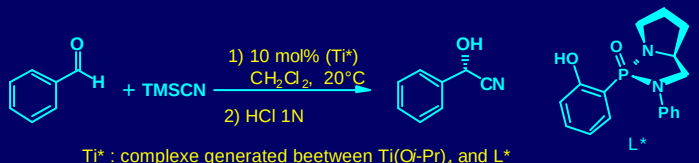


Tetrahedron Lett. **2000**, *41*, 2105-2109

Positive Nonlinear Effect: Interpretation



Enantioselective Addition of TMSCN
Optimisation of Catalytic System

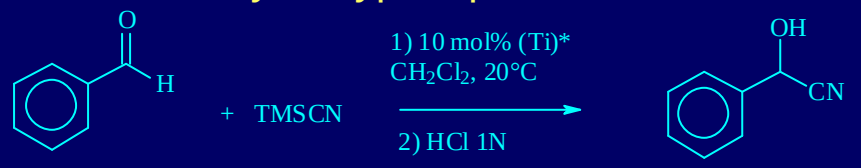


Ti* : complexe generated beetween Ti(O*i*-Pr)$_4$ and L*

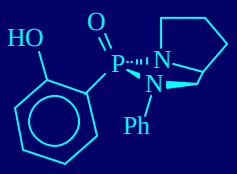
Catalytic System (Ti*) (10 mol%)	Yield (%)	e.e. (%)	Conf.
Ti(O*i*-Pr)$_4$ + **L*** (2 equiv.)	90	20	*S*
Ti(O*i*-Pr)$_4$ + **L*** (4 equiv.)	92	31	*S*
Ti(O*i*-Pr)$_4$ + **L*** (4 equiv.) – *i*-PrOH	89	29	*S*
Ti(O*i*-Pr)$_4$ + **L*** (4 equiv.) + Mol.Sieves 4Å	71	15	*S*
Ti(O*i*-Pr)$_4$ + **L*** (4 equiv.) + *i*-PrOH (1 equiv.)	95	75	*S*
Ti(O*i*-Pr)$_4$ + **L*** (4 equiv.) + *i*-PrOH (2 equiv.)	**95**	**94**	***S***

Tetrahedron: Asymmetry **1999**, *10*, 1979

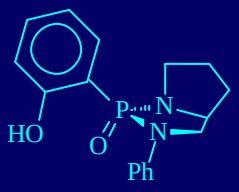
Enantioselective Addition of TMSCN on Aldehydes Catalyzed by Ti(O*i*-Pr)$_4$ Chiral *o*-Hydroxyphosphonamides



