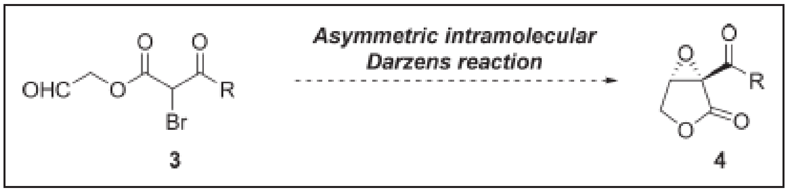
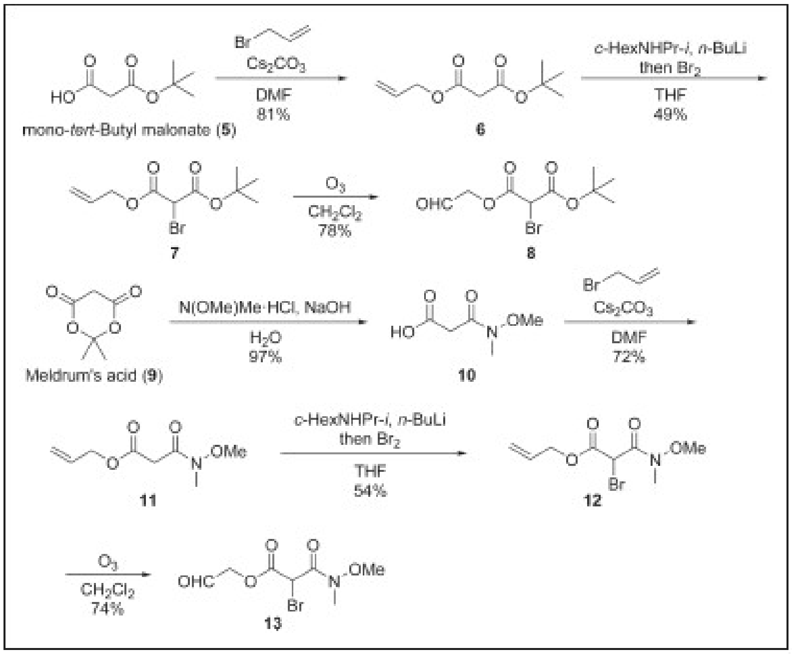
Epoxylactams

By: Robert B. Login rloginconsulting.com

Recently, a paper appeared that caught my attention. It showed how the Darzens reaction can be employed to prepare certain epoxy lactones and lactams. For example:



Scheme 2. Proposed asymmetric intramolecular Darzens reaction.



Scheme 3. Synthesis of aldehydes **8** and **13** for intramolecular Darzens reaction.

Kobayashi, K., Tanaka, K., Suzuki, M., & Kogen, H. (2019). Catalytic Asymmetric Intramolecular Darzens Reaction of 2-Halomalonate Derivatives. *Natural Product Communications*, *14*(10), 1934578X19884409.

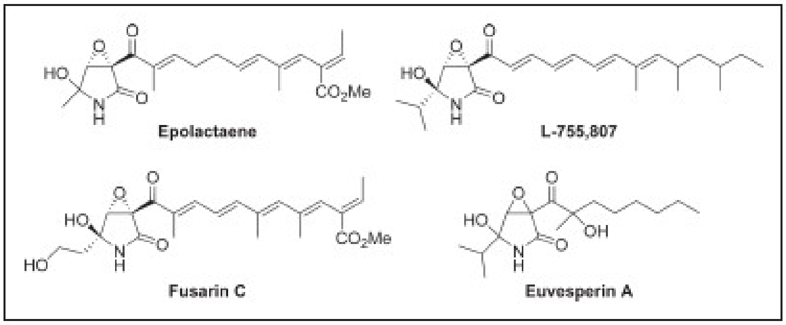
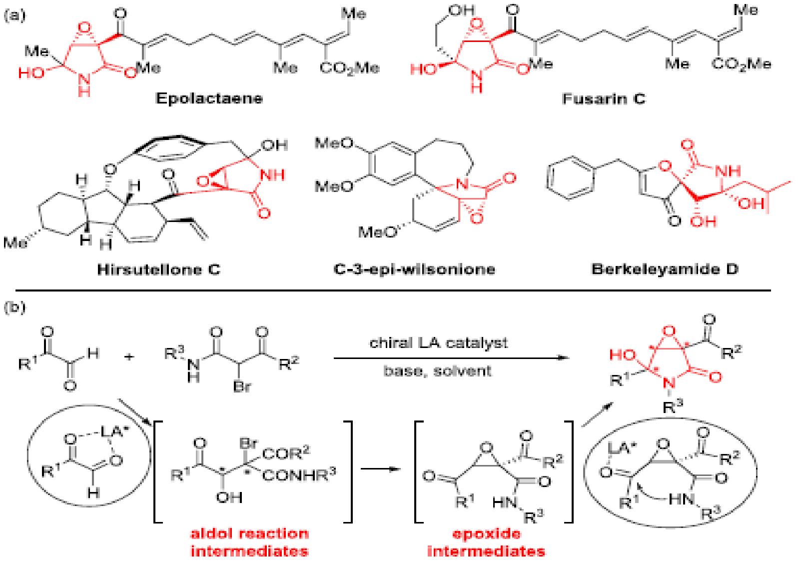


Figure 1. Structures of epolactaene, L-755,807, fusarin C, and euvesperin A.

