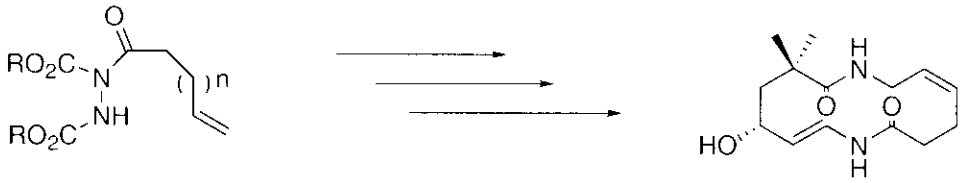
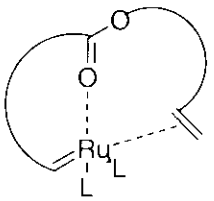
Use of N-N Bond Stereodynamics in Ring-Closing Metathesis to Form Medium-Sized Rings and Macrocycles

Yi Jin Kim and Daesung Lee

Org. Lett. **2004** ASAP



Ring Closing Metathesis



Macrocyclic framework plays a significant role in natural products.

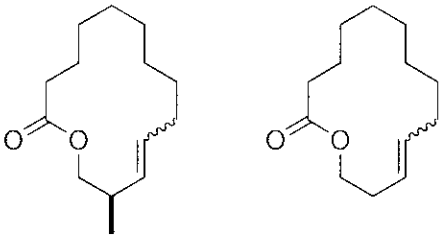
- RCM is one way to gain entry into such systems and has been widely used.

Factors that affect the efficiency of RCM:

i) presence of functional groups that serve to assemble the reacting sites

ii) low steric congestion near double bonds

iii) appropriate distance b/n polar groups and alkenes to be metathesized

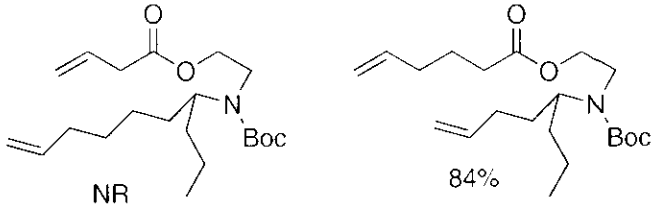


10% 52%

Recently,

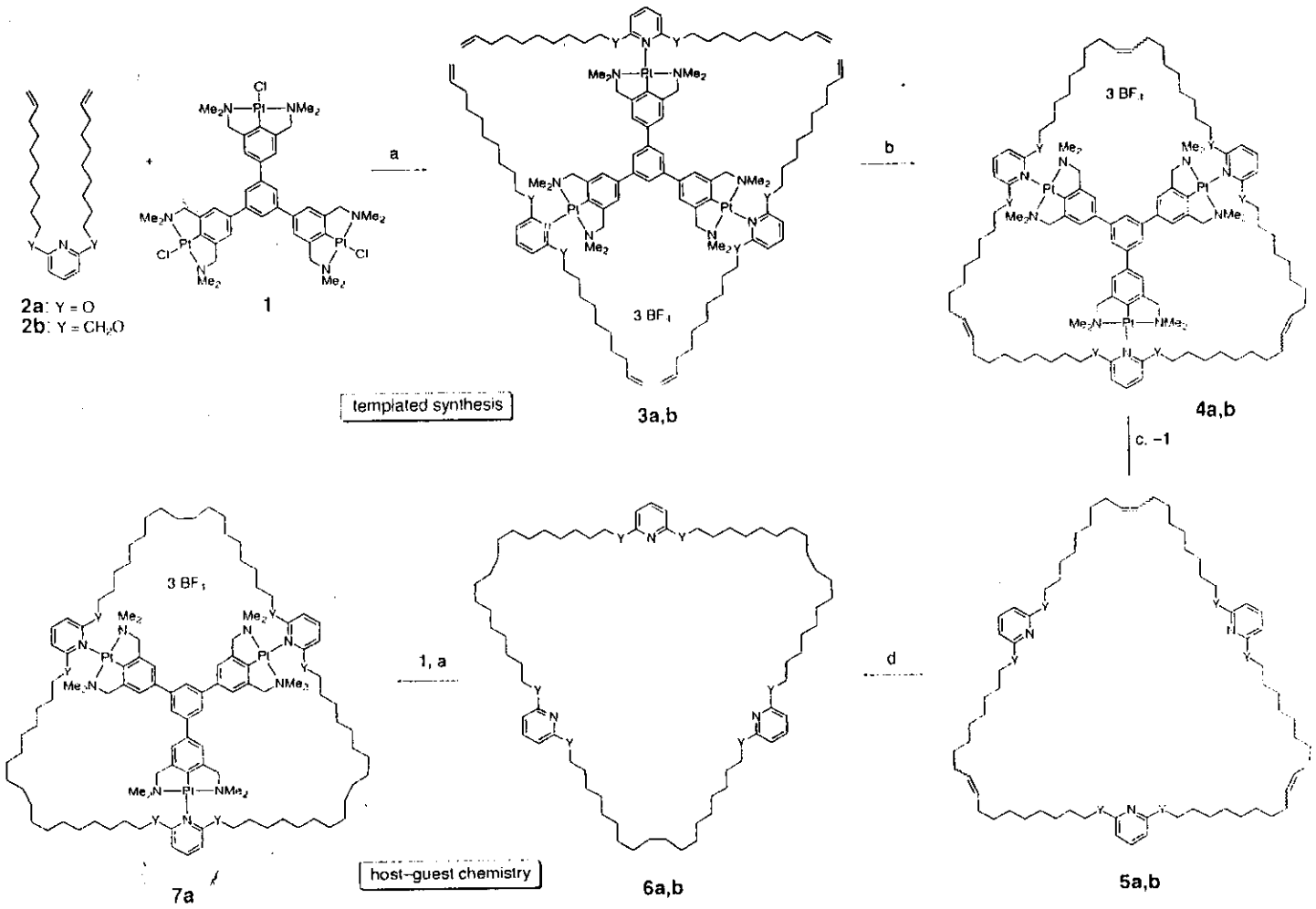
i) template effect

ii) conformational and stereoelectronic constraints



Langemann, K.; Furstner, A. *Synthesis* **1997**, 792.

Shape-Persistent Tricationic Platinum Template



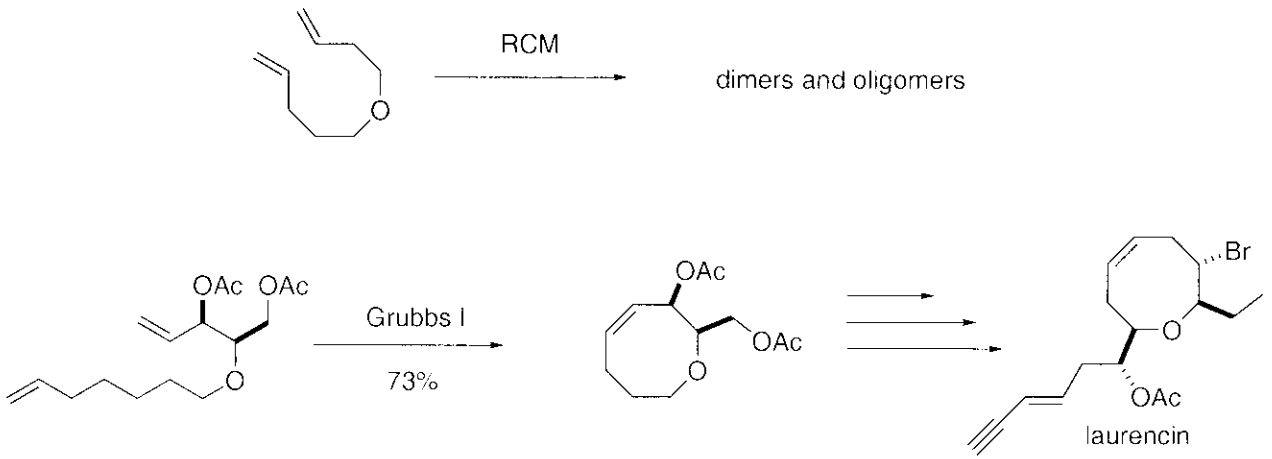
Scheme 1. a) $AgBF_4$, CH_2Cl_2; b) $[Cl_2(PCy_3)_2Ru{=}CHPh]$ 5 mol%, CH_2Cl_2; c) NaCl, H_2O/CH_2Cl_2; d) H_2, Pd/C.

