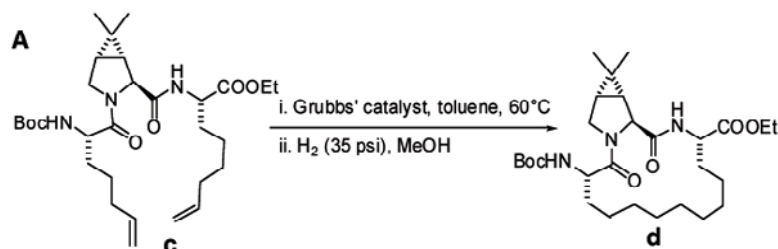


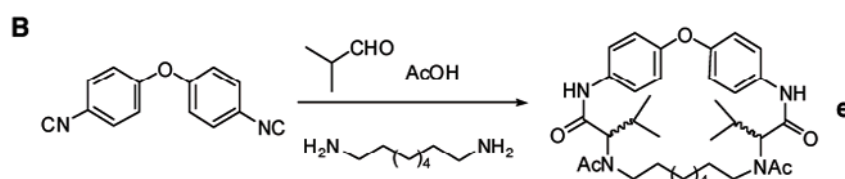
S2 box | **Examples of improved methods for macrocycle synthesis.**

A number of synthetic methods are being used frequently to generate macrocycles in more consistent yields.

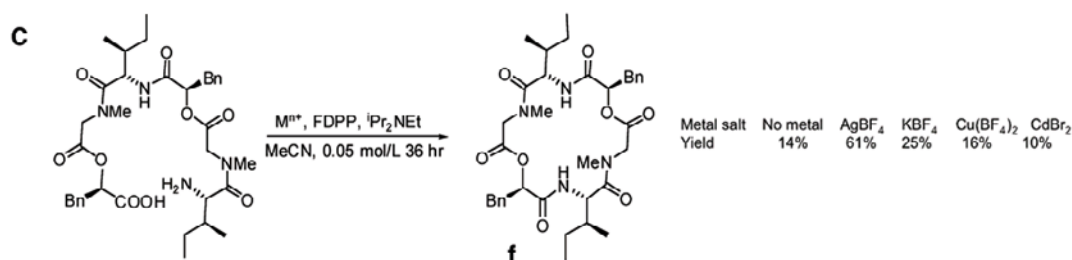
a | The olefin metathesis reaction has been used by numerous groups for macrocyclisations. For example, reaction of the bis-olefin (part c) with the first generation Grubbs catalyst, followed by hydrogenation in methanol has been used to make HCV protease inhibitors via intermediate (part d)¹.



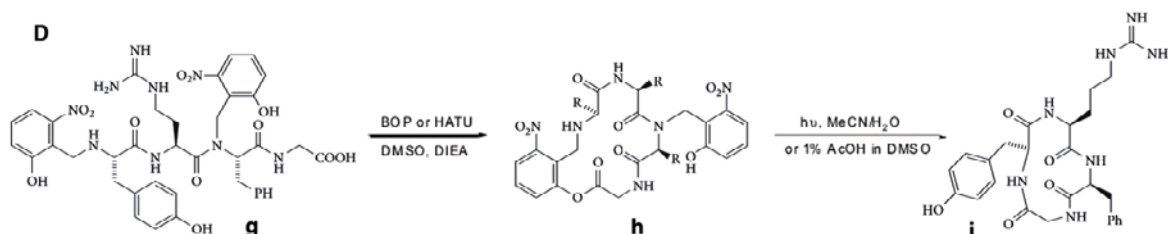
b | Multicomponent reactions have been used to generate macrocycles including compounds such as **S5** that contain the biaryl ether moieties found in naturally-occurring macrocycles such as vancomycin².



c | Cyclisations of linear peptides to give depsipeptide macrocycles (part f) have been found to result in improved yields when executed in the presence of a metal ion³. Various metal ions were explored, and silver was found to be the best catalyst.



d | Linear tetrapeptides (for example, part **g**) have been cyclised via a cyclisation and ring-contraction method⁴. Use of a 2-hydroxy-6-nitrobenzyl derivative on the N-terminus of the linear precursor permits cyclisation to a larger ring (part **h**) before ring contraction and photolytic cleavage of the benzyl group to generate the desired cyclic tetrapeptide (part **i**).



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2. Velázquez, F. *et al.* Application of ring-closing metathesis for the synthesis of macrocyclic peptidomimetics as inhibitors of HCV NS3 protease. *Org. Lett.* **9**, 3061–3064 (2007).
3. Xu, Y., Chen, L., Ma, Y., Li, J. & Cao, X. Silver-ion-mediated macrocyclization to form cyclohexadepsipeptide. *Synlett.* 1901–1904 (2007).
4. Meutermans, W. D. F. *et al.* Difficult macrocyclizations: new strategies for synthesizing highly strained cyclic tetrapeptides. *Org. Lett.* **5**, 2711–2714 (2003).