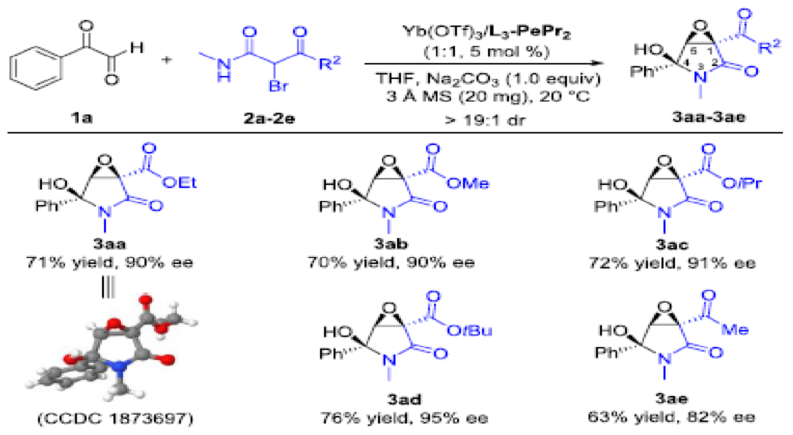
From the same reference above, are examples of the importance of these lactam structures in medicine.

At about the same time, the following reference was published.

Scheme 1. (a) Selected Natural Products Bearing *α,β*-Epoxy-*γ*-Lactam Structure; (b) Darzens/Hemiaminalization Reaction for the Construction of Epoxypyrrolidinone Derivatives



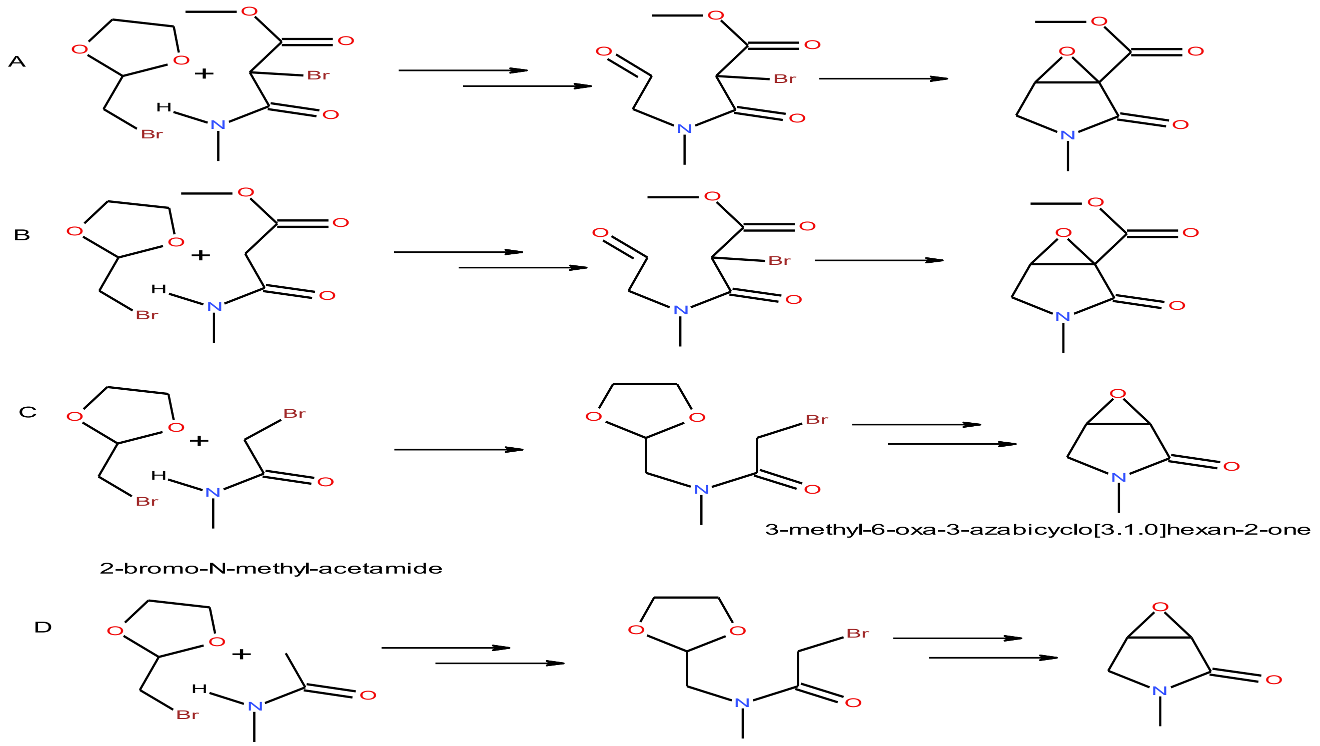
Scheme 2. Substrate Scope of the α-Bromoamides[a]