-69 membered macrocycle

-this template synthesis is applied to large heteroatomic crown ether rings.

van Koten, G. *Angew. Chem. Int.* **2003**, *42*, 228.

Stereoelectronic Constraints

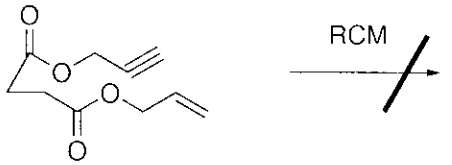


- vicinal stereogenic centers provide acess to conformations where the olefinic chains are gauche which facilitate ring closing -----> gauge effect of 1,2 dioxygen substituents

Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**,*118*,4291.

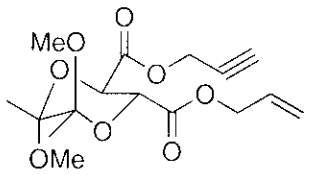
Choy, A.; Crimmins, M. *J. Am. Chem. Soc.* **1999**, *121*, 5653.

Tartrate based Enyne Metathesis

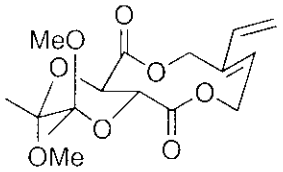


RCM

tartrate linker to facilitate RCM

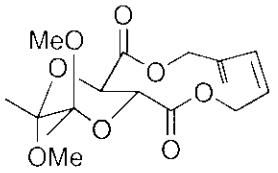


Grubbs 1 or 2



exo

and/or



endo

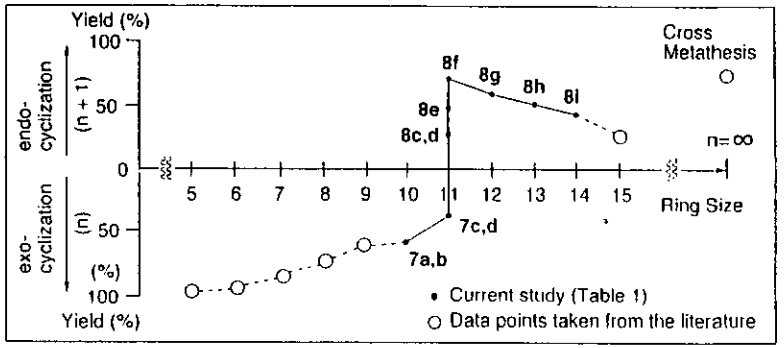
Hansen, E.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582-9583.

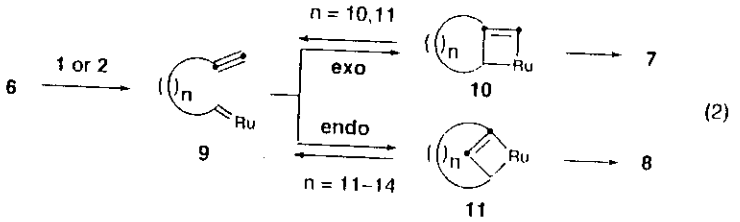
Tartrate based Enyne Metathesis:

Table 1. RCM of Enynes to Form Macrocycles[a]

