Síntesi estereoselectiva de fosfines amb quiralitat al fòsfor. Aplicacions en catàlisis

Thierry León Serrano

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Aplicacions en catàlisis

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Tesi Doctoral, Barcelona **2011**

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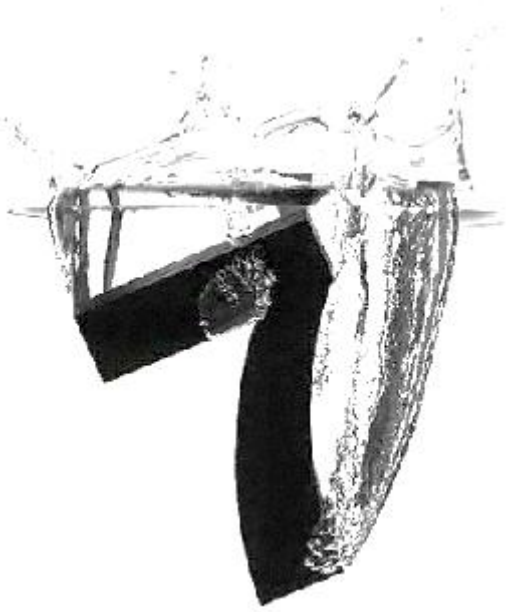
Departament de Química Orgànica – Facultat de Química

Universitat de Barcelona

Programa de doctorat de l'EEES: Química Orgànica

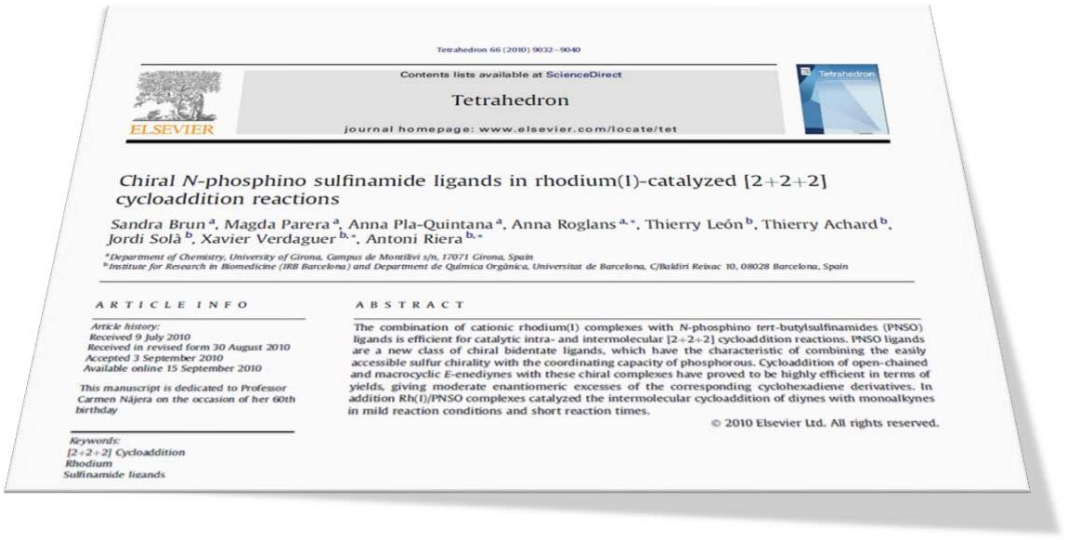
Director de tesi: Xavier Verdaguer i Espaulella



Publicacions i congressos

7.1 Publicacions

"Chiral *N*-phosphino sulfinamide ligands in rhodium(I)-catalyzed [2+2+2] cycloaddition reactions" Brun, Sandra; Parera, Magda; Pla-Quintana, Anna; Roglans, Anna; León, Thierry; Achard, Thierry; Solà, Jordi; Verdaguer, Xavier; Riera, Antoni *Tetrahedron* **2010**, *66*, 9032.



