**Chemical challenge of macrocycles**

Both entropic (how to get reactive termini into proximity) and enthalpic (how to handle ring strain in TS) challenges. For direct cyclization, dimerization always a competing reaction.

- **Typically,** no substantial enthalpy cost
- **Take-home:** 9, 10, 11-membered rings are most synthetically challenging because of both enthalpic and entropic costs.

**Ring Expansion approaches**

Useful when: (a) Final macrocycle is difunctionalized in a 1,4 or 1,5 manner; and (b) making macrocycle size of n-5 or n-6 is substantially easier than final size n. Thus, common for 9 (from 5/6 fused system) and 10 (from 6/6)-membered rings.

**Bin 1: Fragmentative ring expansion**

**Take-home:** Rates of enthalpically-challenging reactions are more temperature dependent. Rates of entropically-challenging reactions have low temperature dependence.

**Within a macrocyclization context:** For unstrained, large macrocycles, just ‘heating it up’ may not increase reaction rates at all!

**Macrocyclization strategy**

- **Direct cyclization**
- **Ring expansion**
- **Insertive/conjunctive**
- **Ring contraction (loss of linker)**

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**Grob or Echenmoser approaches common**

- **Paquette’s jatrophatrione,** *JACS* 2002, 124, 6542.
- **Danishefsky’s tetracyclines,** *JOC,* 1992, 57, 7052.

**Strain release of cyclobutanes also useful**

- **Ikeda’s, phoracantholid,** *Heterocycles* 1983, 20, 1005.
  - Note: modern manufacturing route uses EDCI in higher yield.

**Analogous reductive fragmentations also prevalent**

  - *JOC,* 1998, 63, 7338.
The most literal examples are from the polymer literature


but driving force is necessary…


Also known with carbon nucleophiles

Trost’s Muscone, *JACS* 1980, 102, 5680


Alternate to nucleophilic add’n: pericyclic insertive ring expansion

Tetrahedron 1999, 55, 6577.

Can also be iterative

*Org Lett.* 2010, 12, 2040.

**Key concept:** enthalpic benefit of termini’s coordination to catalyst ‘prepays’ for entropic penalty. Catalyst loading, temperature, and substrate concentration controls MW of polymer.
Ring Contraction Approaches
Useful for three sets of strategy: (a) to contract a less strained pre-macrocycle into a strained target; or (b) to switch atom count by an odd number, and thus invert dissonant/consonant relationships, or (c) introduce a turn-supporting element to decrease entropic penalty of cyclization.

Take-home: Majority of use cases are in medium rings where strain is the primary challenge.

Native chemical ligation is very useful for strain relief.

Conceptually similar approach via traceless Staudinger was developed by Bertozzi.

Salicaldehyde-derived ligands can offer analogous reactivity.

Ramberg-Backlund can preorganize, and also control olefin geometry.

Sigmatropic macrocycle contractions

Direct cyclization approaches
Excellent review: Nat prod rep. 10.1039/c8np00094h

Mostly used in large, unstrained rings. Overriding competitive dimerization is major challenge. Because of large entropic cost, heating reactions can offer limited (or no) kinetic benefit.

Macrocyclizing aldol

Often very stereoselective, but extremely difficult to predict a priori — “A strategy born out of pure hope”

Not always so lucky:

Very distal conformational effects can relay across large rings:
**Macrocyclizations**

**Direct cyclization approaches (cont.)**

**Bin 2: Carbonyl addition chemistry**

NHK is overrepresented

![Chemical reaction diagram](image)

Take-home logic with NHK: “matching reaction kinetics with cyclization kinetics”

Carbenoid chemistry also well-precedented

**Reformatsky is common, but stereocontrol tends to be bad in unconstrained systems**

![Chemical reaction diagram](image)

**Direct cyclization approaches**

**Bin 3: Palladium chemistry**

Advantages are: (a) coordination to metal ‘prepays’ entropic penalty; (b) For highly strained macrocycles of size n, the size (n+1) metallacycle is often much less strained, and (c) reductive elimination is generally irreversible and far downhill.

Cross-coupling is ubiquitous and too numerous to mention

Key takehomes is again ‘kinetic matching;’ thus Cu (Ullmann) often better than Pd (Buchwald)

Tsujii-trost is also common:

Oxidative examples equally successful

Carbonylation also works intramolecularly

Alkyne hydrometallation also extremely popular

Macrolactonization also works to close ring. However, intramolecular aldehyde addition has no dr. Cyclization allows for stereocontrol!

Jamison’s amphidinolides, JACS 2005, 127, 4297.

Direct cyclization approaches (cont.)

Bin 4: addition into cations (oxocarbeniums, carbocations)

Useful for biomimetic approaches, often highly simplifying. Rarely used on highly strained scaffolds, or where cyclization is entropically difficult. Usually used to form a fused system (macrocycle + 5 or 6-membered ring).

Prins and Sakurai abound, but almost always to form fused system. Exception:

\[
\begin{align*}
\text{Me} & \text{O} \\
\text{Me} & \text{O} \\
\text{TMS} & \\
\end{align*}
\]

prins version (sans TMS) works too in low yield

Enev's laulimalide, JACS 2001, 123, 10764.

Harran, the king of cationic macrocyclizations

both aryl-aryl bonds....

and extensive experimentation on intramolecular indole alkylation

very consistently exo for irreversible, intermolecular. \( E = \text{Br, I, Cl, SePh, carbon, alkyl, etc} \)

Even enantioselective DA is possible in macrocyclizing setting

Corey/Snyder's palominol, JACS 2006, 128, 3908.

(Baran/Burns' haouamine synthesis is of course relevant to this subsection.)

