Dibenzo-24-Crown-8 as a Temporary Non-Covalent Protection of a Weinreb Amide Against Grignard Reagent in a [2]Rotaxane Molecular Shuttle

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Introduction

During the past decades, endeavours have been made in the design of new interlocked molecular architectures by investigating new sites of interactions between supramolecular species. The improvement of the efficiency of template-synthesis led to the conception of novel *stimuli*-responsive interlocked molecular machines. Among the interlocked molecules, rotaxanes belong to a family of molecular assemblies that consist of at least one macrocycle surrounding one or several molecular axle(s) through a so-called mechanical bond.[1] In such interlocked molecular structures, the presence and the localization of a macrocycle around the molecular axle dramatically affect the physical and chemical properties of the encircled molecular thread. The motion of the macrocycle along the axle can be controlled if the encircled molecular axle holds several interaction sites (*i.e.* molecular stations) for the macrocycle, and if their affinities are switchable.

In this poster communication, we report on the non-covalent protection of a Weinreb amide by the dibenzo-24-crown-8 (DB24C8) macrocycle in an original [2]rotaxane molecular shuttle.[2] This latter consists of a DB24C8 that surrounds a molecular axle containing an ammonium station and a Weinreb amide as a novel secondary molecular station. After demonstrating the actuation of the new molecular machine, the post-interlocking modification of the [2]rotaxane was studied through the cleavage of the Weinreb amide bond using a Grignard reagent (Figure 1). While the non-interlocked molecular axle was cleaved after a short time in mild conditions, the Weinreb amide bond remained unaltered in the [2]rotaxane species over time. This result highlights the protection shield of the macrocycle around the encircled axle and could be of interest for *stimuli*-responsive protection or cleavage of a wide range of moieties through molecular machinery.

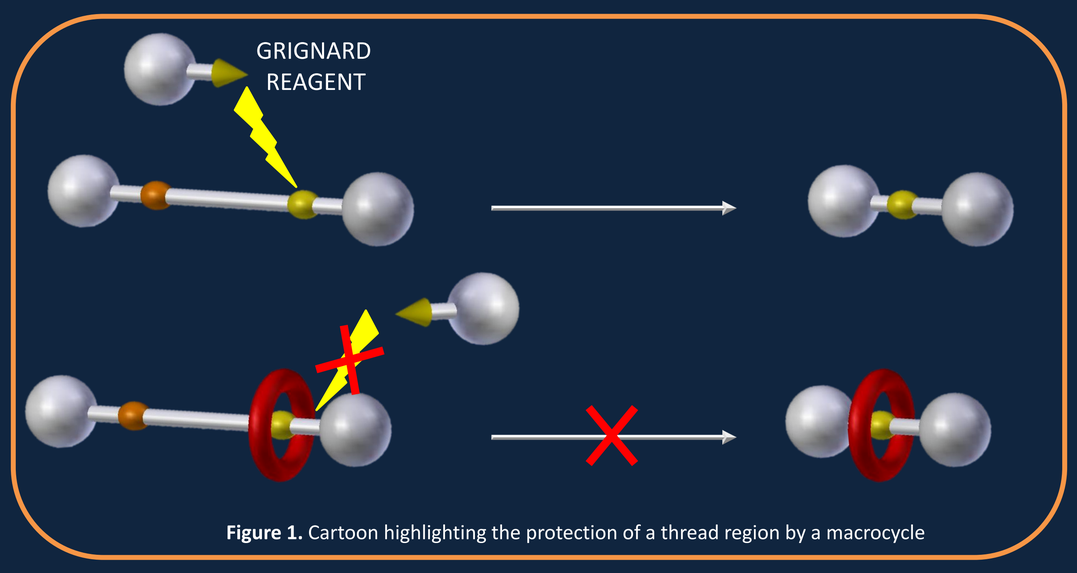
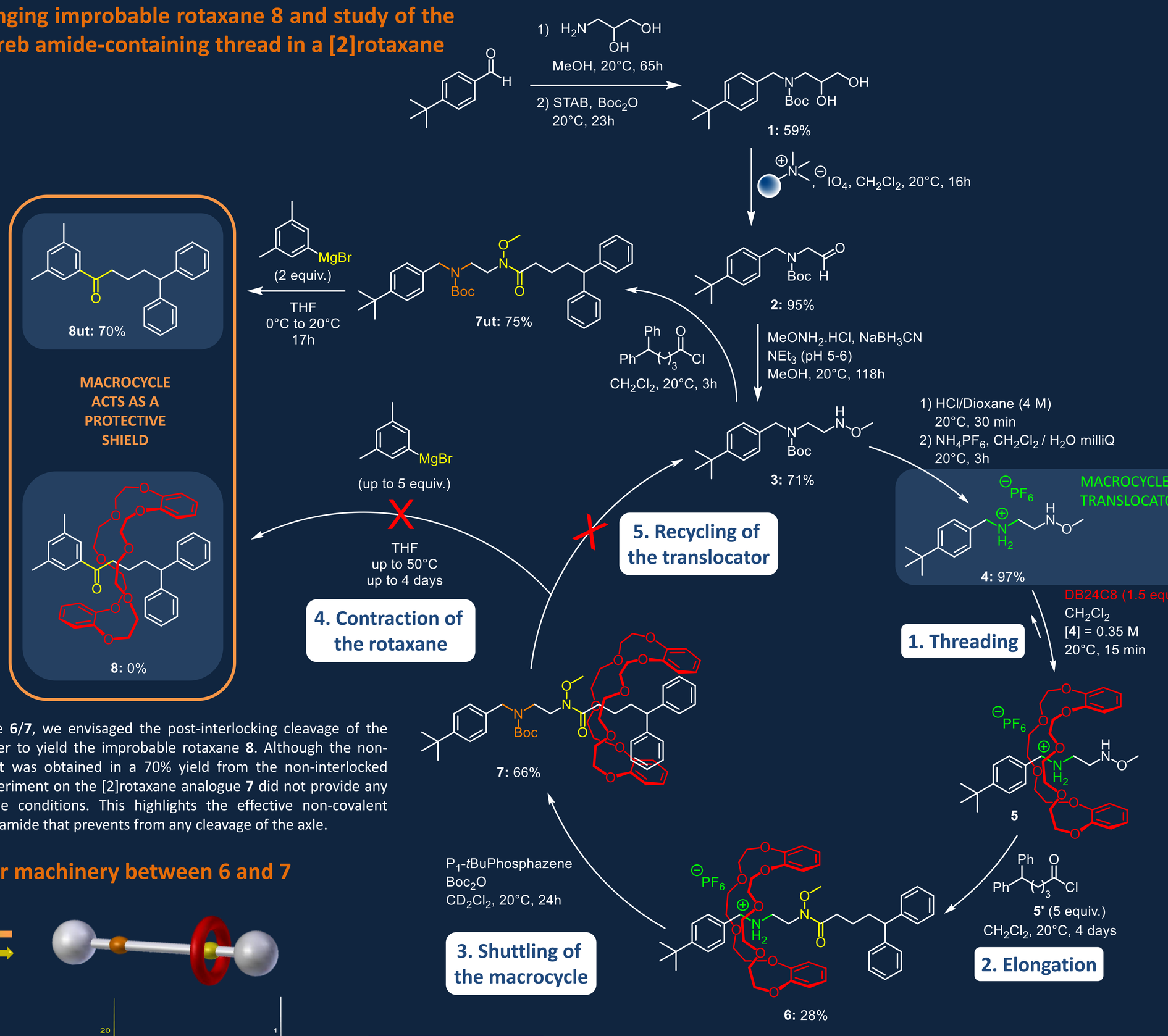


