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

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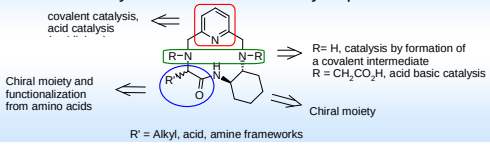
## INTRODUCTION

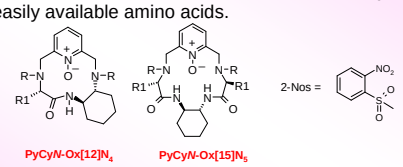
During the last few years, chiral pyridine-based *N*-oxides have emerged as powerful Lewis base catalysts. The oxygen atom of pyridine *N*-oxide possesses Lewis basicity and, hence, it should potentially be capable to activate nucleophilic reagents bearing a Lewis acidic moiety. They have been widely used in various catalytic processes including the asymmetric allylation of aldehydes.[1]

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). [2-4]



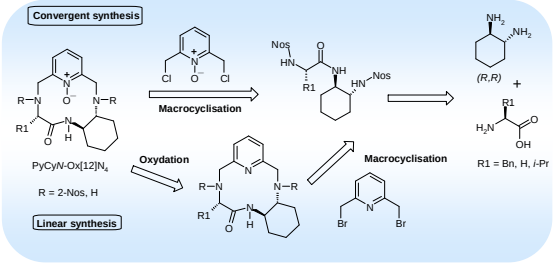

## GOAL

**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.



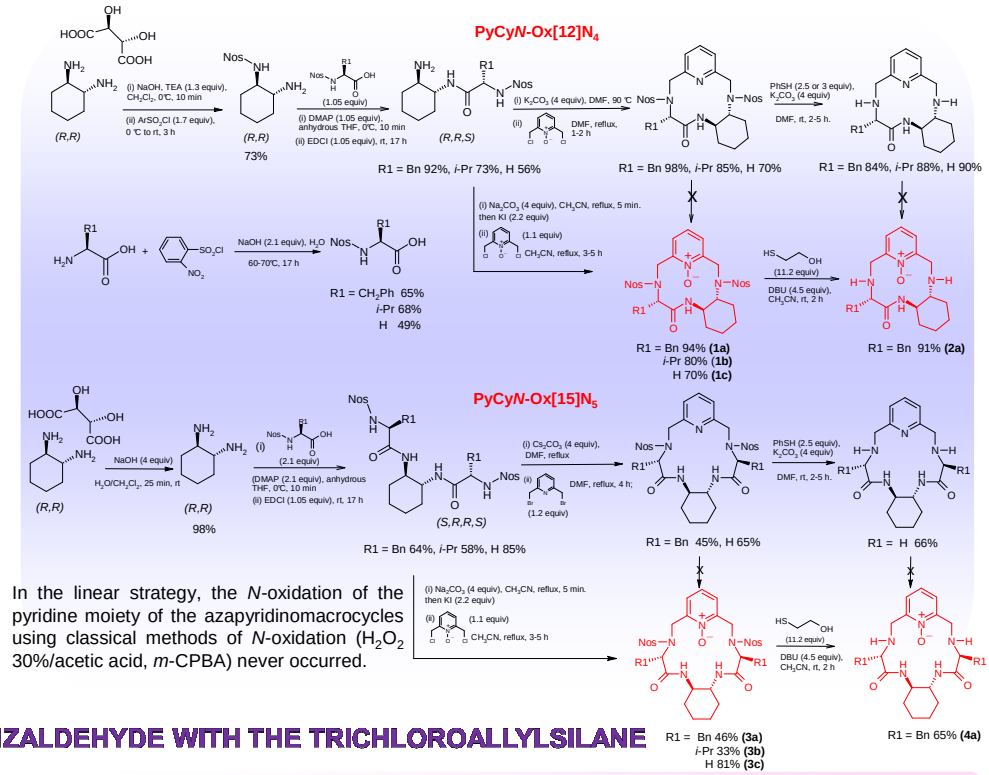

**2.** Their application as chiral organocatalysts in the asymmetric allylation of *p*-nitrobenzaldehyde with allyltrichorosilane

## SYNTHETIC STRATEGIES

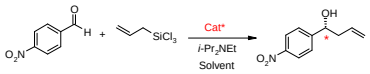



In the linear strategy, the *N*-oxidation of the pyridine moiety of the azapyridinomacrocycles using classical methods of *N*-oxidation ($H_2O_2$ 30%/acetic acid, *m*-CPBA) never occurred.