Entry	Enyne substrate	Macrocycle product exo	Macrocycle product endo	E:Z	Yield (%)[b]
1	6a m = n = 1, X = Y = O, R = H	7a (R = H)[c]		0:1	52
2	6b R = Me	7b (R = Me)[c]		0:1	61
3	6c m = 1, n = 2, X = Y = O, R = H	7c (R = H)[c]	8c (R = H) (1 : 1)	1:1 (2:1 for 8c) (E-8c only)	50 (91)[d] (90)[e]
4	6d R = Me	7d (R = Me)[c]	8d (R = Me) (1 : 1)	1:1 for 8d	92
5	6e m = 1, n = 2, X = NH, Y = O, R = H		8e	1:0	35 (60)[e]
6	6f m = 2, n = 1, X = Y = O, R = H		8f	1:1	70
7	6g m = 2, n = 2, X = Y = O, R = H		8g	0:1	61
8	6h m = 3, n = 2, X = Y = O, R = H		8h	2:1	54
9	6i m = 3, n = 3, X = Y = O, R = H		8i	1:1	55

[a] Reactions performed with 5 mol % of 2 at 0.2 M in refluxing CH_2Cl_2. [b] Isolated yield. [c] The stereochemistry of 7a–d was determined by nOe, and that of 8e–i was determined by coupling constant. [d] RCM under ethylene in refluxing CH_2Cl_2. [e] RCM under ethylene at 25 °C.



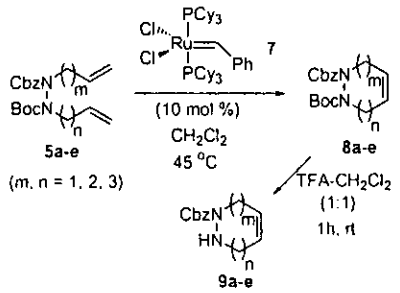


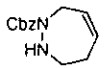
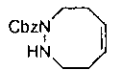
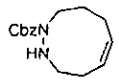
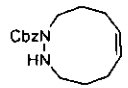
Hansen, E.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582-9583.

Synthesis of Cyclic Hydrazines

- Unlike the 6-membered cyclic hydrazines, only limited synthetic methods are available for 7-10 membered rings.
- 1st. RCM utilizing a 1,2-diaza skeleton

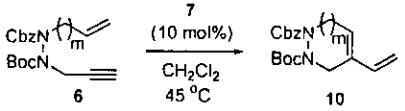
Table 1. Ring-closing metathesis of **5** and deprotection of the Boc in **8**

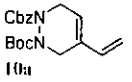
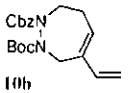
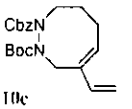


Entry	5	Conditions[a]	Yields (%)[b] 8	9
1	**5a** $m = 1$ $n = 1$	8 h 0.02 M	**8a** (93)	 **9a** (96)
2	**5b** $m = 1$ $n = 2$	8 h 0.02 M	**8b** (98)	 **9b** (80)
3	**5c** $m = 2$ $n = 2$	16 h 0.008 M	**8c** (74)	 **9c** (97)
4	**5d** $m = 3$ $n = 2$	16 h 0.006 M	**8d** (72)	 **9d** (95)
5	**5e** $m = 3$ $n = 3$	16 h 0.005 M	**8e** (70)	 **9e** (84)[c]

[a] Reaction time and concentration for the RCM.
[b] Isolated yields.
[c] Conditions for the deprotection of the Boc in **8e**: $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, CH_2Cl_2.