[a]Unless otherwise noted, the reactions were performed with $Yb(OTf)_3$/L_3-$PePr_2$ (1:1, 5 mol %), **1a** (0.10 mmol), **2** (1.0 equiv), Na_2CO_3 (1.0 equiv), and 3 Å MS (20 mg) in THF (1.2 mL) at 20 °C for 48 h. >19/1 dr.

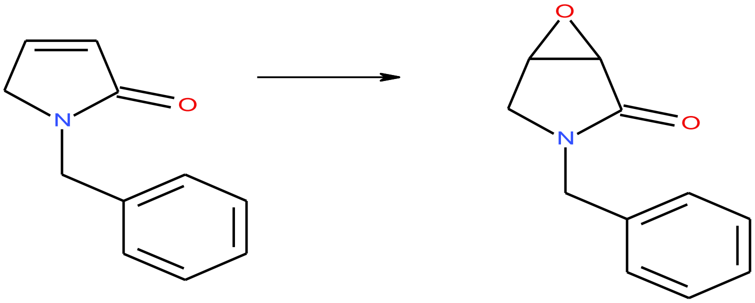
Shen, B., Liu, W., Cao, W., Liu, X., & Feng, X. (2019). Asymmetric Synthesis of α, β-Epoxy-γ-lactams through Tandem Darzens/Hemiaminalization Reaction. *Organic letters*, *21*(12), 4713-4716.

I knew nothing about epoxypyrrolidones before reading the above excellent references. Although both are very interesting, I thought there might be other ways to prepare epoxypyrrolidones.



Scheme 1: Although I show routes A & B, I really would like C or D to be possible. The Darzens literature shows that the yields with chlorine are higher so keep that in mind. Also all of the above reagents are known compounds that should be readily available.

At this point I speculated that there must be easier routes to epoxylactams so the logical thing is to look in SciFinder.



91% yield

R:mCPBA, S:$CHCl_3$
Reactants: 1, Reagents: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation and epoxidation of conjugated lactams: influence of ring size on epoxidation
By Li, Bing and Smith, Michael B.
From Synthetic Communications, 25(8), 1265-75; 1995......91% yield

1. Preparation and epoxidation of conjugated lactams: influence of ring size on epoxidation
By Li, Bing; Smith, Michael B.
From Synthetic Communications (1995), 25(8), 1265-75. Language: English, Database: CAPLUS, DOI:10.1080/00397919508012690

α,β-Epoxy-lactams can be prepd. from conjugated lactams by treatment with m-chloroperoxybenzoic acid. Good yields are obtained, however, only with 2-pyrrolidinone derivs. The yield of epoxy-lactam diminishes dramatically as the size of the lactam ring increases. Epoxidn. of 1,5-dihydro-1-(phenylmethyl)-2H-pyrrol-2-one gave 3-(phenylmethyl)-6-oxa-3-azabicyclo[3.1.0]hexan-2-one.

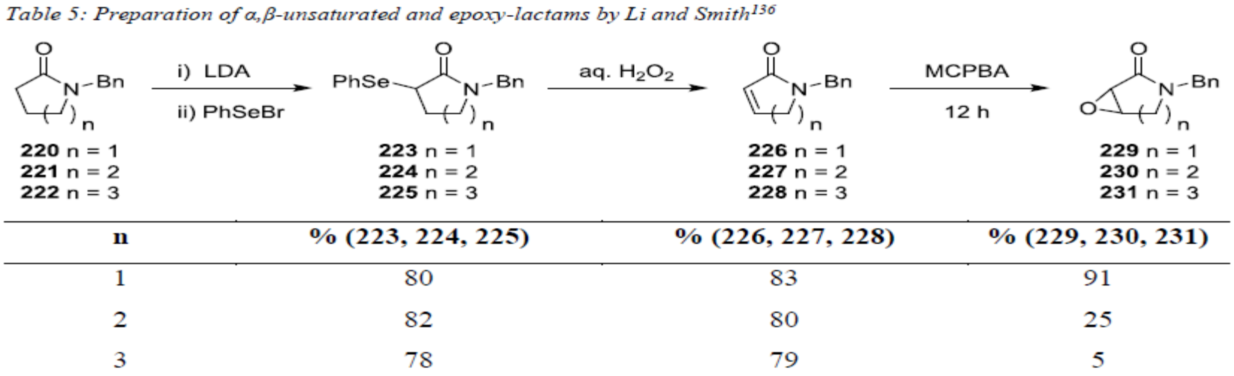


Table 5: Preparation of α,β-unsaturated and epoxy-lactams by Li and Smith[136]