Tetrahedron 66 (2010) 9032–9040

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Chiral *N*-phosphino sulfinamide ligands in rhodium(I)-catalyzed [2+2+2] cycloaddition reactions

Sandra Brun [a], Magda Parera [a], Anna Pla-Quintana [a], Anna Roglans [a,*], Thierry León [b], Thierry Achard [b], Jordi Solà [b], Xavier Verdaguer [b,*], Antoni Riera [b,*]

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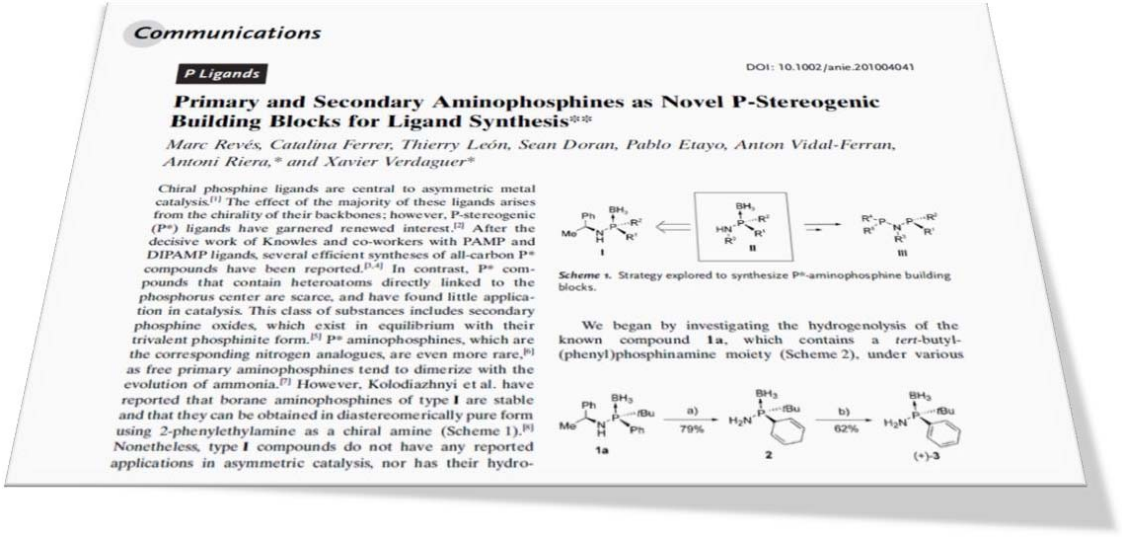
This manuscript is dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

Keywords:
[2+2+2] Cycloaddition
Rhodium
Sulfinamide ligands

ABSTRACT

The combination of cationic rhodium(I) complexes with *N*-phosphino tert-butylsulfinamides (PNSO) ligands is efficient for catalytic intra- and intermolecular [2+2+2] cycloaddition reactions. PNSO ligands are a new class of chiral bidentate ligands, which have the characteristic of combining the easily accessible sulfur chirality with the coordinating capacity of phosphorous. Cycloaddition of open-chained and macrocyclic *E*-enediynes with these chiral complexes have proved to be highly efficient in terms of yields, giving moderate enantiomeric excesses of the corresponding cyclohexadiene derivatives. In addition Rh(I)/PNSO complexes catalyzed the intermolecular cycloaddition of diynes with monoalkynes in mild reaction conditions and short reaction times.

"Primary and secondary aminophosphines as novel P-stereogenic building blocks for ligand synthesis" Revés, Marc; Ferrer, Catalina; León, Thierry; Doran, Sean; Etayo, Pablo; Vidal-Ferran, Anton; Riera, Antoni; Verdaguer, Xavier *Angew. Chem. Int. Ed.* **2010**, *49*, 9452.



Communications

P Ligands

DOI: 10.1002/anie.201004041

Primary and Secondary Aminophosphines as Novel P-Stereogenic Building Blocks for Ligand Synthesis**

