SYNTHESIS OF CHIRAL AZAPYRIDINOMACROCYCLES *N*-OXIDES, NEW POTENTIAL LEWIS BASE CATALYSTS IN ASYMMETRIC ALLYLATION OF *p*-NITROBENZALDEHYDE

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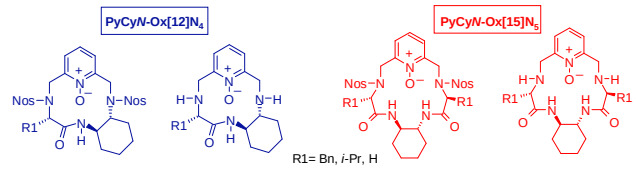
INTRODUCTION

During the last few years, pyridine-based *N*-oxides have emerged as highly versatile compounds, since they possess notable nucleophilicity and basicity properties which allow them to function as Lewis base catalysts and as ligand for metal complexes. In each case, an oxygen atom serves as a basic/ligating site.[1] In asymmetric synthesis, chiral pyridine-based *N*-oxides have been widely used in various catalytic processes including the asymmetric allylation of aldehydes.[2]

Since several years, our laboratory is interested in the synthesis of azapyridinomacrocycles. These polyamine ligands are recognized for their capacity to complex metallic cations, particularly those of the lanthanide family. Under their complexed form, these structures are involved in a wide field of applications such as diagnostic area as contrast agents in Magnetic Resonance Imaging (MRI).[3]

