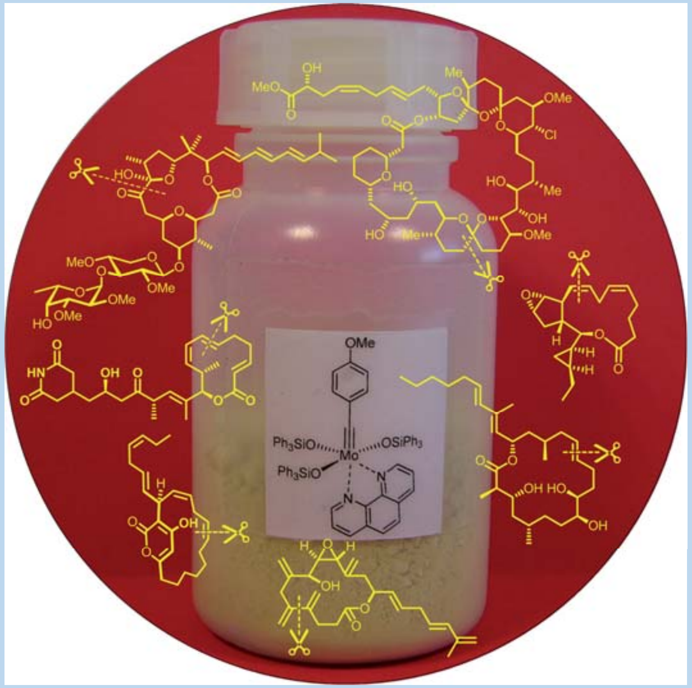
DUDOGNON Yohan

28 04 2016

Bibliographic seminar

The rise of Alkyne Metathesis and its application in Total Synthesis



Introduction - Historic development

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Catalyst Development

1. Lessons learnt from Schrock-Type Tungsten Alkylidynes
2. Molybdenum-Based Catalyst
3. From Nitrile/Alkyne Cross-Metathesis to Improved Catalyst Design
4. From the Glovebox to the Benchtop: Catalysts with Improved Activity and Stability
5. Structural Considerations and Adaptable Electronic Features
6. Factors Influencing the Catalyst Lifetime
7. Molecular Sieves as Butyne Scavengers

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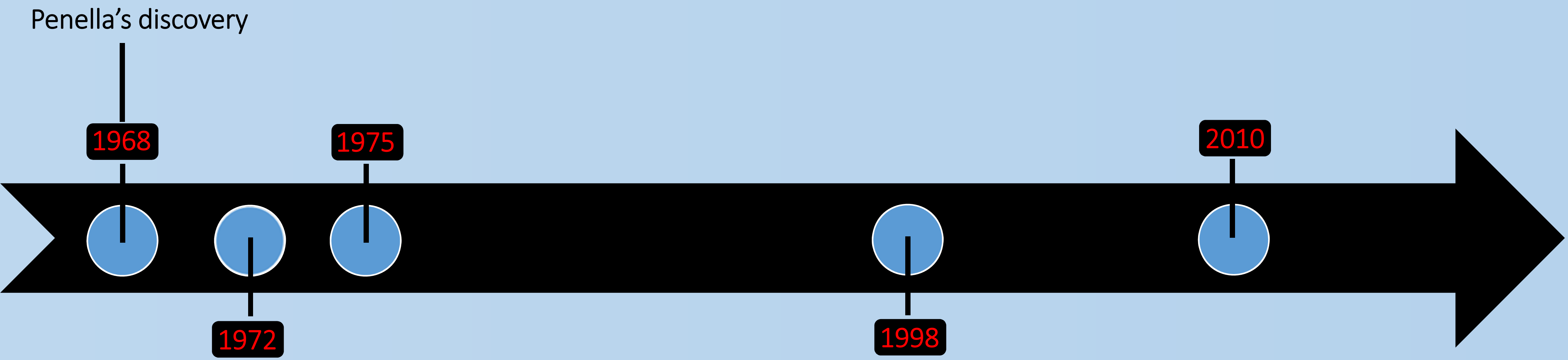
Application in Total Synthesis

1. Alkyne metathesis vs Alkene Metathesis in Total Synthesis?
2. RCAM for the Preparation of Z Alkenes - Hybridalactone and Haliclonin A
3. RCAM for the Preparation of E Alkenes - Tulearin C
4. Enyne-Yne Metathesis - Preparation of Stereodefined 1,3-Dienes - Lactimidomycin
5. Trisubstituted alkene synthesis - 5,6-Dihydrocineromycin B
6. How to further use that alkyne? - Kendomycin

Conclusion - Sum up and Prospects

- Alkyne Metathesis Chronology



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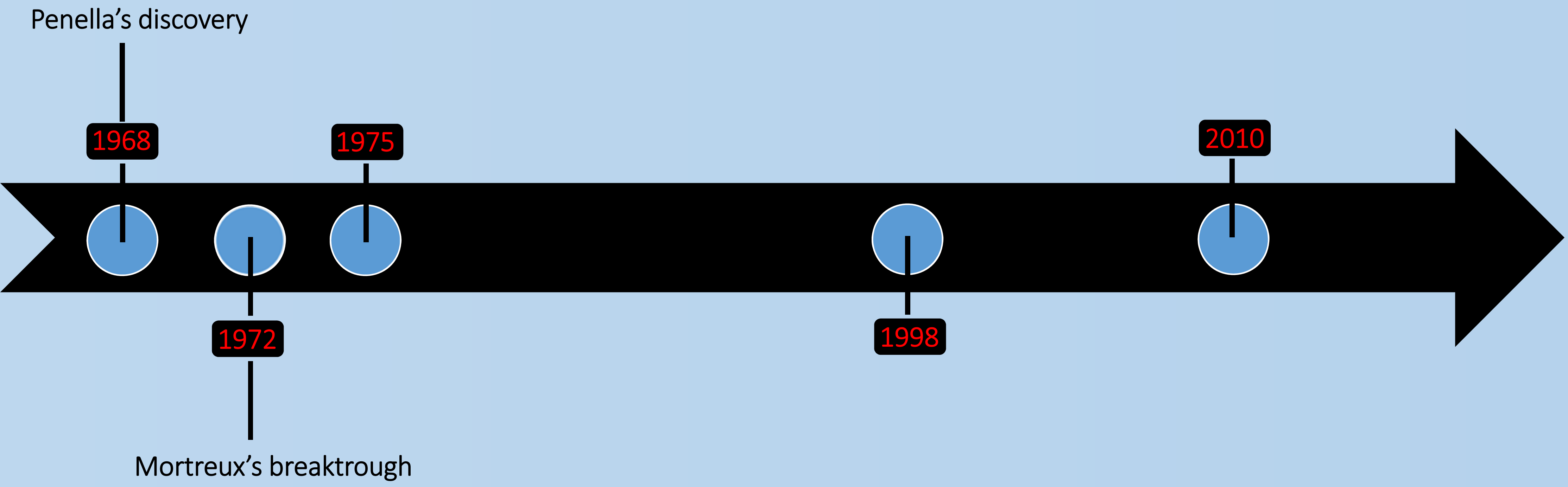

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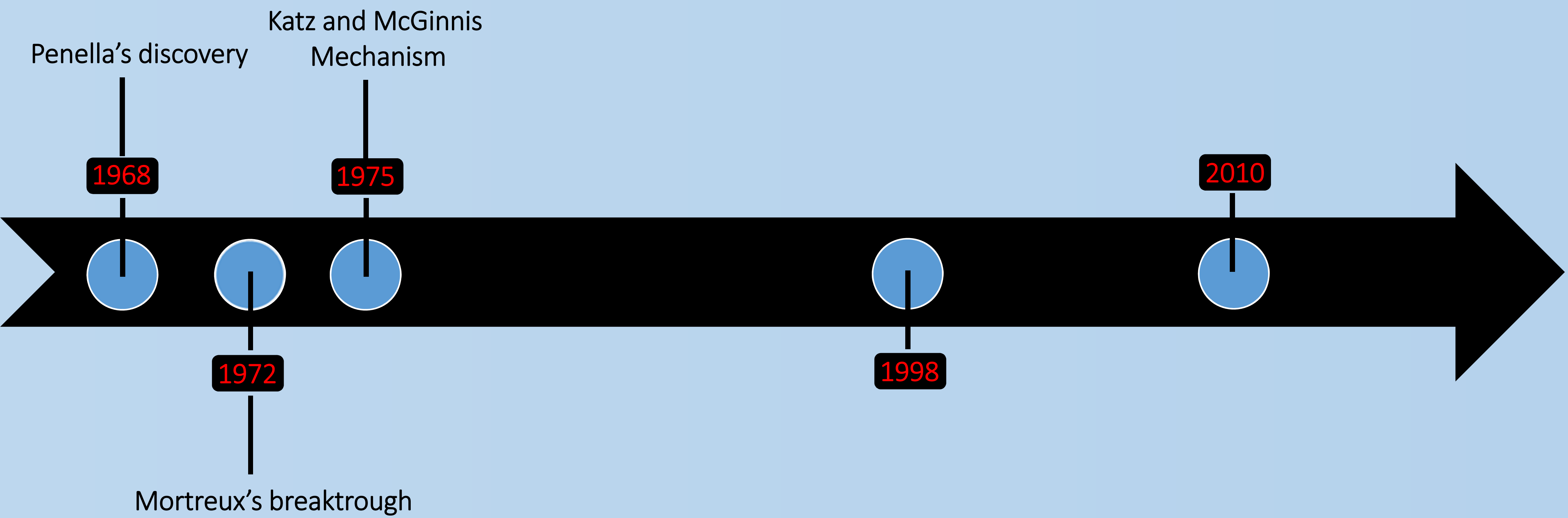

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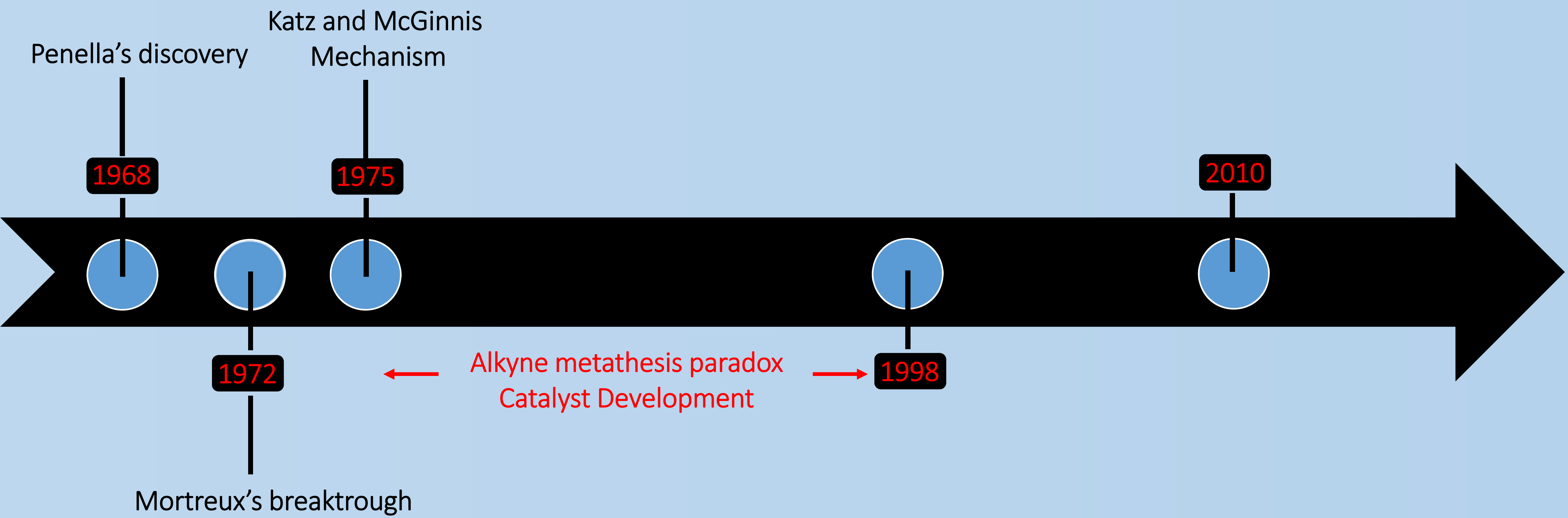

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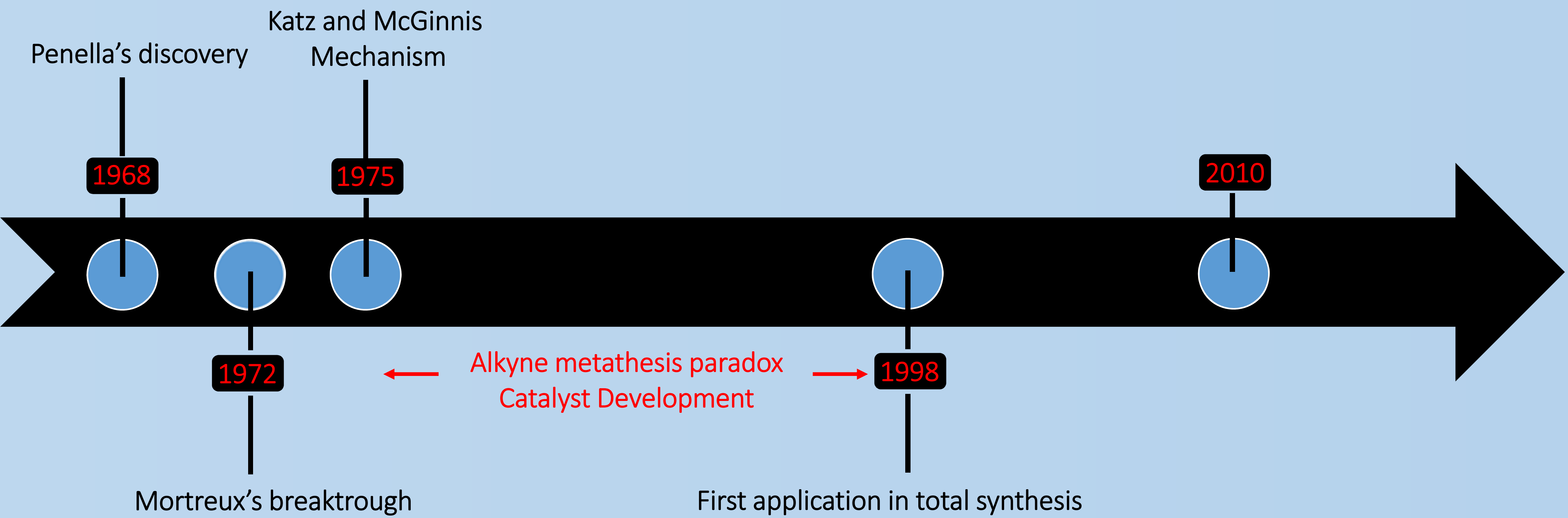

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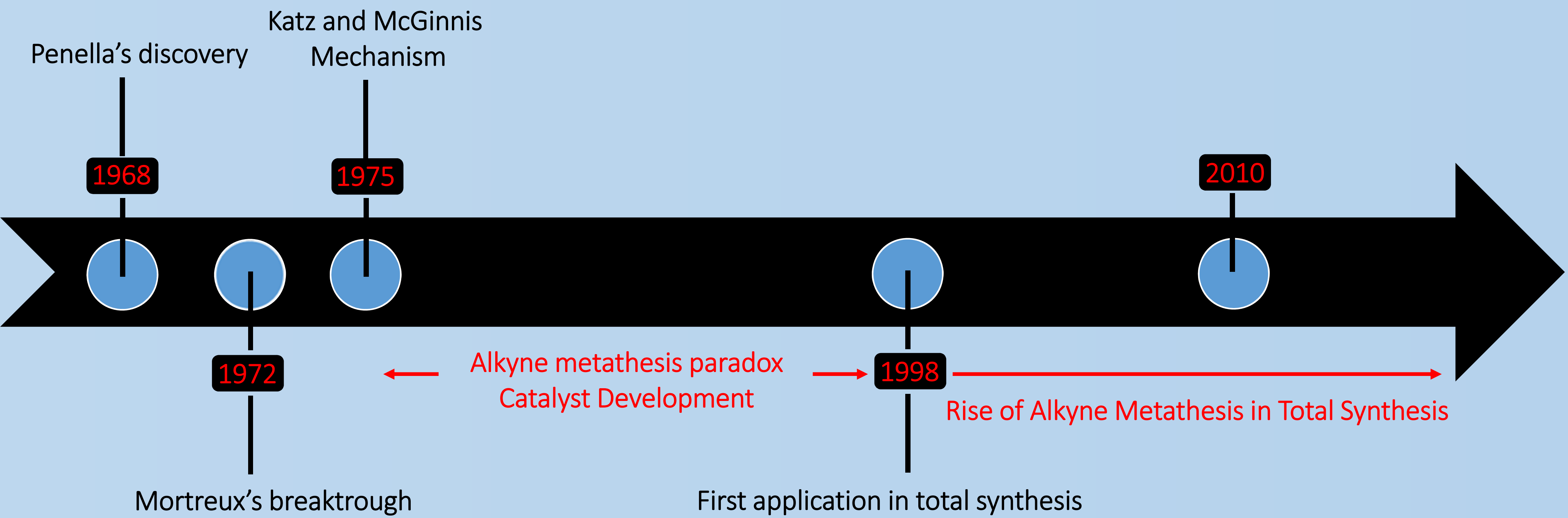

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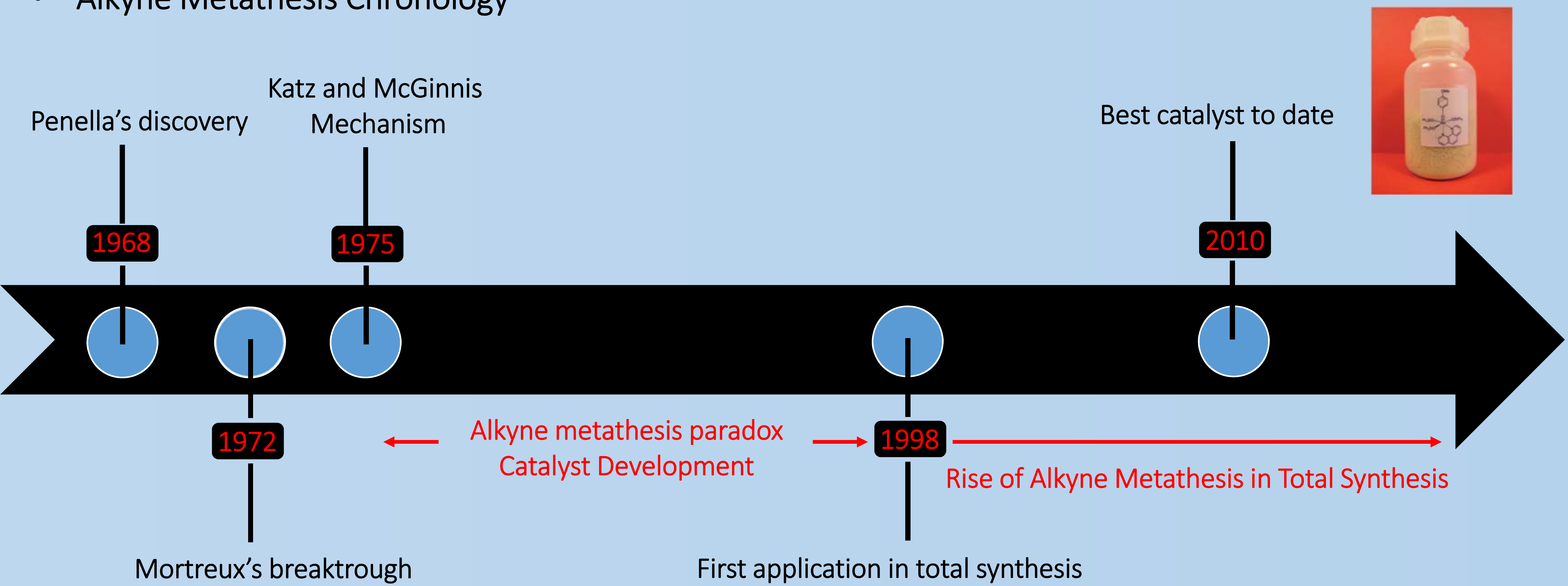
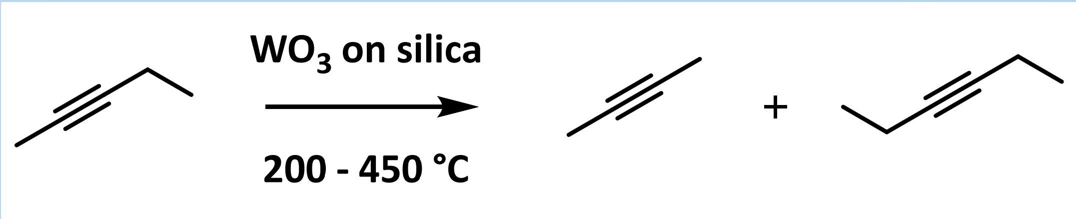


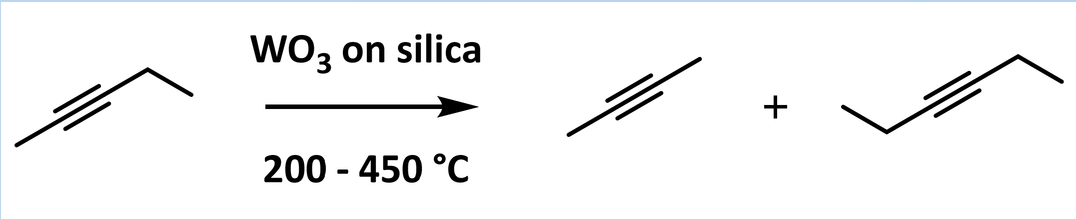
- Penella's discovery



As early as **1968**

F. Penella, R. L. Banks, G. C. Bailey, *J. Chem. Soc. Chem. Commun.* **1968**, 1548 - 1549.

- Penella's discovery



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Originates from **heterogeneous catalysis**

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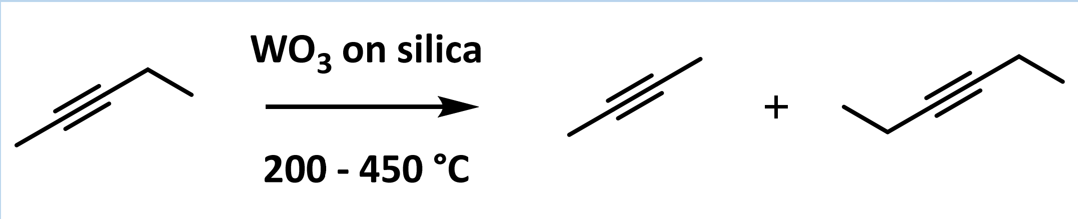

As early as **1968**

Originates from **heterogeneous catalysis**

Limited impact:

- **Polymerization** under reaction conditions
- **Low yield** and **mixture of alkynes**

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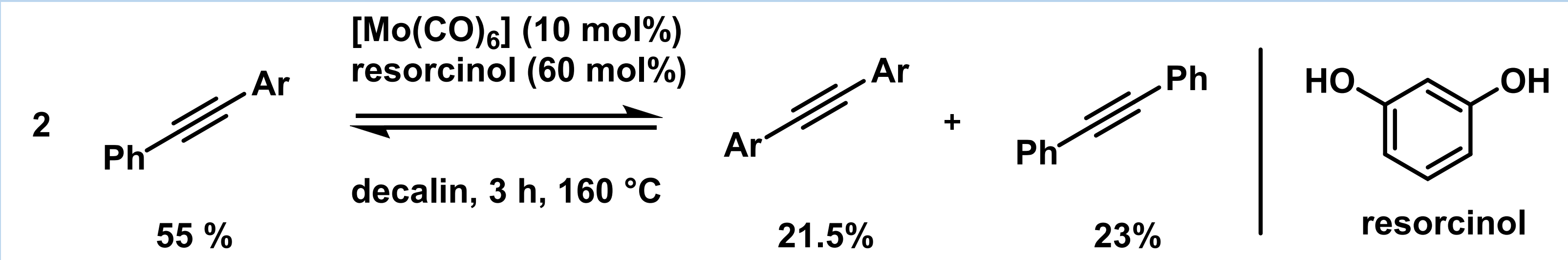
- Mortreux's breaktrough



