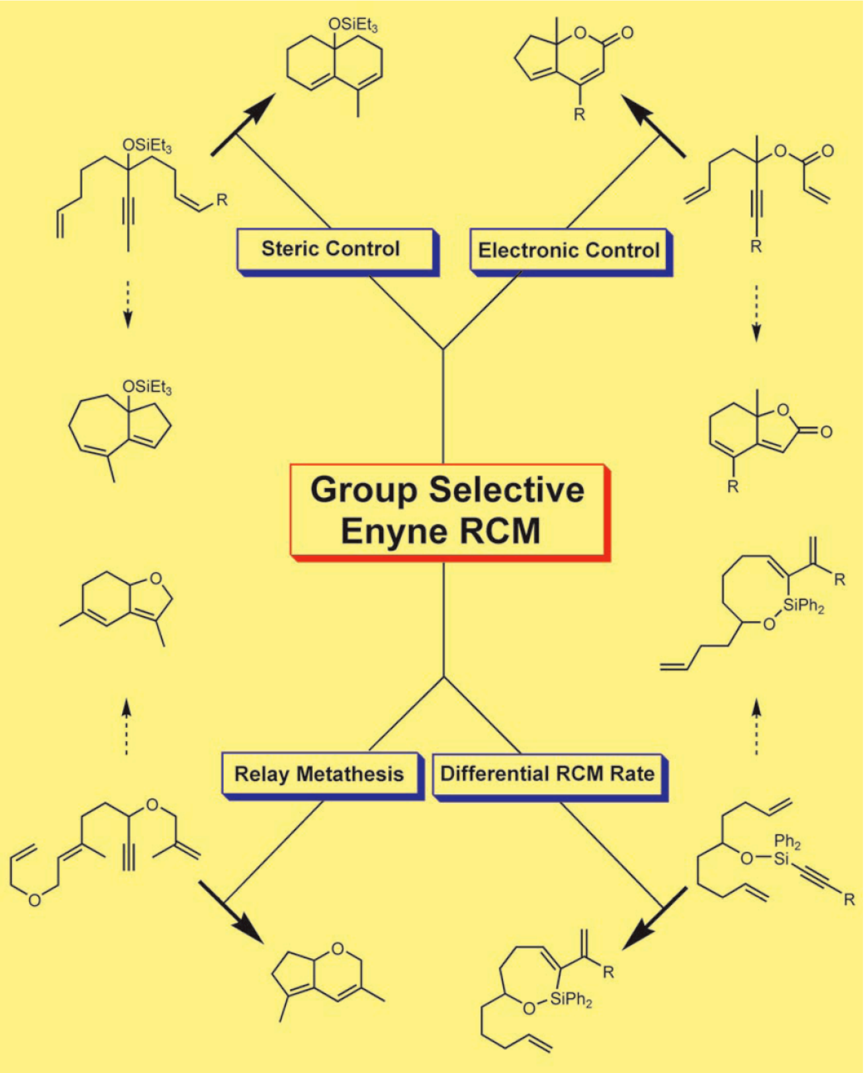
Group Selective Enyne RCM



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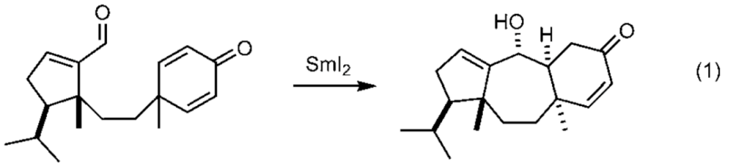
Chemistry A European Journal
Early view

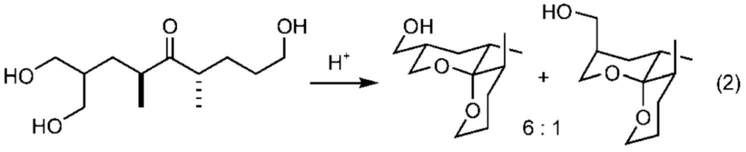
Initial remarks, Nobel and etc...