Table 2. Ring-closing enyne metathesis of **6**

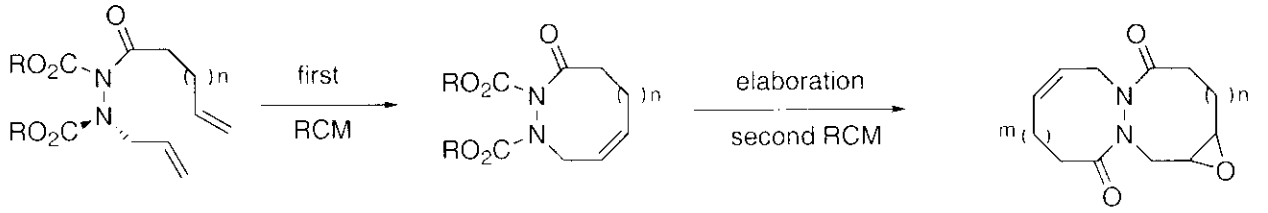


Entry	Substrate	Conditions[a]	Product	Yield (%)[b]
1	**6a** $m = 1$	4 h 0.02 M	 **10a**	99
2	**6b** $m = 2$	8 h 0.02 M	 **10b**	70
3	**6c** $m = 3$	10 h 0.02 M	 **10c**	70

[a] Reaction time and concentration.
[b] Isolated yields.

Hahn, D-W.; Tae, J. *Tetrahedron Lett.* **2004**, *45*, 3757.

Double RCM



N-N functionality in RCM

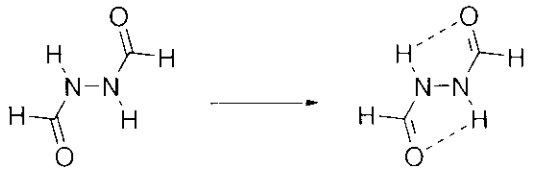
- generate new info about conformational properties of N-N bonds constained in macrocycles

- new route to produce hydrazine derivatives

-resulting double bond in product can serve as a conformationally constrained peptidomimetic

Stereodynamic Behavior of N-N

unsubstituted

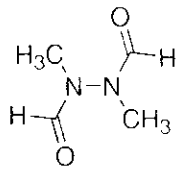


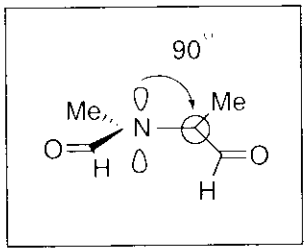
- E_a = 1 kcal/mol

- Planar structure is more stable due to the hydrogen bonding.

- Due to the hydrogen bonding, electron density is withdrawn from the N-lone pair, which reduces repulsive interactions between the nitrogens.

substituted





E_a = ~19 kcal/mol

-E_a = 19 kcal/mol

- No Hydrogen bonding --->
Planar structure is much less stable.

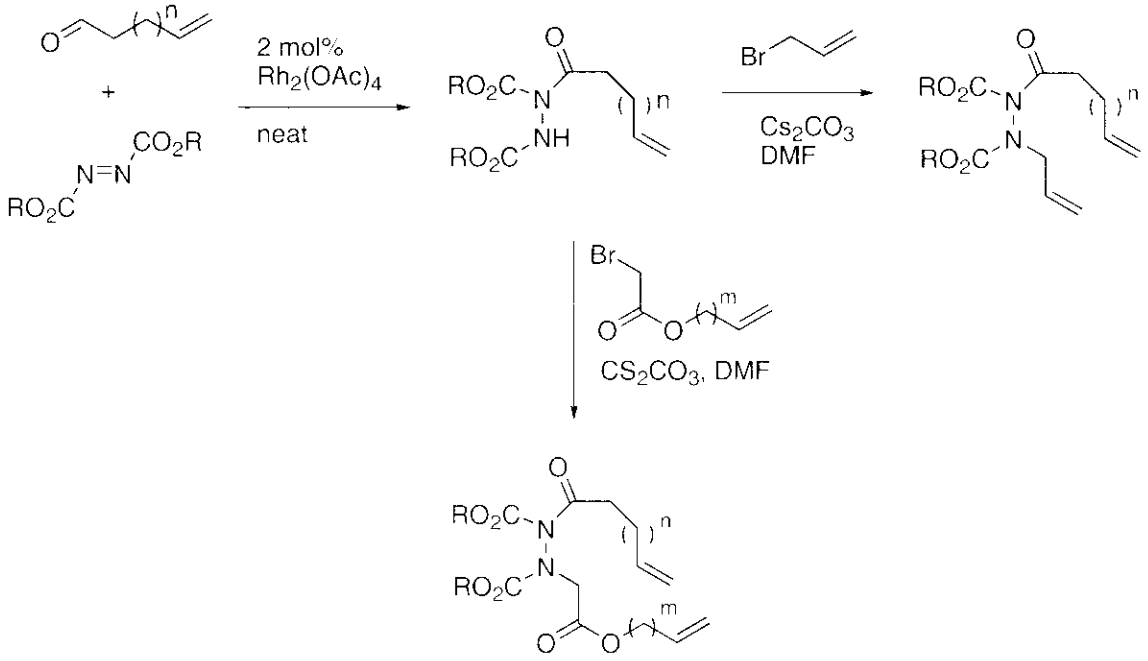
-Much more repulsive interactions between the nitrogens.