First homogeneous alkyne metathesis

Mixture of separable alkynes

A. Morteux, M. Blanchard, *Bull. Soc. Chem. Fr.* **1972**, 1641 - 1643; J. A. Moulijn, H. J. Reitsma, C. Boelhouwer, *J. Catal.* **1972**, *25*, 434 - 436; A. Mortreux, F. Petit, M. Blanchard, *J. Mol. Catal.* **1980**, *8*, 97 - 106; A. Morteux, M. Blanchard, *J. Chem. Soc. Chem. Commun.* **1974**, *786 - 787.*

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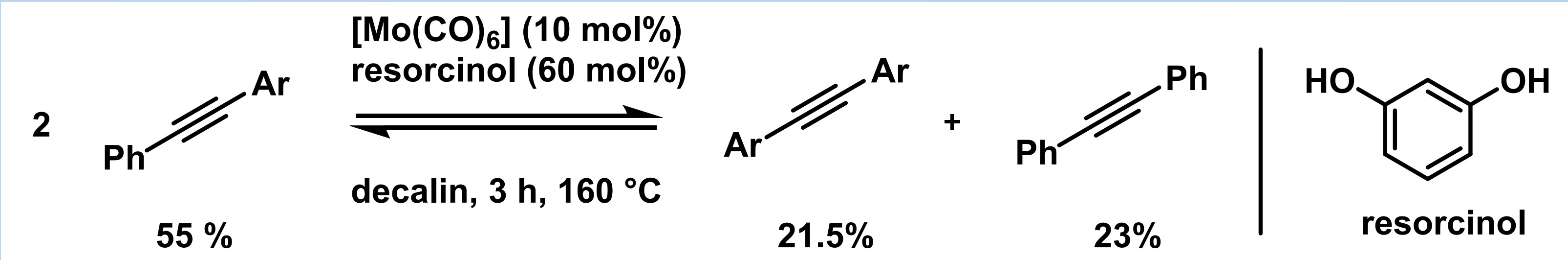

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Mixture of separable alkynes

Operationally simple: Numerous attempts at optimizing

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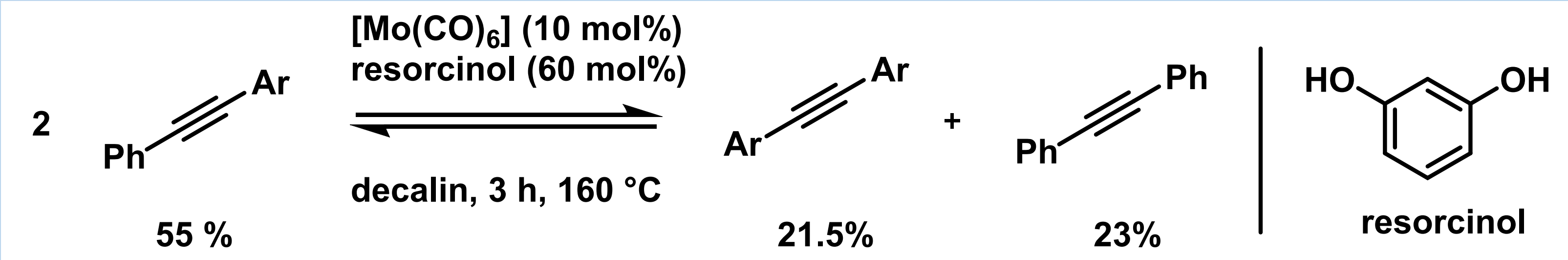
- Further developpement of Mortreux's catalyst



Various **Mo sources**, **phenols**, **solvents** and **additives** were **tested**

Selected examples: L. Kloppenburg, D. Song, U. H. F. Bunz, *J. Am. Chem. Soc.* **1998**, *120*, 7973 - 7974; K. Grela, J. Ignatowska, *Org. Lett.* **2002**, *4*, 3747 - 3749; V. Maraval, C. Lepetit, A.-M. Caminade, J.-P. Majoral, R. Chauvin, *Tetrahedron Lett.* **2006**, *47*, 2155 - 2159.

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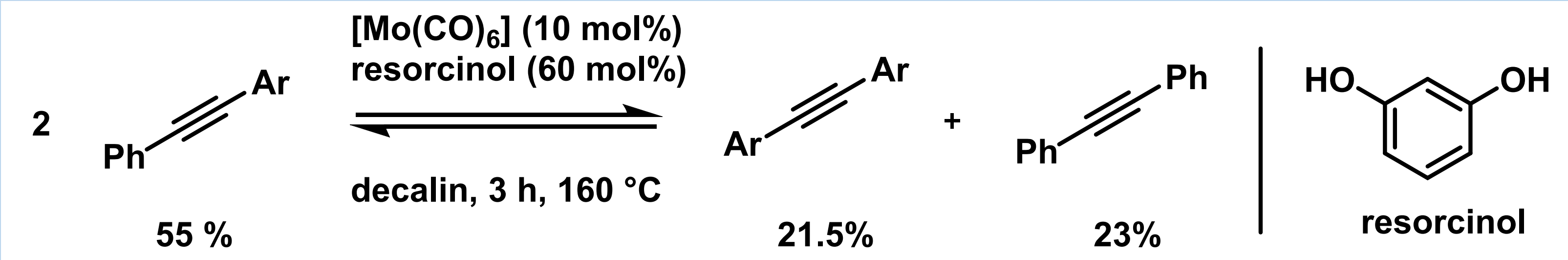

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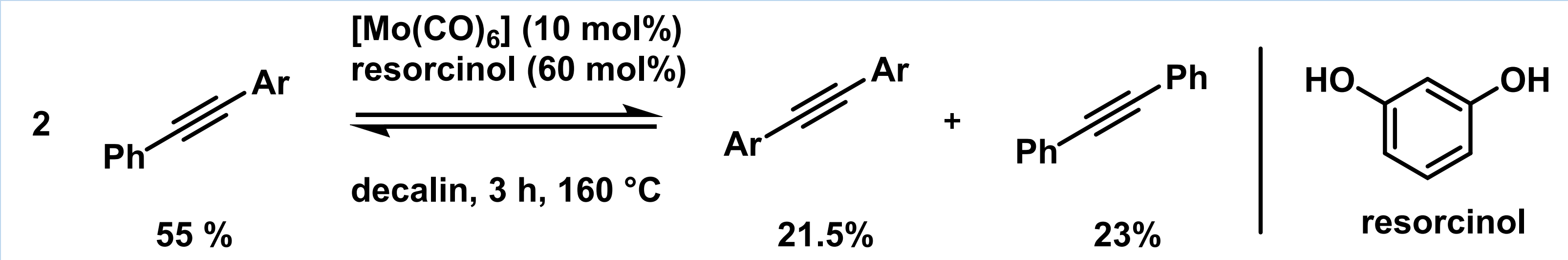

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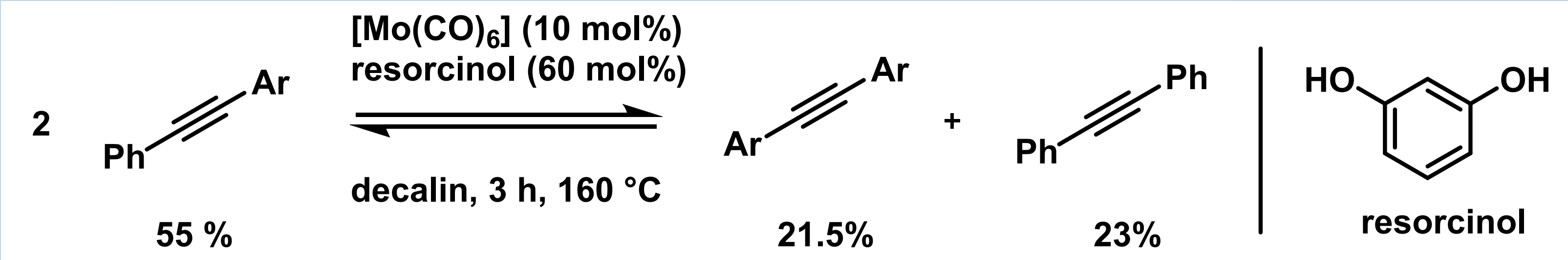

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Main problem: narrow functional-group tolerance

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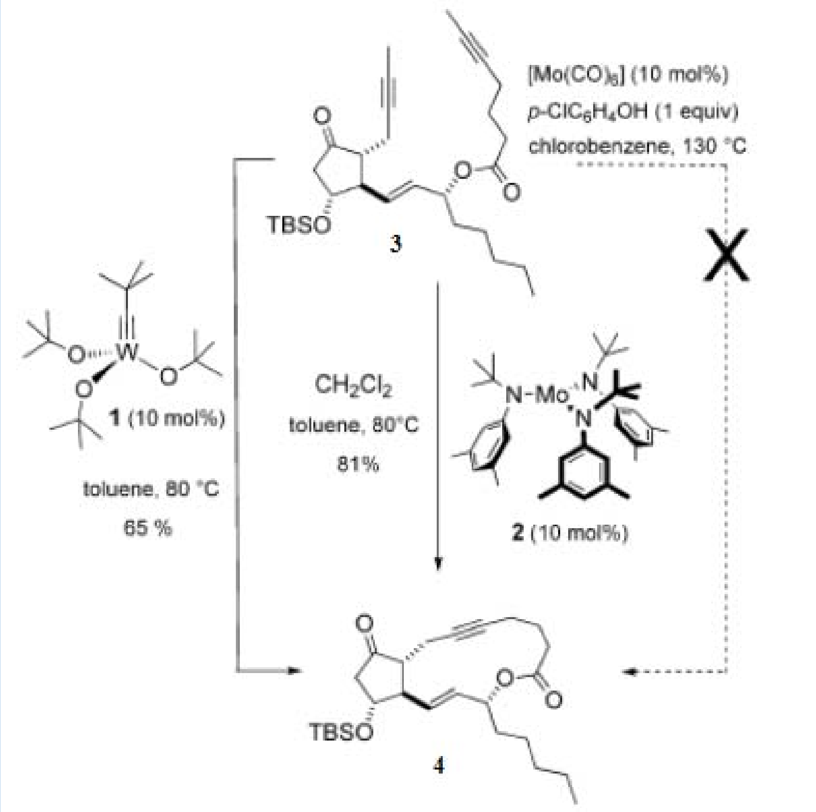
- A concrete example - Prostaglandin E2-1,15-Lactone

  - Phenols may endanger many polar substituents



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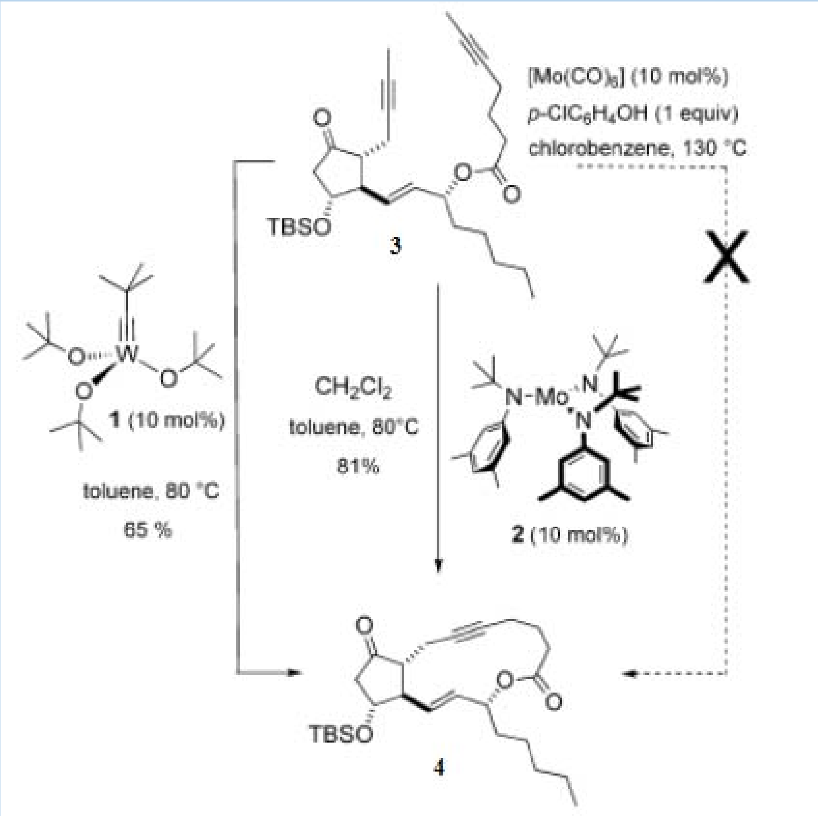

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  - Decomposition of 3 with Mortreux's catalyst (right)

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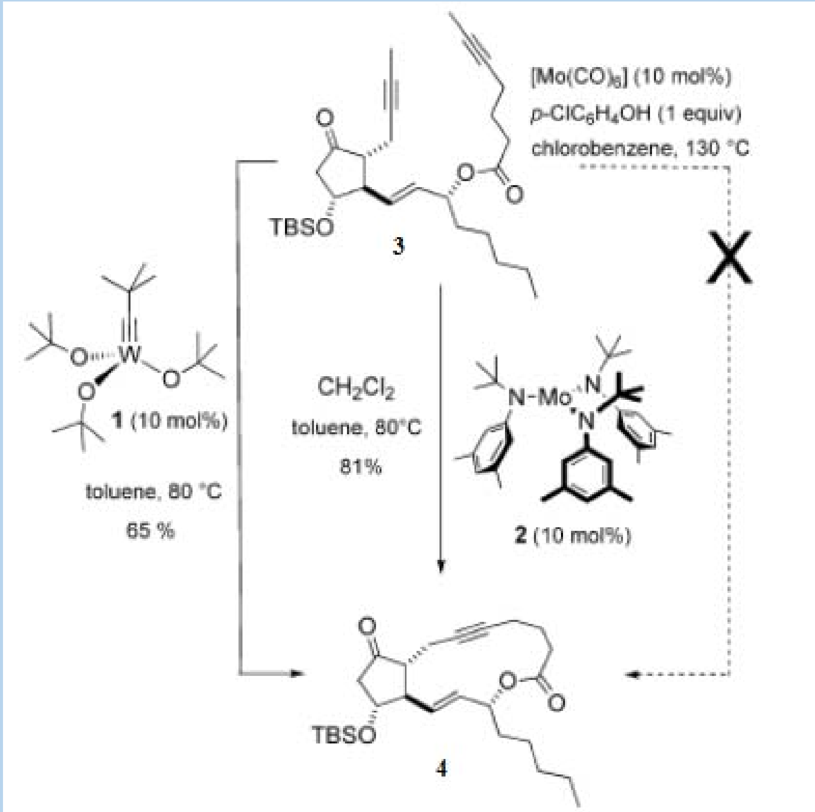

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  - Decomposition of 3 with Mortreux's catalyst (right)
  - No problem with more recent W and Mo catalysts (left and middle)

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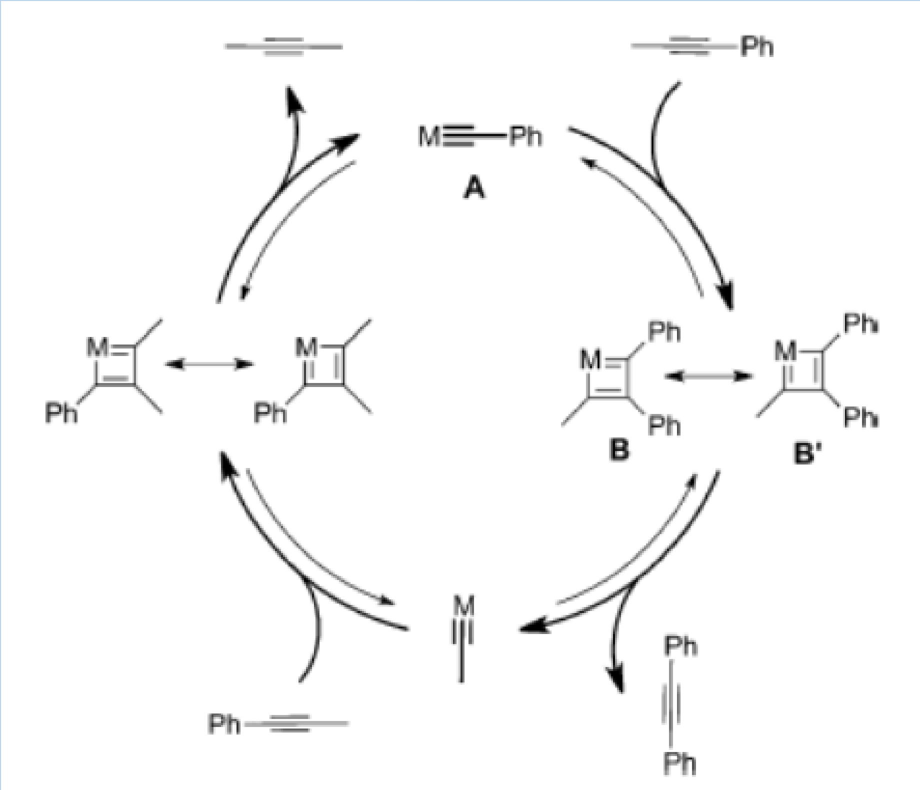
- Katz and McGinnis mechanism
  - Following **Chauvin's cycle** for **olefin metathesis**



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    - ➢ **High-valent** alkylidyne complexes of Mo, W and Re
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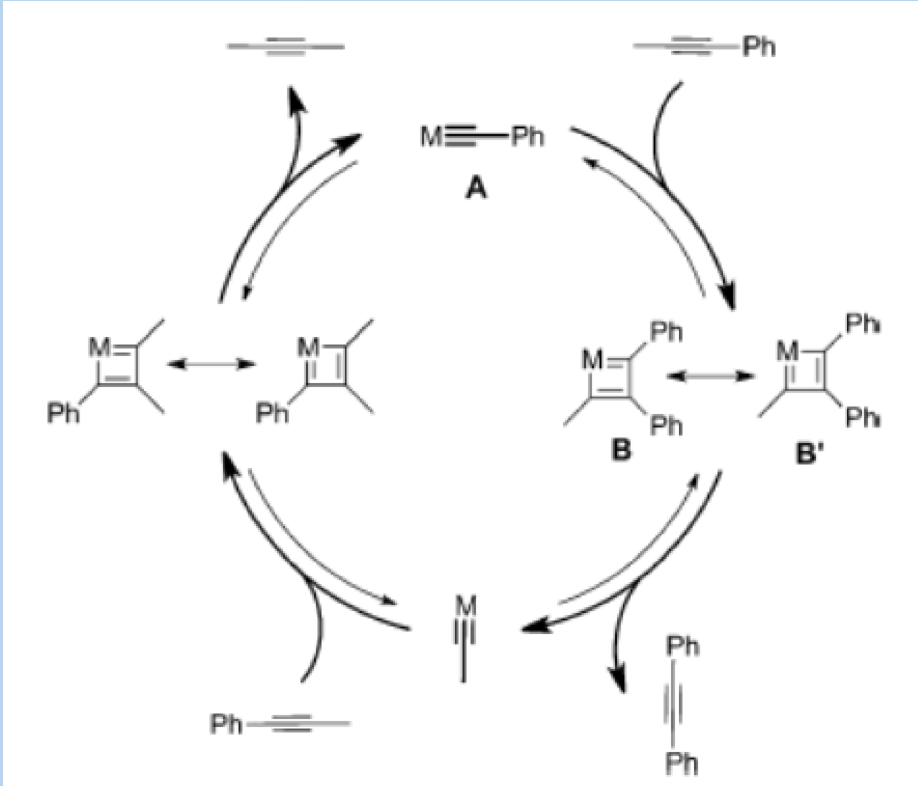

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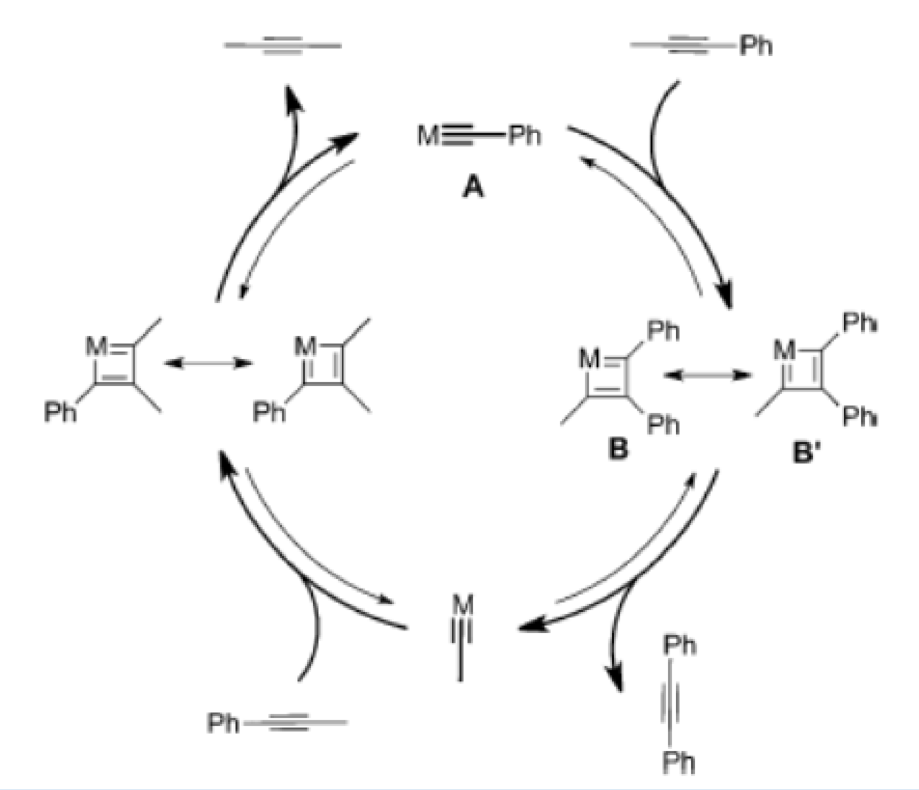
  - **Metallacyclobutadienes:**
    - **Intermediates** rather than **transition states**
    - Likely **represent** the **catalyst resting state (W)**



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- Alkyne metathesis paradox

  - **Facts:** By the **early 1980s**

    - **Validated mechanism**
    - Already several **competent catalyst** systems
    - **Detailed insights** into the comportment of Schrock-type alkylidyne complexes
    - **Limited impact** on organic and polymers chemistry

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  - **Turning point: 1998**

    - **First application** of **Alkyne Metathesis** in the **total synthesis** of a complex molecule
    - **Rise** of **Alkyne Metathesis** in **Total Synthesis**

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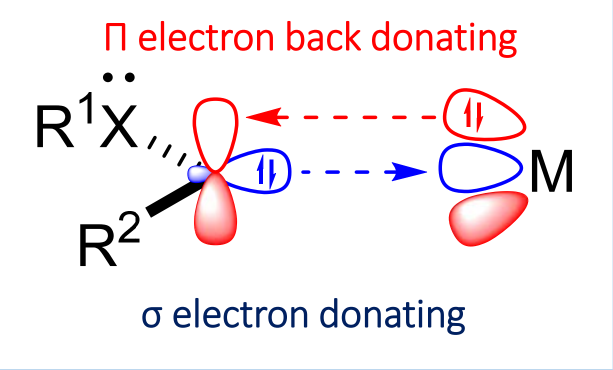

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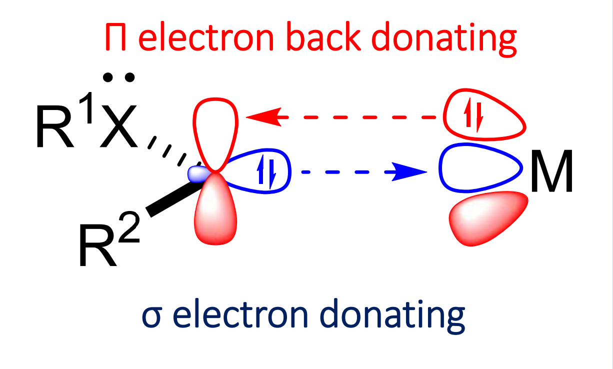
    - Complexes of singlet carbenes
    - Low oxidation state metals
    - Middle and late transition metals (Fe^0, Mo^0, Cr^0, W^0)