220 n = 1
221 n = 2
222 n = 3

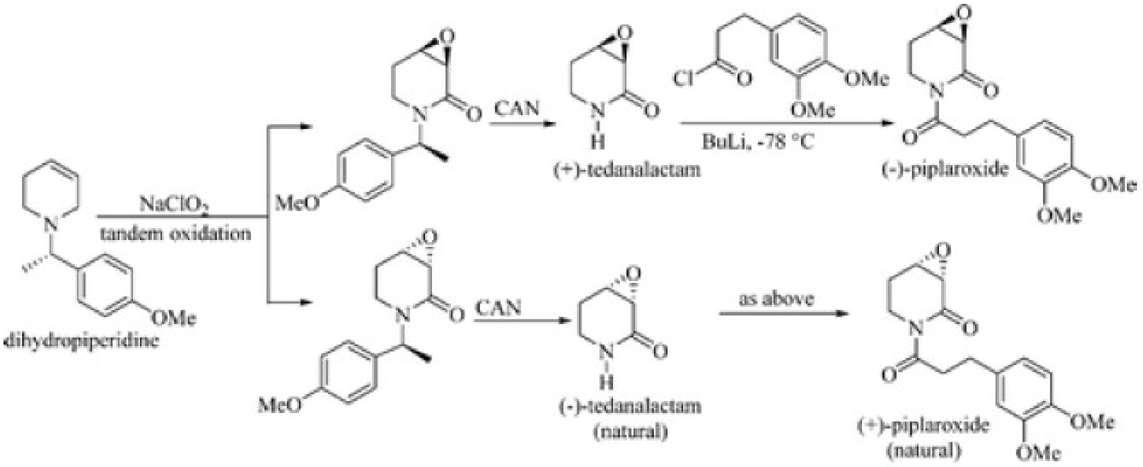
223 n = 1
224 n = 2
225 n = 3

226 n = 1
227 n = 2
228 n = 3

229 n = 1
230 n = 2
231 n = 3

n	% (223, 224, 225)	% (226, 227, 228)	% (229, 230, 231)
1	80	83	91
2	82	80	25
3	78	79	5

Claret, E. M. thesis, see below.



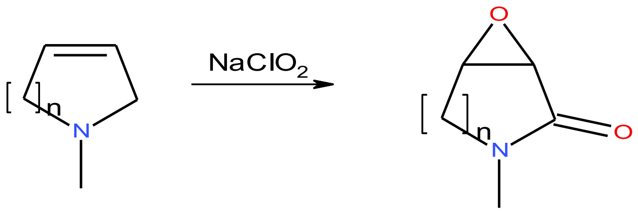
2. Synthesis of the Enantiomers of Tedanalactam and the First Total Synthesis and Configurational Assignment of (+)-Piplaroxide

By Romero-Ibanez, Julio; Xochicale-Santana, Leonardo; Quintero, Leticia; Fuentes, Lilia; Sartillo-Piscil, Fernando

From Journal of Natural Products (2016), 79(4), 1174-1178. Language: English, Database: CAPLUS, DOI:10.1021/acs.jnatprod.5b01041

Highlighting the recently established methodology. for the direct synthesis of glycidic amides from tertiary allyl amines, the synthesis of the enantiomers of tedanalactam, (+)-I and (-)-II, were completed in two steps from the corresponding chiral dihydropiperidine. Addnl., the (+)- and (-)-enantiomers of piplaroxide, III and IV, resp., were obtained from their resp. tedanalactam precursor, and the abs. configuration of the naturally occurring (+)-piplaroxide was detd. The present approach represents not only the shortest synthesis of (-)-tedanalactam, II, but also the first total synthesis of (+)-piplaroxide, a repellent against the leafcutter ant Atta cephalotes.

I think that this NaClO2 reaction would also work with pyrrolidine and larger rings?



Obviously it would react on the allylic side of larger rings.

RM preparation:

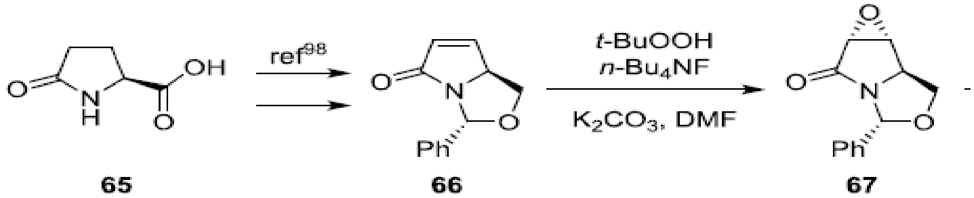
Alves, J. C. (2007). Preliminary studies towards the preparation of reactive 3-pyrrolin-2-ones in conjugate addition reactions for the syntheses of potentially bioactive 2-pyrrolidinones and pyrrolidines. *Journal of the Brazilian*

Chemical Society, *18*(4), 855-859.

