MANAGING TIGHT-BINDING RECEPTORS FOR NEW SEPARATION TECHNOLOGIES

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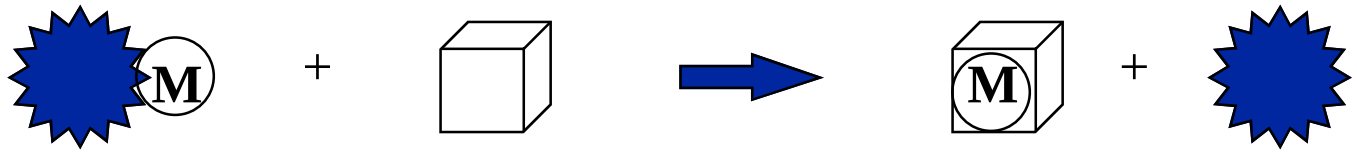
ADVANTAGES OF TIGHT-BINDING LIGANDS IN METAL ION SEPARATIONS

- Competing Equilibria:

  Metal ions can be taken away from other reasonably strong binding sites



Competing Site Powerful Ligand

- Effective at Various Concentration Levels:

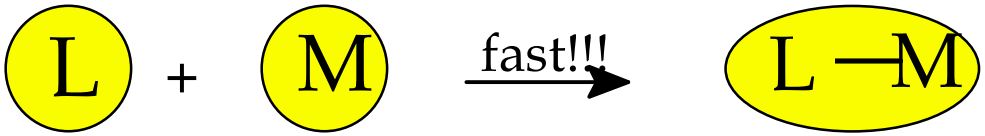
  Metal ions can be abstracted from extremely dilute solutions, making ligands appropriate for low concentration receptee streams

- Selectivity:

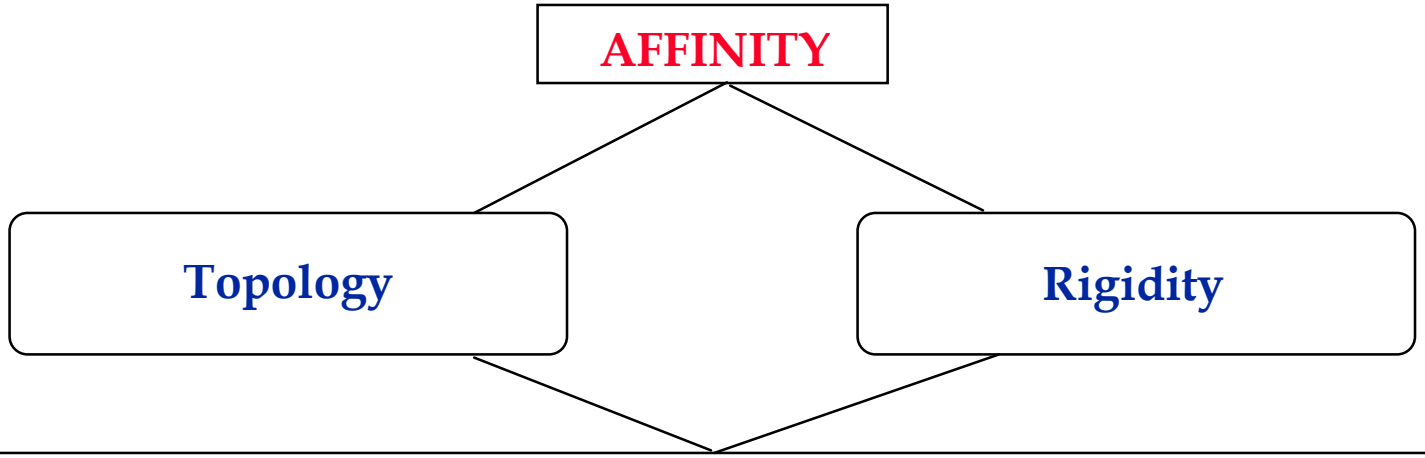
  If a ligand has a high affinity for a metal ion, with proper optimization, it may also have a high selectivity

Given these attributes, why are powerful ligands not commonly employed in the separation of metal ions?

Traditional separation methods like ion exchange and solvent extraction require *rapid* interaction between ligands and metal ions:



However, the most tight-binding receptors invariably bind *slowly* due to their affinity for appropriate metal ions:



Slow Kinetic Processes Result:

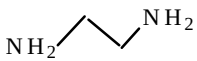
- **Constraints imposed by topology and rigidity restrict motion during binding**
- **Rigidity and topology even more drastically inhibit dissociation**

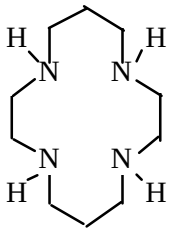
THE INFLUENCE OF VARIABLE TOPOLOGY IN THE FORMATION OF COMPLEXES

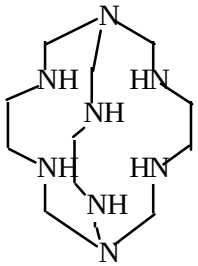
Stability of Complexes

	monodentate	<	chelate	<	macrocycle	<	cryptate
Relative Thermodynamic Stabilities:	1		10^3 -10^4		10^6 -10^8		10^{10} -10^{13}

NH_3







Complexation Kinetics

	monodentate	≥	chelate	>>	macrocycle	>>	cryptate
Relative Rates of Complexation (k_f, $M^{-1}\,s^{-1}$)	1		1		10^{-1} -10^{-2}		10^{-2} -10^{-5}
Relative Rates of Dissociation(k_d, $M^{-1}\,s^{-1}$)	1		10^{-3}		10^{-7} -10^{-10}		10^{-12}-10^{-18}

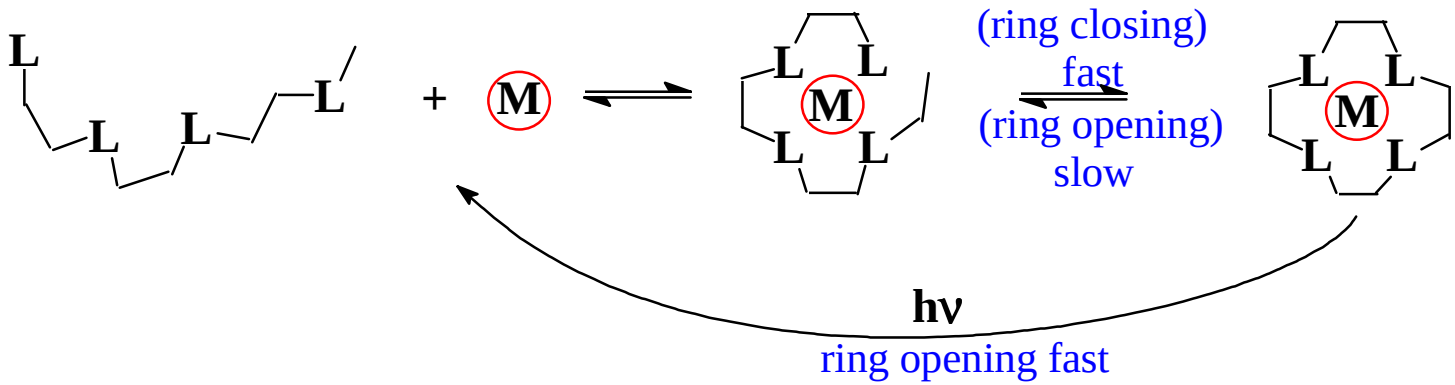
NEEDED: Rate processes with the velocity of simple chelation giving a product with the stability of a macrocycle