- Greek words *meta* (change) and *thesis* (position), metathesis is the exchange of two parts of two substances;
- Propene produces ethylene and 2-butene at 725 ^{O}C, 1931;
- Heterogeneous propene disproportionation catalysts: $M(CO)_6$ (Mo or W) on alumina, silica, Re_2O_7 (150 – 500 ^{o}C). Eleuterio et al, 1960-64;
- The Yves Chauvin (Nobel 2005) mechanism: metal-alkylidene + olefin and intermediacy of metallacyclobutanes, 1971;
- First isolated metal-alkylidene complex $[Ta{=}CHBu^t(CH_2Bu^t)_3]$, Schrock (Nobel 2005), 1974;
- Chauvin´s mechanism verified by Schrock with an isolated metal-alkylidene complex and first isolated unimolecular metathesis catalyst $[LnTa{=}CHBu^t]$, Schrock, 1980;
- First isolated Ru=carbene metathesis catalyst complex, air stable, by Robert Grubbs (Nobel 2005), 1992;
- First chiral metathesis catalyst, Mo-alkylidene by Schrock, 1993;
- Commercial catalyst $[Ru{=}CHPh(PCy_3)_2Cl_2]$ active with functional olefins, Grubbs, 1995;
- First very efficient asymmetric metathesis reaction by Schrock and Hoveyda, 1998;
- Second generation Grubbs catalyst $[Ru{=}CHPh(PCy_3)(L)Cl_2]$ with a diaminocarbene ligand, air stable, more reactive and commercial, Grubbs et al, 1999;
- 2nd generation chiral version, Grubbs, 2001.

Introduction

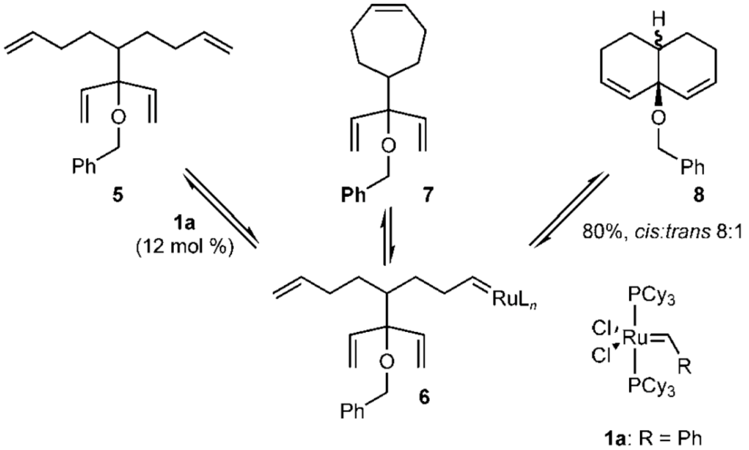
The group-selective transformations concept.





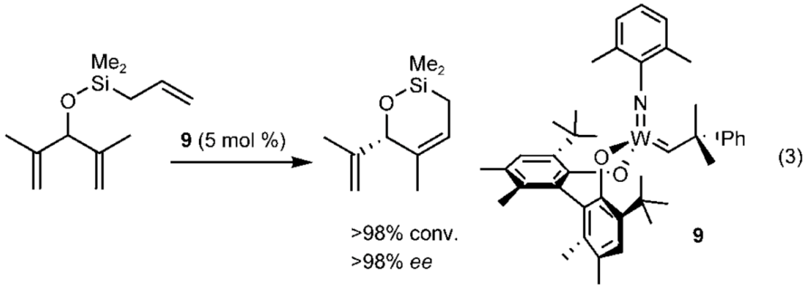
Nguyen, Seifert, Mowrey, Lee, *Org. Lett.* **2002**, 3959.
Schreiber and Wang, *JACS*, **1985**, 5503.

The reversibility of metathesis reactions as a tool for group-selection.



Lautens and Hughes, *Angew. Chem.* **1999**, 160;
Angew. Chem. Int. Ed. **1999**, 129.