3+2 cycloaddition also prevalent. Next to Click chemistry for triazole peptide stapling, isoxazoline synthesis is most common.

reminder, isoxazoline is nice beta-hydroxy ketone equivalent!


Direct cyclization approaches

Bin 5: Macrocycle-closing cycloadditions

Again, useful for fused or bridging systems (macrocycle + 5 or 6-membered ring). Prediction of stereochemistry is complex — secondary orbital overlap and conformational predisposition of the macrocycle are both important, and if in conflict, there is no clear rationale for which one trumps.

Diels-Alder stereochemistry exemplifies this problem:

intermolecular variant goes exclusively exo (above, desired)

Easy fix: undesired imine hydrolyzes, desired is stable!

Direct cyclization approaches (cont.)

Bin 6: magic radicals (charge transfer, photochem, etc)

Artisanal and unpredictable. Used for cool-looking ‘trick-shots’ but rarely advantaged practically. Frequent core issue: radical lifetime is too short to “find” other chain terminus

Boger’s Giese macrocyclization

works for ring sizes 11 to 20
HOWEVER, if backbone is at all branched or substituted, fails

JACS 1990, 112, 4009.

Addition into phthalamides

Works for ring sizes up to 26. No dimers observed even at .1 M. Potassium salt is critical; with Na₂CO₃ or pyridine, only reductive decarboxylation is observed.

Authors initially postulate pre-organizing chelate, but then show this experiment:

More Harran, a different diazonamide route
dramatic NMR pH dependence on indoline shifts.

Conclusion: charge transfer complex


Direct cyclization approaches

Bin 7: Macrolactamizations

Cyclopeptides are the single largest class of macrocyclic natural products, so lactamization is the most obvious approach. Fundamentally more challenging than macrolactonization because the nucleophile cannot be ‘turned off’ in absence of base. Thus, pre-activation of the acid is not possible.


Key enablers of cyclization

- Turn-inducing element (proline, pyrroloindoline, cis-olefin, DKP, etc)
- Steric preference at cyclization point (glycine, D to L peptide junction, etc)
- Templating effects (see later section for metal templates)
- Conformational freedom; i.e., chaotropic additives can help

Acetal provides turn-inducing element


Thioamides are useful, especially because of epimerization protection

Hutton, ACIE 2019, 58, 4998.

Secondary amines are DRAMATICALLY less reactive. This can be used to advantage:

Note: Attempts to cyclize at pyrroloindoline/indole C-N bond failed!

Strategy to “store” carboline as pyrroloindoline

Baran’s Kapakahine, JACS 2009, 131, 6360.
Contrast with Rainier’s synthesis, which carries carboline throughout. Org. Lett., 2010, 12, 2154.
Direct cyclization approaches (cont.)

Bin 8: Macrolactonizations


EDCI; Yamaguchi; Corey-Nicolau are of course first resort.

For beta-keto lactones, Boeckman approach is often best

HATU failed in this context

JOC 2003, 68, 2200.

Umpolung (e.g., Mitsunobu or epoxide opening) is useful if ester is hindered or sensitive


Benzylic/allylic alcohols can be prone to elimination in Mitsunobu macrocyclization

KEY TRICK: Add an equiv of TsOH to prevent elimination. In this system, exclusively elimination product observed without TsOH.

With Yamaguchi conditions, complete epimerization observed.

JACS 1996, 118, 7237.

Macrolactols are often thermodynamic well

sp³ of lactol is key — direct lactonization on acid was unsuccessful

JACS 2002, 124, 13670.

Comparing RCM to other technologies… Reproduced from Chem. Rev. 2013, 113, PR1.
Direct cyclization approaches (cont.)

Bin 10: reductive amination / imine strategies
Imines often are thermodynamic well for kinetically unfeasible macrocycles

1. OsO₄, NaIO₄
2. BnNH₂, NaBH(OAc)₃

Because process is thermodynamically driven, there is EXTREME sensitivity to conformational preferences


Bin 11: carbenoid addition strategies

pi pre-complexation drives macrocyclization lactonization fails in this system. Synlett 2001, 9, 1364.

Bin 12: The importance of templating
Most classic example, vitamin B12 For an excellent review on templating, see: Chem. Rev., 2015, 115, 8736.

Dozens of examples of M⁺ and halide or SO₄²⁻ templating poly-ethers or poly- amines in a similar fashion. A more esoteric example:

Without cobalt, no reaction Pure Appl. Chem. 1973, 33, 145.

Oxidative amidation along similar lines is also known

KEY TIP: AglO₃ shifts imine/hemiaminal equilibrium away from imine JACS 2006, 128, 13064.

Fun and random: chiral shift via imine macrocycles

Chiral amino acid of interest helical bis-imine macrocycle. Direction of helix reliably determines amino acid configuration.


Baran has expansion of this work, see JACS 2017, 139, 5233.
Macrocylizations

Solomon H. Reisberg

Baran Group Meeting
1/18/20

Macrocycles in drug discovery

Key benefits: (a) conformational locking; access to binding-like ground-state conformations; (b) decreased surface-area to volume ratio; often improved membrane permeability; and (c) privileged proteolytic stability


Even without crystal, nOE can guide cyclization. Merck FTase inhibitors

\[
\text{IC}_{50} = 5490 \text{nM} \\
\text{nOE observed, only in presence of enzyme}
\]

No atropisomerism observed in acyclic analogs. Cyclization done via SnAR of naphthol onto fluoro-cyanobenzene. JACS 2001, 123, 2107.

As always, potency is extremely conformationally sensitive

Physical properties are also dramatically affected

MCL1, a breeding ground for rationally-designed macrocyclic inhibitors

The AMG176 story

Reproduced from: Cancer Disc., 2018, 8, 1582.