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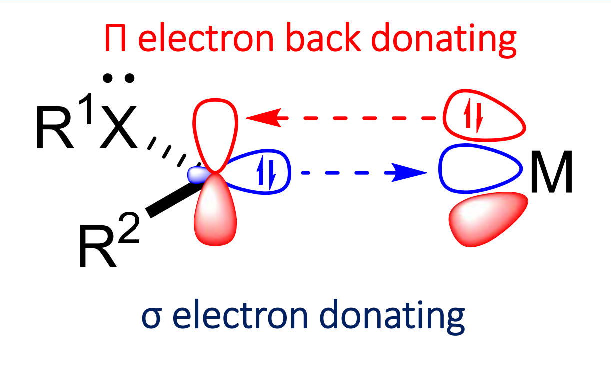
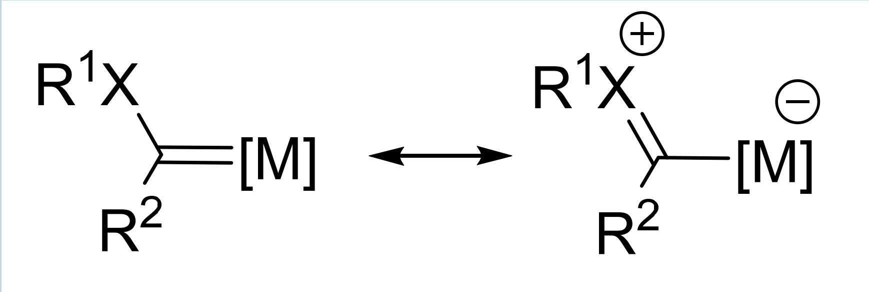
    - ➢ **Low oxidation** state metals
    - ➢ **Middle** and **late transition metals** (Fe^0, Mo^0, Cr^0, W^0)
    - ➢ **Π-acceptor ligand, Π-donor α-substituent**
    - ➢ **High electrophilic** character





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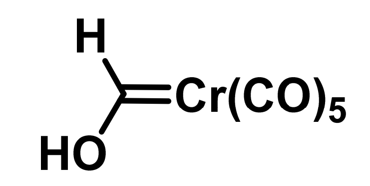
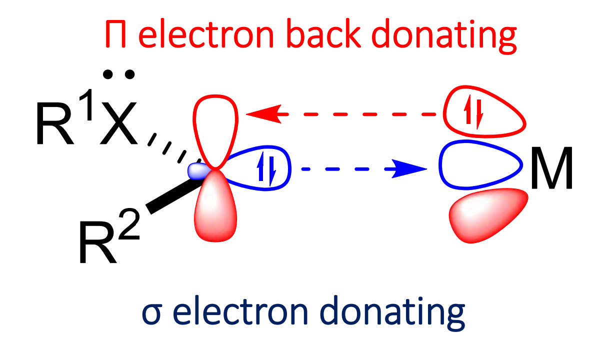
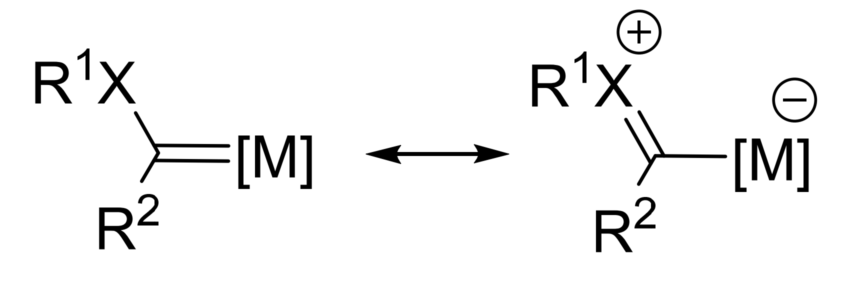


Cr=C bond energy
184 kJ.mol^{-1}





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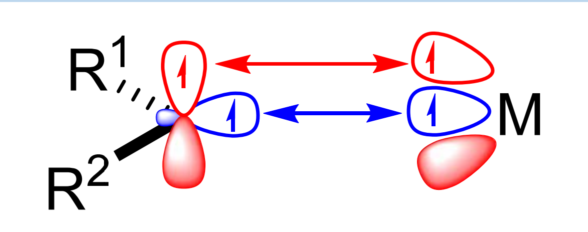
    - Complexes of **triplet carbenes**



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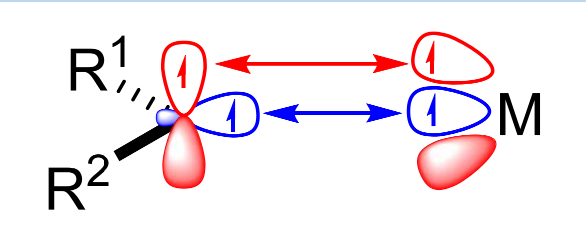

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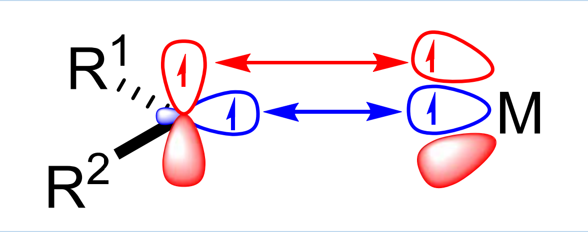
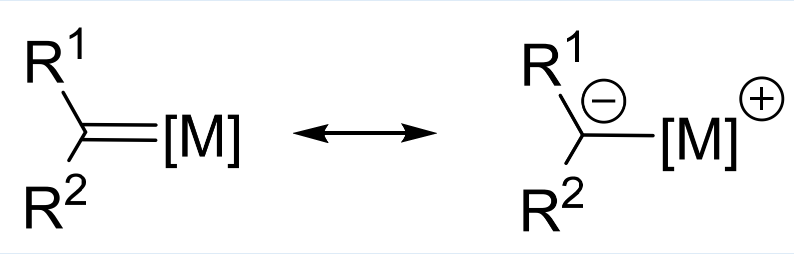
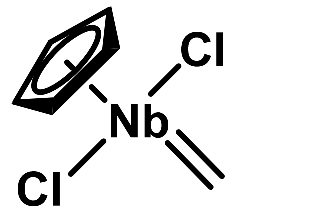
    - ➢ **Π-donor ligand, no α-heteroatom**
    - ➢ **Nucleophilic** character



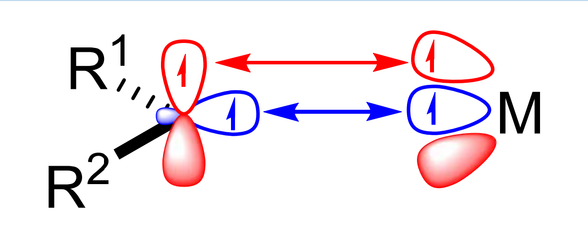


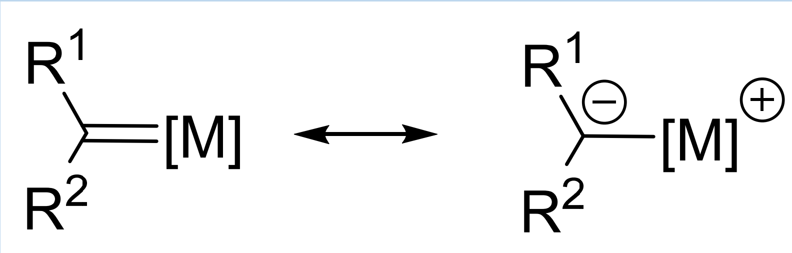
R. R. Schrock, *Chem. Rev.* **2002**, *102*, 145 - 179; **Nobel lecture:** R. R. Schrock, *Angew. Chem. Int. Ed.* **2006**, *45*, 3748 - 3759.

- Schrock carbenes
  - R. R. Schrock: **Nobel Prize** in **2005**, along with Y. **Chauvin** and R. H. **Grubbs**
    - ➢ Complexes of **triplet carbenes**
    - ➢ **High oxidation** state metals
    - ➢ **Early transition metals** (Ti^{IV}, Ta^{IV} ...)
    - ➢ **Π-donor ligand, no α-heteroatom**
    - ➢ **Nucleophilic** character



Nb=C bond energy
309 kJ.mol^{-1}





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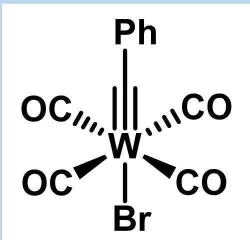
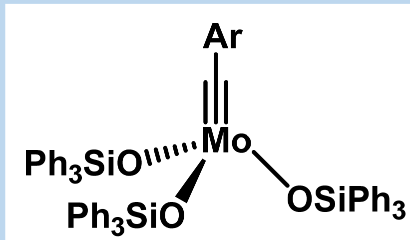
- Fischer carbynes vs Schrock carbynes

Fischer carbynes	Schrock carbynes
Low oxidation state TM	High oxidation state TM
Monoanionic alkylidyne	Trianionic alkylidyne (formalism)
Electrophilic	Nucleophilic





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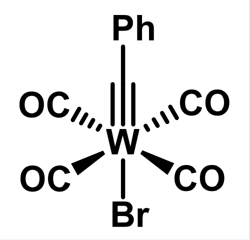
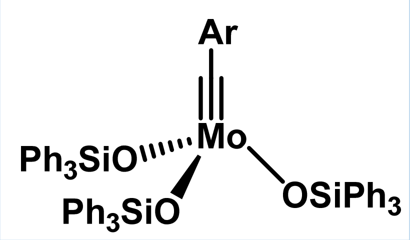
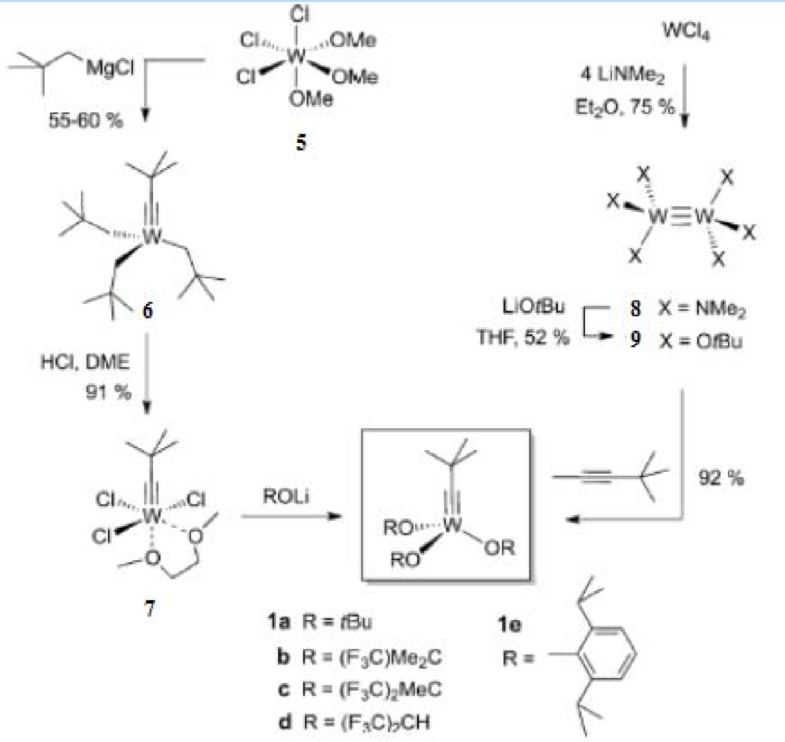
Fischer carbynes	Schrock carbynes
Low oxidation state TM	High oxidation state TM
Monoanionic alkylidyne	Trianionic alkylidyne (formalism)
Electrophilic	Nucleophilic
Not efficient for Alkyne Metathasis	Efficient for Alkyne Metathasis



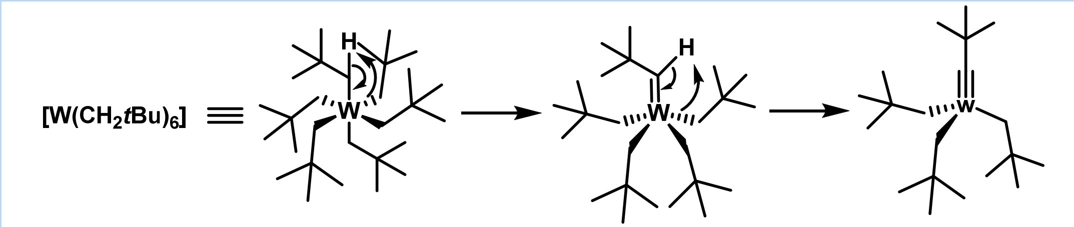


1. Lessons learnt from Schrock-Type Tungsten Alkylidynes: Catalyst Preparation



W

- First method: Classical Schrock method
  - Alkylation of a W^{VI} precursor
  - Two consecutive α-elimination



1st α-elimination 2nd α-elimination

J. H. Wengrovius, J. Sancho, R. R. Schrock, *J. Am. Chem. Soc.* **1981**, *103*, 3932 - 3934; S. F. Pedersen, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *J. Am. Chem. Soc.* **1982**, *104*, 6808 - 6809; M. H. Chisholm, J. D. Martin, J. E. Hill, I. P. Rothwell, *Inorg. Synth.* **1992**, *29*, 137 - 140;
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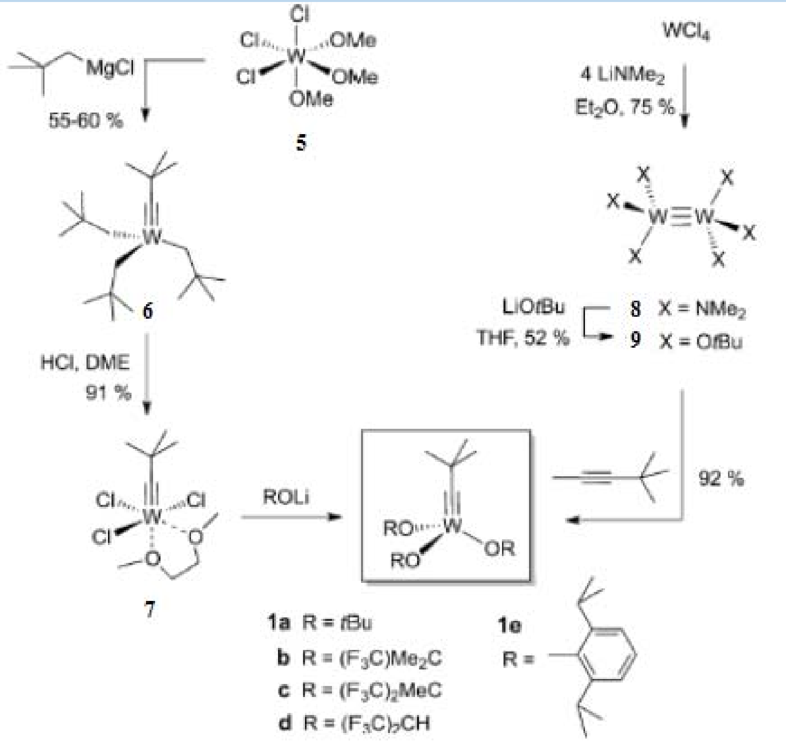

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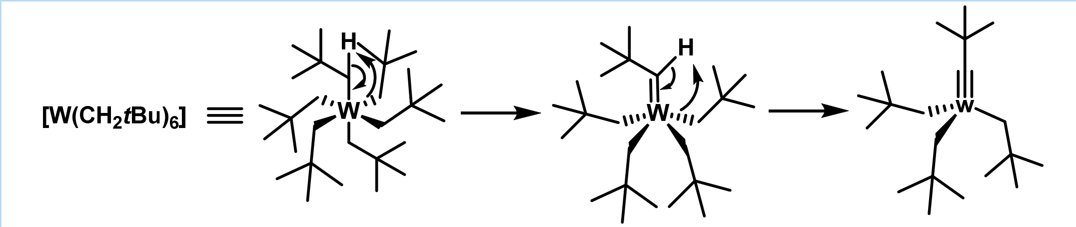

1st α-elimination 2nd α-elimination

- **Second method**: Metathetic cleveage
  - ➢ Complexe **1a** is now **commercially available**

J. H. Wengrovius, J. Sancho, R. R. Schrock, *J. Am. Chem. Soc.* **1981**, *103*, 3932 - 3934; S. F. Pedersen, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *J. Am. Chem. Soc.* **1982**, *104*, 6808 - 6809; M. H. Chisholm, J. D. Martin, J. E. Hill, I. P. Rothwell, *Inorg. Synth.* **1992**, *29*, 137 - 140;
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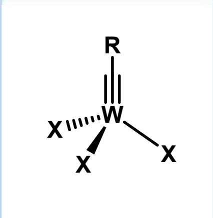
1. Lessons learnt from Schrock-Type Tungsten Alkylidynes: Role of R and X

- Complexe of the general type [$X_3W\equiv CR$]



W

R. R. Schrock, D. N. Clark, J. Sancho, J. H. Wengrovius, S. M. Rocklage, S. F. Pedersen, *Organometallics* 1982, *1*, 1645 - 1651.
M. A. Stevenson, M. D. Hopkins, *Organometallics* 1997, *16*, 3572 - 3573.

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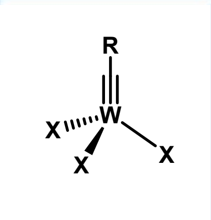

W

- Complexe of the general type [$X_3W\equiv CR$]
- Influence of R
  - Little bearing on the inherent activity
  - Affect the **stability** and **rate of initiation**
  - Ease of preparation

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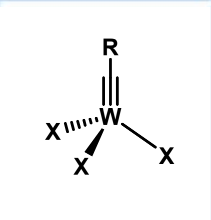
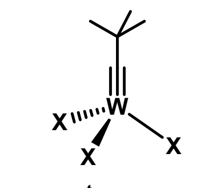
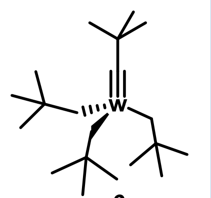


W

- Complexe of the general type $[X_3W{\equiv}CR]$
- Influence of R
  - Little bearing on the inherent activity
  - Affect the **stability** and **rate of initiation**
  - Ease of preparation
- Influence of X
  - Plays a **decisive role**: **1a**: commercially available vs **6** and **7**: not reactive
  - Bulk important to **shield W atom**
    - ➢ Prevent dimerization and bimolecular decomposition
  - **Electronic properties** are important



X = O^{t}Bu **1a**



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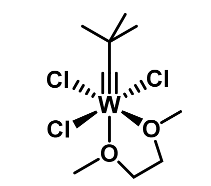

7

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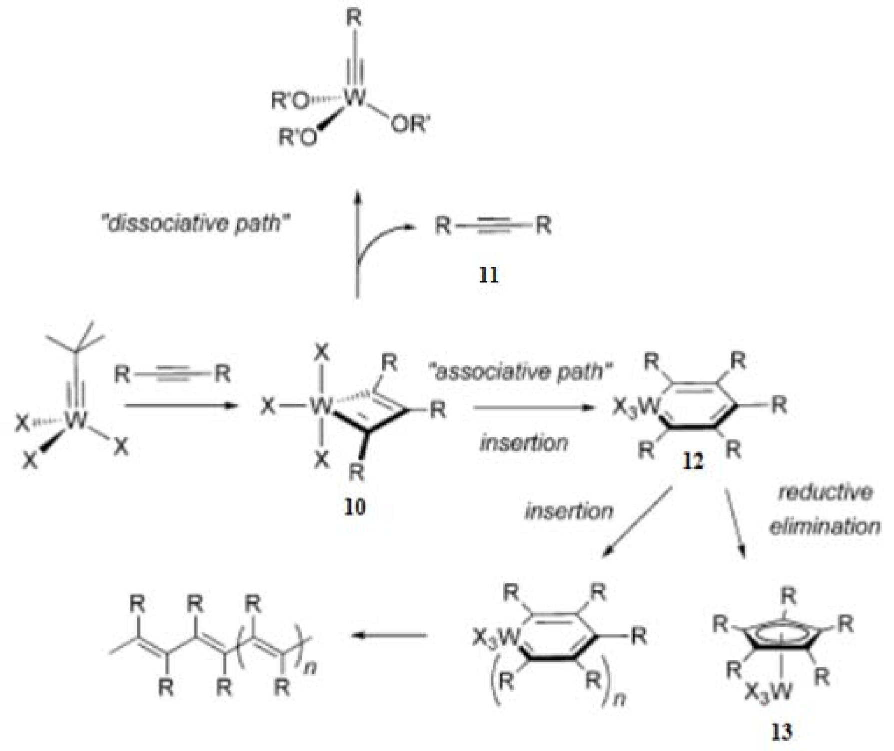

- Metallacyclobutadienes 10: Isolated and analysed

M. R. Churchill, J. W. Ziller, J. H. Freudenberger, R. R. Schrock, *Organometallics* 1984, *3*, 1554 - 1562.
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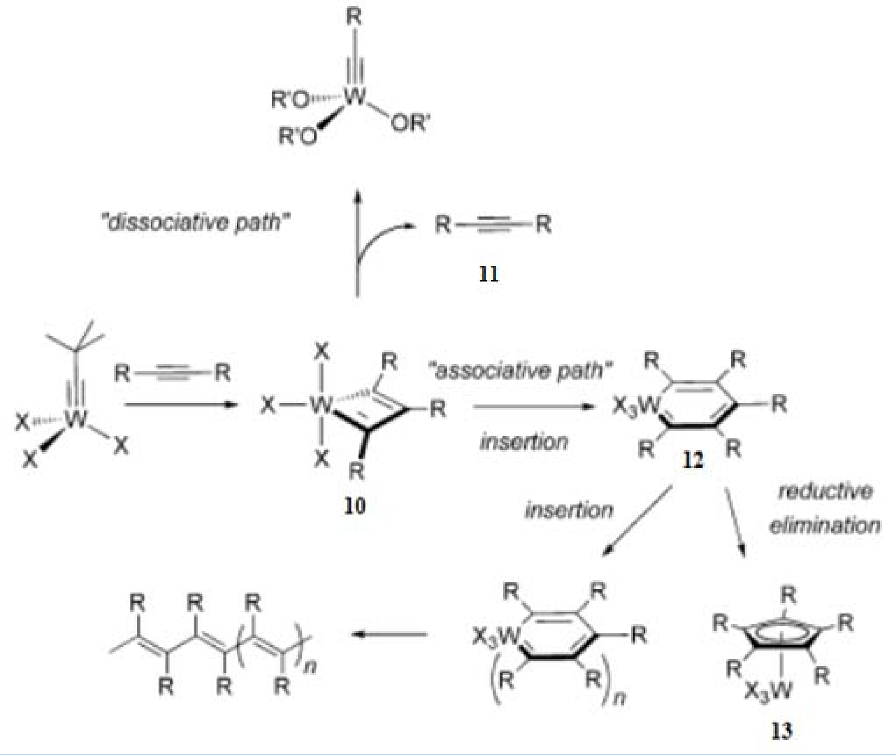