PROPOSED: For Formation

Design linear molecules capable of undergoing *template macrocyclization* in the process of complex formation

For Dissociation

Design a macrocyclic ligand in a complex that can be converted into a linear chelating ligand following cleavage via a ligand reaction

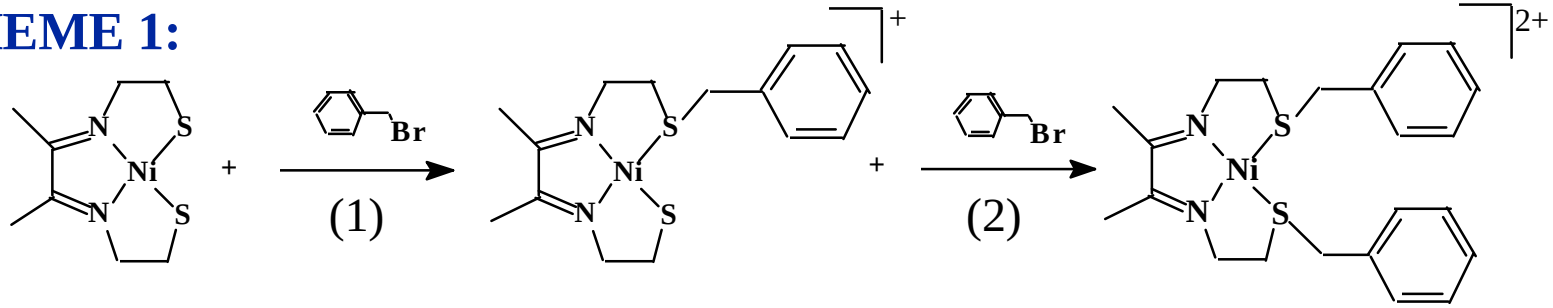


TEMPLATE MACROCYCLIZATION AS A MEANS TO ACCELERATE BINDING

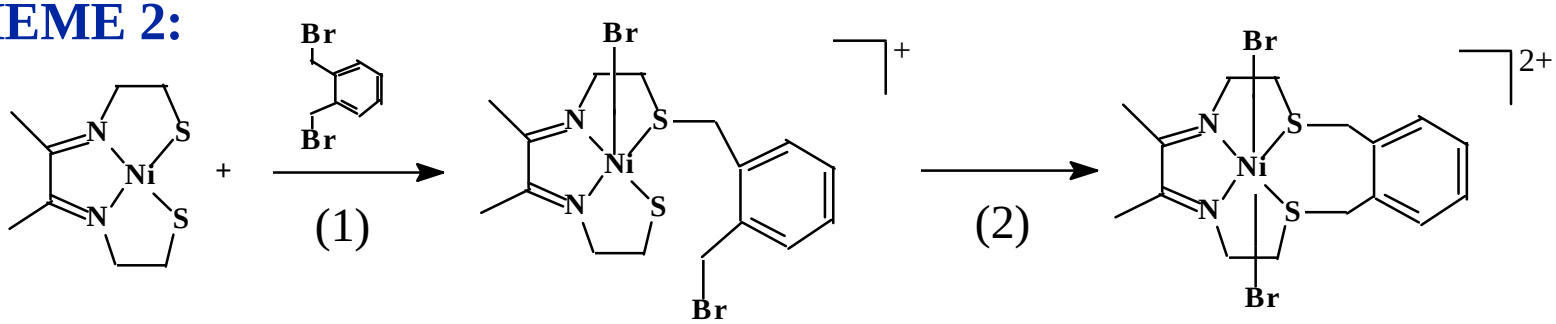
Linear Chelate ⇨ Macrocycle

Supporting Evidence: Blinn, E. L. and Busch, D. H. *Inorg. Chem.*, **7**, 820 (1968).

SCHEME 1:



SCHEME 2:

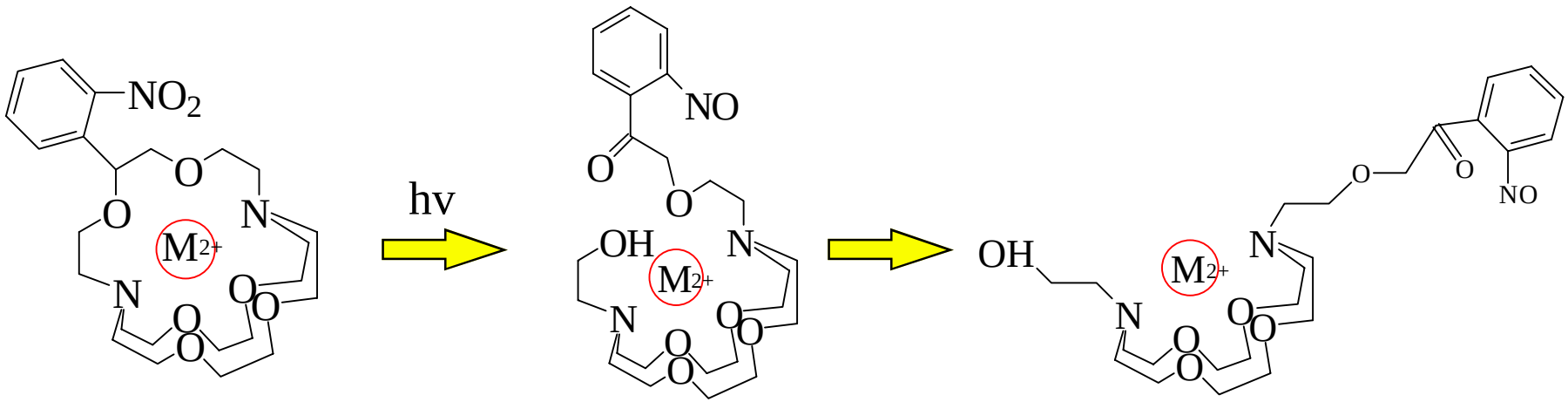


The relative rates of the consecutive steps (1) and (2) change minimally by a factor of 350 between Scheme 1 (monomer) and Scheme 2 (chelate)

PHOTOLYSIS ACCELERATES METAL ION RELEASE BY DECREASING TOPOLOGICAL CONSTRAINTS:

Macrocycle → Linear Chelate

Supporting Evidence: Grell, E. and Warmuth, R. *Pure & Appl. Chem.*, **65**, 373 (1993).
Lehn, J.-M. *et al*. *Helv. Chim. Acta*, **74**, 671 (1991).



