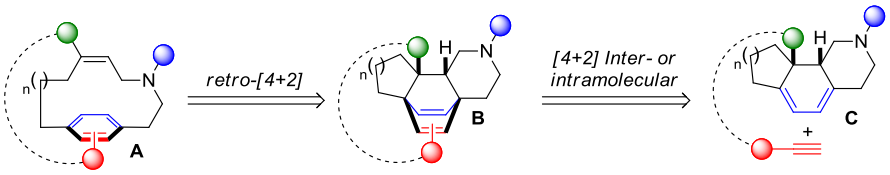
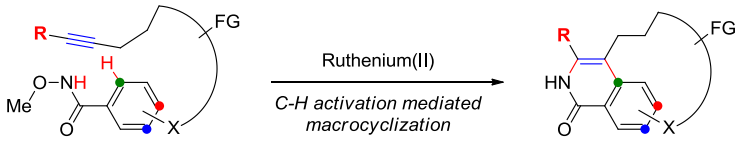
Ring Rearrangement and C-H Activation. Synthesis of Macrocycles.

Macrocycles have been the subject of a growing interest in the field of drug discovery.[1] They offer a compromise between conformational rigidity and flexibility, which enables them to show a degree of preorganization enhancing their affinity and specificity for a given biological target.[2] Despite these promising features, the use of synthetic macrocycles as therapeutic agents is still scarce.[3] The goal of the work presented here was to develop efficient new methodologies to enable the access to otherwise challenging cyclophane structures.

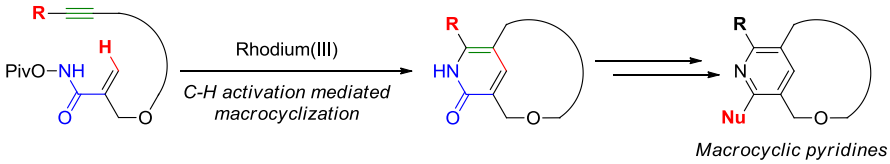
In the first part of our work, an efficient and modular access to structurally diverse and functionalized [n]Paracyclophanes **A** was devised. The strategy relied on the use of retro-[4+2] fragmentation of 1,4-dienes **B** which in turn arose from a [4+2] cycloaddition of acetylenic dienophiles with tricyclic 1,3-dienes **C**, capitalizing on a transformation originally applied to steroid derivatives.[4] The [4+2] cycloaddition could be performed either in an intermolecular fashion or in an intramolecular to give, in the latter case, an access to unprecedented cage-like [n]paracyclophanes.[5]



The second part of the work presented was dedicated to the synthesis of functionalized cyclophanes incorporating heteroaromatic moieties, by a C-H activation mediated macrocyclization. The ruthenium(II)-catalyzed cyclization of benzhydroxamates possessing an ω-acetylenic chain was investigated to access new structurally diverse macrocyclic isoquinolones that features an excellent functional-group compatibility.[6]



This concept could be successfully extended to the synthesis of macrocyclic pyridin-2-ones from unsaturated α,β-hydroxamic acids in the presence of a rhodium(III) catalyst. The resulting pyridones can then be easily converted to polysubstituted macrocyclic pyridines, which are of potential great interest for pharmaceutical applications.[7]



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[3] E. A. Villar, D. Beglov, S. Chennamadhavuni, J. A. Porco Jr *et al.*, *Nat. Chem. Biol.* **2014**, *10*, 723.
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[5] J.-P. Krieger, G. Ricci, D. Lesuisse, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2014**, *53*, 8705.
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