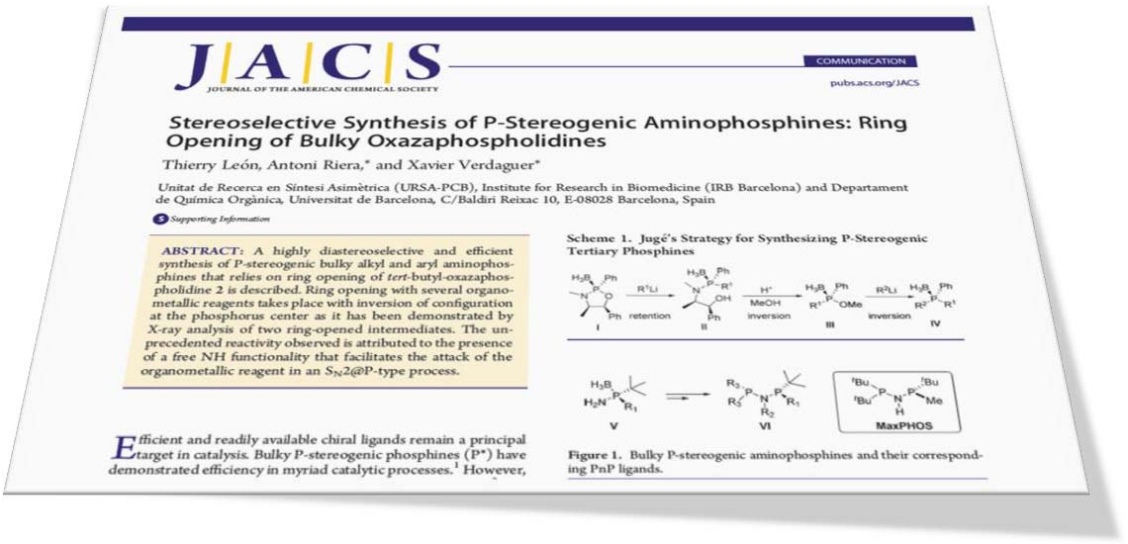
Marc Revés, Catalina Ferrer, Thierry León, Sean Doran, Pablo Etayo, Anton Vidal-Ferran, Antoni Riera,* and Xavier Verdaguer*

Chiral phosphine ligands are central to asymmetric metal catalysis.[1] The effect of the majority of these ligands arises from the chirality of their backbones; however, P-stereogenic (P*) ligands have garnered renewed interest.[2] After the decisive work of Knowles and co-workers with PAMP and DIPAMP ligands, several efficient syntheses of all-carbon P* compounds have been reported.[3,4] In contrast, P* compounds that contain heteroatoms directly linked to the phosphorus center are scarce, and have found little application in catalysis. This class of substances includes secondary phosphine oxides, which exist in equilibrium with their trivalent phosphinite form.[5] P* aminophosphines, which are the corresponding nitrogen analogues, are even more rare,[6] as free primary aminophosphines tend to dimerize with the evolution of ammonia.[7] However, Kolodiazhnyi et al. have reported that borane aminophosphines of type **I** are stable and that they can be obtained in diastereomerically pure form using 2-phenylethylamine as a chiral amine (Scheme 1).[8] Nonetheless, type **I** compounds do not have any reported applications in asymmetric catalysis, nor has their hydro-

Scheme 1. Strategy explored to synthesize P*-aminophosphine building blocks.

We began by investigating the hydrogenolysis of the known compound **1a**, which contains a *tert*-butyl-(phenyl)phosphinamine moiety (Scheme 2), under various

"Stereoselective synthesis of P-stereogenic aminophosphines: Ring opening of bulky oxazaphospholidines" León, Thierry; Riera, Antoni; Verdaguer, Xavier *J. Am. Chem. Soc.* **2011**, *133*, 5740 [*ChemInform* **2011**, *42*, issue 37].



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COMMUNICATION

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Stereoselective Synthesis of P-Stereogenic Aminophosphines: Ring Opening of Bulky Oxazaphospholidines

Thierry León, Antoni Riera,* and Xavier Verdaguer*

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Institute for Research in Biomedicine (IRB Barcelona) and Departament de Química Orgànica, Universitat de Barcelona, C/Baldiri Reixac 10, E-08028 Barcelona, Spain

Supporting Information

ABSTRACT: A highly diastereoselective and efficient synthesis of P-stereogenic bulky alkyl and aryl aminophosphines that relies on ring opening of *tert*-butyl-oxazaphospholidine **2** is described. Ring opening with several organometallic reagents takes place with inversion of configuration at the phosphorus center as it has been demonstrated by X-ray analysis of two ring-opened intermediates. The unprecedented reactivity observed is attributed to the presence of a free NH functionality that facilitates the attack of the organometallic reagent in an S_N2@P-type process.