Ti* : Ti(Oi-Pr)$_4$ / Ligand/ i-PrOH : 1/4/2



S_P-**1**



R_P-**2**

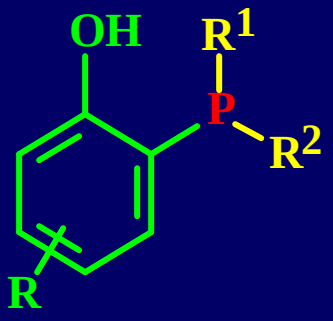
S_P-**1** C.y: 95%
E.e: 94%
Conf.: *S*

R_P-**2** C.y: 89%
E.e: 98%
Conf.: *R*

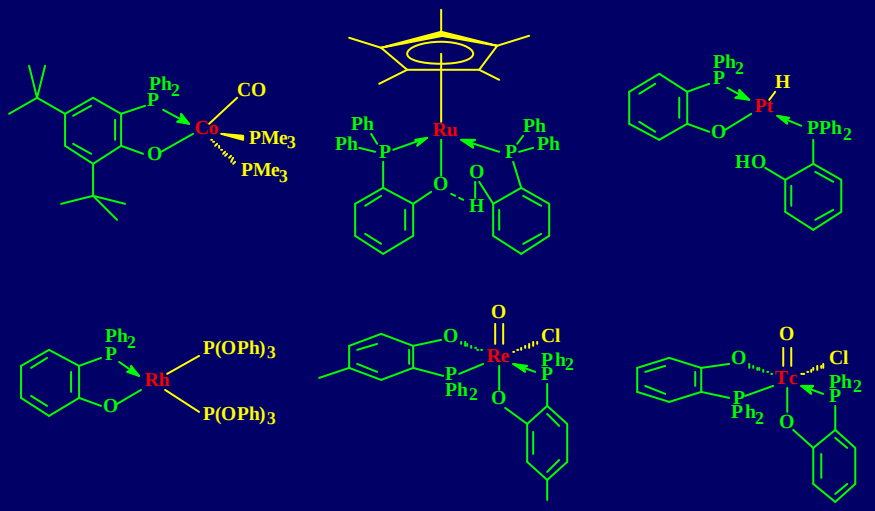
Tetrahedron: *Asymmetry* **1999**, *10*, 1979-1984

Application of the 1,3 Anionic Rearrangment:

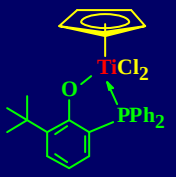
New Chiral Phosphinophenols

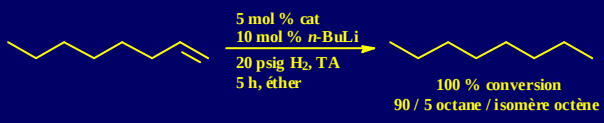


Example of *ortho*-Phosphinol Complexes



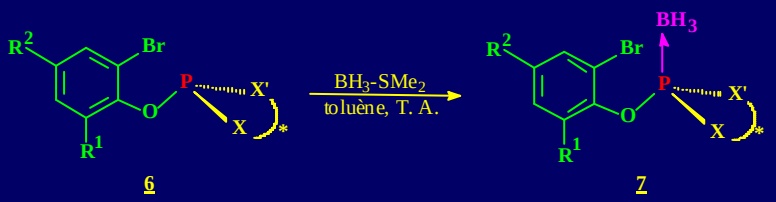
Application in Olefine Hydrogenation





C. A.Willoughby, R. R. Duff, W. M. Davis, S.L.Buchwald, *Organometallics* **1996**, 15, 472.

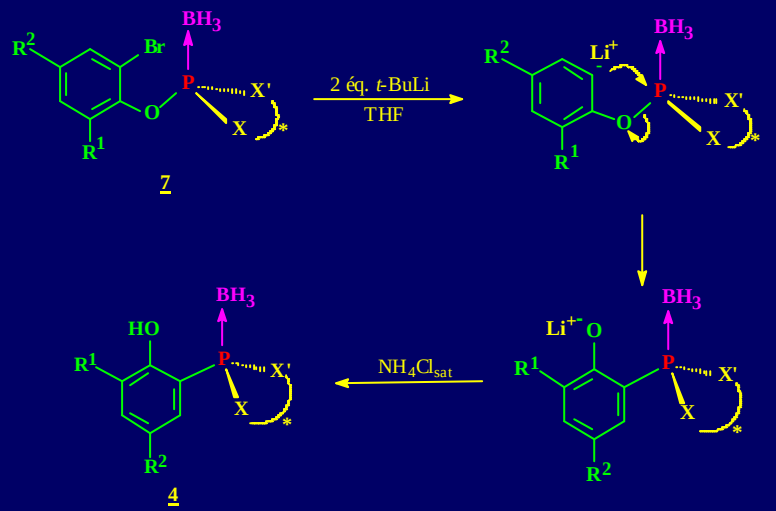
Synthesis of *ortho*-Hydroxyaryl Phosphine-Borane Complexes.



6 7

J. Organomet. Chem . **2002**, *643-644*, 237 and *Eur. J. Org. Chem under press*

Synthesis of *ortho*-Hydroxyaryl Phosphine-Borane Complexes.