- Maintains a CO-N-N-CO near 90°

-vicinal N, N" substituents will arrange in a gauche like arrangement ----> facilitate RCM

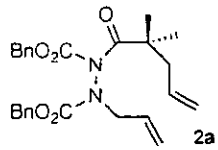
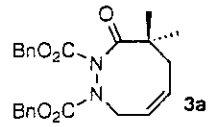
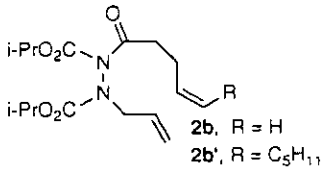
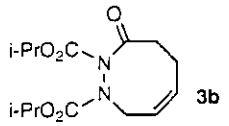
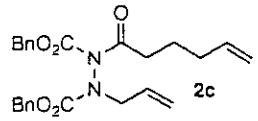
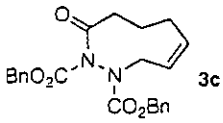
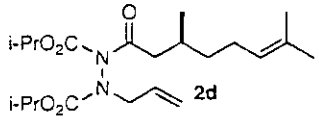
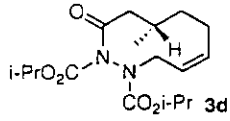
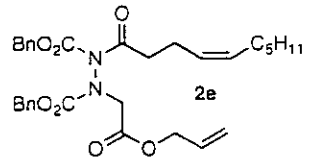
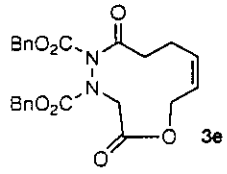
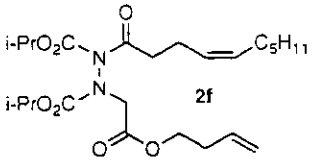
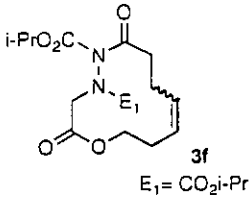
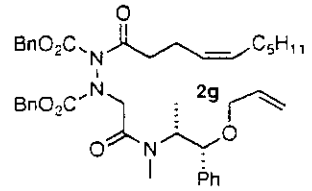
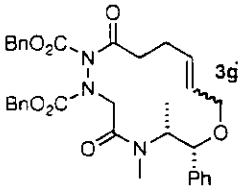
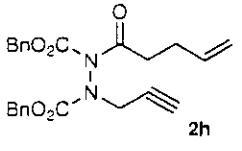
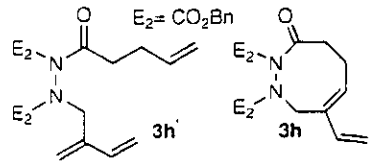
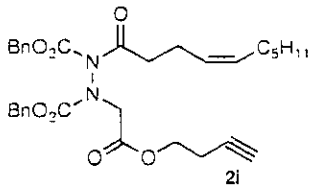
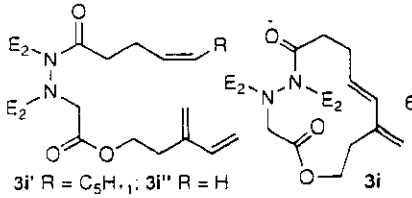
Hormann, R.; Reynolds, C. *J. Am. Chem. Soc.* **1996**, *118*, 9395-9401.