Efficient and readily available chiral ligands remain a principal target in catalysis. Bulky P-stereogenic phosphines (P*) have demonstrated efficiency in myriad catalytic processes.[1] However,

Scheme 1. Jugé's Strategy for Synthesizing P-Stereogenic Tertiary Phosphines

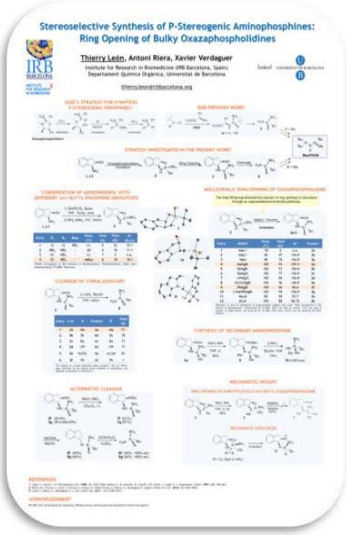
Figure 1. Bulky P-stereogenic aminophosphines and their corresponding PnP ligands.

7.2 Congressos

VI Trobada de Joves Investigadors (IEC-SCQ)

València (España). 1 – 2 Febrer 2010.

Contribució: *Assistència*

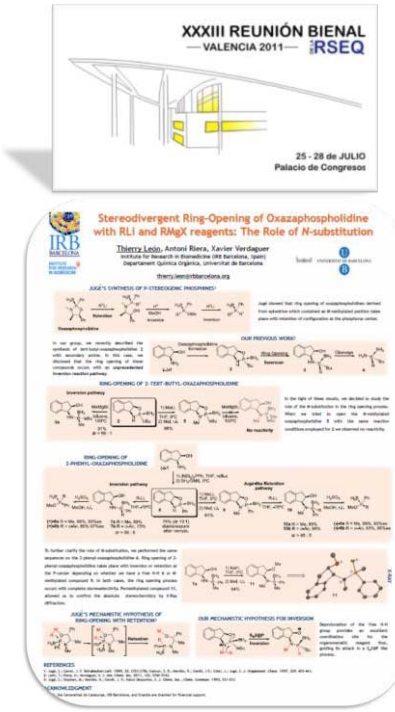


12th Tetrahedron Symposium (Elsevier)

Sitges (España). 21 – 24 Juny 2011.

Contribució: *1 póster (nostre)*

1 pòster (col·lab. UdG)



XXXIII Reunión Bienal de Química (RSEQ)

València (España). 25 – 28 Juliol 2011.

Contribució: *1 póster i presentación oral*

1 pòster (col·lab. UdG)

Stereoselective Synthesis of P-Stereogenic Aminophosphines: Ring Opening of Bulky Oxazaphospholidines

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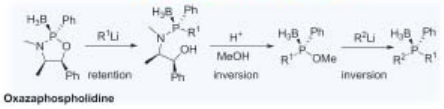
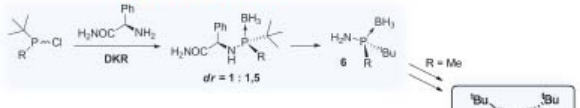
JUGÉ'S STRATEGY FOR SYNHTESIS P-STEREOGENIC PHOSPHINES[1]

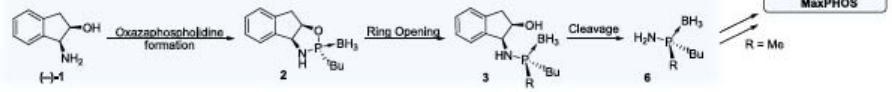


Oxazaphospholidine

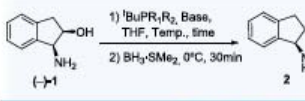
OUR PREVIOUS WORK[2]



STRATEGY INVESTIGATED IN THE PRESENT WORK[3]

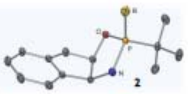


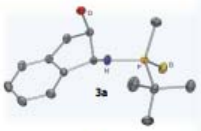
CONDENSATION OF AMINOINDANOL WITH DIFFERENT *tert*-BUTYL-PHOSPHINE DERIVATIVES

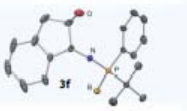


Entry	R_1	R_2	Base	Temp. (°C)	Time (h)	Yield (%)[a]	dr[b] (R_p:S_p)
1	Cl	Cl	NEt_3	r.t.	5	22	10:1
2	NEt_2	NEt_2	-	60	4	18	11:1
3	Cl[c]	NEt_2	-	r.t.	7	0	n.a.
4	Cl[c]	NEt_3	-	reflux	8	78	18:1

[a]Yields correspond to the mixture of diastereomers. [b]Diastereomeric ratios were determined by ^{31}P-NMR. [c]Racemic.