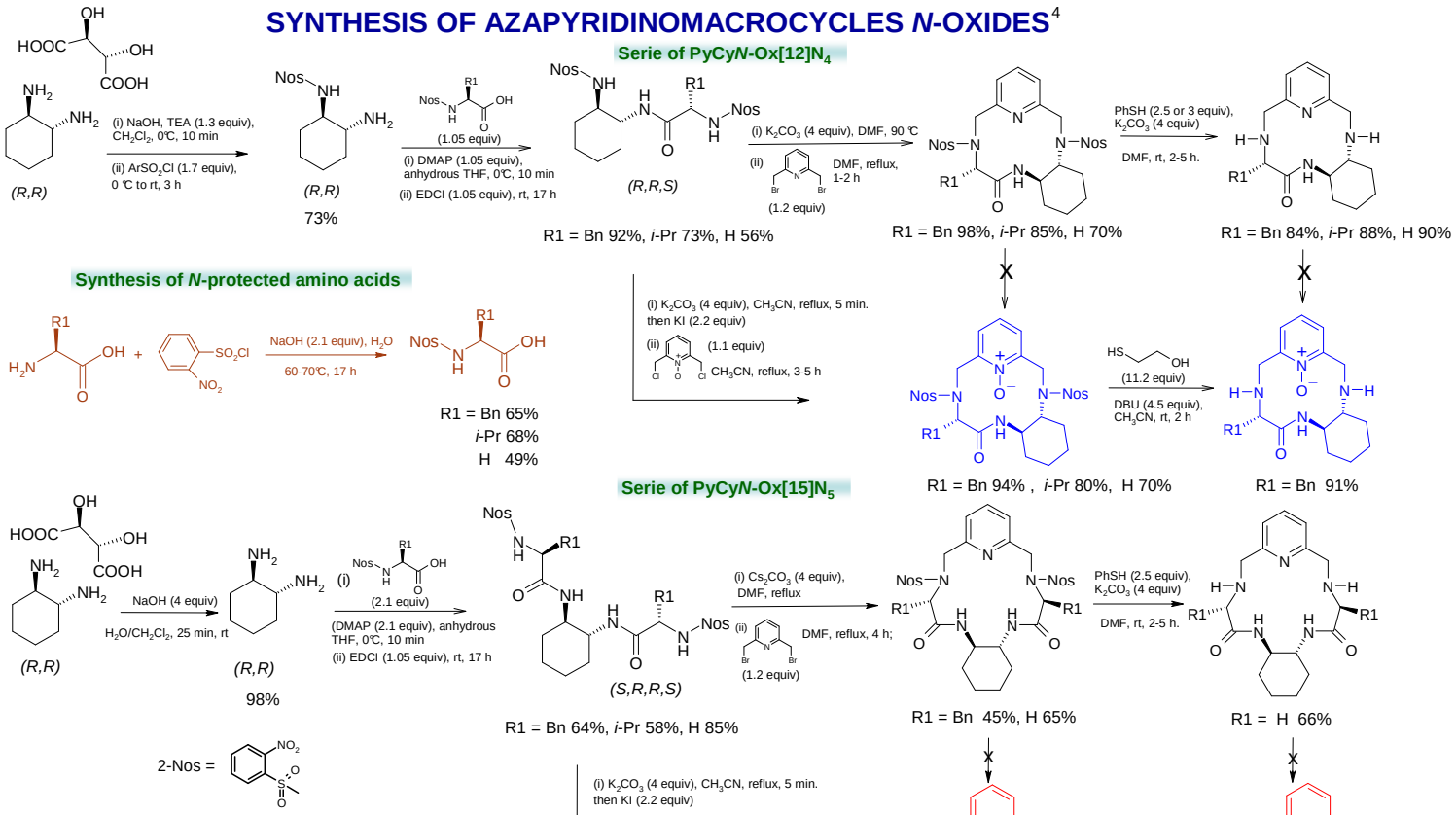
GOAL

1. The preparation of two series of chiral azapyridinomacrocycles *N*-oxides, PyCy*N*-Ox[12]N_4 and PyCy*N*-Ox[15]N_5 from natural and easily available amino acids.



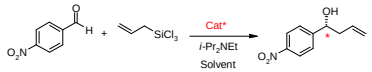
2. Their application as chiral organocatalysts in the asymmetric allylation of *p*-nitrobenzaldehyde with allyltrichorosilane

SYNTHESIS OF AZAPYRIDINOMACROCYCLES *N*-OXIDES[4]



ASYMMETRIC ALLYLATION OF *p*-NITROBENZALDEHYDE

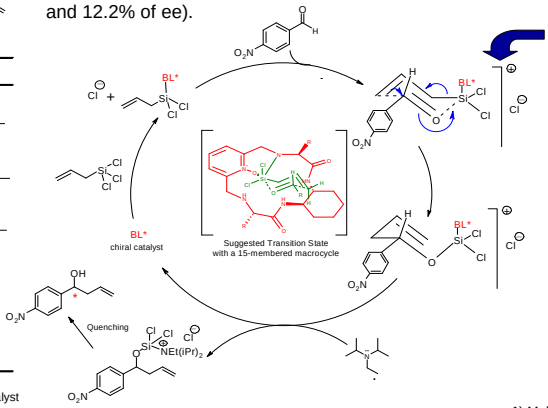
The catalytic efficiency of the azapyridinomacrocycles *N*-oxides synthesized was investigated and the rate conversions and ees were determined by HPLC. Different parameters were studied, such as the solvent, the amount of additives and the temperature.[4]



Entry	Catalyst	Temp/°C	Time/h	Yield (%) [a]	ee (%) [b]
1		20	72	28	10
2		20	72	48	2.3
3		0	72	27	3.2
4		20	48	60	4.5
5		0	48	42	6.1
6		20	24	83.2	13.4
7		0	24	72	7.8
8		-30	24	58	14.1
9	More efficient catalyst	-38	24	43	40.2
10[c]		-38	24	65	4.6

The reaction was carried out in CH_3CN at 0.15 mmol scale with 2.4 equiv of allyltrichorosilane in the presence of the corresponding catalyst (20 mol%) and DIPEA (3 equiv).
[a] Conversion was determined by HPLC.
[b] Established by chiral HPLC.
[c] 6 equiv of DIPEA were used.

The first results showed that azapyridinomacrocycles *N*-oxides 12-membered PyCy*N*-Ox[12]N_4 are unsuccessful catalysts (48% yield and 12.2% of ee).



Proposed mechanism and transition state in catalysed allylation

The reaction proceeds via a closed chair like transition structure highly crowded organized around the silicon atom.

The organocatalysis study gives some new insights into the relationship between catalytic activity and/or stereoselectivity, the presence of electron withdrawing groups on the macrocycle structure and the size of the macrocycle in the steroselective allylation process

CONCLUSION

- The optimization of the reaction conditions allowed us to obtain the 12-membered chiral azapyridinomacrocycles *N*-oxides PyCy*N*-Ox[12]N_4 in 40% to 78% overall yields and the 15-membered PyCy*N*-Ox[15]N_5 in 20% to 68% overall yields.
- The macrocycles were tested as potential catalyts in the enantioselective allylation of *p*-nitrobenzaldehyde with trichloroallylsilane and resulted in good conversion above 80% and promising enantioselectivity (40% ee).
- Further studies are in progress in order to use larger macrocycles and to assess these original ligands in other enantioselective organocatalyzed reactions.

1) Malkov, A. V. and Kocovsky, P. *Eur. J. Org. Chem* 2007, 29-36 and references cited therein.
2) Denmark S.E. and Chung W.-J. *J. Org. Chem.*, 2008, 73, 4582.
3) Dioury, F.; Ferroud, C.; Guy, A.; Port, M. *Tetrahedron*, *65*, 2009, 7573-7579. 29-36 and references cited therein.
4) Sylla, M.; Joudat, M.; Wagner, M.; Falguières, A.; Guy, A.; Ferroud, C. *submitted to Heterocycles* 2011.