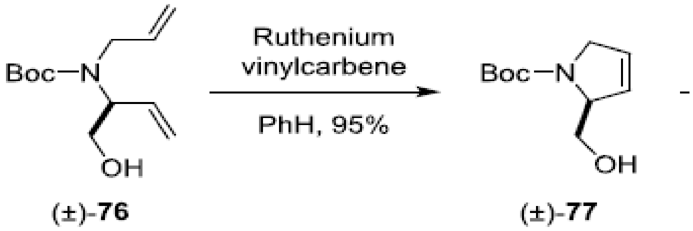
Cuiper, A. D., Brzostowska, M., Gawronski, J. K., Smeets, W. J., Spek, A. L., Hiemstra, H., ... & Feringa, B. L. (1999). Determination of the Absolute Configuration of 3-Pyrrolin-2-ones. *The Journal of Organic Chemistry*, *64*(7), 2567-2570.

At this point I discovered an excellent thesis that covered in great detail the above chemistry:
Claret, E. M. (2018). *Design and Synthesis of Pyrrolidine-Based Nucleotide Mimetics for Use as Inhibitors of the DNA Repair Enzyme AAG*(Doctoral dissertation, University of Surrey (United Kingdom)).
(Note that the following book chapters also are very thorough: Pelkey, E. T., Pelkey, S. J., & Greger, J. G. (2015). De Novo Synthesis of 3-Pyrrolin-2-Ones. In *Advances in Heterocyclic Chemistry* (Vol. 115, pp. 151-285). also see vol.128 Academic Press.)

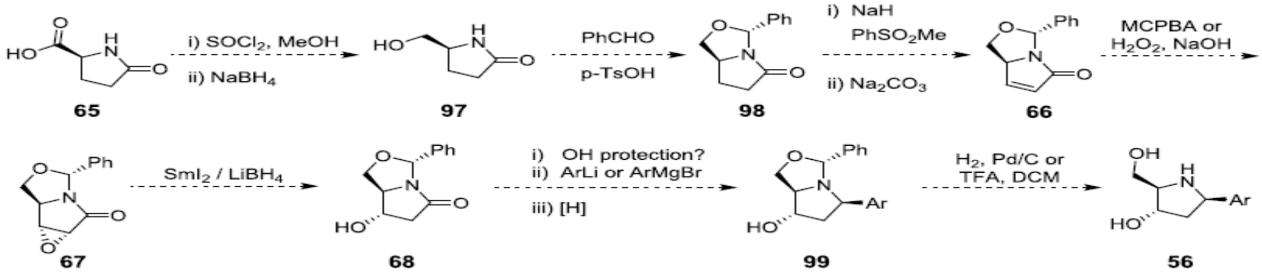
I've copied the following from Claret thesis:



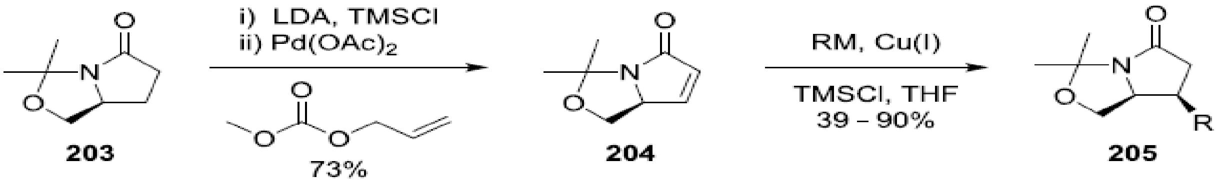
(Partial scheme 14&15 ...75% yield)



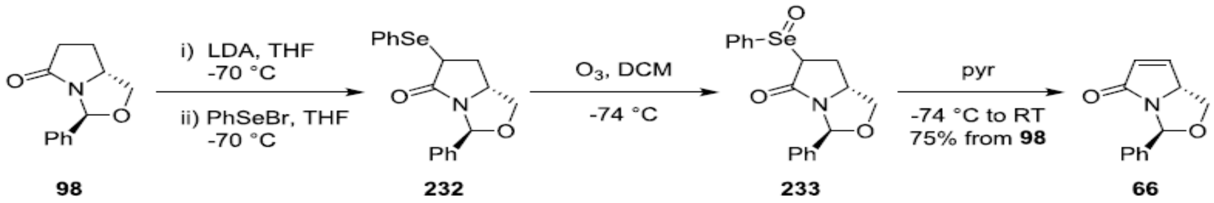
(Partial scheme 17)