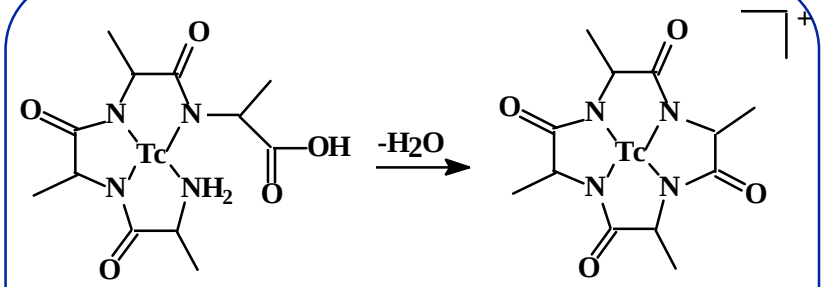
- Developed in research to facilitate concentration jumps
- Ca^{2+} and Mg^{2+} were released in such systems
- Using photolysis, a macrocyclic ligand in a complex can be converted to the corresponding linear ligand, concomitantly releasing the metal ion

Project 1:
Accelerated Binding Rates for Tightly-bound Adducts

LIGAND DESIGN FOR RAPID RING CLOSURE

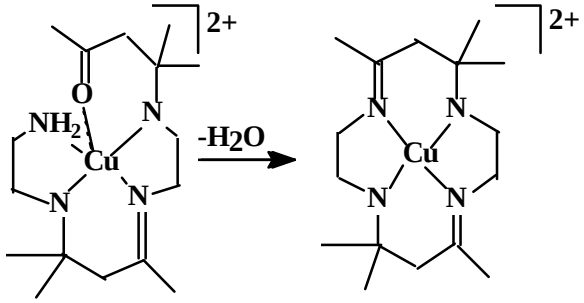
- Ligands must begin as open chain structures to facilitate rapid binding
- Ligands must have reactive groups that close into macrocycles upon chelation to metal ions
- No literature precedent exists for such free ligands; high reactivity of termini complicate design and isolation

Examples of Serendipitously Isolated Open Chain Precursors Bound to Metal Ions that Close into Macrocycles:



Verbruggen, A. et al. *Inorg. Chem.*, **35**, 6240 (1996)

- Amide formation in aqueous solution
- Ring closure slow: 4.91×10^{-3} min^{-1} ($25^{\circ}C$, pH = 4)



Hay, R. W. et al. *Inorg. Chim. Acta*, **246**, 395 (1996)

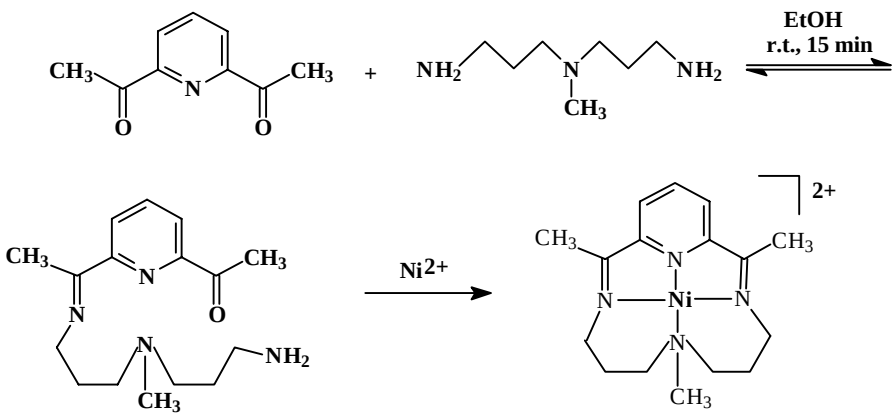
- Base-catalyzed imine formation
- Rapid ring closure occurs via hydroxo-complex: $k_{obs} = 4.98 \times 10^{4}$ s^{-1} ($30.1^{\circ}C$)

VALIDATION OF CONCEPT

METAL TEMPLATED RING CLOSING STUDIES ON A TERNARY COMPONENT SYSTEM

Pre-equilibration of Ligand Components:

Metal Ion Complexation

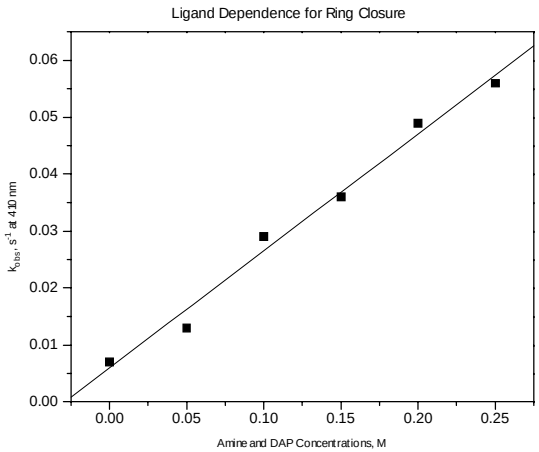


^{1}H NMR, ^{13}C NMR, and IR confirm linear tetradentate generated in situ

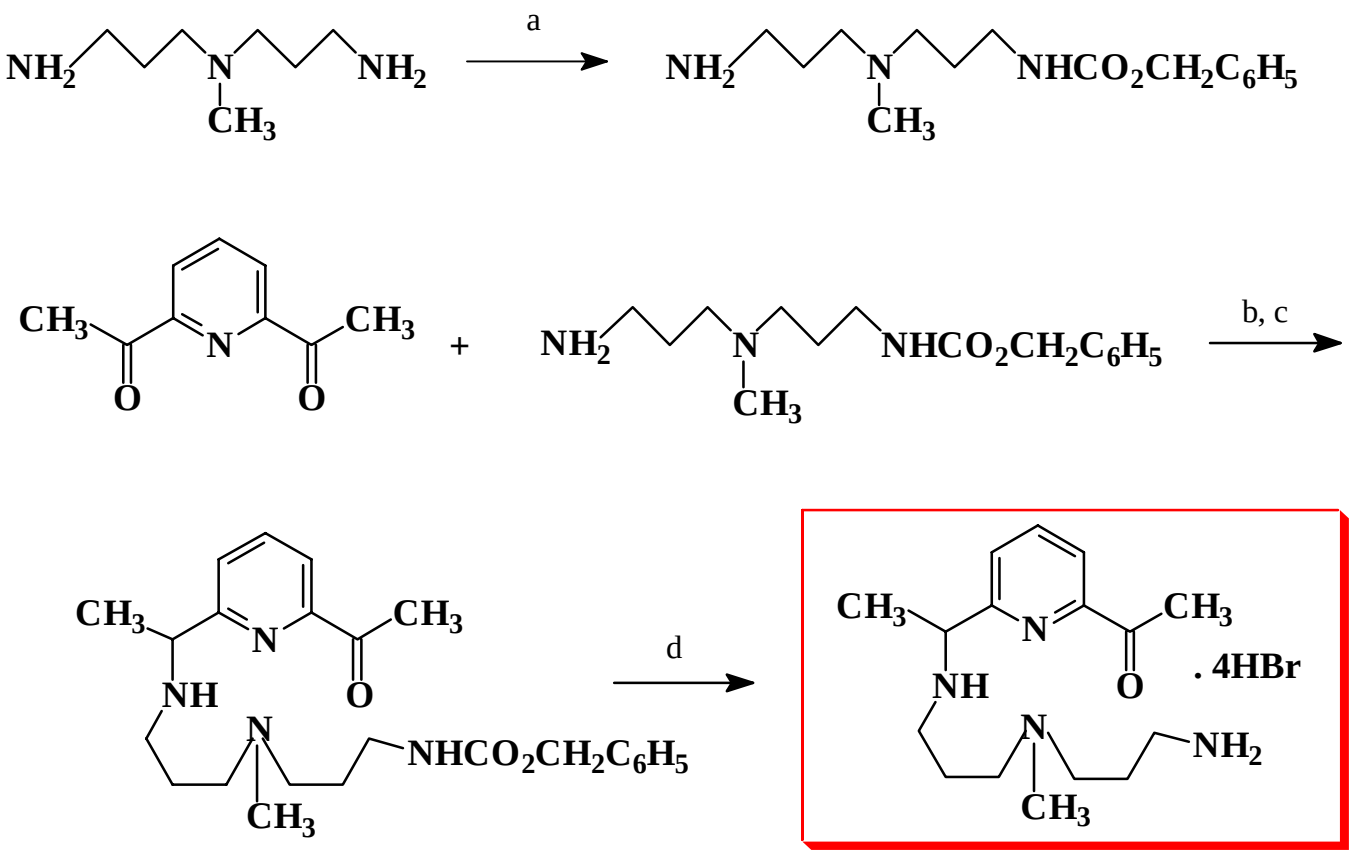
UV/VIS, IR, and MS confirm formation of macrocyclic complex

Kinetic Studies

- Single wavelength UV/VIS scans used to monitor complexation of Ni^{2+} with monocondensed species and subsequent ring closure into complete macrocycle.
- Linear dependence on ligand concentration noted and k, the rate constant of ligand complexation to the metal ion, was found to be 0.21 s^{-1}.
- The rate of consequent ring closure was unobservable, validating the notion that open chain ligands are capable of binding rapidly to form very stable macrocycles.



FIRST GENERATION LIGAND



Structure determined by NMR, IR, MS, and EA.
Overall yield: 60%

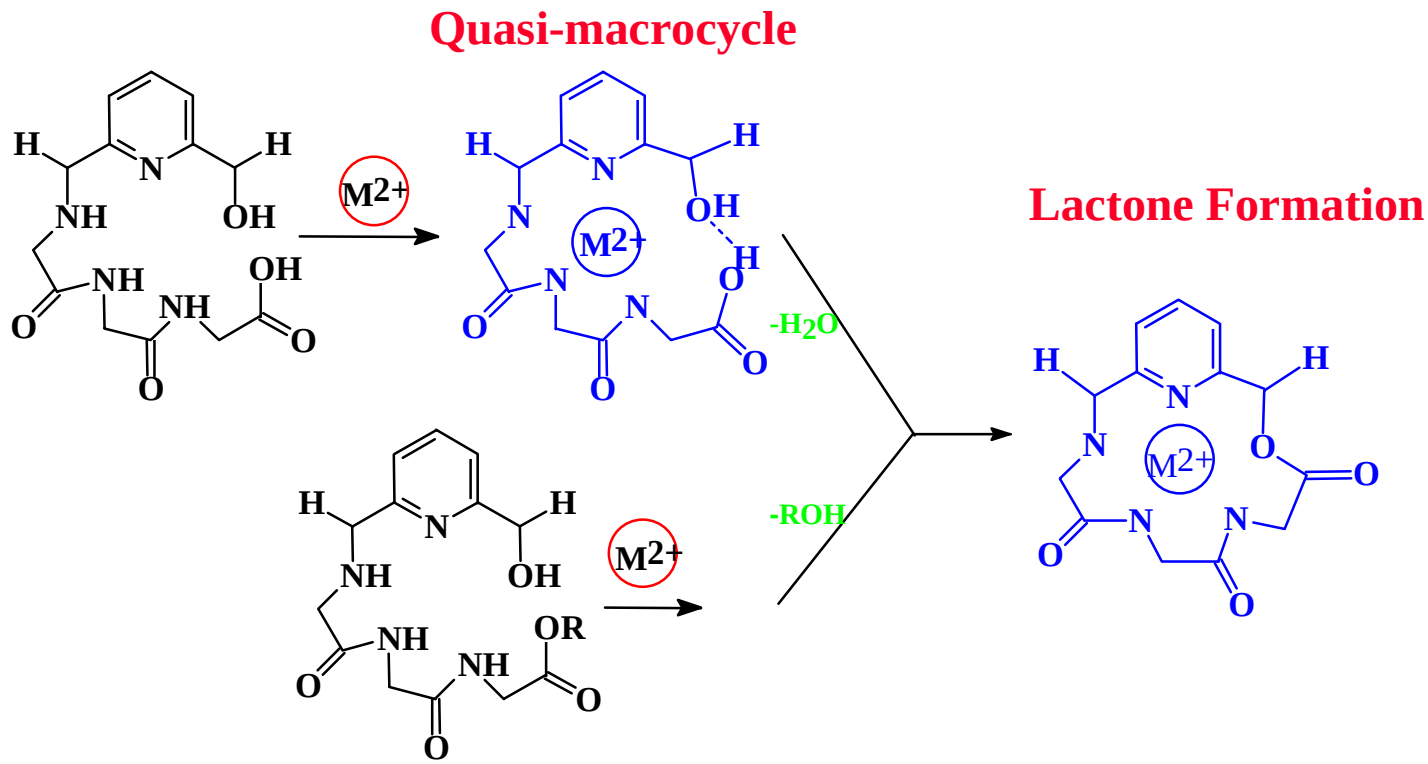
a) Benzylchloroformate, EtOH/H_2O, r.t., 8 h b) EtOH, reflux, 24 h, N_2 c) $NaBH_4$, r.t., 24 h, N_2