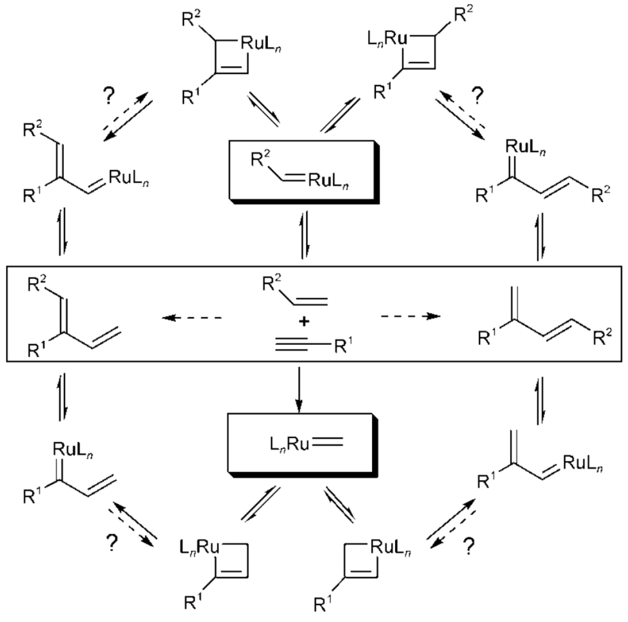
Asymmetric diene RCM reaction.



Tsang, Hultzsch, Alexander, Bonitatebus, Schrock and Hoveyda, *JACS* **2003**, 2652.

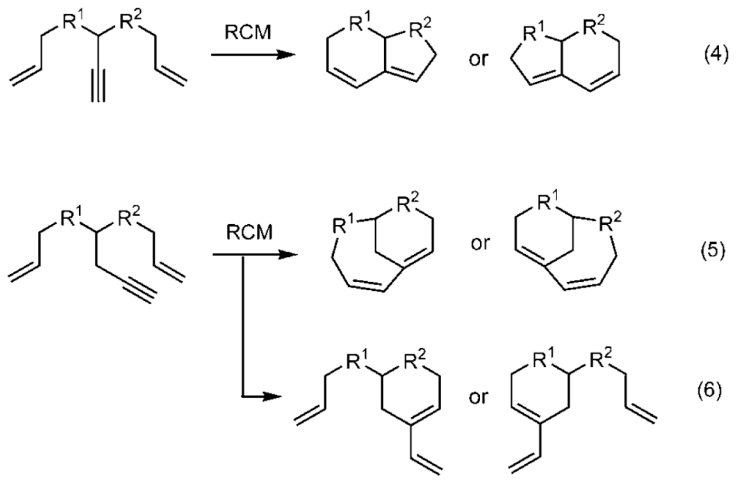
When concerning Enyne RCM...

...product distribution is still a challenge...



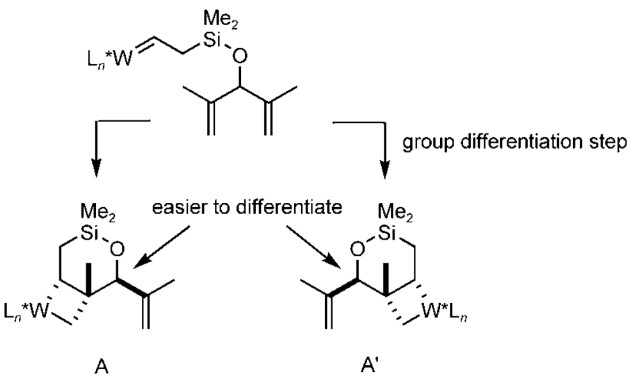
- Diene metathesis regenerates the initial functionality and is reversible in nature.
- Enyne metathesis forms a 1,3-diene from the alkene + alkyne reaction.
- Reversibility is assumed but not confirmed because of competing pathways with multiple intermediates.

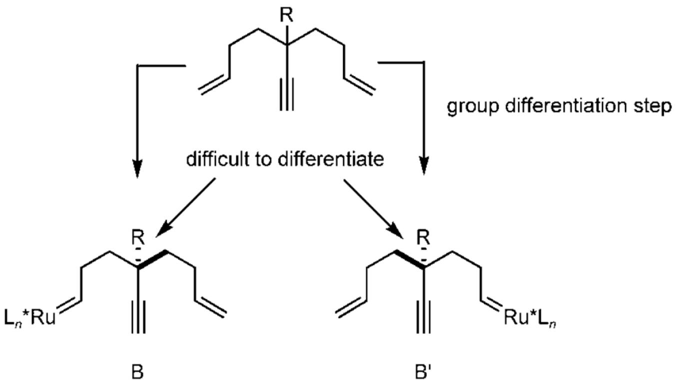
Desymmetrization of dienynes systems.