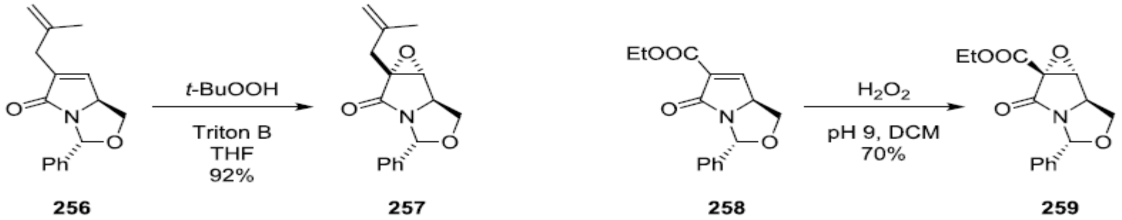
Scheme 20: Proposed synthesis of 2-(hydroxymethyl)pyrrolidines



Scheme 49: Unsaturation and alkyl cuprate conjugate addition by Wright et al.[137]

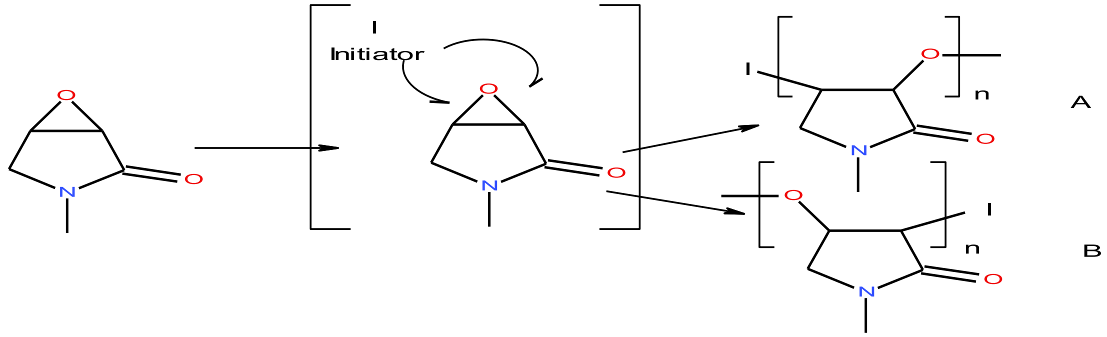


Scheme 53: Bicyclic lactam unsaturation by Hamada et al.[99]

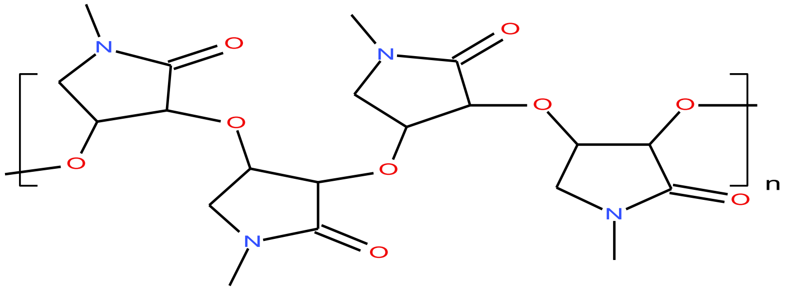


Scheme 68: Epoxidation reactions by Jao et al. and Cottrell et al.[167, 168]

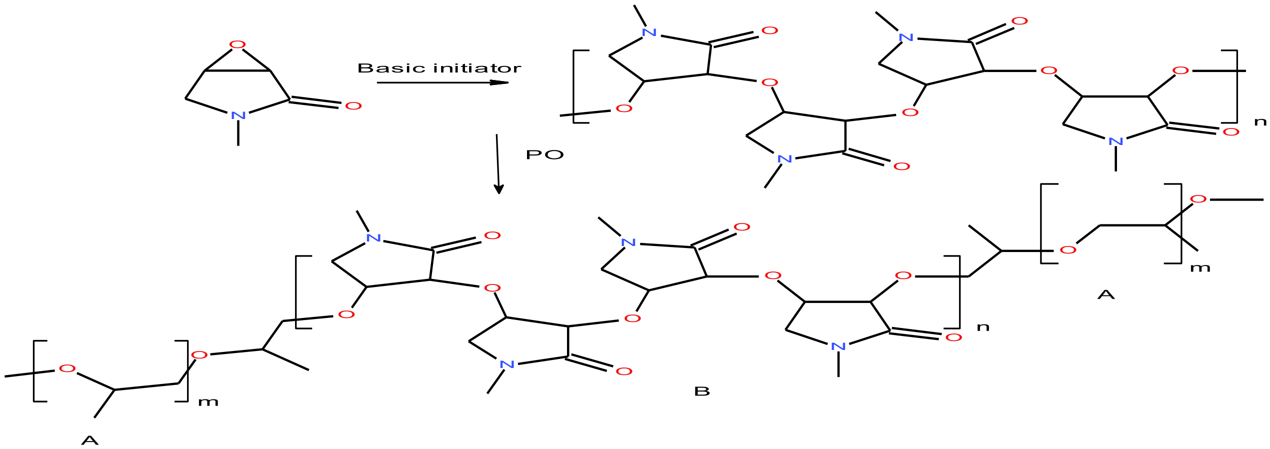
What then are epoxypyrrolidones good for?