Figure 1. Cartoon highlighting the protection of a thread region by a macrocycle

Attempt of synthesis of the challenging improbable rotaxane 8 and study of the non-covalent protection of a Weinreb amide-containing thread in a [2]rotaxane

The main aim of the project was to synthesize rotaxanes that are devoid of any template. As such, the targeted rotaxane **8** can be seen as very challenging to obtain because of the lack of interaction between the embedded elements and that's the reason why we call it an "improbable" rotaxane. We proposed a diverted strategy[3] that employs the molecular auxiliary **4**, named translocator of macrocycle because it can trap the DB24C8 before releasing it to another axle through molecular machinery, even though the novel axle to be encircled has very few nay no interaction for it.

By this way, the targeted Weinreb amide-containing [2]rotaxane molecular shuttle **6**/**7** was synthesized according to the adjacent multi-step sequence. The translocator **4** was synthesized from the *tert*-butylbenzaldehyde in a 5-step chemical sequence. As it contains the ammonium template, it was able to thread the DB24C8 to afford the semi[2]rotaxane **5**. This latter was not isolated but directly capped at its methoxyamine end through the condensation of the freshly prepared acyl chloride **5'** to provide the mechanically locked extended [2]rotaxane **6**. At the protonated state, in **6**, the DB24C8 is localized around the best ammonium station, while deprotonation-carbamoylation of the ammonium triggers the shuttling of the macrocycle around the Weinreb amide site ([2]rotaxane **7**). The ^{1}H NMR evidences of the molecular machinery are reported Figure 2.



Beyond the synthesis of the new molecular shuttle **6**/**7**, we envisaged the post-interlocking cleavage of the encircled thread **7** using a Grignard reagent in order to yield the improbable rotaxane **8**. Although the non-interlocked ketone-containing molecular thread **8ut** was obtained in a 70% yield from the non-interlocked molecular axle **7ut** in mild conditions, the same experiment on the [2]rotaxane analogue **7** did not provide any expected ketone-containing rotaxane whatever the conditions. This highlights the effective non-covalent protective shield of the DB24C8 around the Weinreb amide that prevents from any cleavage of the axle.