Synthesis of RCM Substrates



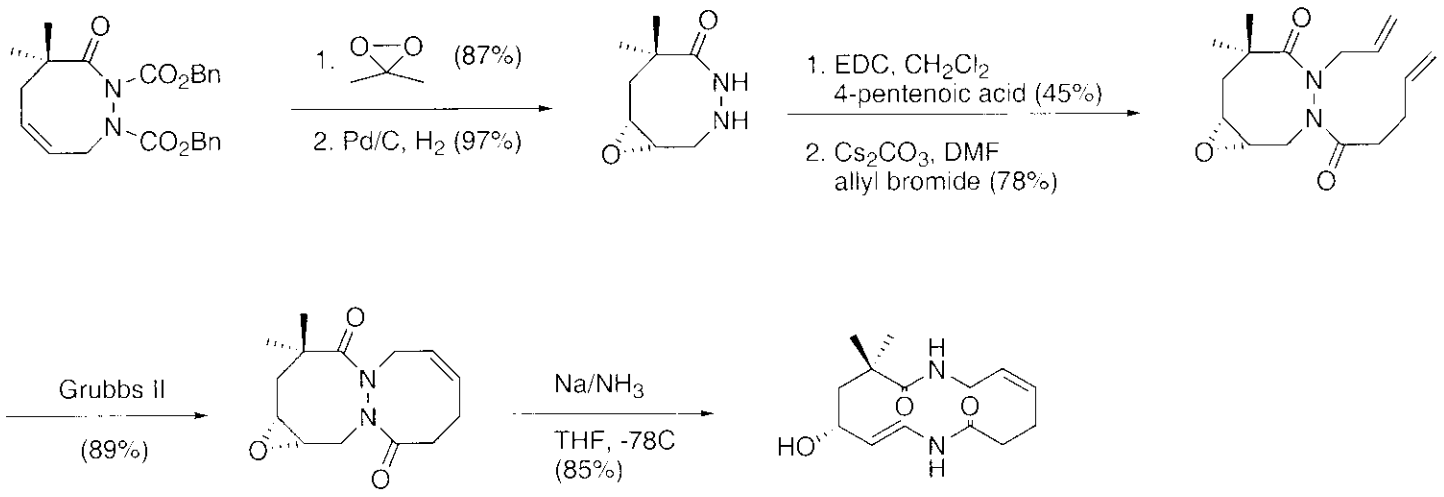
Formation of Cyclic Hydrazines via RCM

Table 1. Formation of Cyclic Hydrazine Derivatives via RCM[a]

entry	RCM substrate (2)	product (3)	yield (%)[b]
1	 2a	 3a	93
2	 2b, R = H 2b', R = C_5H_{11}	 3b	88 (65)[c]
3	 2c	 3c	42
4	 2d	 3d	46
5	 2e	 3e	65
6	 2f	 3f E_1= CO_2i-Pr	72 2:1 *Z:E*
7	 2g	 3g	94 3:2 *Z:E*
8	 2h	 E_2= CO_2Bn 3h' 3h	47[d,e]
9	 2i	 3i' R = C_5H_{11}; 3i'' R = H 3i	60[d,f]

[a] Reactions are carried out in CH_2Cl_2 (0.002 M) with 5−10 mol % of **8** for 2−5 h. [b] Isolated yield. [c] Yield for **2b'**. [d] Reaction under ethylene. [e] 1:1 for **3h**:**3h'**. [f] 2:1:1 for **3i**:**3i'**:**3i''**.

Synthesis of Macrocycle



Future Work:

- Elaboration of final macrocycles
- study of biological performance as cyclic peptide mimics
- nanotube-forming propensity

Summary:

- RCM utilizes the conformational constraints of N-substituted diacyhydrazines.
- RCM of N-substituted diacylhydrazines result in 8-14 membered cyclic hydrazines in good yield.
- New strategy to gain rapid acess to macrocyclic amides from hydrazines