- Tandem bond-forming allows for construction of conjugated double bonds.
- Fused (4) and bridged bicycles (5) and monocyclic structures (6).
- The asymmetric enyne version of eq. 3 is more difficult to accomplish and it prevents advancement of the method.

The asymmetric desymmetrization on enyne metathesis:



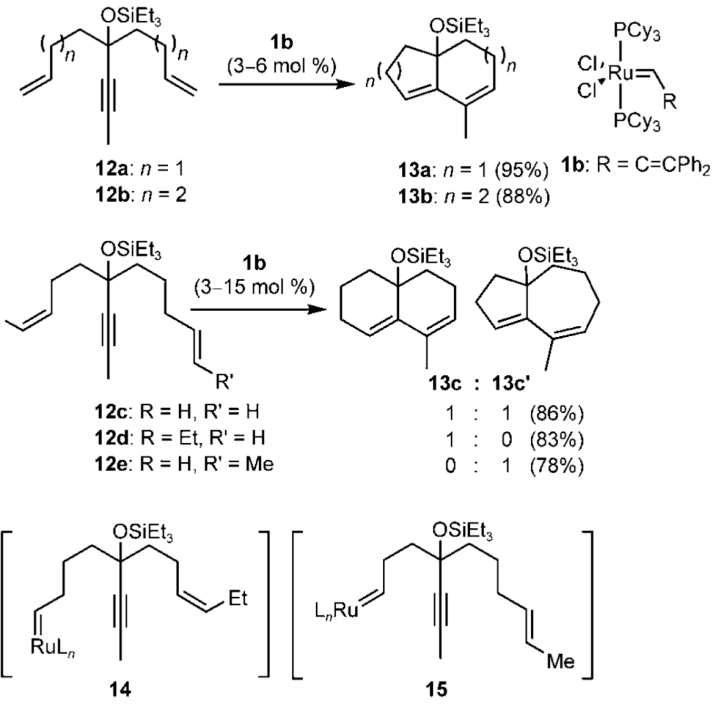


- Differentiation between B and B’ in a tandem enyne RCM can expand the scope of metathesis.

Four strategies have been investigated:

1. Steric perturbation;
2. Electronic perturbation;
3. Relay metathesis;
4. Ring closure rate-based differentiation.

1. Steric perturbation.



12a: $n = 1$
12b: $n = 2$

13a: $n = 1$ (95%)
13b: $n = 2$ (88%)

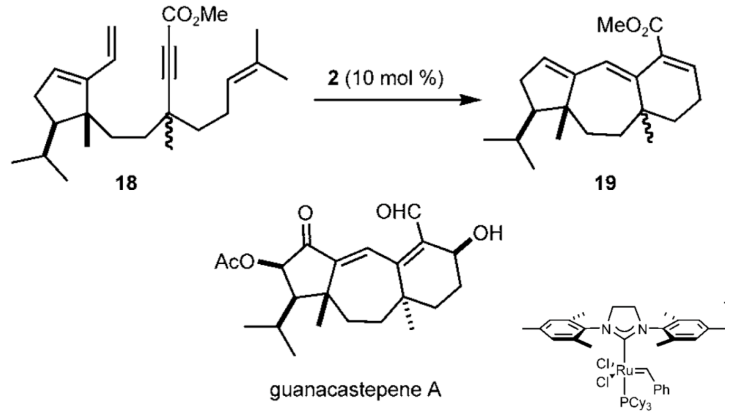
1b: R = C=CPh$_2$

12c: R = H, R' = H — 1 : 1 (86%)
12d: R = Et, R' = H — 1 : 0 (83%)
12e: R = H, R' = Me — 0 : 1 (78%)

14 **15**

Kim, Bowden and Grubbs, *JACS*, **1994**, 10801;
Kim, Zuercher, Bowden and Grubbs, *JOC*, **1996**, 1073.