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  - Dissociative Path

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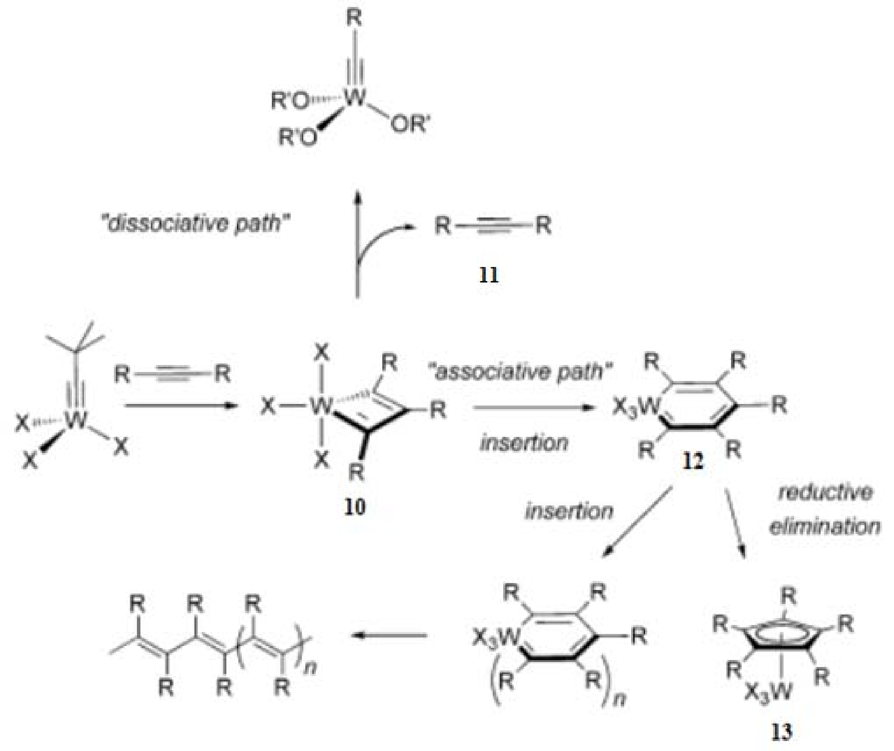

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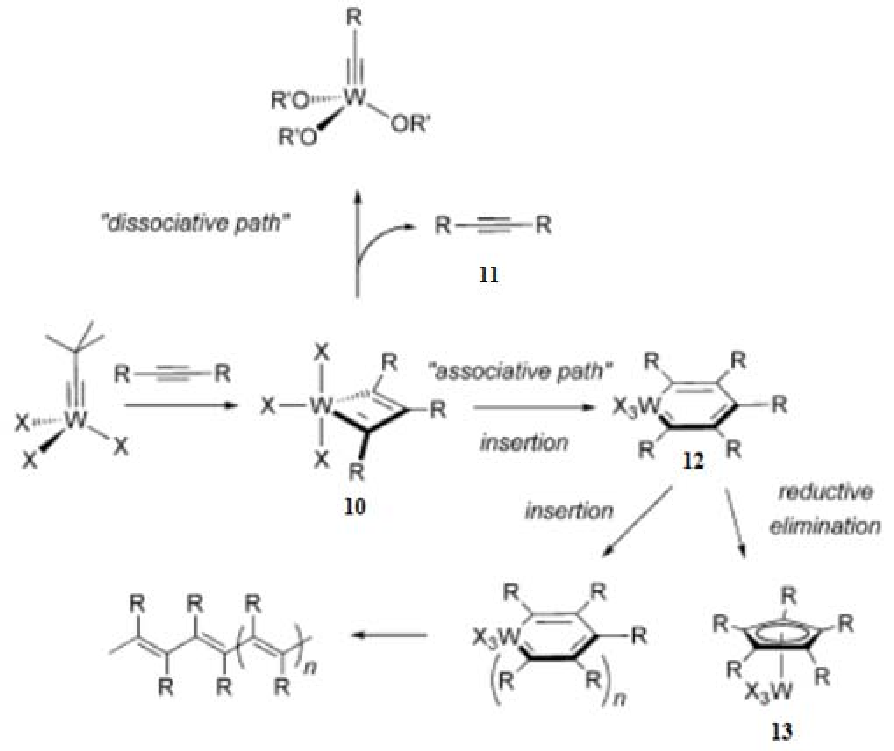

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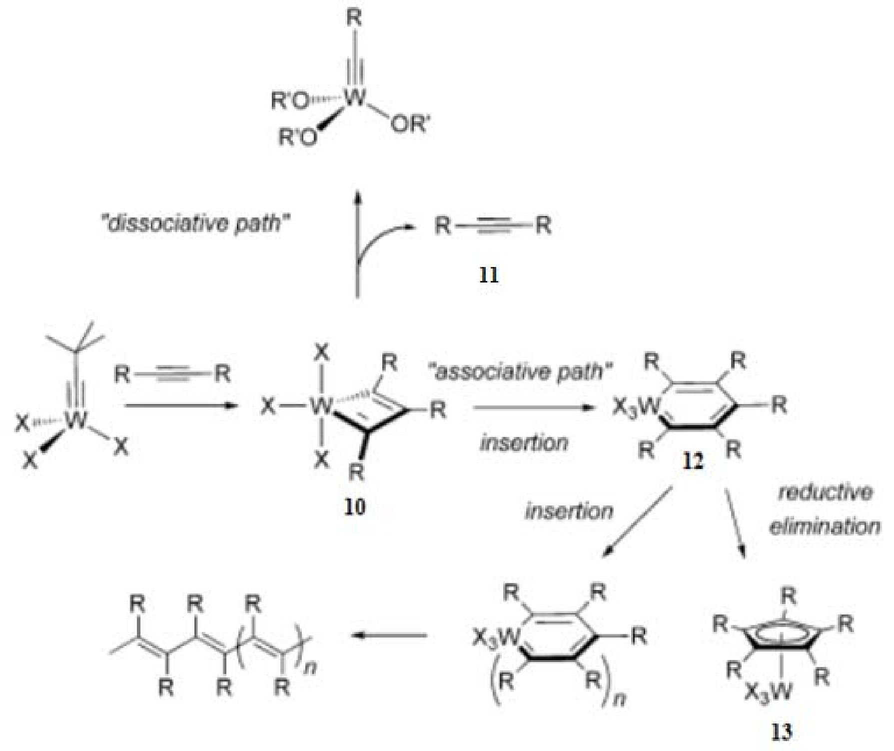

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X. Wu, C. G. Daniliuc, C. G. Hrib, M. Tamm, *J. Organomet. Chem.* **2011**, *696*, 4147 - 4151; Z. J. Tonzetich, Y. C. Lam, P. Mller, R. R. Schrock, *Organometallics* **2007**, *26*, 475 - 477; S. Beer, C. G. Hrib, P. G. Jones, K. Brandhorst, J. Grunenberg, M. Tamm, *Angew. Chem. Int. Ed.* **2007**, *46*, 8890 - 8894.
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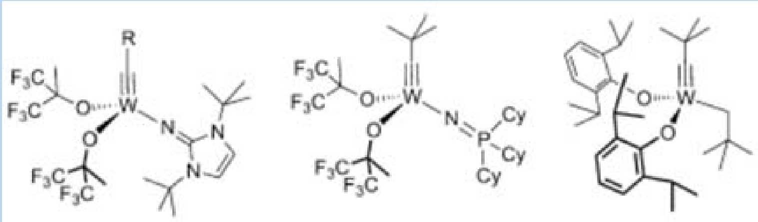

- **Solution: Heteroleptic push/pull environment** around **W**

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2. Molybdenum-Based Catalyst: Early preparation

Mo

- Original syntheses of [$X_3Mo \equiv CR$] :
  - ➢ low yields and problems with scale-up

L. G. McCullough, R. R. Schrock, *J. Am. Chem. Soc.* **1984**, *106*, 4067 - 4068; I. A. Weinstock, R. R. Schrock, W. M. Davis, *J. Am. Chem. Soc.* **1991**, *113*, 135 - 144; L. G. McCullough, R. R. Schrock, J. C. Dewan, J. C. Murdzek, *J. Am. Chem. Soc.* **1985**, *107*, 5987 - 5998; Y.-C. Tsai, P. L. Diaconescu, C. C. Cummins, *Organometallics* **2000**, *19*, 5260 - 5262; J. M. Blackwell, J. S. Figueroa, F. H. Stephens, C. C. Cummins, *Organometallics* **2003**, *22*, 3351 - 3353.

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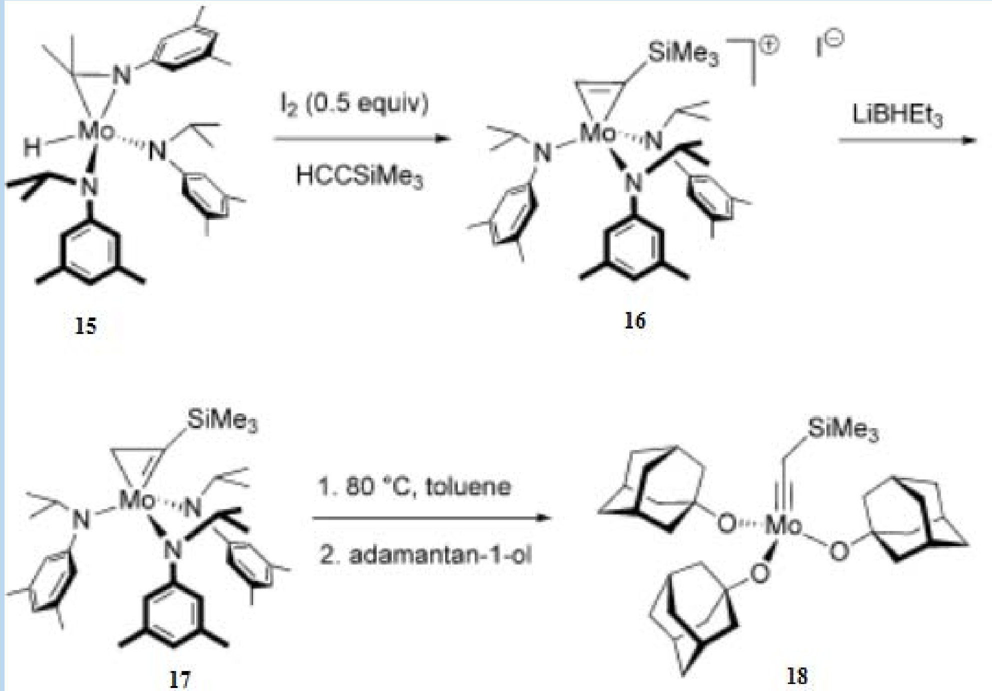
- Contrary to tungsten series, [$(t\text{BuO})_3Mo{\equiv}CCMe_3$]
  - performs poorly
- When X = phenolates or branched fluorinated alkoxides:
  - good activity
- First reliable preparation: Cummins 2000
  - No systematic screening



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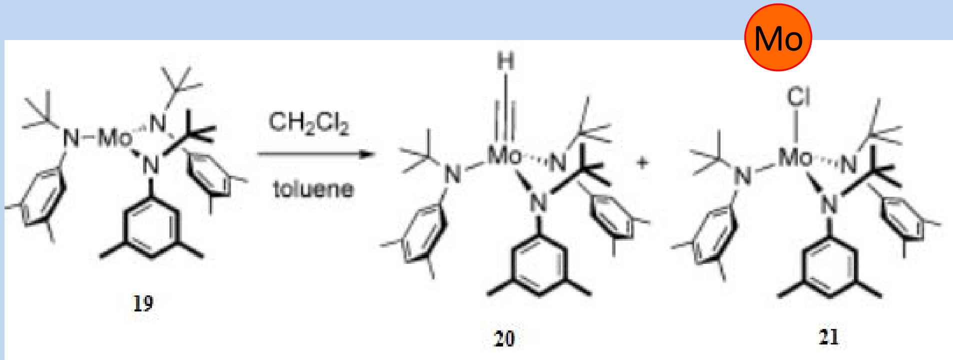
2. Molybdenum-Based Catalyst: Upgraded Preparation

- Precursor 19 provides great oppotunities



A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* 1999, *121*, 9453 - 9454; A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* 2001, *7*, 5299 - 5317.

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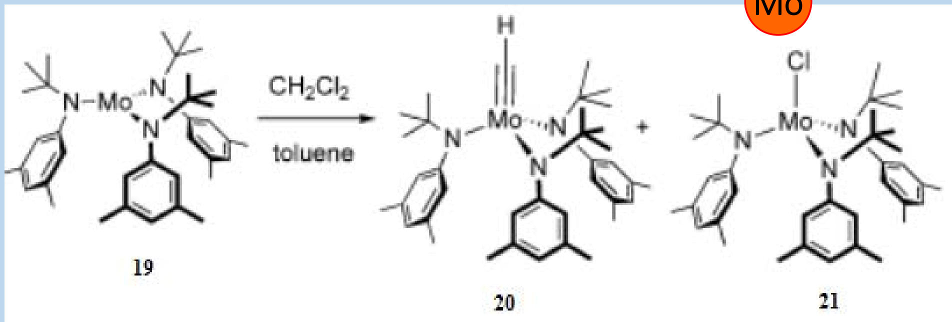
- 20 catalyzes many alkyne metathesis

Mo



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2. Molybdenum-Based Catalyst: Upgraded Preparation

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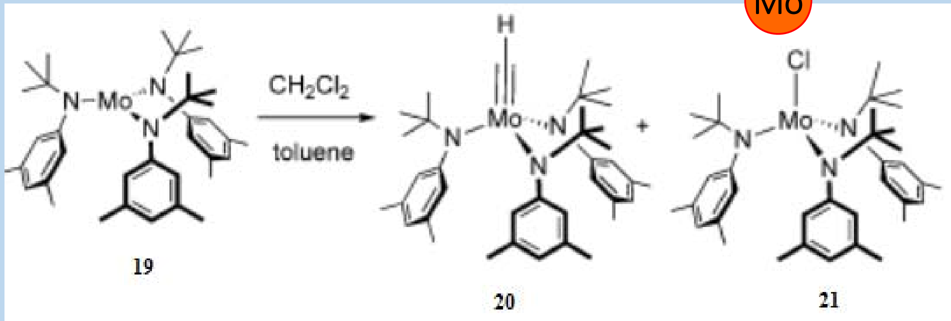

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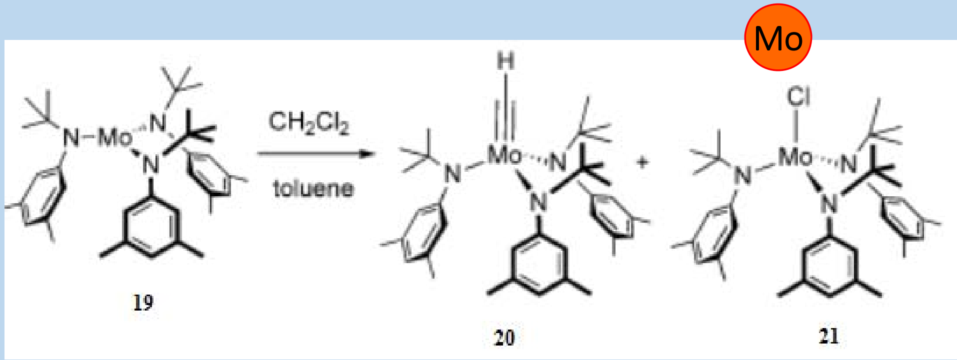

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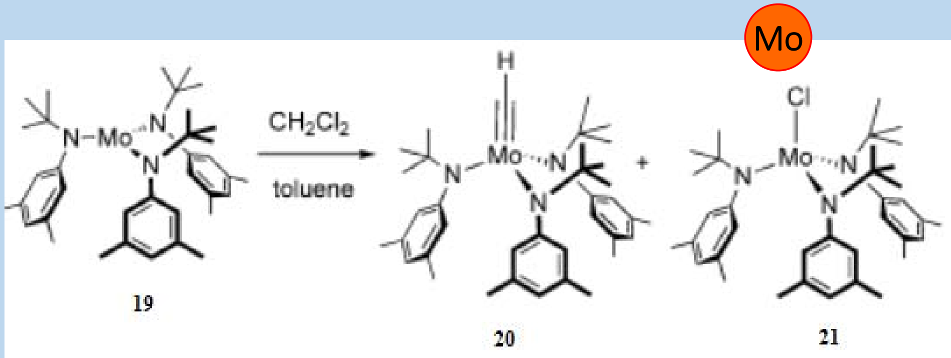

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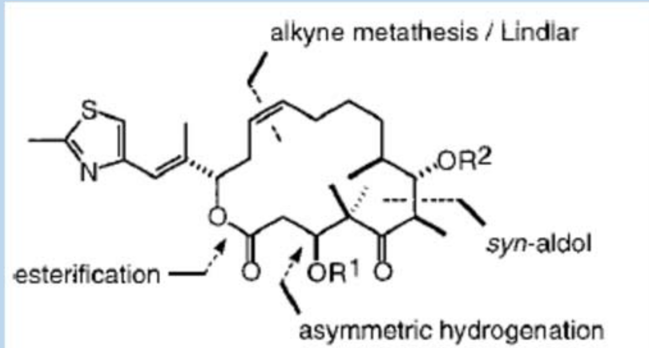

Epothilone C

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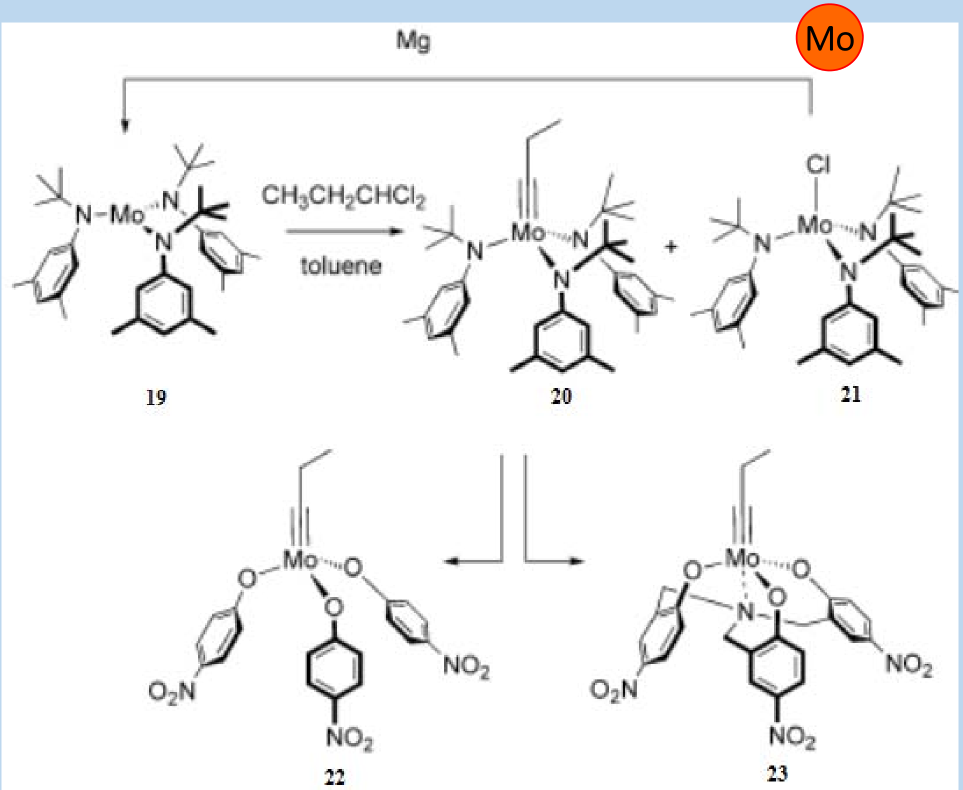

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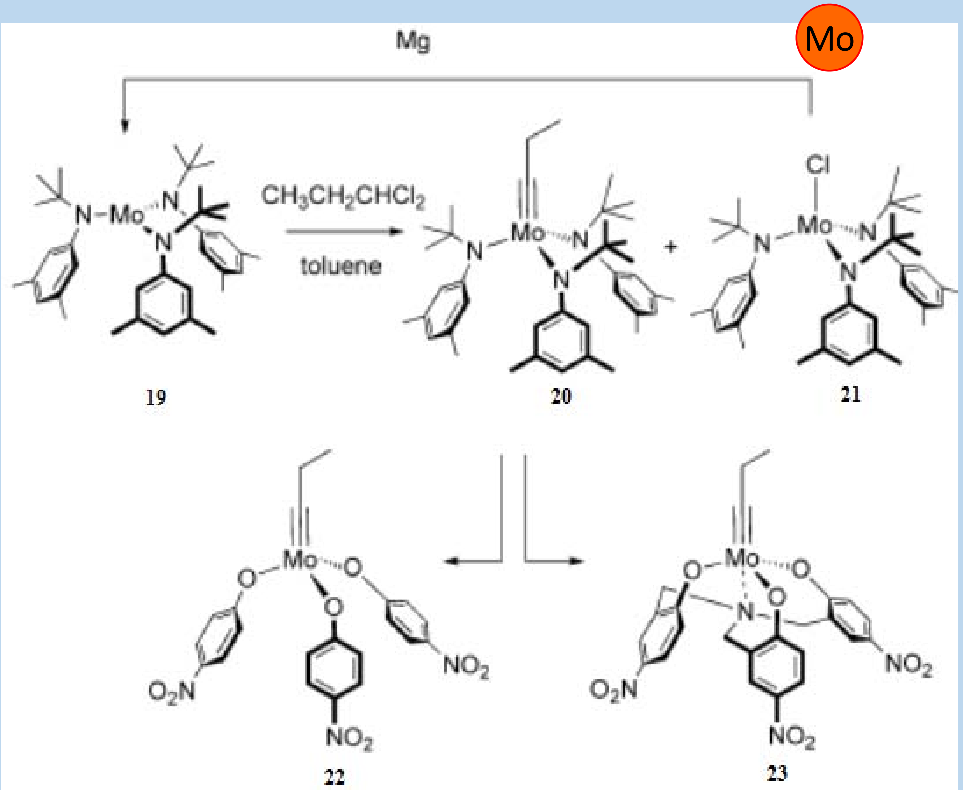

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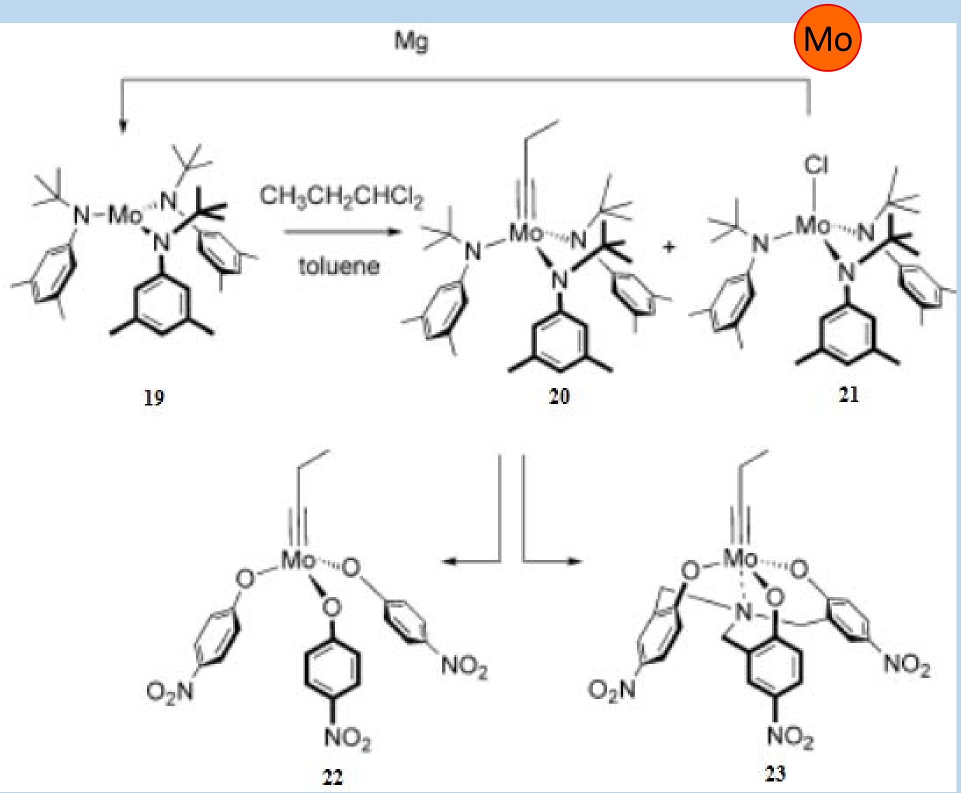