d) HBr/HOAc, r.t., 12 h, N_2

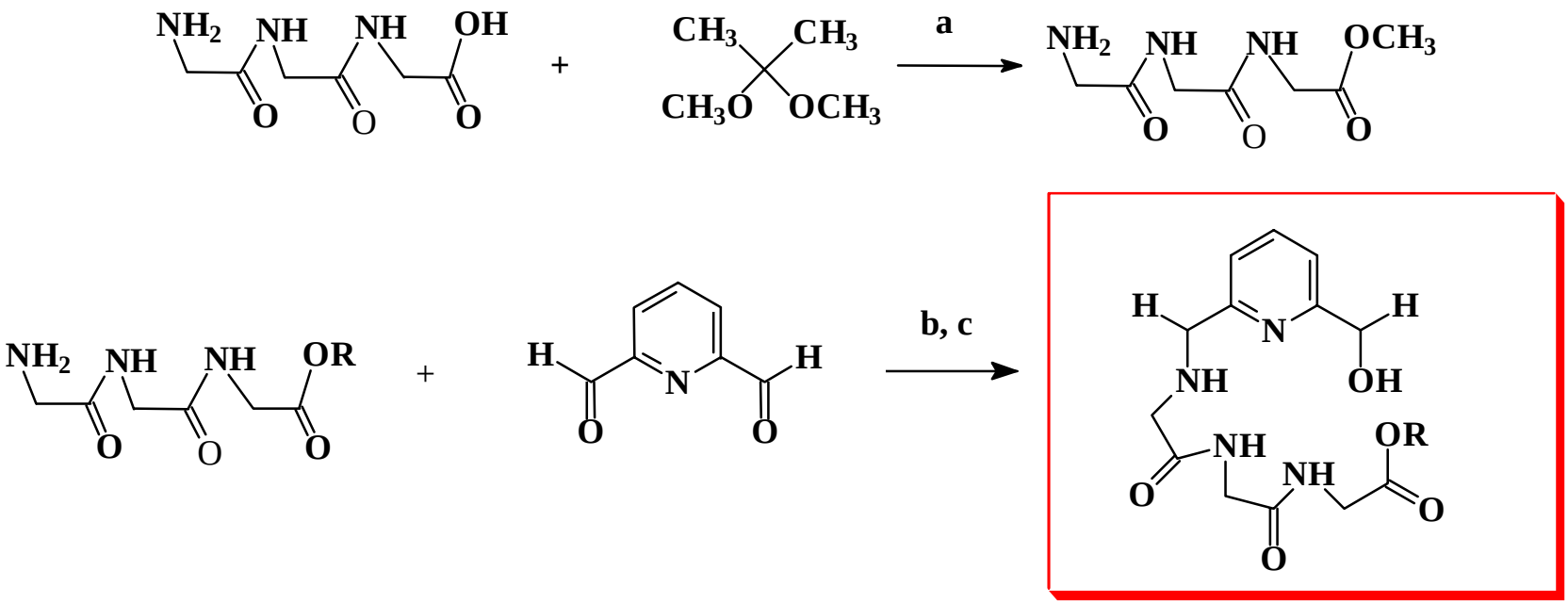
SECOND GENERATION LIGANDS

- **Ionophores bind and transport ions quite selectively in biological systems, undergoing cyclization to quasi-macrocycles through hydrogen bonding only after coordination to suitable metal ions.**

- **Tetradentate ligands designed to mimic ionophores have been fashioned.**



GENERAL SYNTHESIS



R = H: Structure determined by NMR, IR, MS, and EA, overall yield: 65%

R = CH_3: Structure determined by NMR, IR, MS, and EA, overall yield: 40%

a) 12M HCl, r.t., 24 h b) EtOH, reflux, 24 h, N_2 c) $NaBH_4$, r.t. 24 h, N_2

FUTURE DIRECTIONS:

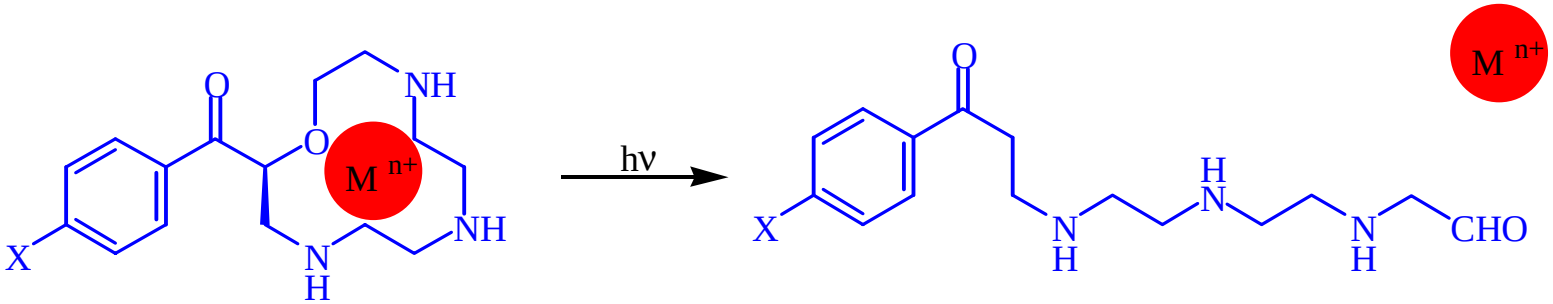
•Potentiometric studies on first and second generation ligands with metal ions are being used to establish species distribution over a range of pHs.

•Complexation studies using both slow (single wavelength scan) and fast (stopped flow) UV/VIS spectroscopic techniques are being patterned to examine the kinetics of complexation and ring closing. IR, NMR, and MS will be used in conjunction with these efforts to elucidate observed processes.

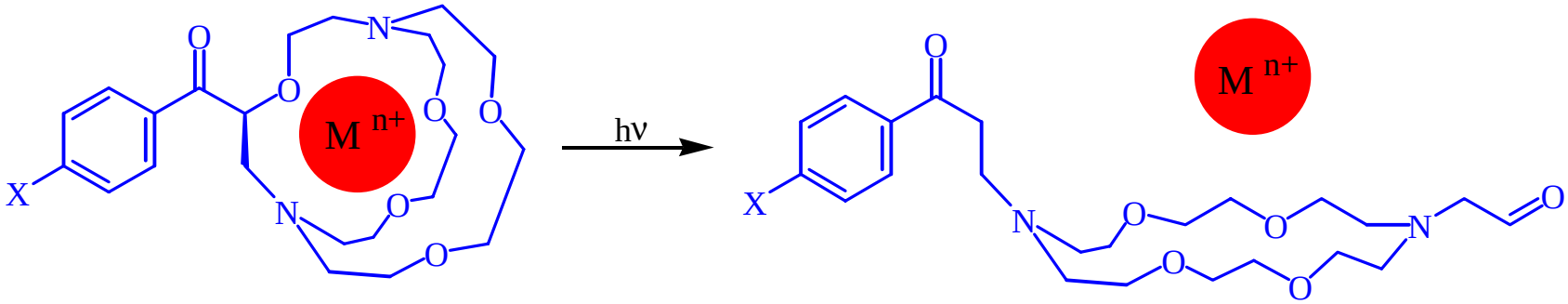
•Given the results from the above studies, the ligands will be “tuned” and third generation ligands will be designed.