Formation of the guanascastepene skeleton



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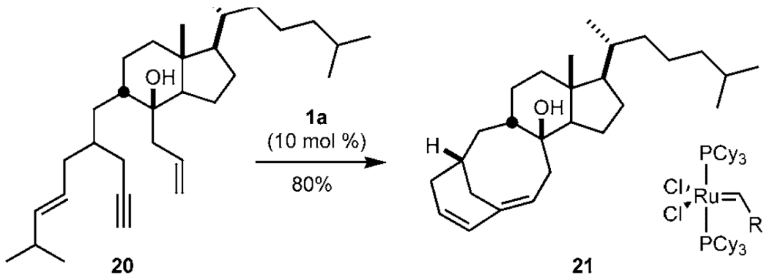
guanacastepene A

Boyer, Hanna and Ricard, *Org. Lett.* **2001**, 3095.

Rare bridged bicycle with a bridgehead double bond



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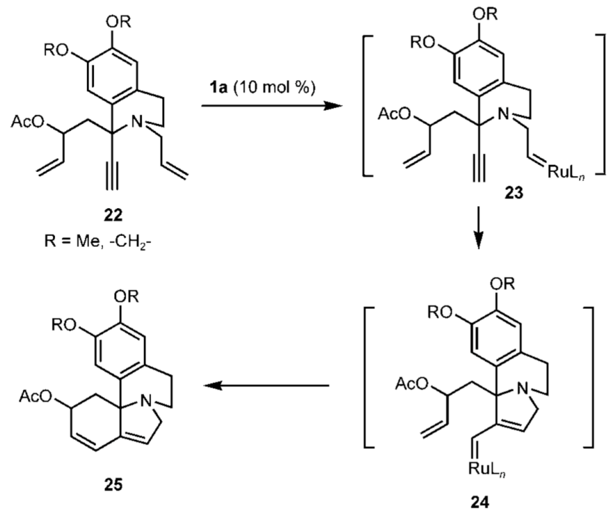
21

1a: R = Ph

Garcia-Fandino, Codesido, Sobarzo-Sanchez, Castedo and Granja, *Org. Lett.* **2004**, 193.



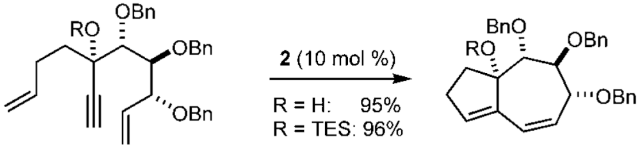
22

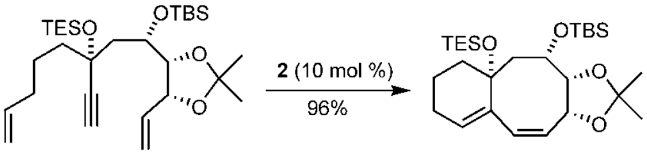
R = Me, -CH$_2$-

23

24

25



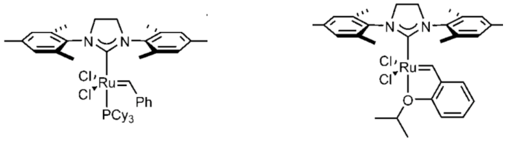


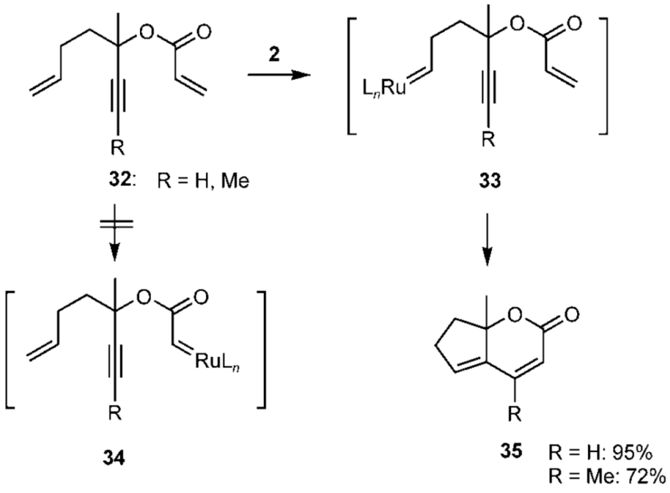
Mori et al, *Org. Lett.* **2003**, 2323.
Hatakeyama et al, *THL*, **2003**, 8047.
Hanna et al, *Org. Lett.* **2004**, 1817.