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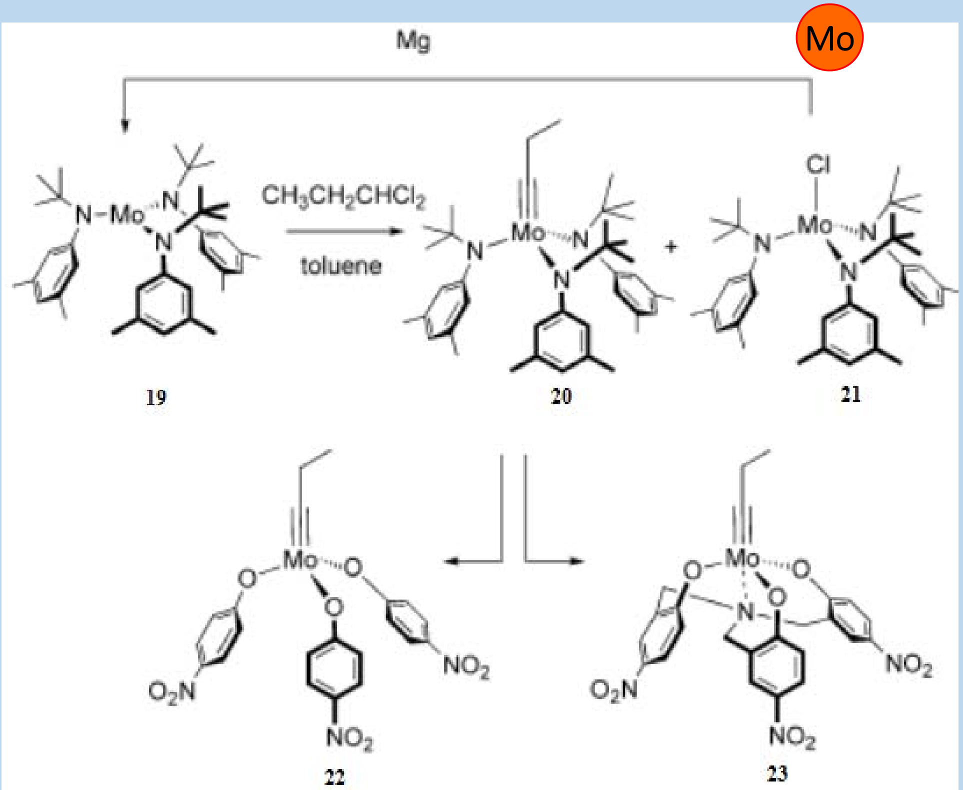

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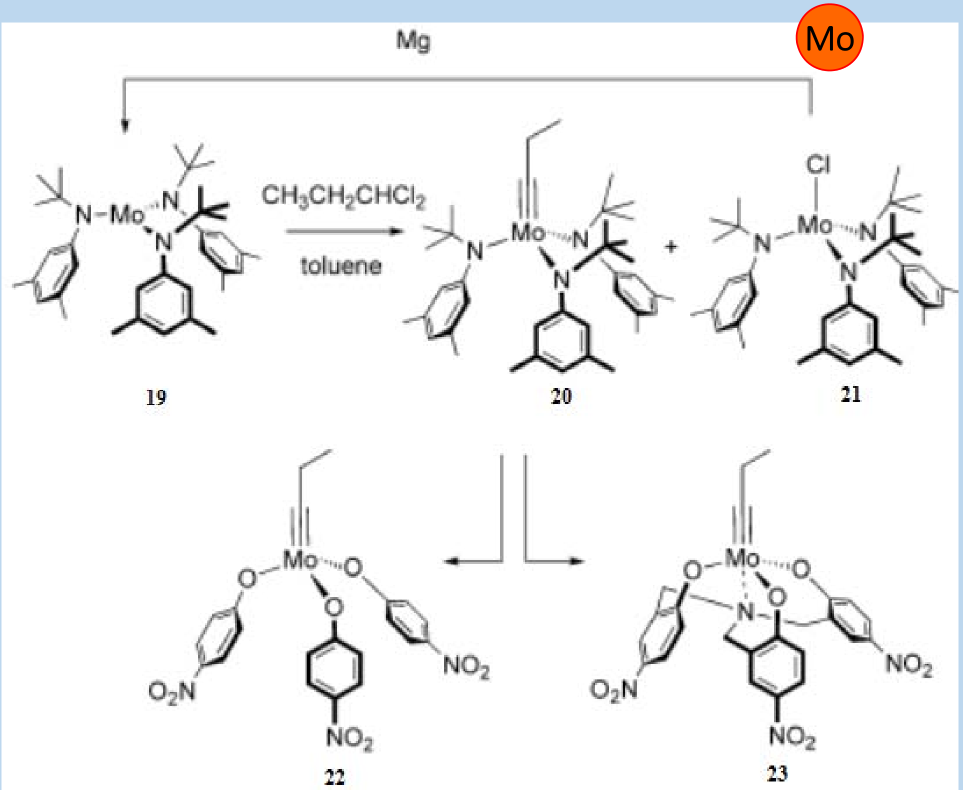
- Catalyst 23
  - Tridendate ligand increase catalyst lifetime and scope
  - High metathesis activity
  - Tolerate aldehyde and nitro groups



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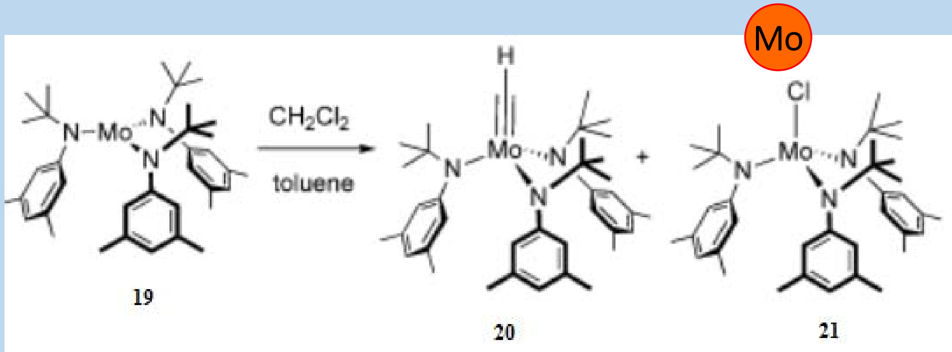

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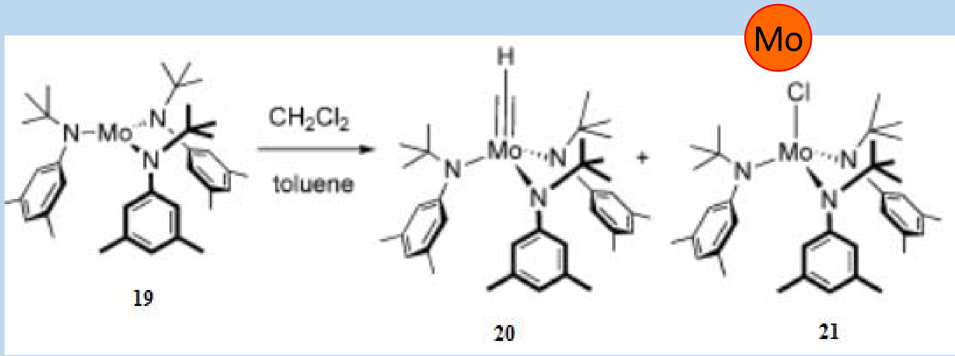

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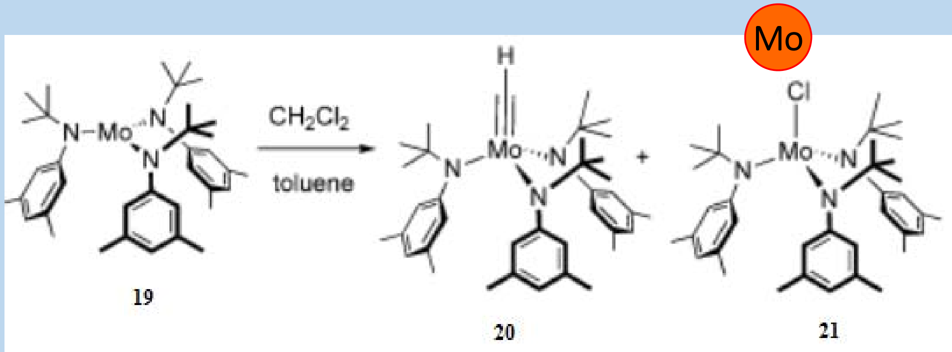

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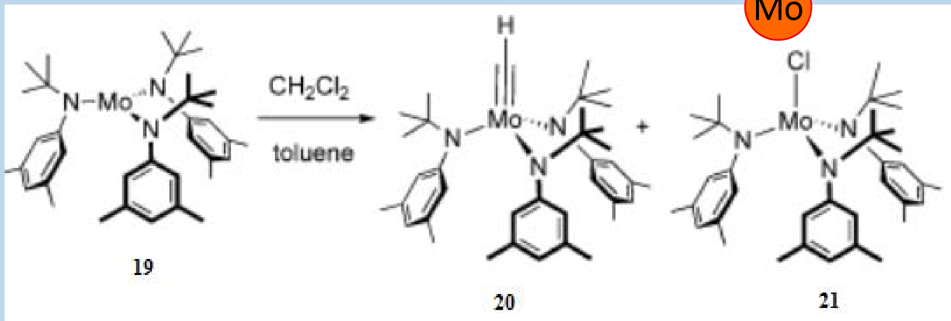

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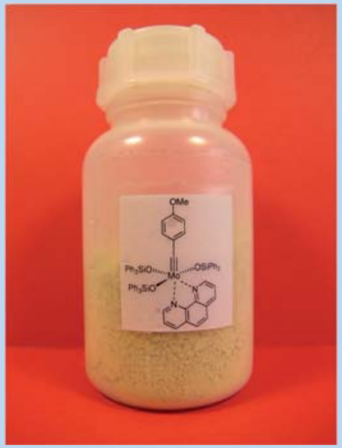

- Importance to **develop more robust, more user-friendly alternatives**

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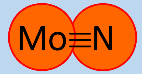
3. From Nitrile/Alkyne Cross-Metathesis to Improved Catalyst Design



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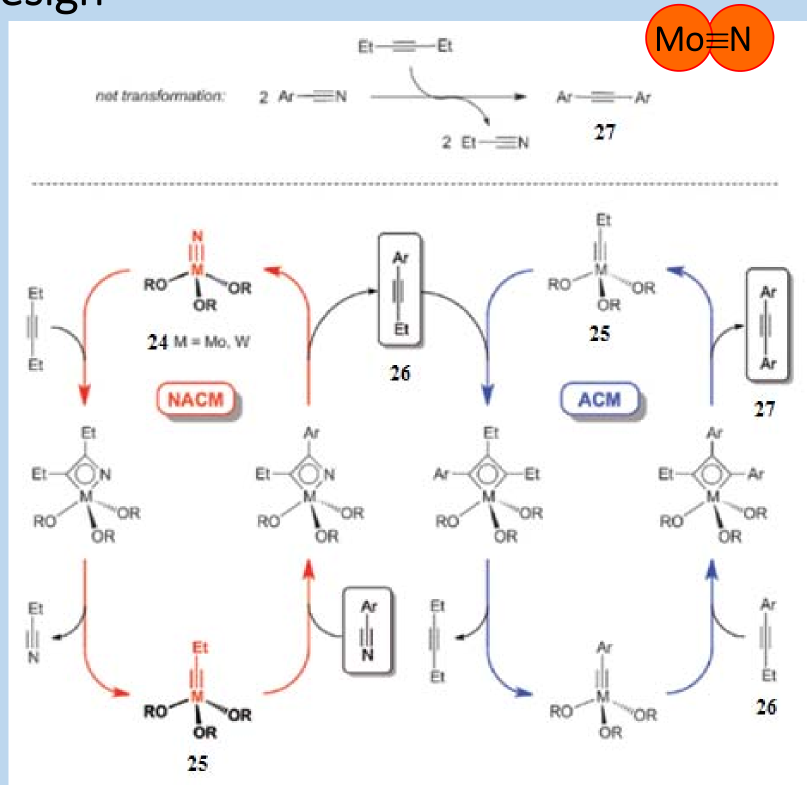

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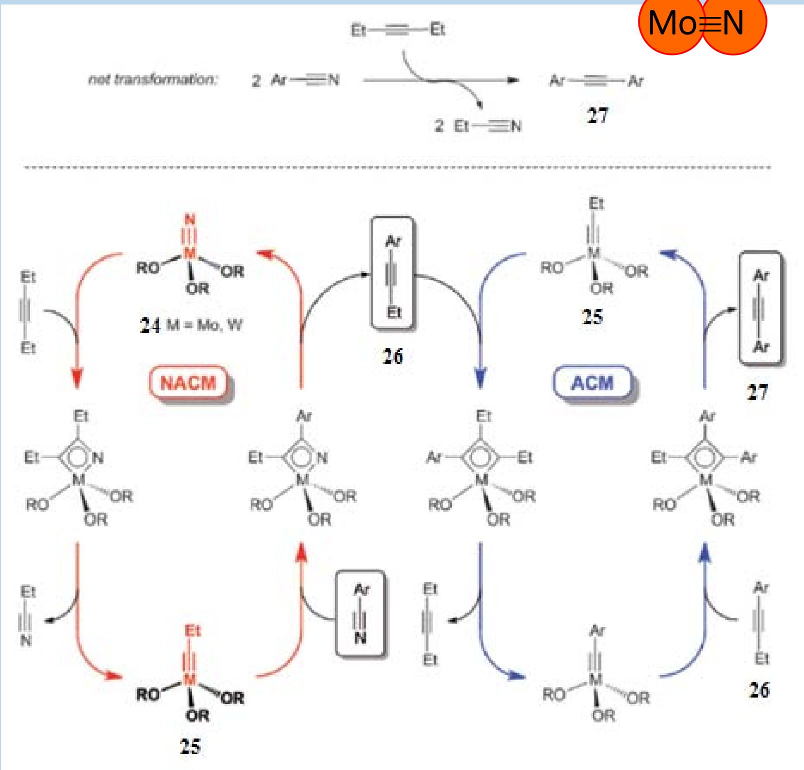

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- Two lessons learnt:
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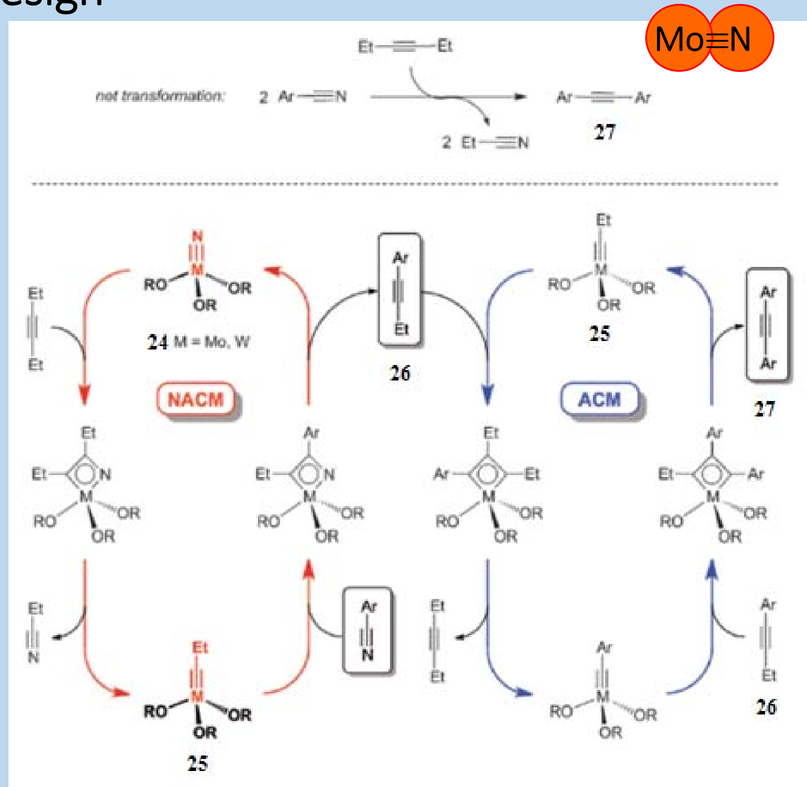
  - W or Mo nitrides as precatalysts for alkyne metathesis



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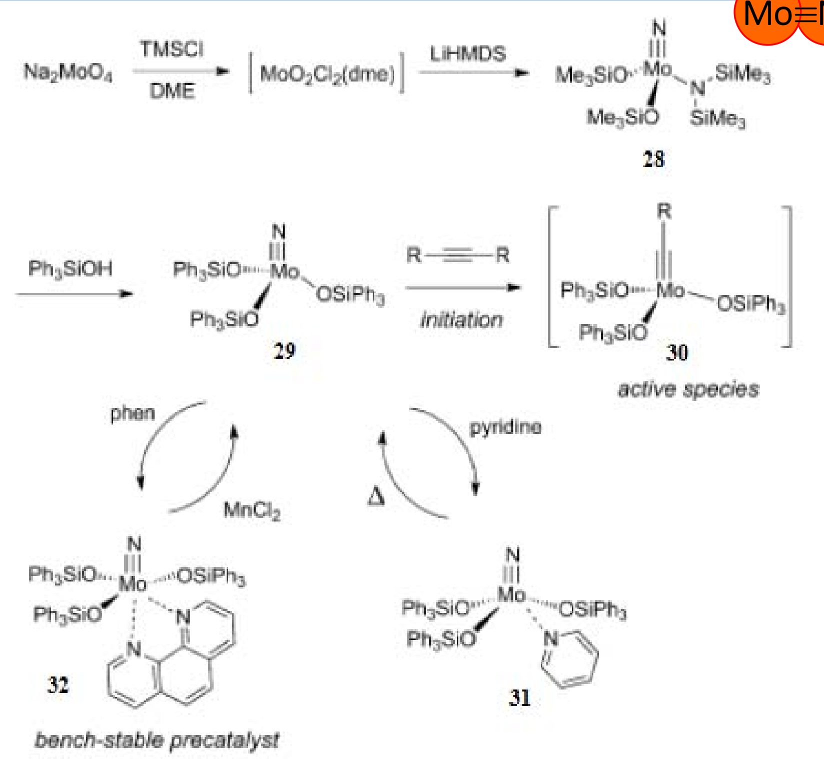

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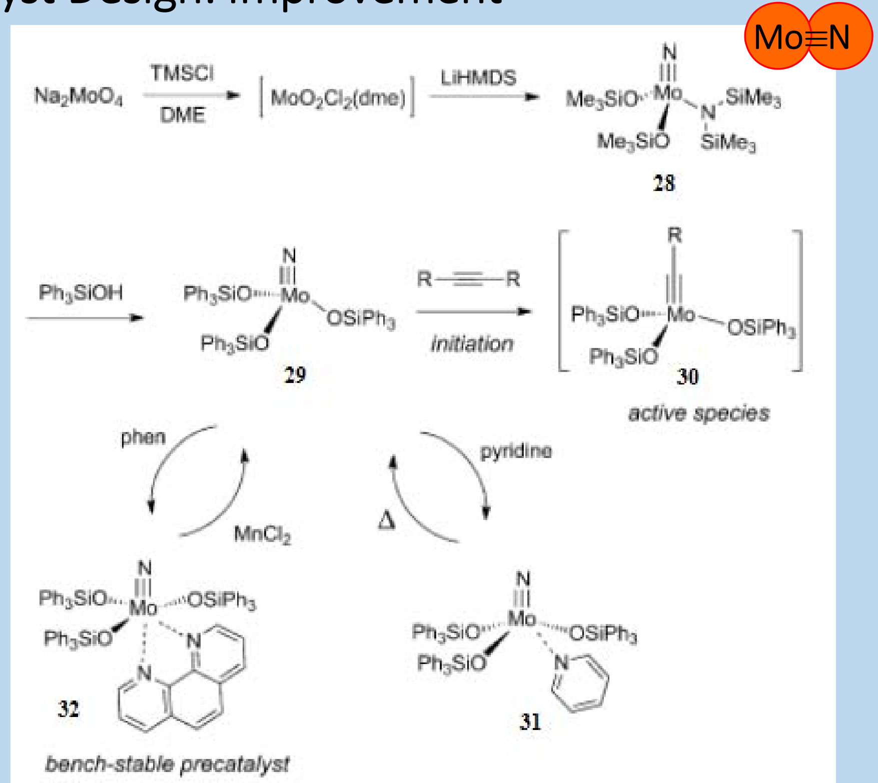

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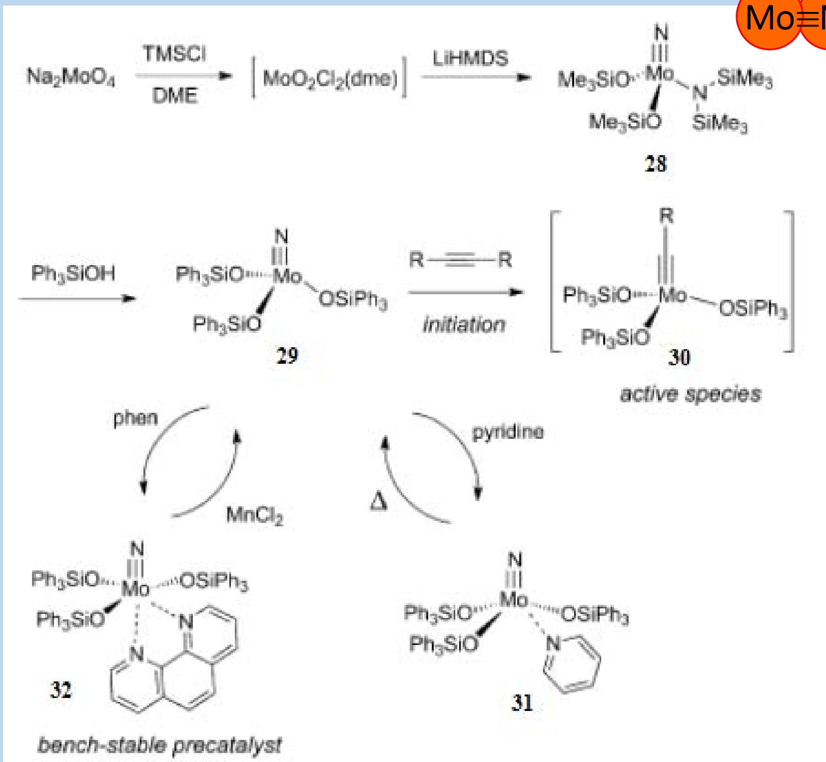

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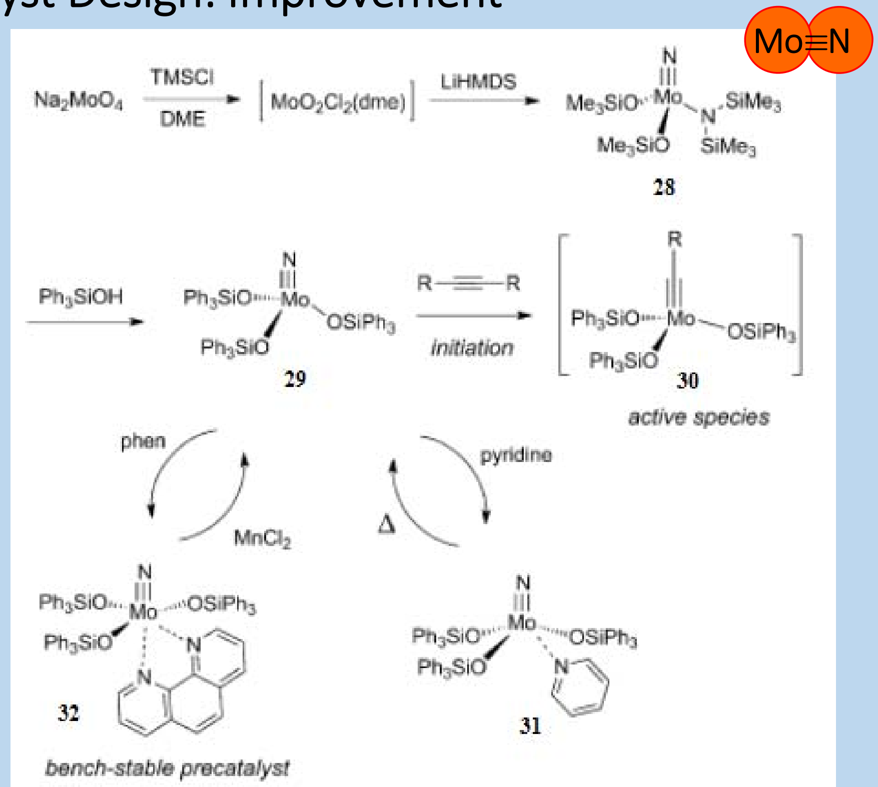