## SYNTHESIS OF AZAPYRIDINOMACROCYCLES *N*-OXIDES[5]




## ASYMMETRIC ALLYLATION OF *p*-NITROBENZALDEHYDE WITH THE TRICHLOROALLYLSILANE




| Entry | Catalyst | # | Solvent | Additive/equiv | Temp/°C | Time/h | Yield (%)[a] | ee (%) [b] |
|---|---|---|---|---|---|---|---|---|
| 1 | PyCy*N*-Ox[12]$N_4$ | **1a** | $CH_3CN$ | DIPEA/3 equiv | 20 | 48 | 9.2 | - |
| 2 | PyCy*N*-Ox[12]$N_4$ | **1a** | THF | DIPEA/3 equiv | 20 | 48 | 11 | - |
| 3 | PyCy*N*-Ox[12]$N_4$ | **1b** | $CH_3CN$ | DIPEA/3 equiv | 20 | 24 | 9 | - |
| 4 | PyCy*N*-Ox[12]$N_4$ | **1b** | $CH_2Cl_2$ | DIPEA/3 equiv | 20 | 24 | 0 | - |
| 5 | PyCy*N*-Ox[12]$N_4$ | **1b** | THF | DIPEA/3 equiv | 20 | 24 | 48 | 3.5 |
| 6 | PyCy*N*-Ox[12]$N_4$ | **1c** | $CH_3CN$ | DIPEA/3 equiv | 20 | 48 | 2 | - |
| 7 | PyCy*N*-Ox[12]$N_4$ | **1c** | THF | DIPEA/3 equiv | 20 | 48 | 20 | 12.2 |
| 8 | PyCy*N*-Ox[12]$N_4$ | **2a** | $CH_3CN$ | DIPEA/3 equiv | 20 | 72 | 26 | 2 |
| 9 | PyCy*N*-Ox[12]$N_4$ | **2a** | THF | DIPEA/3 equiv | 20 | 48 | 14 | 7.5 |
| 10 | PyCy*N*-Ox[15]$N_5$ | **3a** | $CH_3CN$ | DIPEA/3 equiv | 20 | 72 | 28 | 10 |
| 11 | PyCy*N*-Ox[15]$N_5$ | **3b** | $CH_3CN$ | DIPEA/ 3equiv | 20 | 72 | 48 | 2.3 |
| 12 | PyCy*N*-Ox[15]$N_5$ | **3b** | $CH_3CN$ | DIPEA/3 equiv | 0 | 72 | 27 | 3.2 |
| 13 | PyCy*N*-Ox[15]$N_5$ | **3c** | $CH_3CN$ | DIPEA/3 equiv | 20 | 48 | 60 | 4.5 |
| 14 | PyCy*N*-Ox[15]$N_5$ | **3c** | $CH_3CN$ | DIPEA/3 equiv | 0 | 48 | 42 | 6.1 |
| 15 | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_3CN$ | DIPEA/3 equiv | 20 | 24 | 83.2 | 13.4 |
| 16 | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_3CN$ | DIPEA/3 equiv | 0 | 24 | 72 | 7.8 |
| 17 | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_3CN$ | DIPEA/3 equiv | -30 | 24 | 58 | 14.1 |
| **18** | **PyCy*N*-Ox[15]$N_5$** | **4a** | **$CH_3CN$** | **DIPEA/3 equiv** | **-38** | **24** | **43** | **40.2** |
| 19 | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_2Cl_2$ | DIPEA/3 equiv | -38 | 24 | 10 | 6.4 |
| 20[c] | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_3CN$ | DIPEA/3 equiv | -38 | 24 | 32 | 4.9 |
| 21 | PyCy*N*-Ox[15]$N_5$ | **4a** | $CH_3CN$ | DIPEA/6 equiv | -38 | 24 | 65 | 4.6 |

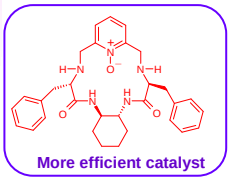
The reaction was carried out at 0.15 mmol scale with 2.4 equiv of allyltrichorosilane in the presence of the corresponding catalyst (20 mol%) and DIPEA (3 equiv).
[a] Conversion was determined by HPLC.
[b] Established by chiral HPLC.
[c] 10 mol% of catalyst was used.

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.[5]

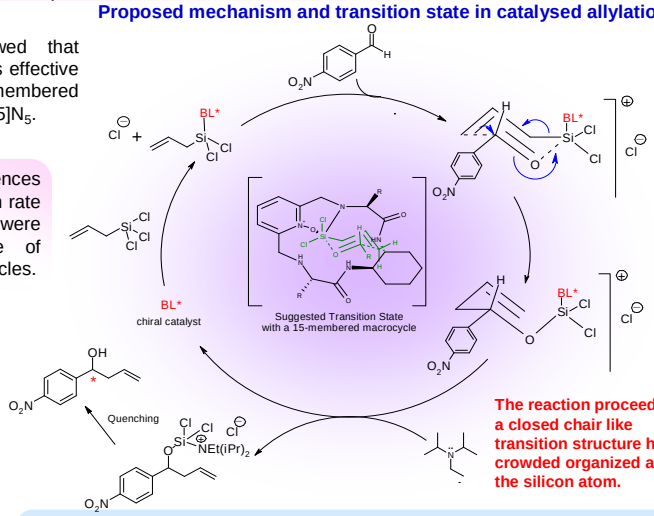
The first results showed that PyCy*N*-Ox[12]$N_4$ are less effective catalysts than the 15-membered macrocycles PyCy*N*-Ox[15]$N_5$.

No significant differences concerning the conversion rate and the enantioselectivity were observed in the serie of PyCy*N*-Ox[12]$N_4$ macrocycles.

The combination of PyCy*N*-Ox[15]$N_5$ **(4a)** and acetonitrile appears to be a well-balanced choice.




**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

- Eight new chiral azapyridinomacrocycles *N*-oxides have been easily synthesized, from inexpensive starting materials.
- 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) for catalyst **(4a)**.
- Further studies are in progress in order to use larger macrocycles and to assess these original ligands in other enantioselective organocatalyzed reactions.

## REFERENCES

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3) Dioury, F.; Sambou, S.; Guéné, E.; Sabatou, M.; Ferroud, C.; Guy, A.; Port, M. *Tetrahedron* **2007**, *63*, 204-214.
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