2. Electronic perturbation.

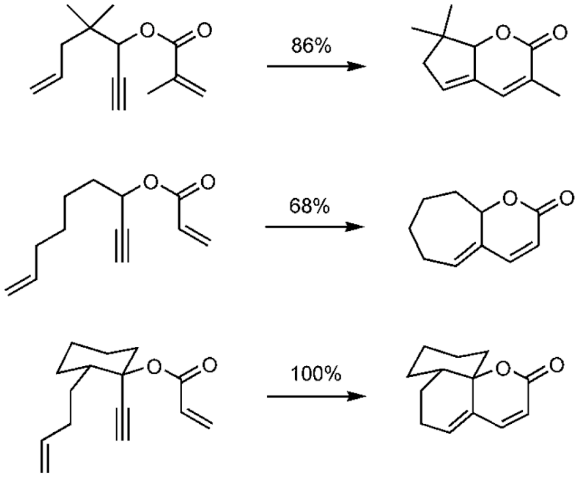
Carbenes derived from α,β-unsaturated carbonyl are less stable.

Chatterjee, Morgan, Scholl and Grubbs, *JACS*, **2000**, 3783.





Choi and Grubbs, *CC*, **2001**, 2648.

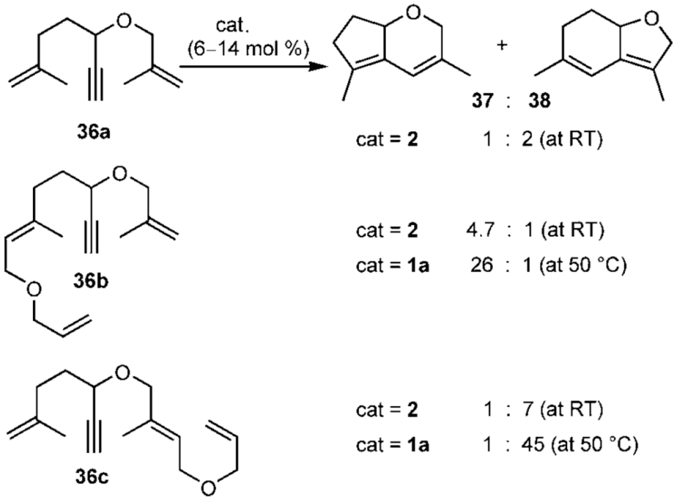


Choi and Grubbs, *CC*, **2001**, 2648.

3. Relay metathesis.

Design of a substrate that propagates the ruthenium carbenoid to a less reactive alkene.

- Atypical alkylidene intermediaries: 17a, 17b and 17c.
- Possibilities.
- Drawbacks.



36a → **37** : **38**

cat = **2** 1 : 2 (at RT)

36b

cat = **2** 4.7 : 1 (at RT)