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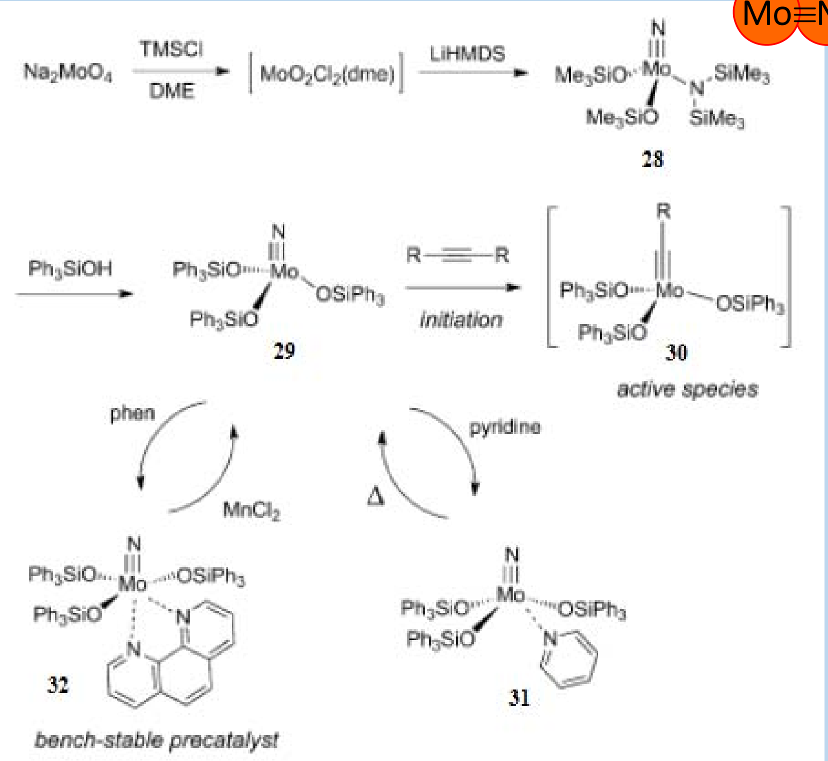
  - **Tolerate** many functional groups
  - **Convert aldehydes and acid chlorides** into **nitriles**

Mo≡N



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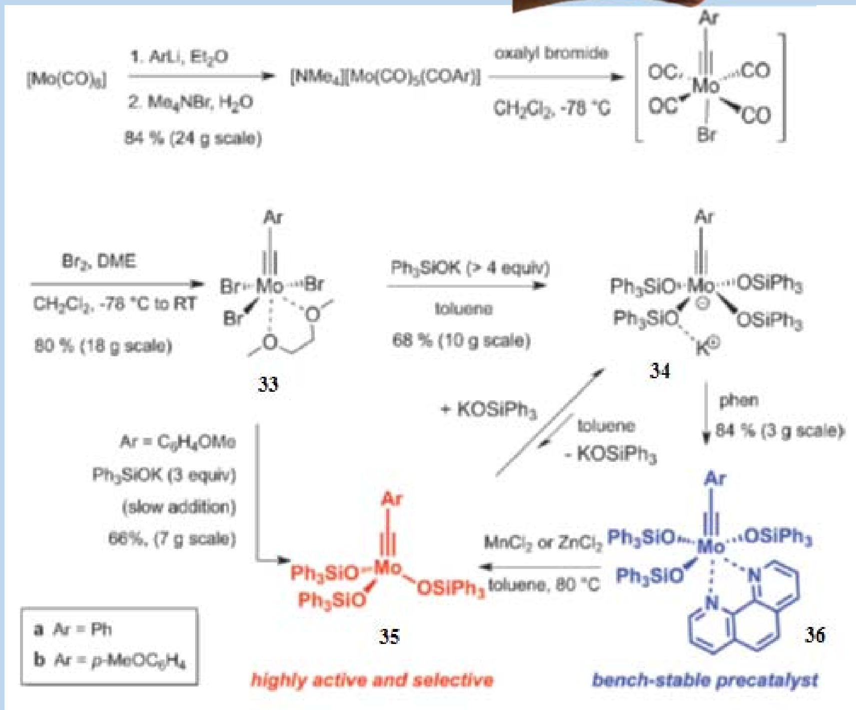
- Design of **new alkylidynes** catalyst **based** on previous **nitride complexes**



B. Haberlag, X. Wu, K. Brandhorst, J. Grunenberg, C. G. Daniliuc, P. G. Jones, M. Tamm, *Chem. Eur. J.* **2010**, *16*, 8868 - 8877.
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- **Bench stable catalyst**
  - Complexation with phenanthroline
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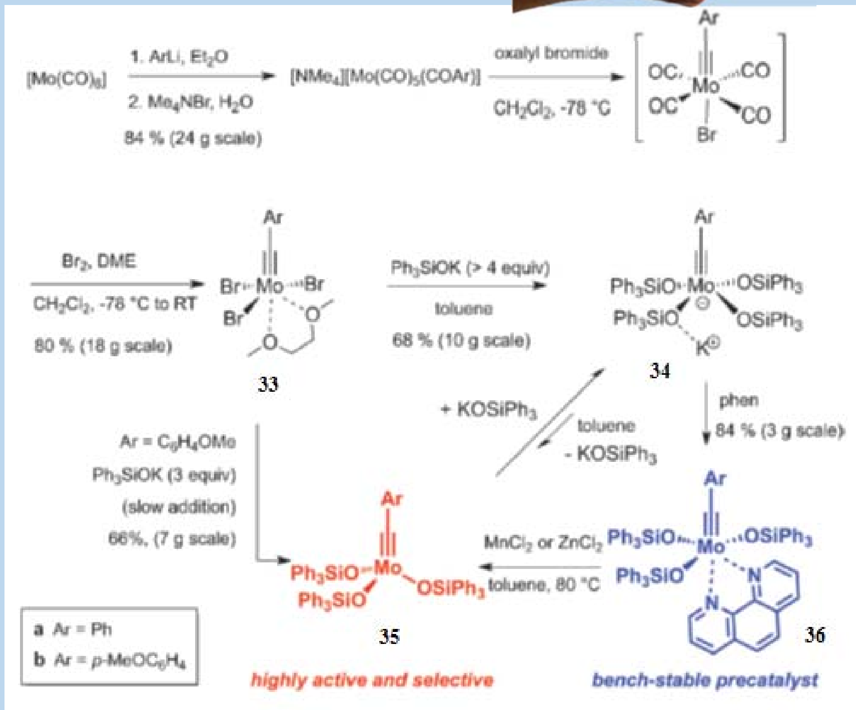

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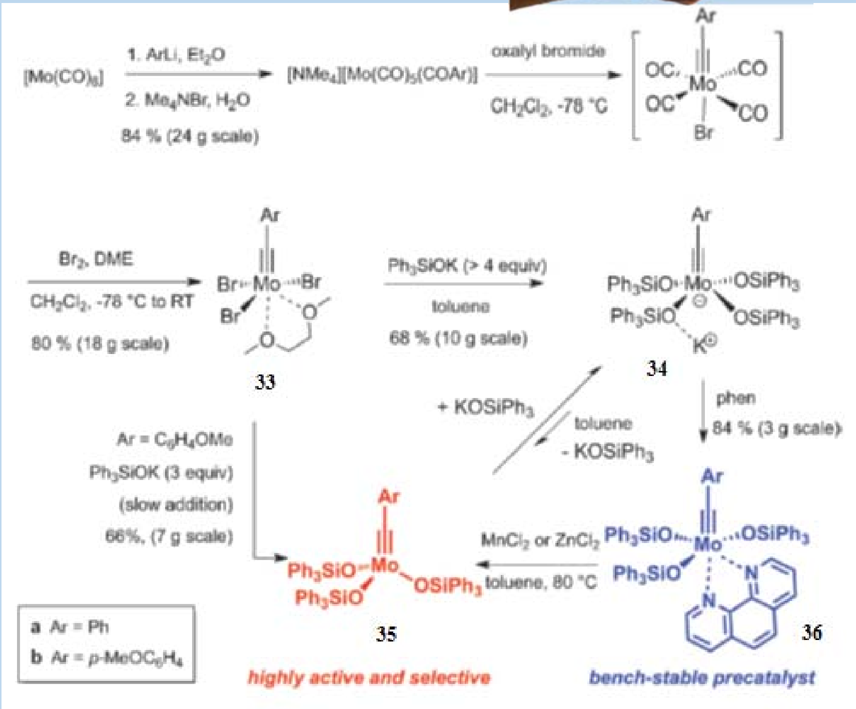

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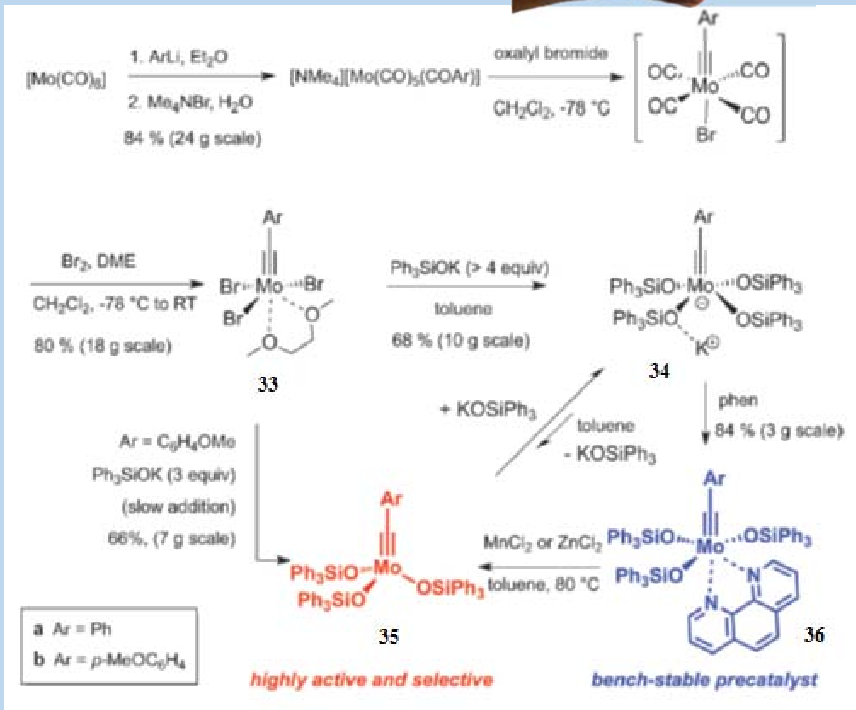

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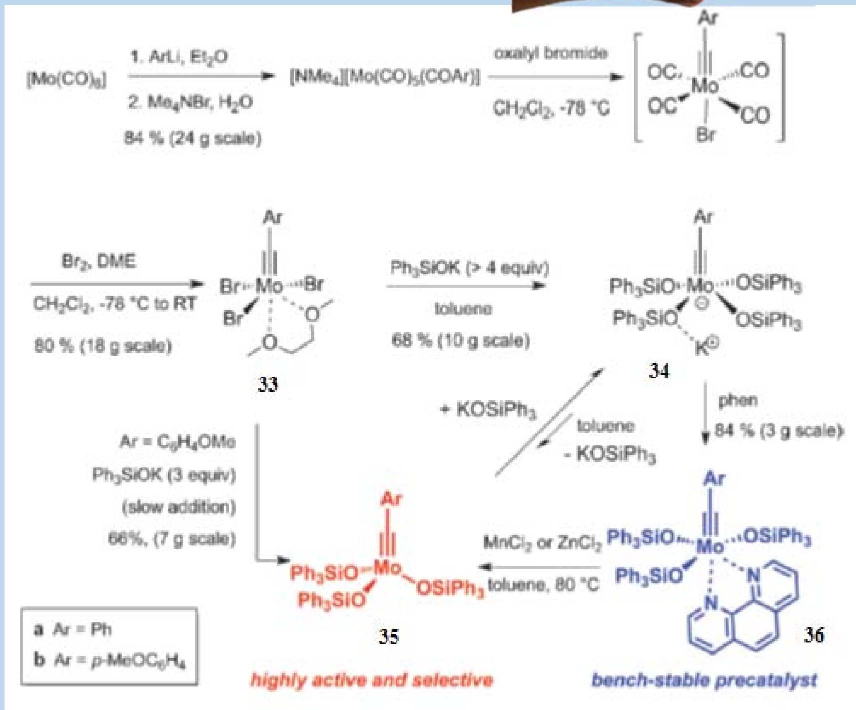
- **Best alkyne metathesis to date**



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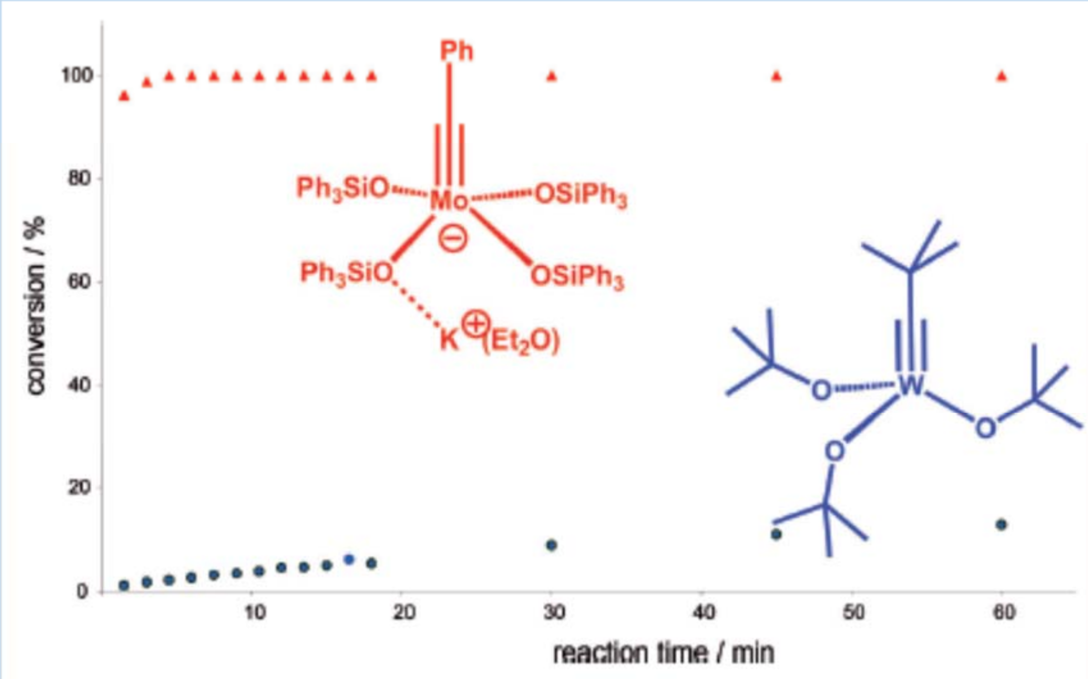
4. From the Glovebox to the Benchtop: Catalysts with Improved Activity and Stability

- Old vs new generation catalyst
- Reaction with **1-phenyl-1-propyne**
- New catalyst:
  - 1 mol% catalyst loading
  - **Quantitative** after **< 5 min** at rt
- Old generation:
  - **< 20% conversion** after 1h



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- Old vs new generation catalyst

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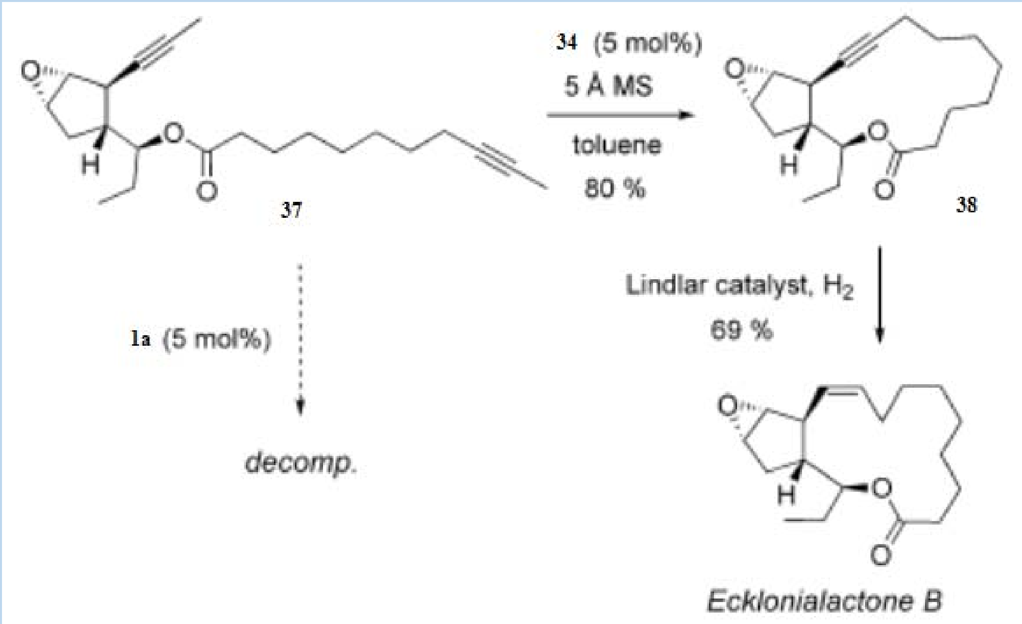

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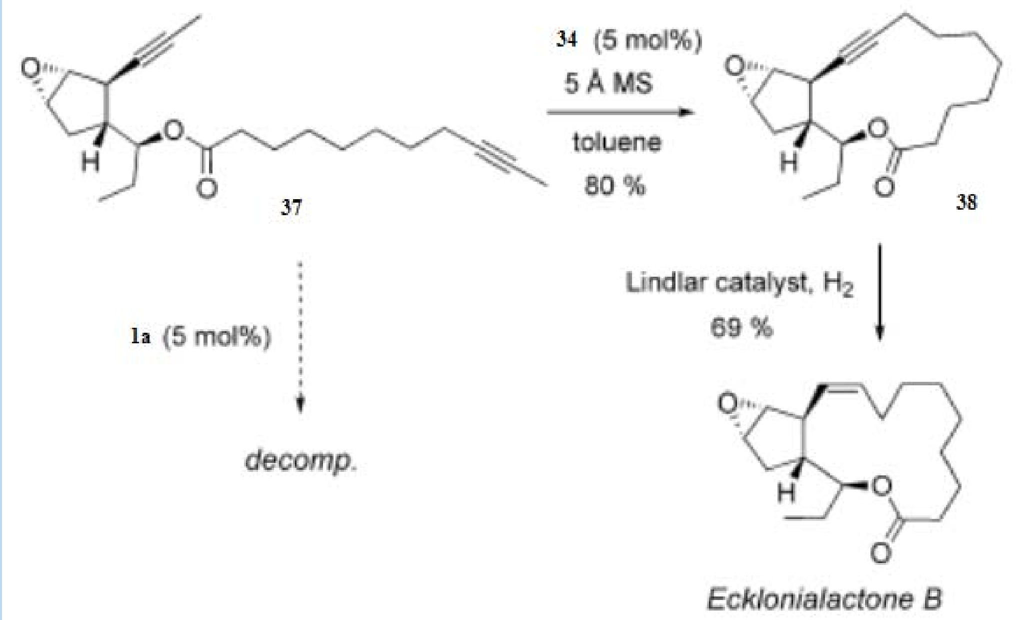
  - **Destroy** acid-sensitive epoxide **37**
  - **Deactivated** by basic nitrogen and divalent sulfur



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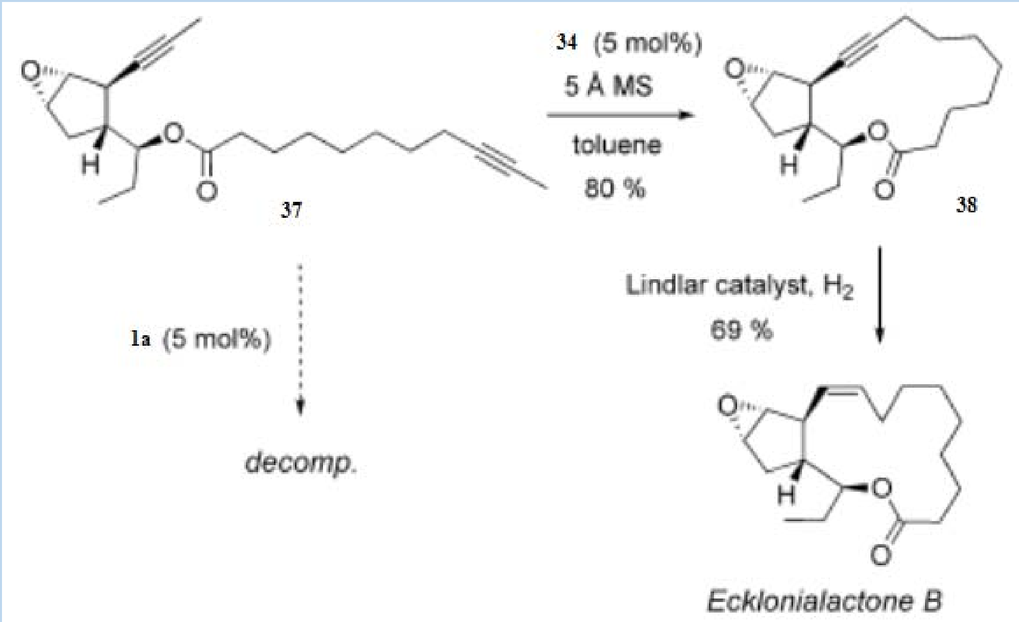
- New catalyst:
  - Lead to product 38 with excellent yield
  - Tolerate pyridines, thiazole and thioethers



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- Avantages and limitations

- Tolerate pyridines, thiazole, thioethers, esters, ethers, silyl ethers tosylates, ketones, amides, carbamates, aldols, acetals, spiroketals, epoxides vinyl epoxides, Aryl-X, alkyls chlorides, propargyl acetates, carbozoles, pyrones, trifluoromethyl, nitro groups

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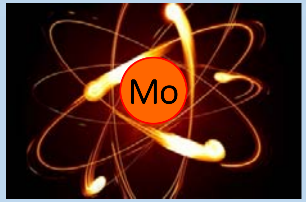
- Limitations
  - Aromatic aldehyde are endangered
  - Grubbs and Schrock **alkene metathesis catalysts react with alkynes**

5. Structural Considerations and Adaptable Electronic Features



- Steric factors
  - Ph_3SiO groups is not that bulky (4 Ph_3SiO)
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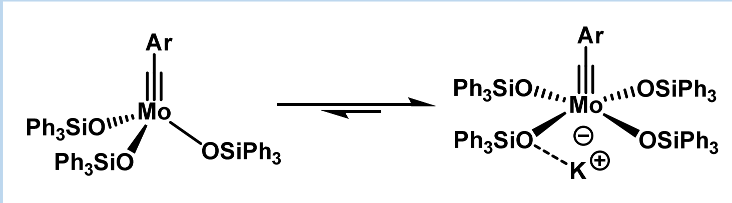

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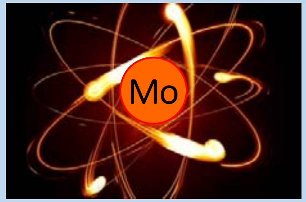

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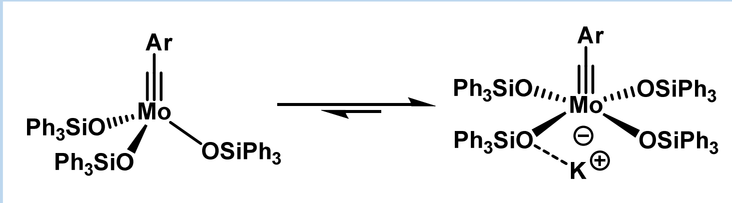