^{1}H NMR evidences of the molecular machinery between 6 and 7

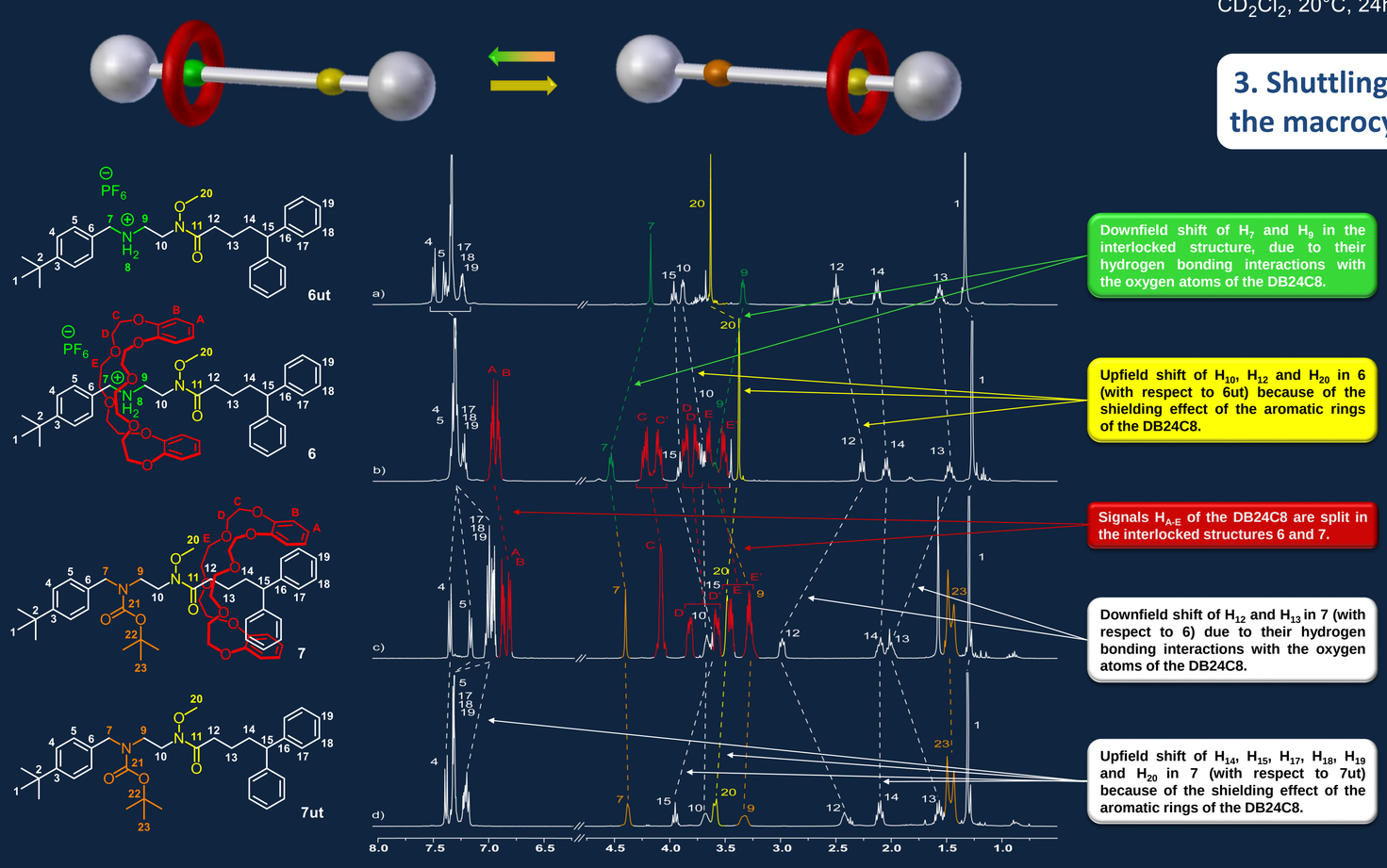


Figure 2. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298K) of (a) the protonated uncomplexed thread **6ut**, (b) the protonated [2]rotaxane **6**, (c) the *N*-carbamoylated [2]rotaxane **7**, (d) the uncomplexed *N*-carbamoylated thread **7ut**.

Conclusion

We have reported the synthesis of a new molecular shuttle that contains an ammonium and a Weinreb amide as molecular stations for the DB24C8. The DB24C8 was localized around the best ammonium station at the protonated state, while Weinreb amide proved to act as an efficient secondary molecular station for the DB24C8 after *N*-carbamoylation of the deprotonated ammonium. In this *co*-conformation, the DB24C8 resides around the amide site, where it acts as a protective shield that prevents the Weinreb amide from any attack by the Grignard reagent, even under drastic experimental conditions.
Using a macrocycle as a temporary non-covalent protection of specific sites of an encircled axle might be valuable for the post-interlocking multi-step modification of rotaxanes. Eventually, *stimuli*-responsive protection of a wide range of moieties through molecular machinery using this strategy is in progress.

References

[1] C. Bruns, J. F. Stoddart, *The Nature of the Mechanical Bond: From Molecules to Machines*, John Wiley & Sons Inc., Hoboken, NJ, **2017.**
[2] M. Gauthier, F. Coutrot, *Eur. J. Org. Chem.* **2019**, *21*, 3391-3395.
[3] S. Chao, C. Romuald, K. Fournel-Marotte, C. Clavel, F. Coutrot, *Angew. Chem. Int. Ed.* **2014**, *53*, 6914-6919.