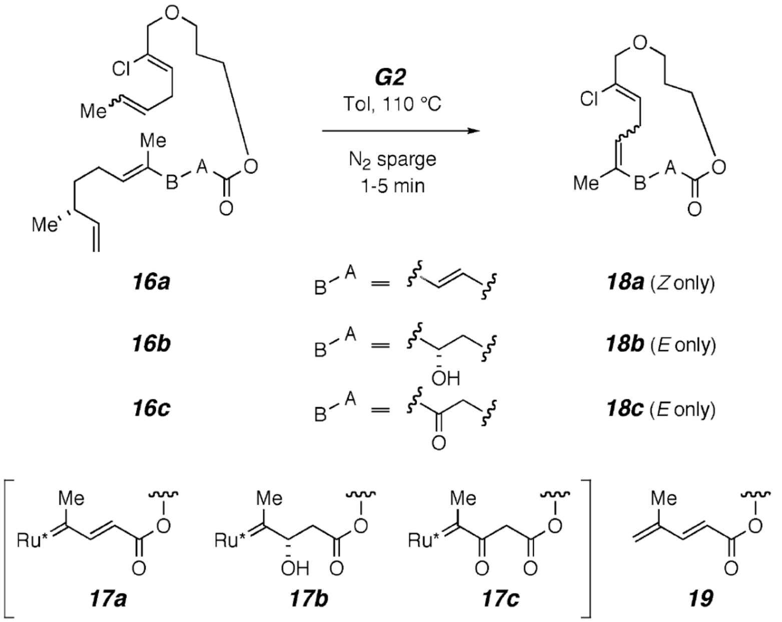
cat = **1a** 26 : 1 (at 50 °C)

36c

cat = **2** 1 : 7 (at RT)

cat = **1a** 1 : 45 (at 50 °C)

Hoye, Jeffrey, Tennakoon, Wang and Zhao, *JACS*, **2004**, 10210.



G2
Tol, 110 °C
N_2 sparge
1-5 min

16a B–A = ***18a*** (*Z* only)

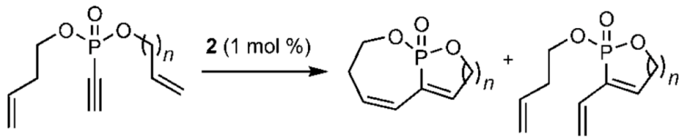
16b B–A = ***18b*** (*E* only)

16c B–A = ***18c*** (*E* only)

[***17a*** ***17b*** ***17c***] ***19***

4. Ring closure rate-based differentiation.

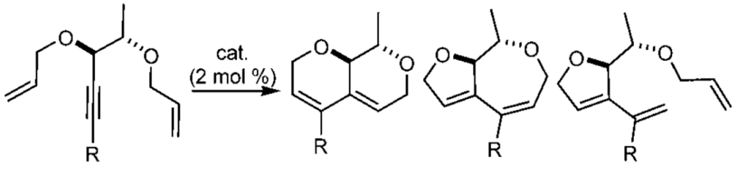
Ring closure rate, rather than rates of initiation influenced by steric and electronic factors, would govern the selectivity of a tandem enyne RCM.



39a: $n = 1$
39b: $n = 2$
39c: $n = 3$

40a:**40a'** (2.9:1): $n = 1$, 89%
40b:**40b'** (4.2:1): $n = 2$, 94%
40c (1.0:0): $n = 3$, 83%

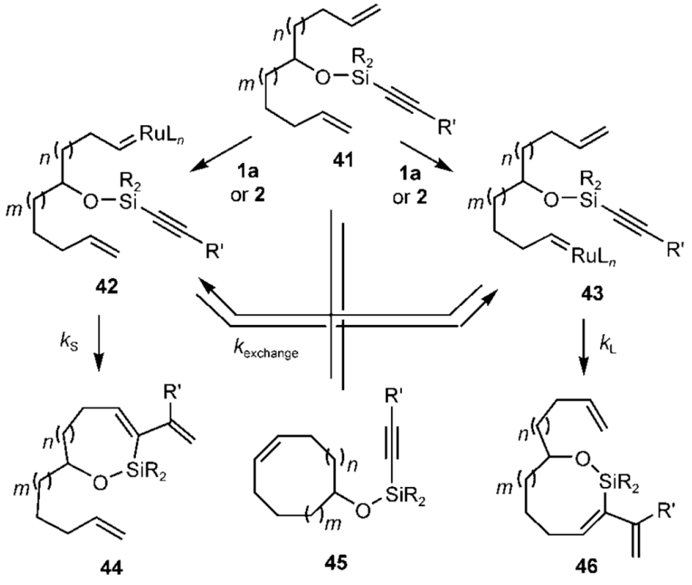
Timmer, Ovaa, Filippov, van der Marel and van Boom, *THL*, **2001**, 8231.