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  - Siloxides **weaker donors** than alkoxides
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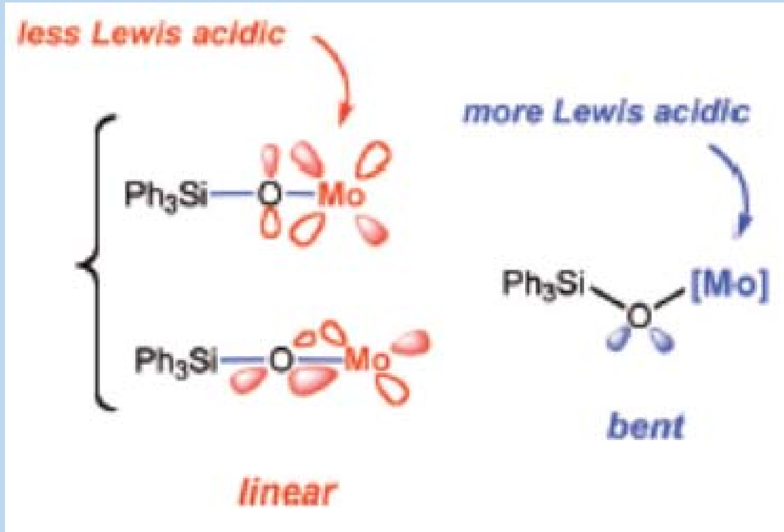
  - Bending, worse O → Mo bonding, **increase Lewis acidity**



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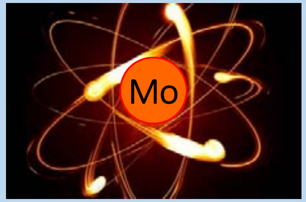

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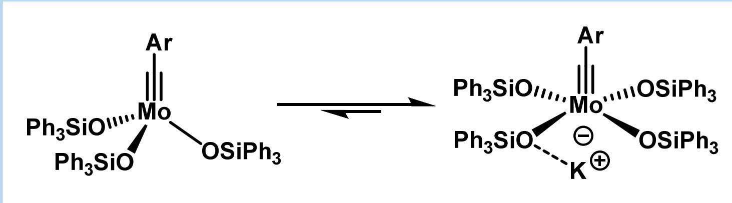

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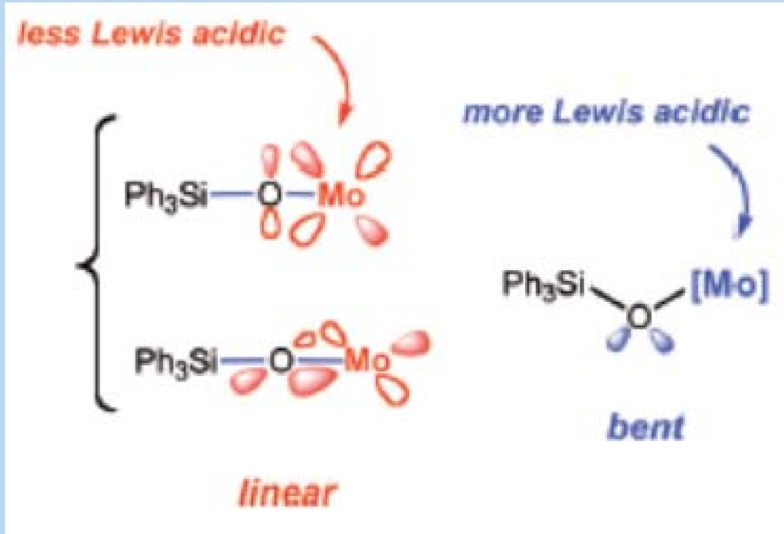

- X-ray: **stretching** and **bending Mo-O-Si** is **facile**
  - **Catalyst may adapt** during the catalytic cycle
    - ➢ Could be **applied in other catalytic transformations**

6. Factors Influencing the Catalyst Lifetime

Mo

- Ph_3SiO ligands exert a **positive effect** on the **catalyst lifetime**
- **Hydrolysis:** anhydrous solvents are mandotory

Development on terminal alkynes metathesis:
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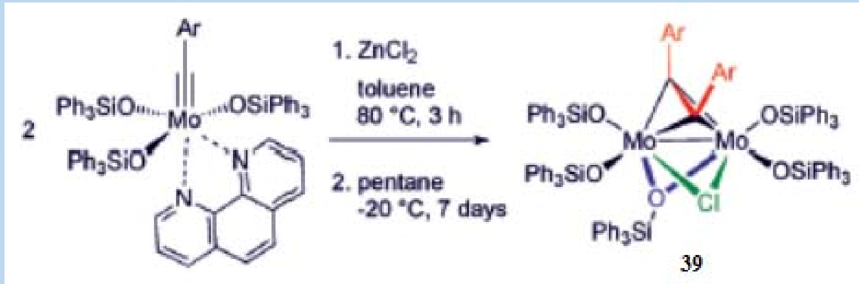

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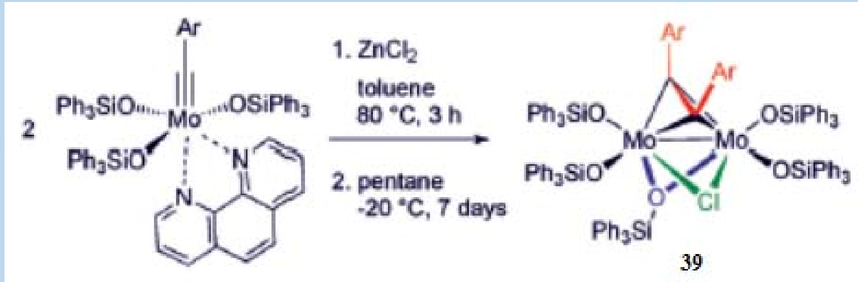
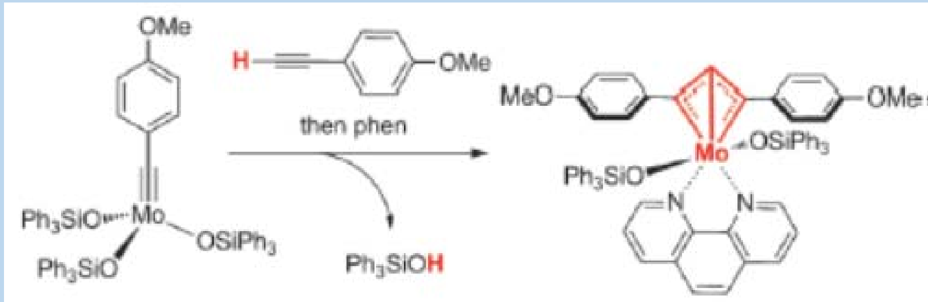


- Alkyne metathesis of **terminal alkynes in development**



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7. Molecular Sieves as Butyne Scavengers

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  - ➢ to shift the equilibrium
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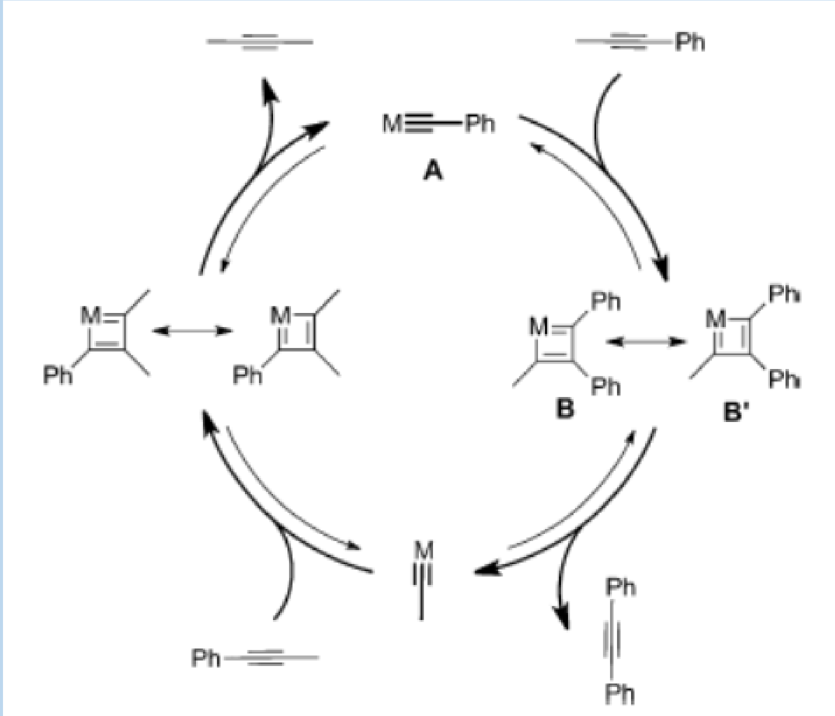

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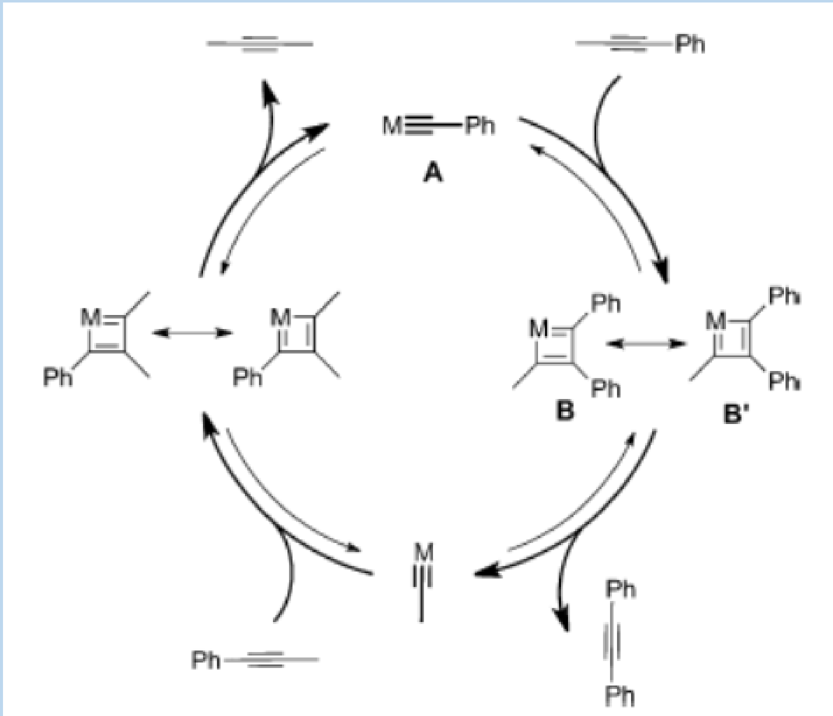

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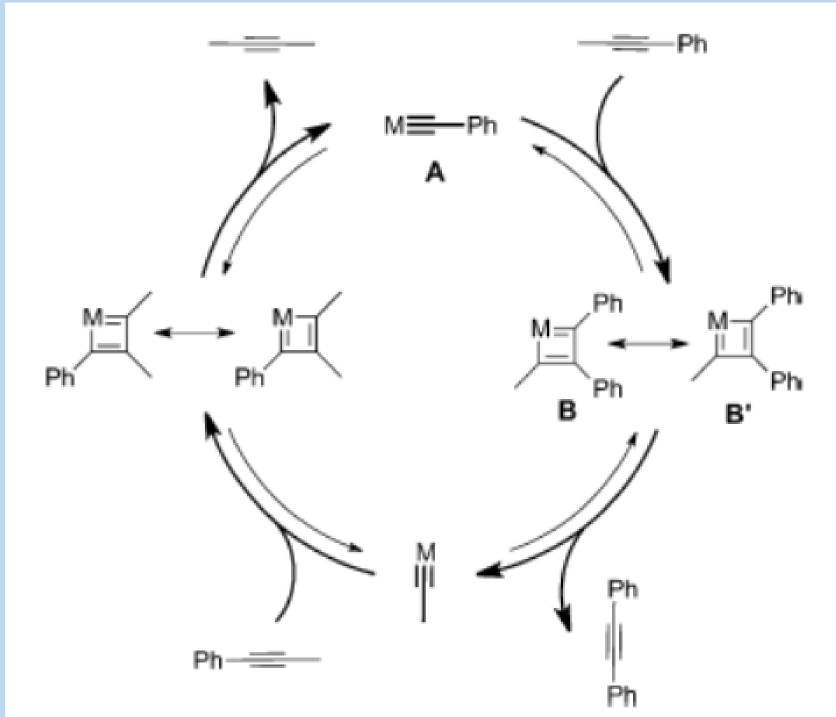

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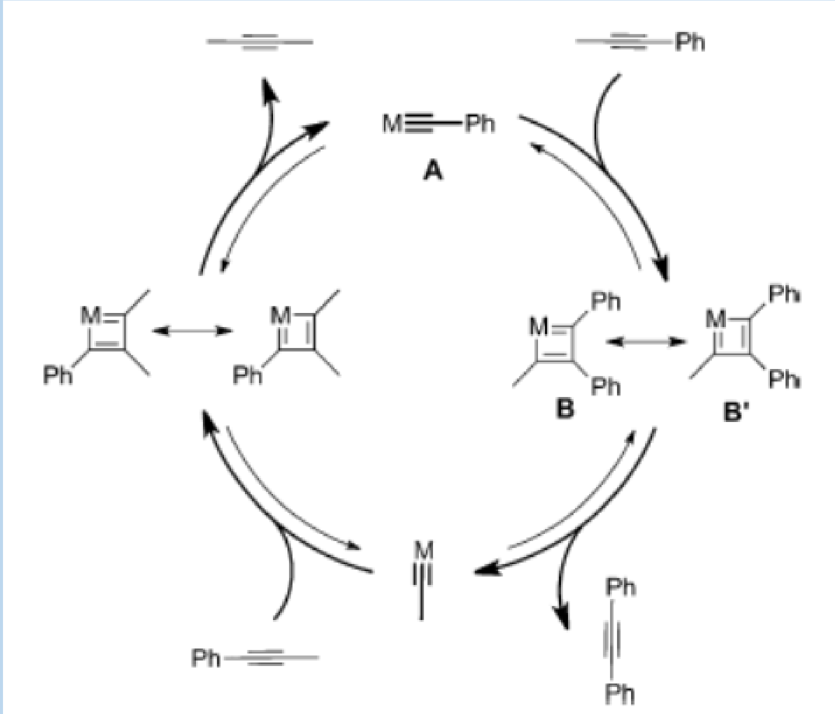

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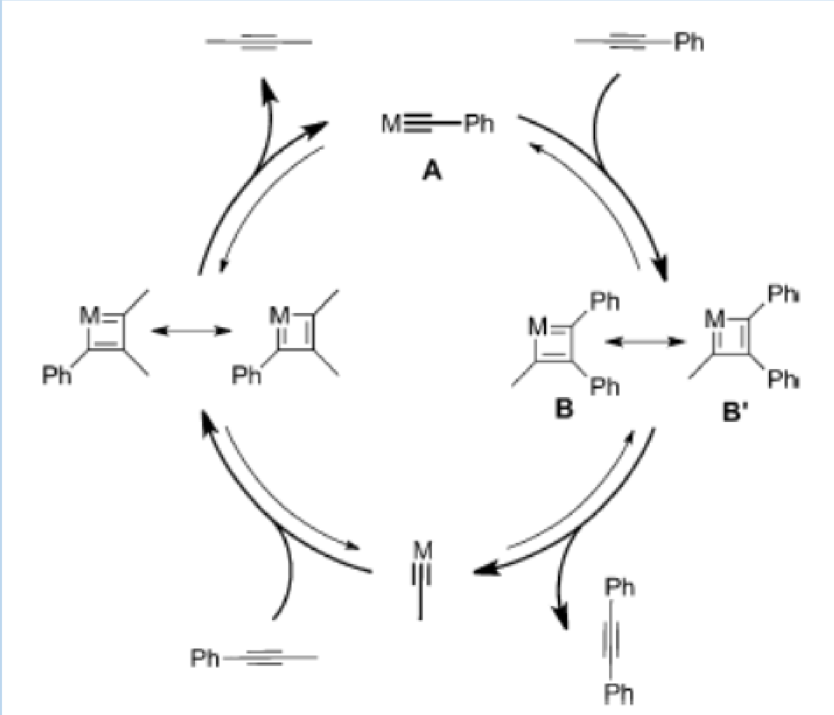

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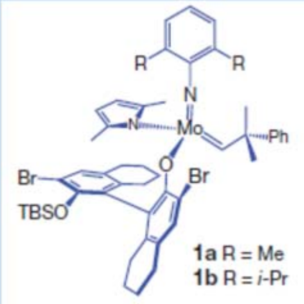

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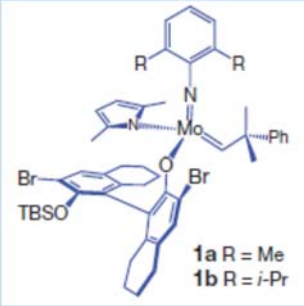
  - **No application** in total synthesis **yet**



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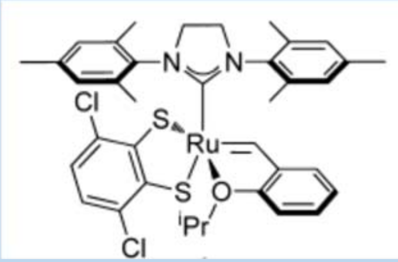

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Introduction → Catalyst Development → **Total Synthesis** → Conclusion

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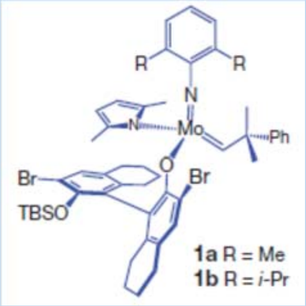
  - **No application** in total synthesis **yet**
- **Alkene synthesis** is **more developped** and **little shorter** than **alkyne synthesis**



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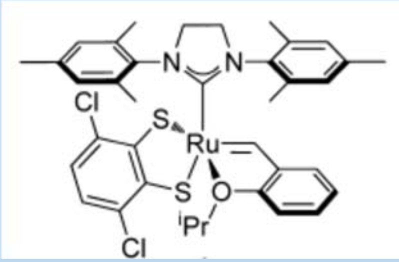

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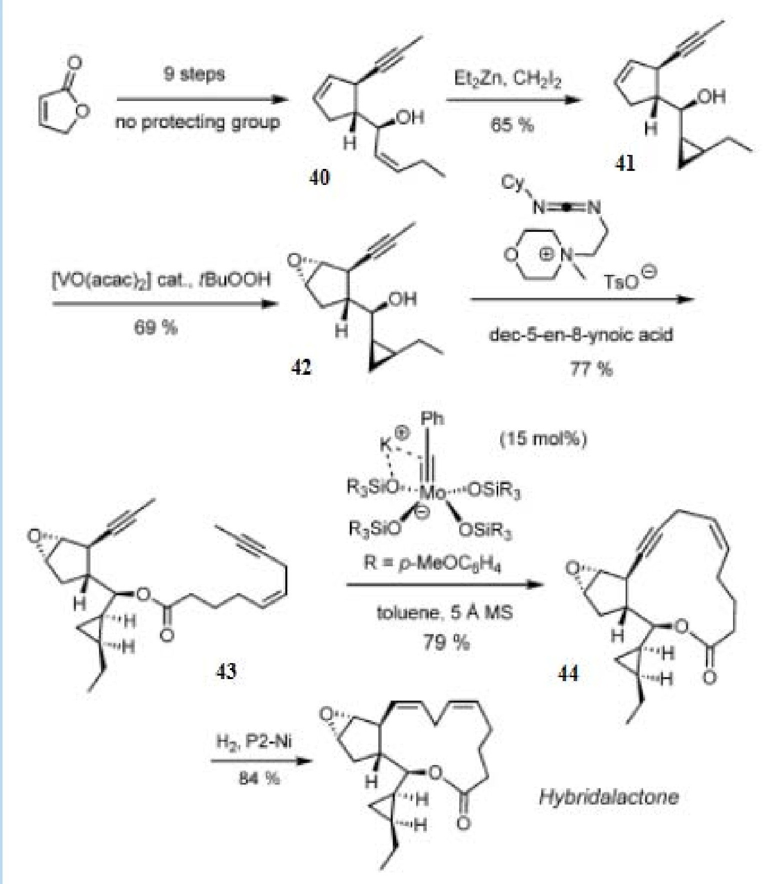
- Butenolide 40 prepared **without protecting group**



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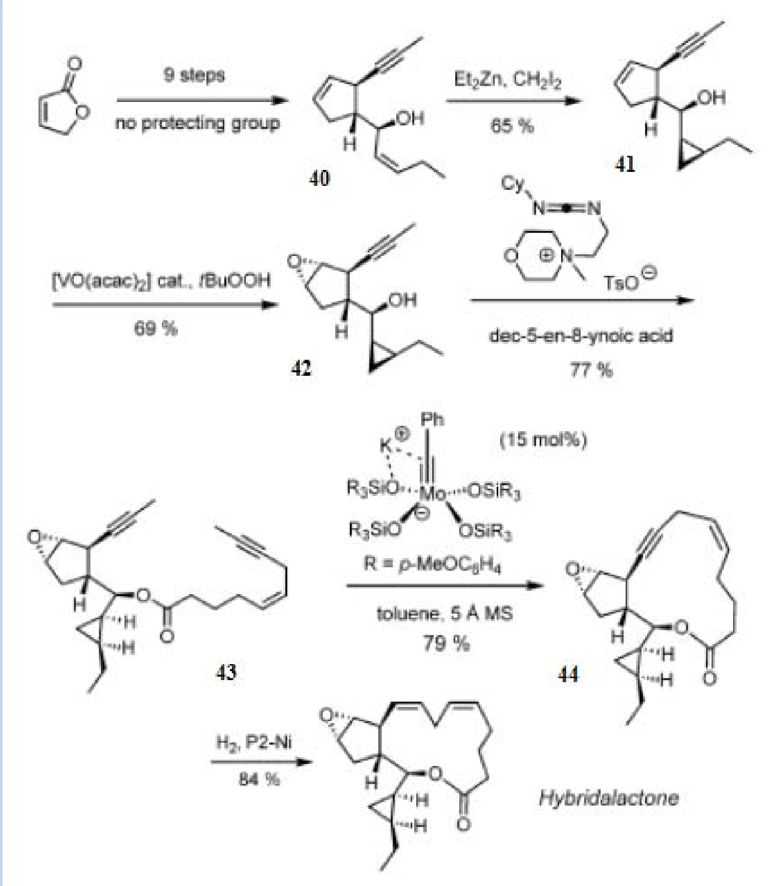

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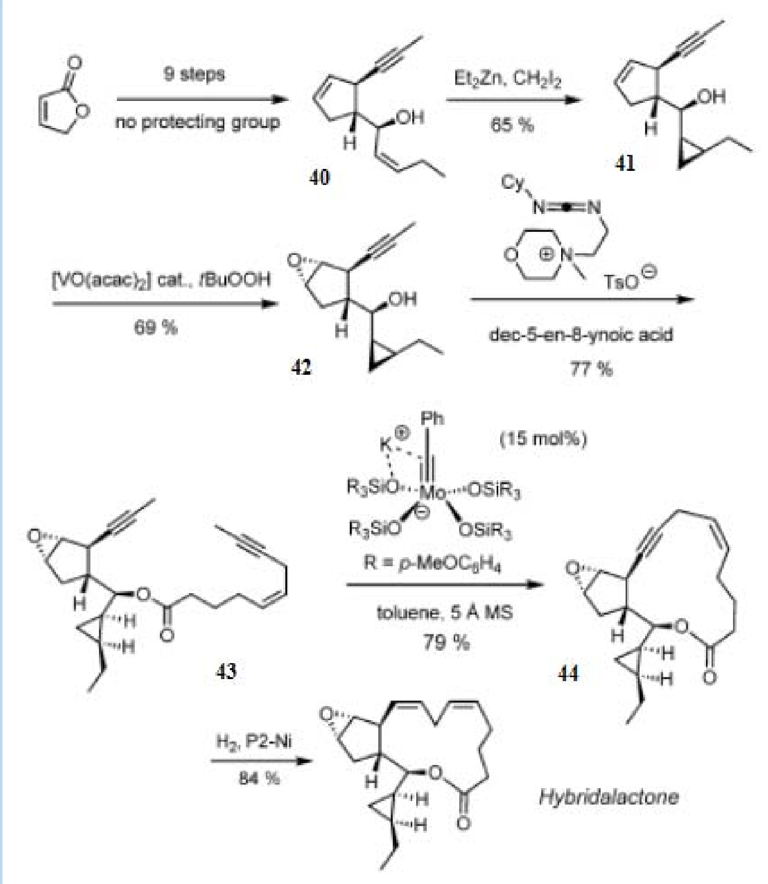