Project 2:
Photorelease of Metal Ions from Tightly-bound Adducts

a) Photofragmentation of oxaza-crown phototriggers:

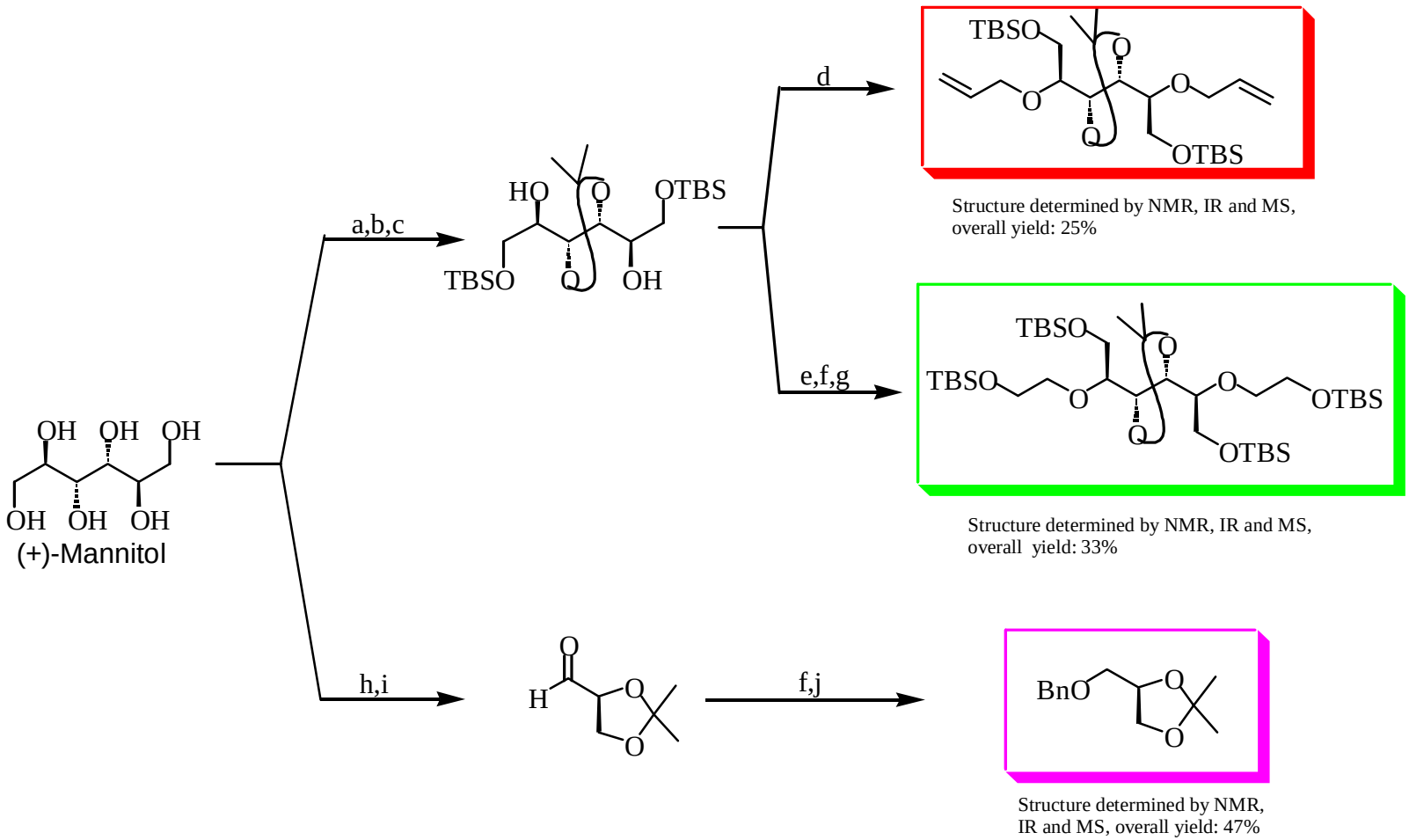


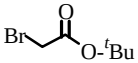
b) Photofragmentation of cryptate phototriggers:

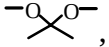


Color code for the structures: **Black** = Synthesized materials
Blue = Materials to be synthesized