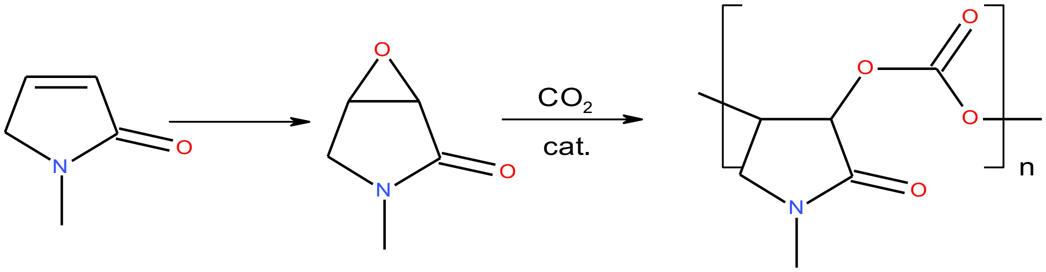
Scheme 2: I would expect the initiator to attack as in B as the 3-position is more electrophilic.



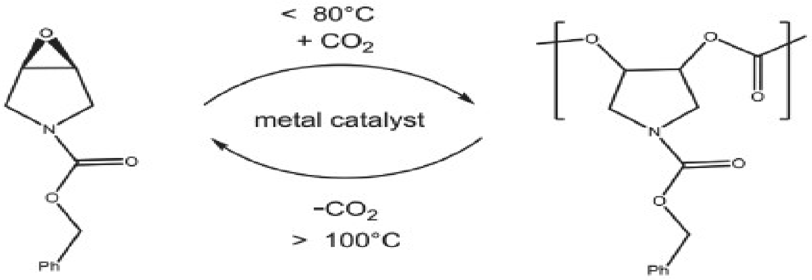
Scheme 3: This is how the resulting polymer can fit together illustrating 4 repeat units.



Scheme 4: Furthermore water soluble polyepoxypyrrolidones could copolymerize with EO or PO resulting in block or heteric combinations. Even if its an oligomer, it could be the central block capped by polyPO for example resulting in unique polymers like the Pluronic surfactants. The pyrrolidone units might be excellent complexing agents with various drugs forming drug delivery micells.



Scheme 4: Cyclic epoxies react with carbon dioxide to form polymers. I found the following references:



Scheme 8.

Completely recyclable monomers and polycarbonate: approach to sustainable polymers

Y Liu, H Zhou, JZ Guo, WM Ren…- Angewandte Chemie …, 2017 - Wiley Online Library

It is of great significance to depolymerize used or waste polymers to recover the starting monomers suitable for repolymerization reactions that reform recycled materials no different from the virgin polymer. Herein, we report a novel recyclable plastic: degradable polycarbonate synthesized by dinuclear chromium-complex-mediated copolymerization of CO2 with 1-benzyloxycarbonyl-3, 4-epoxy pyrrolidine, a meso-epoxide. Notably, the novel polycarbonate with more than 99% carbonate linkages could be recycled back into the…

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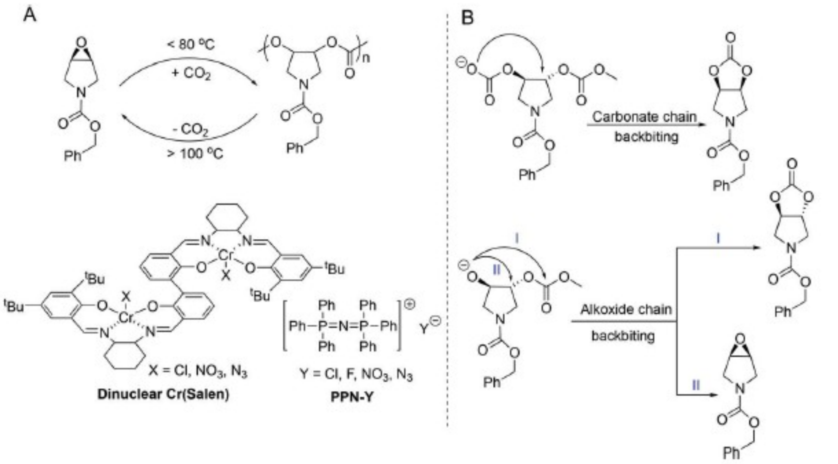
(Note: I have not read this reference)



Scheme 12 (A) Copolymerization–depolymerization cycle between PC and CO_2/BEP monomer in the presence of a dinuclear salen–chromium complex and a PPN-Y cocatalyst; (B) possible depolymerization products.