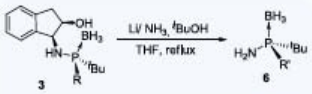
NUCLEOPHILIC RING OPENING OF OXAZAPHOSPHOLIDINE

The free NH group allowed the reaction of ring opening to take place through an unprecedented inversion pathway.

Entry	R[MX][a]	Temp. (°C)	Yield (%)[b]	dr[c]	Product
1	MeLi[d]	-78	0	n.a.	3a
2	MeLi[e]	40	47	>96:4[f]	3a
3	MeLi	40	76	>96:4[f]	3a
4	MeMgBr	100	91	>99:1[g]	3a
5	EtMgBr	100	91	>96:4[f]	3b
6	BuMgCl	100	77	>96:4[f]	3c
7	i-PrMgCl	100	85	>96:4[f]	3d
8	$H_2CCCMgBr$	100	96	>96:4[f]	3e
9	PhMgBr	100	96	96:4	3f
10	2-MeOPhMgBr	100	94	>96:4[f]	3g
11	Me_3Al	80	90	93:7	3a
12	Et_3Al	100	88	90:10	3b

[a]Between 2.2 and 4.5 equivalents of organometallic reagent were used. [b]Yield corresponds to the mixture of diastereomers. [c]Determined by ^{31}P-NMR. CD_2O was used as solvent. [d]THF was used as solvent. [e]A single isomer was observed by ^{1}H NMR. [f]The minor isomer was not detected by HPLC analysis.

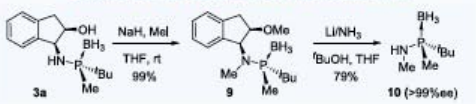
CLEAVAGE OF CHIRAL AUXILIARY



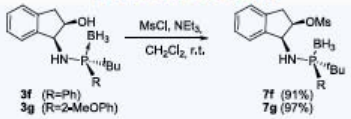
Entry	S.M.	R	Product	R'	Yield (%)
1	3a	Me	6a	Me	71[a]
2	3b	Et	6b	Et	78
3	3c	Bu	6c	Bu	71
4	3d	i-Pr	6d	i-Pr	71
5	3e	H_2CCC	6e	n-C_3H_7	81
6	3f	Ph	6f	Ph	-[b]

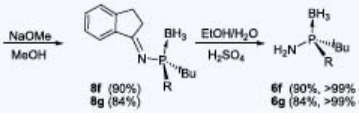
[a]GC analysis on a chiral stationary phase revealed > 99% ee. [b]Birch-type reduction at the phenyl group attached to phosphorus was obtained as described in reference 2.

SYNTHESIS OF SECONDARY AMINOPHOSPHINE



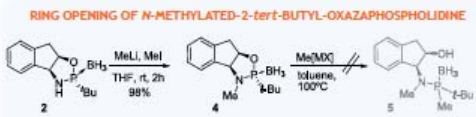
ALTERNATIVE CLEAVAGE



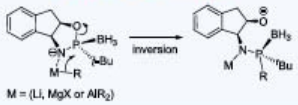


MECHANISTIC INSIGHT

RING OPENING OF *N*-METHYLATED-2-*tert*-BUTYL-OXAZAPHOSPHOLIDINE



MECHANISTIC HYPOTHESIS



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1: Jugé, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783-2786; Kaloun, E. B.; Merdès, R.; Genêt, J-P.; Uziel, J.; Jugé, S. *J. Organomet. Chem.* **1997**, *529*, 455-463.
2: Reyes, M.; Ferrer, C.; León, T.; Doran, S.; Etayo, P.; Vidal-Ferran, A.; Riera, A.; Verdaguer, X. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9452-9455.
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ACKNOWLEDGMENT

MICINN, the Generalitat de Catalunya, IRB Barcelona, and Enantia are thanked for financial support.