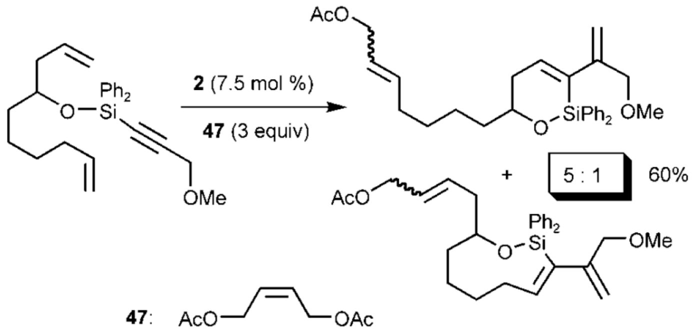
R = H	**1a**	60%	8%	16%
	2	63%	19%	trace
R = C_4H_9	**1a**	62%	trace	23%
	2	64%	21%	trace

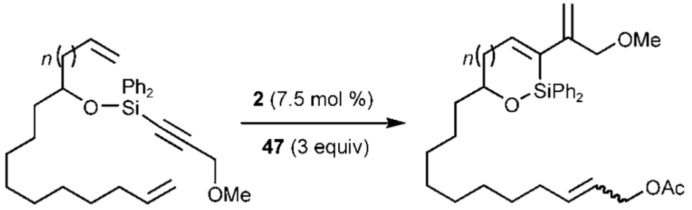
Wu, Madhushaw, and Liu, *JOC*. **2003**, 7889.

Pre-equilibrium of alkylidene intermediates prior to ring closure



Group-selective RCM of dienynes with substantially different tether lengths.



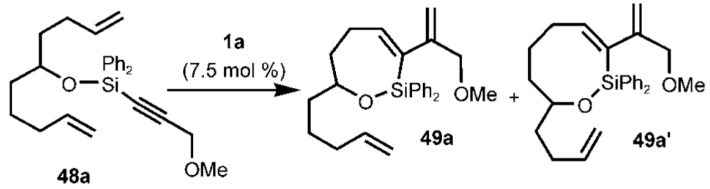


n = 1 only 81%

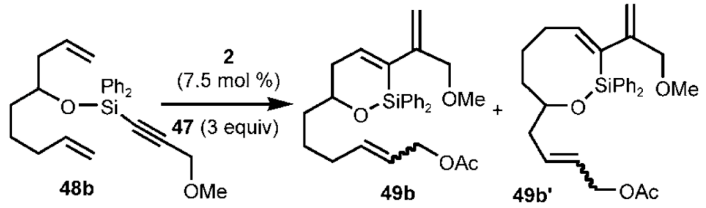
n = 3 24 : 1 77%

Maifeld, Miller and Lee, *JACS*. **2004**, 12228.

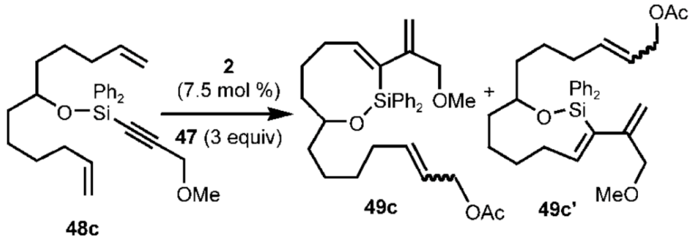
Concentration-dependent group selectivity profile.



Concentration	49a : 49a'	Yield (%)
0.01	6.4 : 1	80
0.07	25 : 1	74
neat	>50 : 1	79



Concentration	49b : 49b'	Yield (%)
0.001	1.1 : 1	80
0.3	3 : 1	79
neat	13.3 : 1	85



Concentration	49c : 49c'	Yield (%)
0.001	2.8 : 1	73
0.1	20 : 1	71
neat	>50 : 1	79

Final Remarks

- Dienynes systems suffer from selectivity issues in RCM reactions;
- Four main strategies were gathered in this concept paper;
- The steric and electronic pertubations are the earliest strategies, although the later has not been as investigated as the former;
- Relay and rate-based ring closure broadens the possibilities of applications.