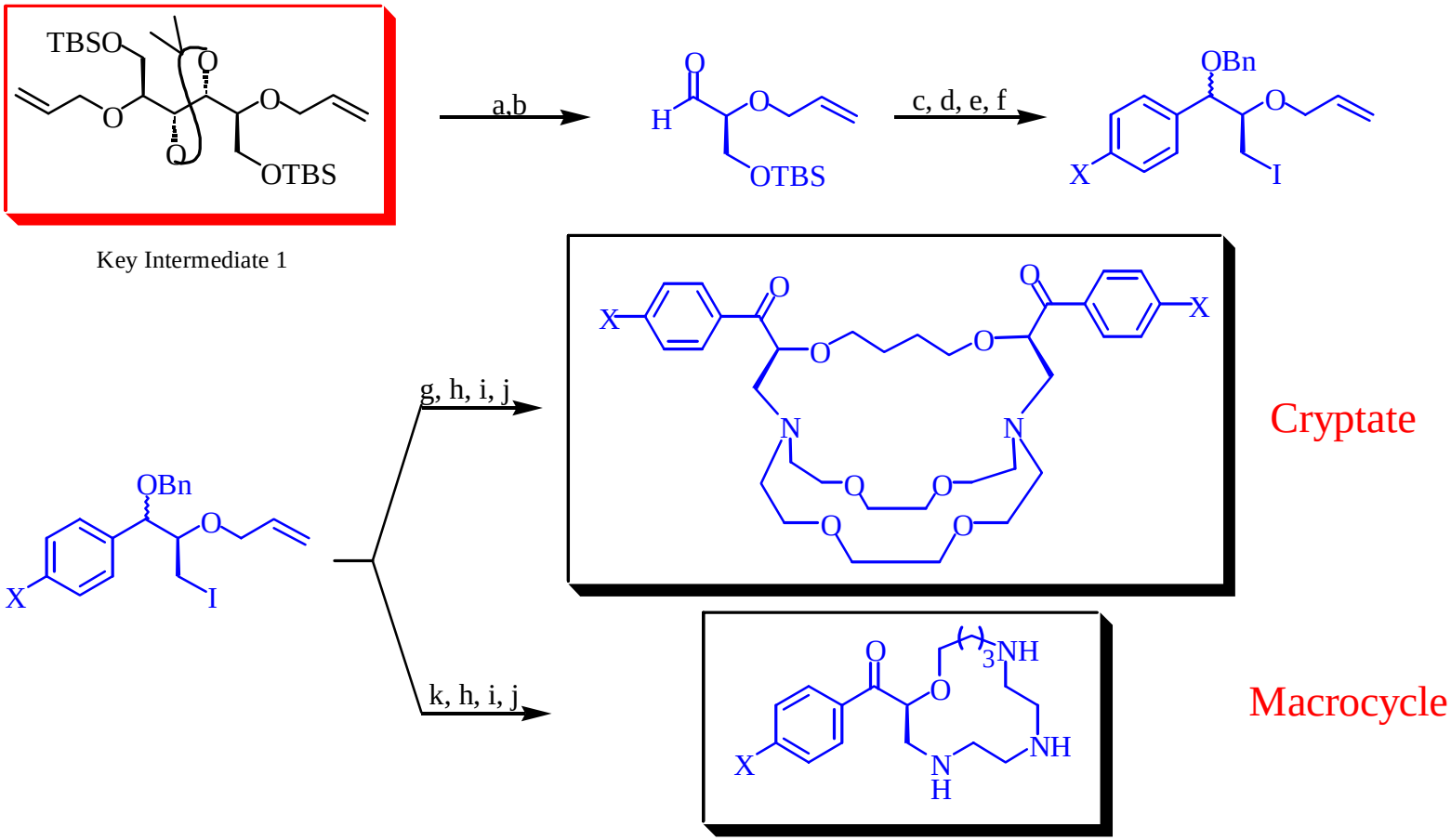
SYNTHESIS OF KEY INTERMEDIATES



a) , H^+ b) 70% HOAc c) TBS-Cl, Et_3N, DMAP d) e)  , NaH, THF f) $LiAlH_4$

g)TBS-Cl, Et_3N, DMAP h)  , $SnCl_2$ i) $NaIO_4$ j) BnBr, KOH

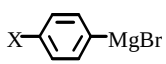
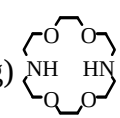
FORMATION OF MACROCYCLES AND CRYPTATES

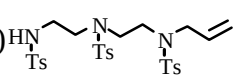


Key Intermediate 1

Cryptate

Macrocycle

a) MeOH, H^+ b) $NaIO_4$ c)  d) BnBr, KOH e) TBAF f) PPh_3, I_2, Imidazole g)  , K_2CO_3

h) Grubb's-Metathesis i) 10% Pd/C, H_2 j) Dess-Martin Periodinane k)  , K_2CO_3

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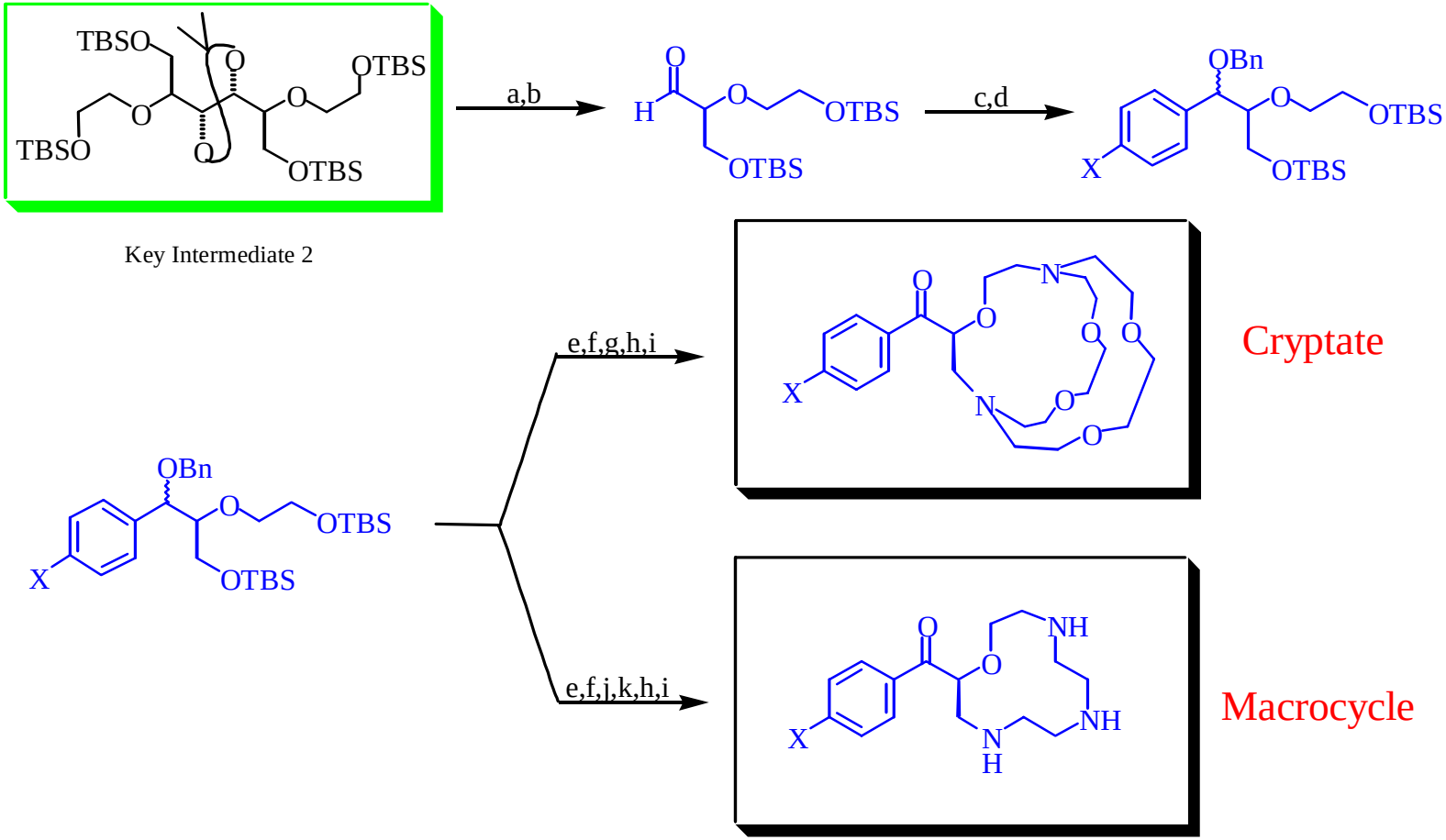
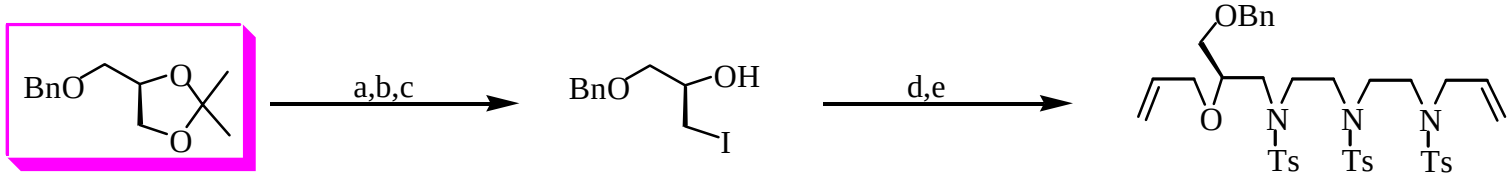