Stereodivergent Ring-Opening of Oxazaphospholidine with RLi and RMgX reagents: The Role of *N*-substitution

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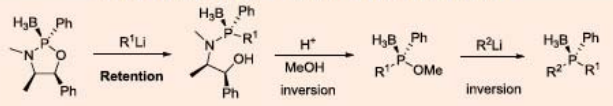
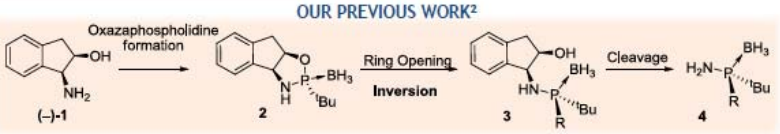
JUGÉ'S SYNTHESIS OF P-STEREOGENIC PHOSPHINES[1]



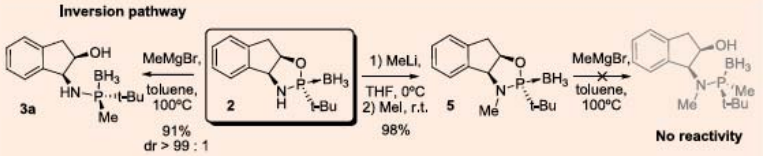
Jugé showed that ring opening of oxazaphospholidines derived from ephedrine which contained an *N*-methylated position takes place with retention of configuration at the phosphorus center.

OUR PREVIOUS WORK[2]

In our group, we recently described the synthesis of *tert*-butyl-oxazaphospholidine **2** with secondary amine. In this case, we disclosed that the ring opening of these compounds occurs with an unprecedented inversion reaction pathway.

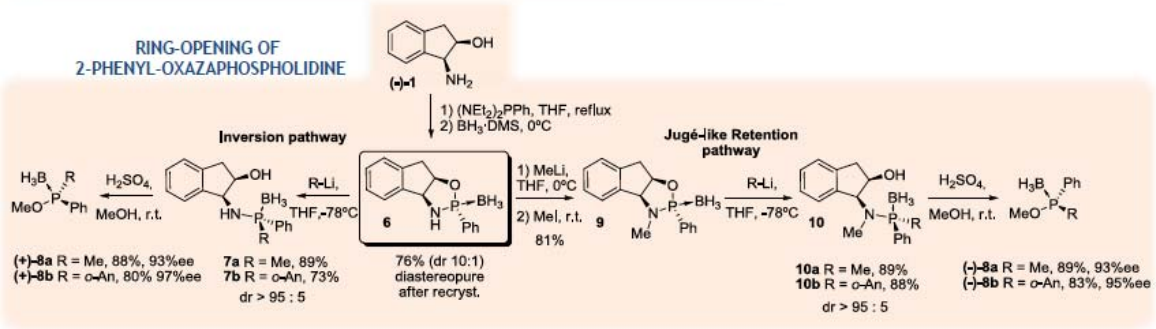


RING-OPENING OF 2-*TERT*-BUTYL-OXAZAPHOSPHOLIDINE



In the light of these results, we decided to study the role of the *N*-substitution in the ring opening process. When we tried to open the *N*-methylated oxazaphospholidine **5** with the same reaction conditions employed for **2** we observed no reactivity.

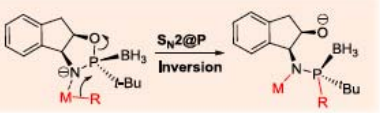
RING-OPENING OF 2-PHENYL-OXAZAPHOSPHOLIDINE



To further clarify the role of *N*-substitution, we performed the same sequences on the 2-phenyl-oxazaphospholidine **6**. Ring opening of 2-phenyl-oxazaphospholidine takes place with inversion or retention at the P-center depending on whether we have a free N-H **6** or *N*-methylated compound **9**. In both cases, the ring opening process occurs with complete stereoselectivity. Permethylated compound **11**, allowed us to confirm the absolute stereochemistry by X-Ray diffraction.

JUGÉ'S MECHANISTIC HYPOTHESIS OF RING-OPENING WITH RETENTION[3]

OUR MECHANISTIC HYPOTHESIS FOR INVERSION



Deprotonation of the free N-H group provides an excellent coordination site for the organometallic reagent thus, guiding its attack in a $S_N2@P$ like process.

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1: Jugé, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783-2786; Kaloun, E. B.; Merdès, R.; Genêt, J-P.; Uziel, J.; Jugé, S. *J. Organomet. Chem.* **1997**, *529*, 455-463.
2: León, T.; Riera, A.; Verdaguer, X. *J. Am. Chem. Soc.* **2011**, *133*, 5740-5743.
3: Jugé, S.; Stephan, M.; Merdès, R.; Genêt, J. P.; Halut-Desportes, S. *J. Chem. Soc., Chem. Commun.* **1993**, 531-533.

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