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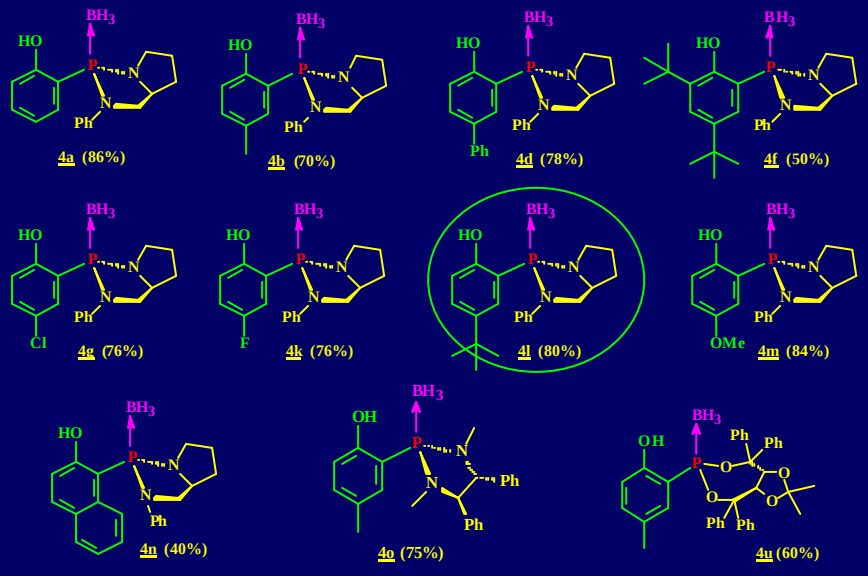
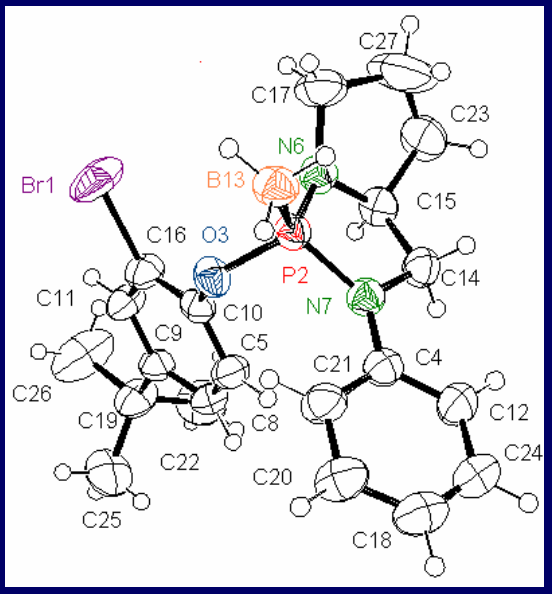
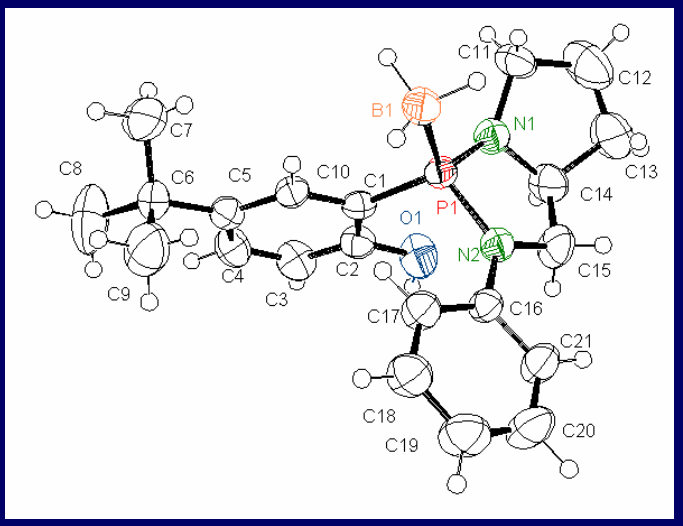
Synthesis *ortho*-Hydroxyaryl Phosphine-Borane Complexes



Structure of Starting Borane Complex



Structure of Borane Complex after the 1,3-Rearrangment



Fédération de Chimie Moléculaire de Marseille FR 1739

U.M.R. « Synthèse, Catalyse, Chiralité »

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