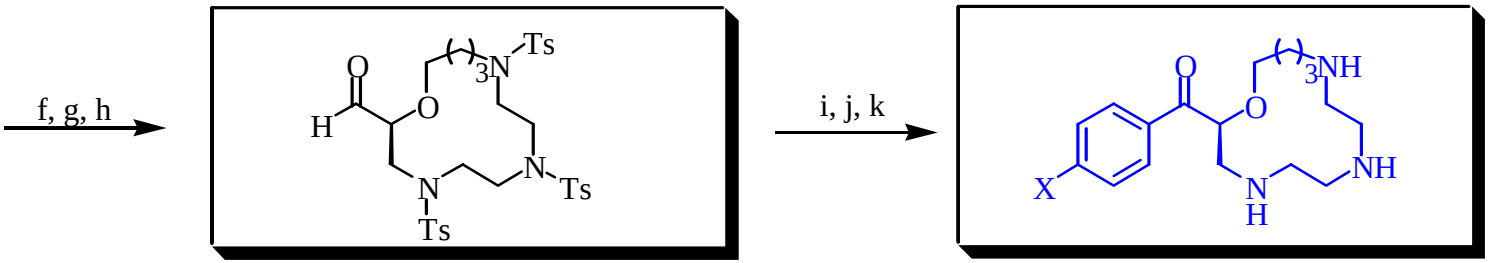
a) MeOH, H^+ b) $NaIO_4$ c) X–⟨benzene⟩–MgBr d) BnBr, KOH e) TBAF f) Ts-Cl, pridine g) ⟨O, O, NH, HN, O, O⟩, K_2CO_3

h) 10% Pd/C, H_2 i) Dess-Martin Periodinane j) NaN(Ts)–⟨chain⟩–N(Ts)–⟨chain⟩–NNa(Ts) k) Detosylation

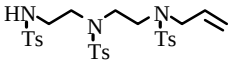
FORMATON OF THE MACROCYCLE

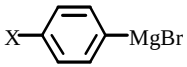


Key Intermediate 3



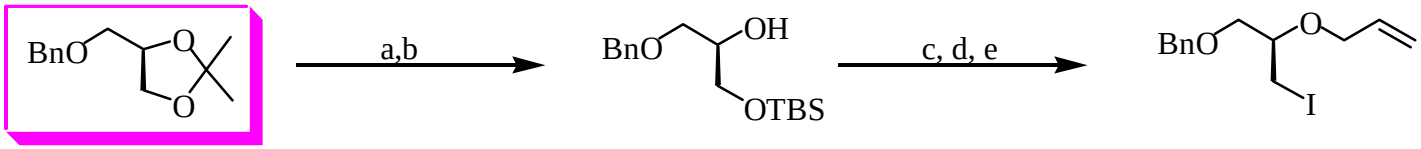
Structure determined by NMR, IR and MS,
overall yield: 9%

a) MeOH, H^+ b) Ts-Cl, pyridine c) NaI, acetone d)  , K_2CO_3 e) , KO^tBu

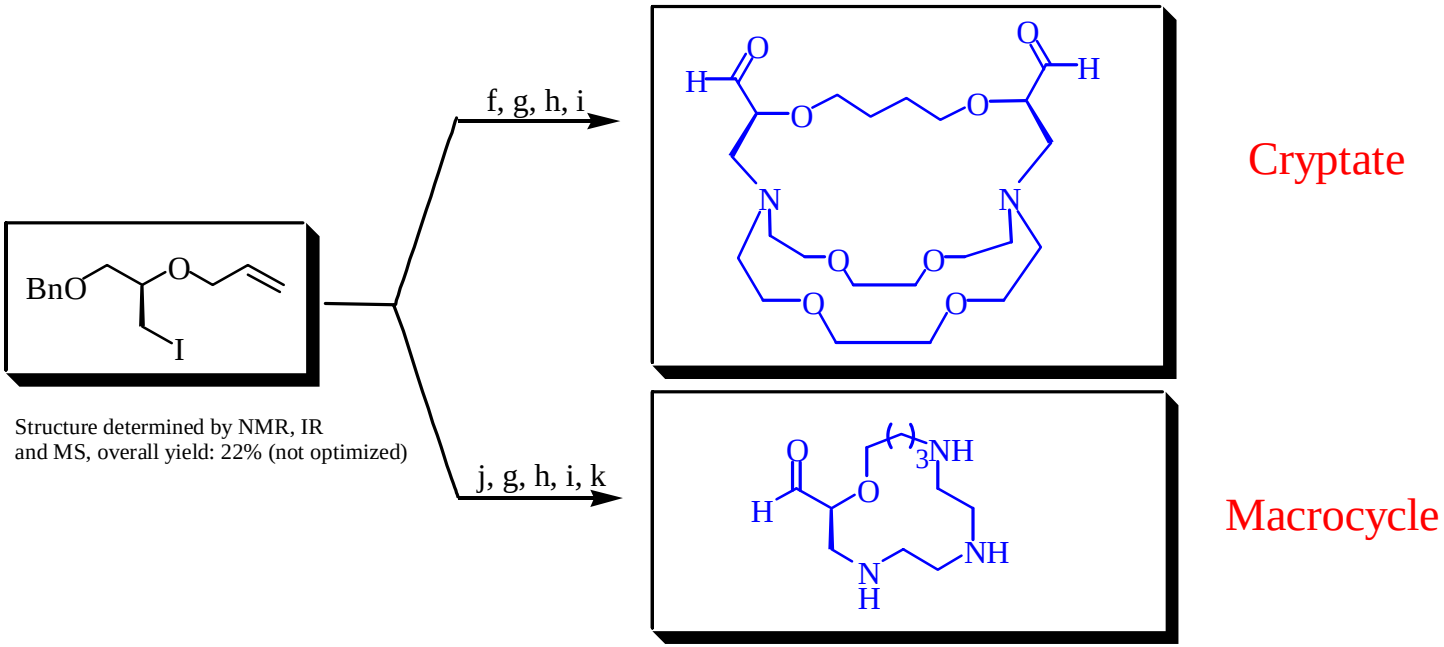
f) Grubb's Metathesis g) 10% Pd/C, H_2 h) Dess-Martin Periodinane i)  j) Oxidation

k) Detosylation

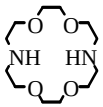
FORMATION OF MACROCYCLES AND CRYPTATES

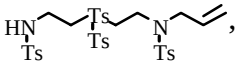


Key Intermediate 3



Structure determined by NMR, IR and MS, overall yield: 22% (not optimized)

a) MeOH, H^+ b) TBSCl, Et_3N, DMAP c) , KO^tBu d) TBAF e) PPh_3, I_2, imidazole f)  , K_2CO_3

g) Grubb's-Metathesis h) 10% Pd/C, H_2 i) Dess-Martin periodinane j)  , K_2CO_3

k) Detosylation

FUTURE DIRECTIONS:

•Irradiation of the oxaza-crown phototrigger in the presence and absence of coordinated metal ions.

•Completion of cryptate synthesis and testing their photochemical behavior in the presence and absence of coordinated metal ions.
•Design, synthesis and exploratory reactions of the oxaza ring of oxaza-crowns and cryptates.

•Attachment of the phototriggerable macrocycles and cryptates to polymer beads for heterogeneous cleaning through column.