Hong, M., & Chen, E. Y. X. (2017). Chemically recyclable polymers: a circular economy approach to sustainability. *Green Chemistry*, *19*(16), 3692-3706.

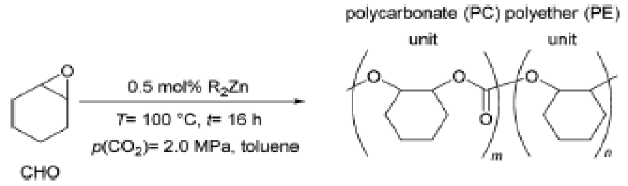
Obviously there is interest in this chemistry. I would think this CO2 copolymerization could be expanded with block or heteric copolymerization. Placing block oligomers of this type, in other polymers might result in on demand thermal scission resulting in degradeable polymers.

Other references to polycarbonates that might be of interest:

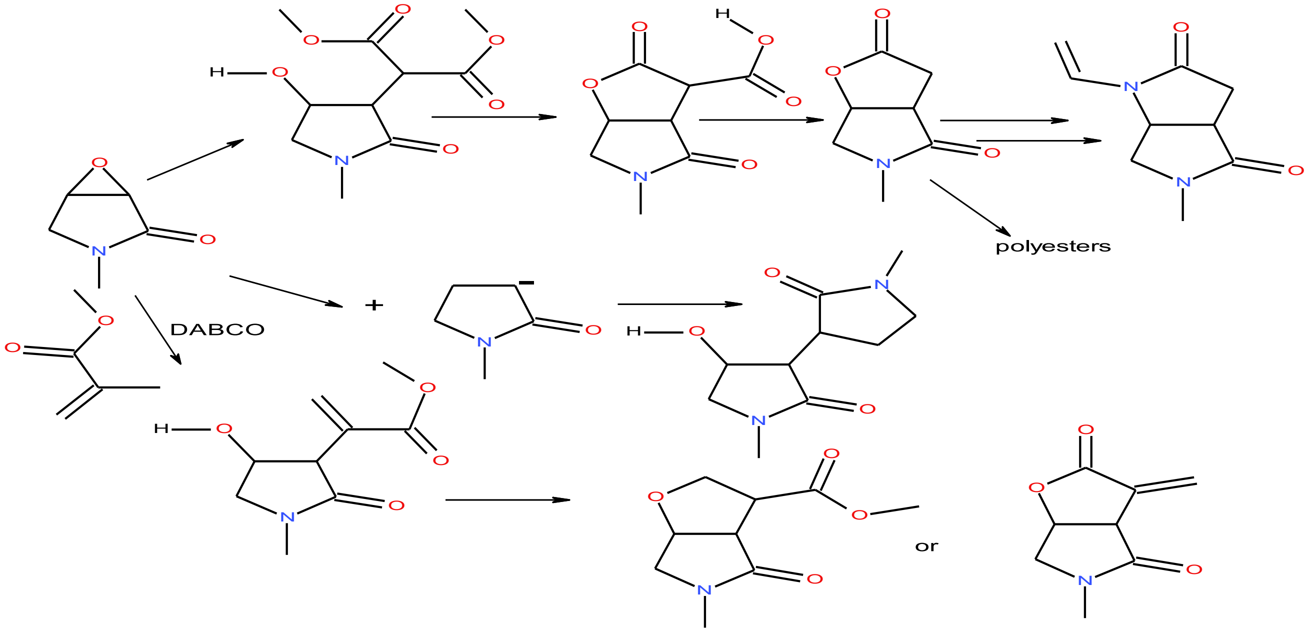
Zhang, D., Zhang, H., Hadjichristidis, N., Gnanou, Y., & Feng, X. (2016). Lithium-assisted copolymerization of CO2/cyclohexene oxide: A novel and straightforward route to polycarbonates and related block copolymers. *Macromolecules*, *49*(7), 2484-2492.

Taherimehr, M., & Pescarmona, P. P. (2014). Green polycarbonates prepared by the copolymerization of CO2 with epoxides. *Journal of Applied Polymer Science*, *131*(21).

Table 1 Screening of readily available zinc organyls R_2Zn for the copolymerization of CHO and CO_2[a]



Wulf, C., Doering, U., & Werner, T. (2018). Copolymerization of CO 2 and epoxides mediated by zinc organyls. *RSC advances*, *8*(7), 3673-3679. I show these references since cyclohexane epoxides are prevalent in the literature. There are many more references.



Scheme 5: Possible derivatives. I'm sure many others are conceivable.

Thank you for reading these proposals!

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