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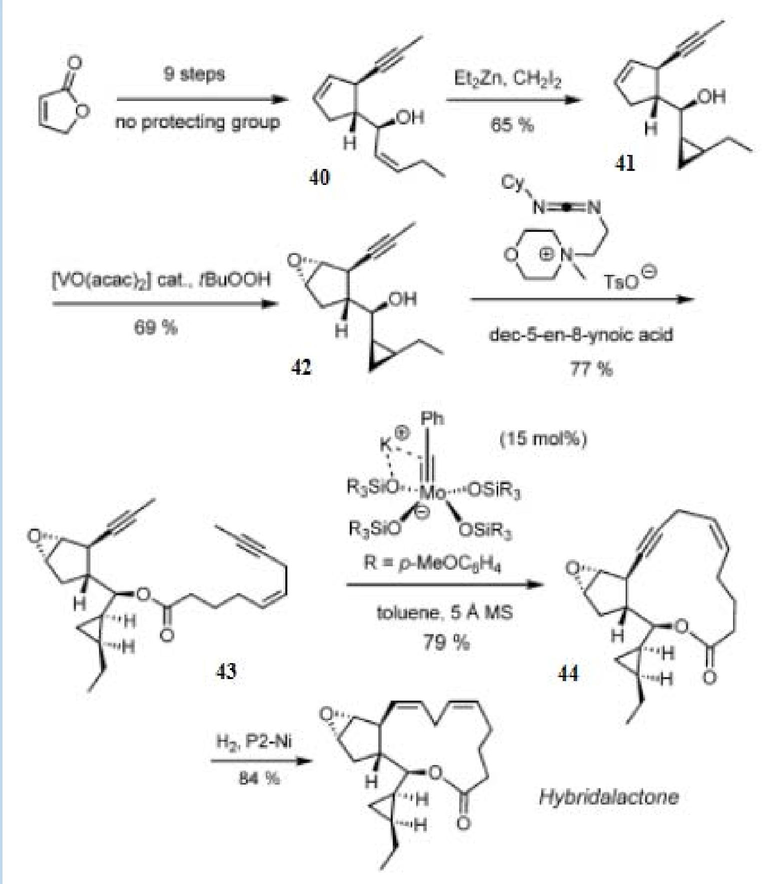
- Did not work with previous catalyst
- Structure **not accessible with RCM** (mixture of rings of different sizes)



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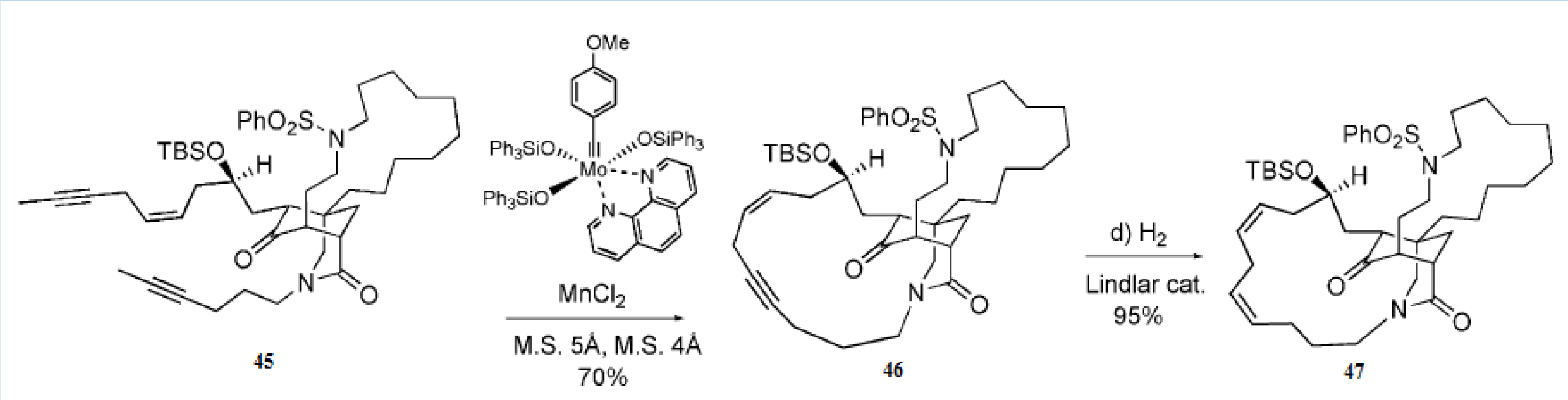

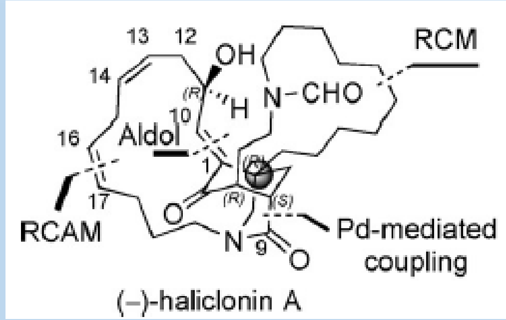

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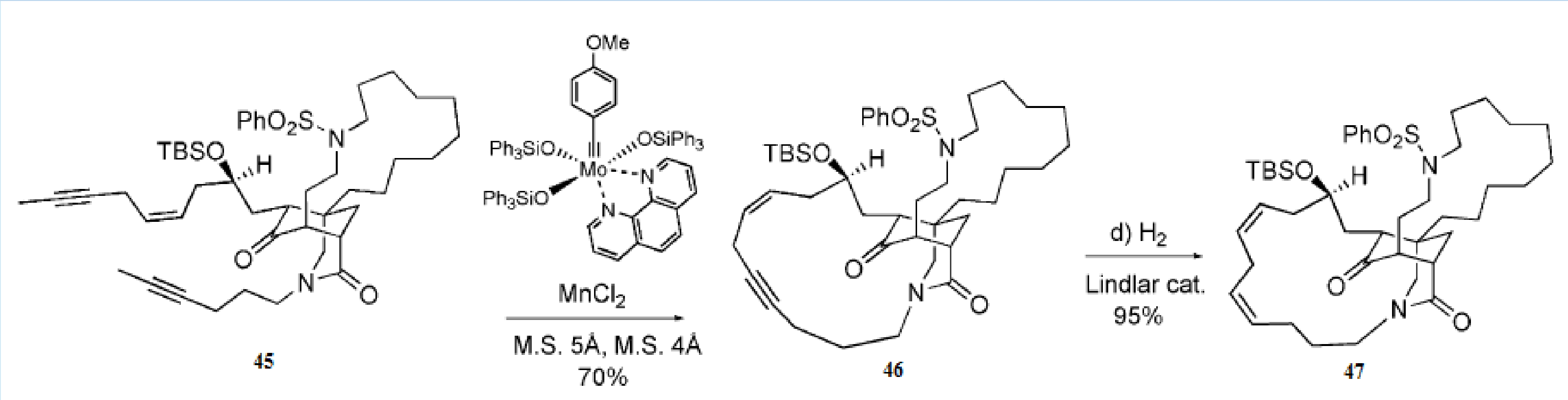

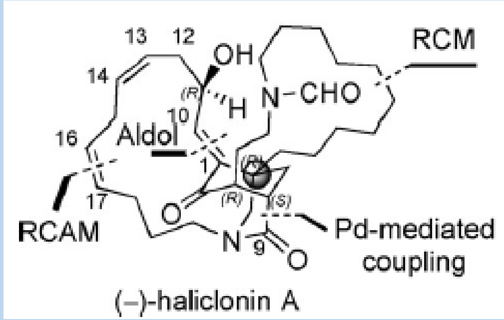

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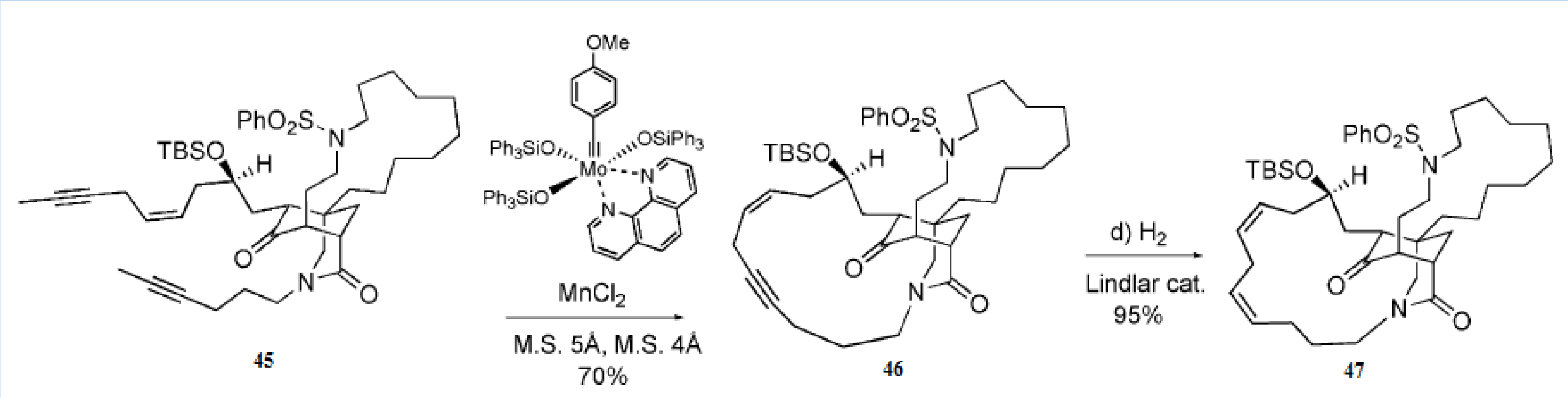

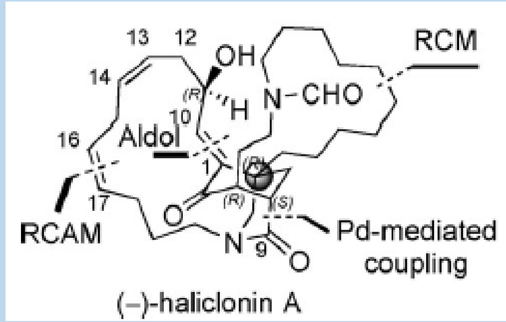

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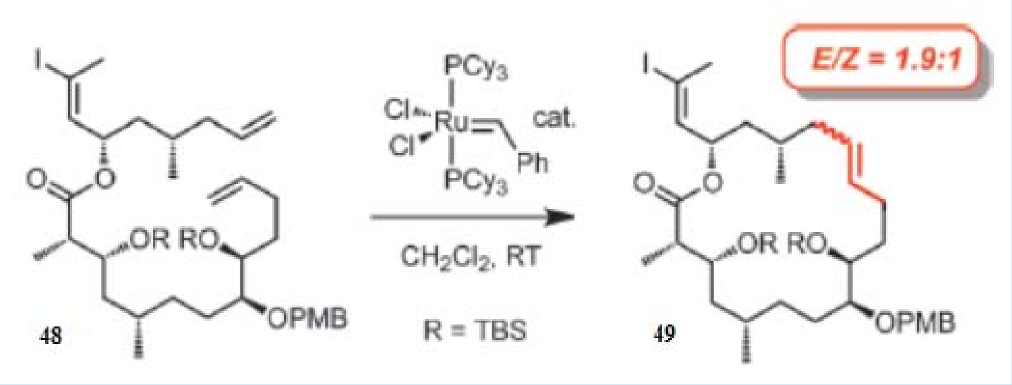

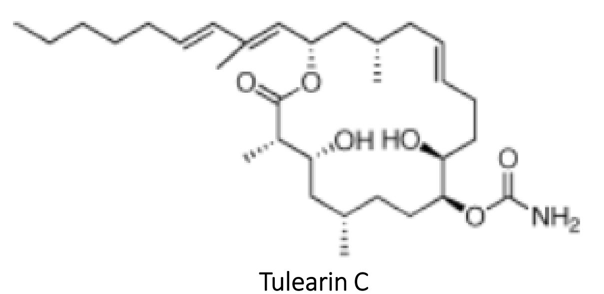

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- **Low diastereoselectivity** on RCM (E/Z = 1.9:1)

A. L. Mandel, V. Bellosta, D. P. Curran, J. Cossy, *Org. Lett.* **2009**, *11*, 3282 - 3285.

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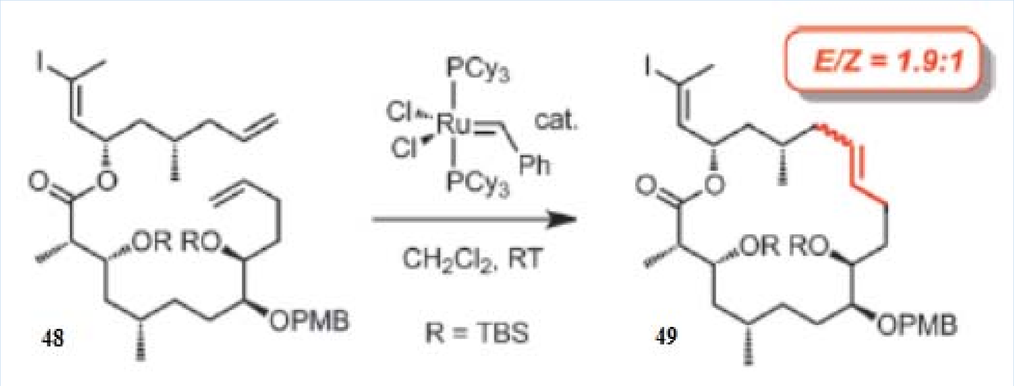

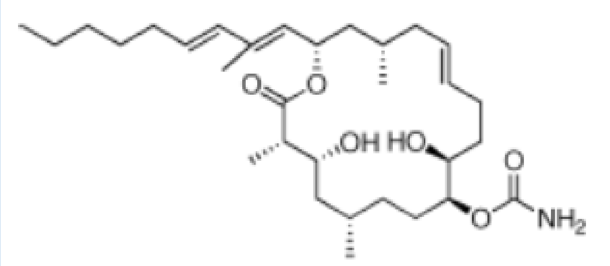

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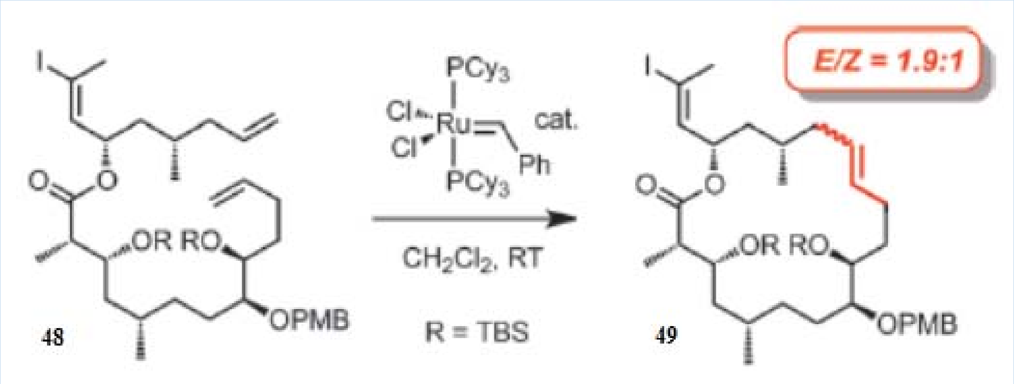

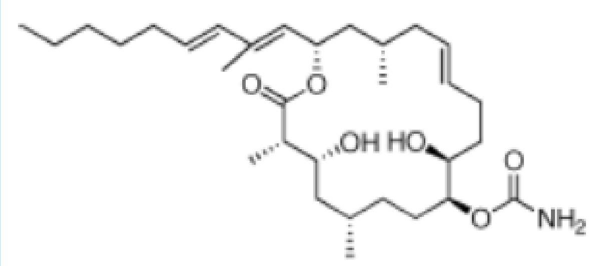

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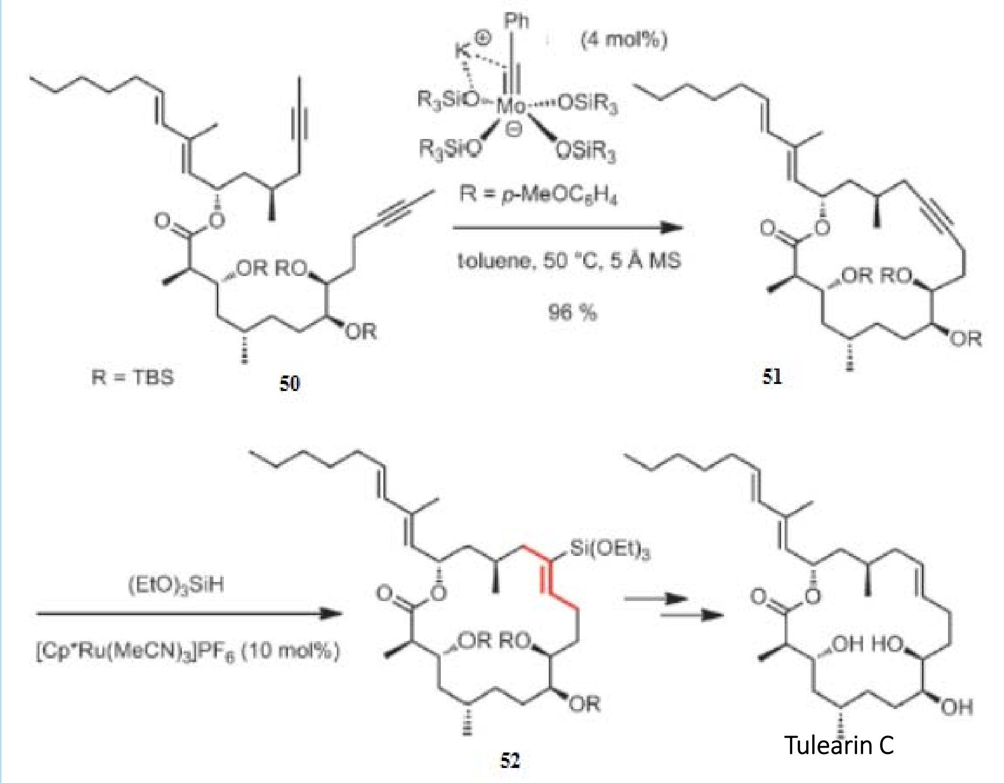

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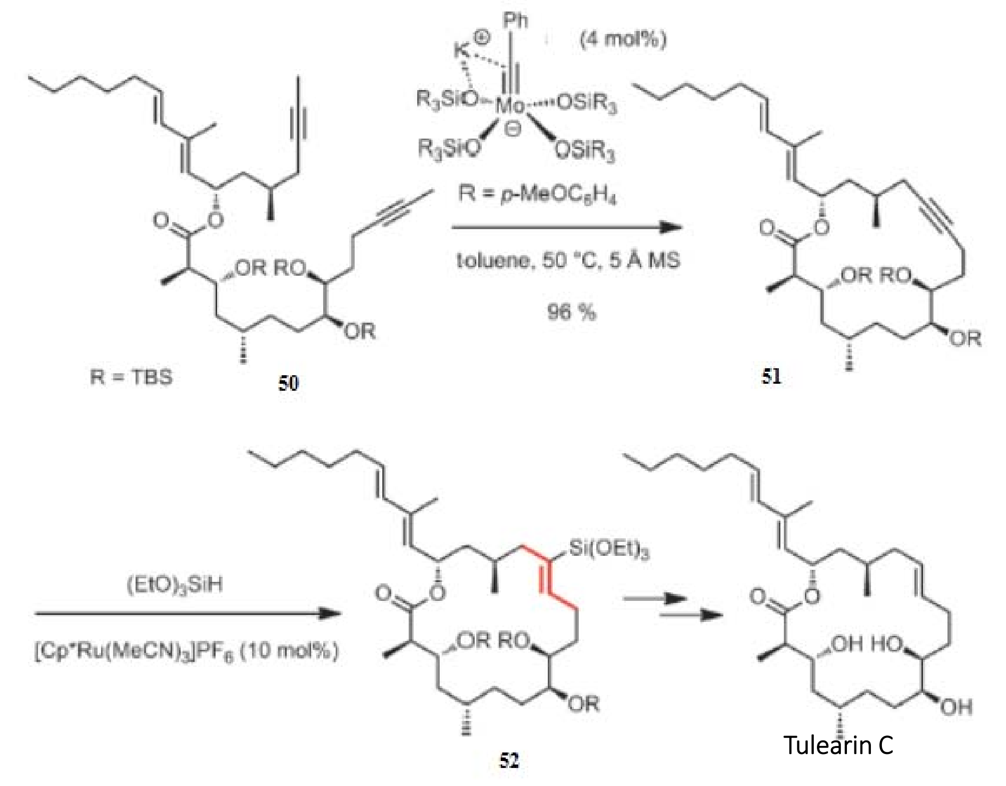

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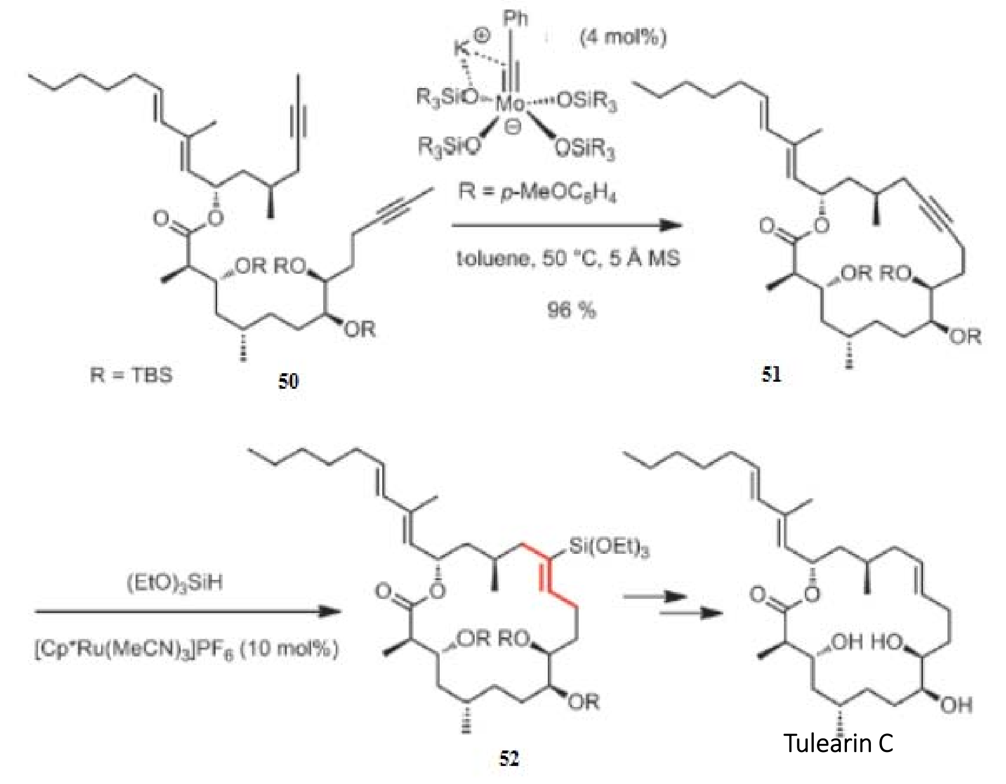

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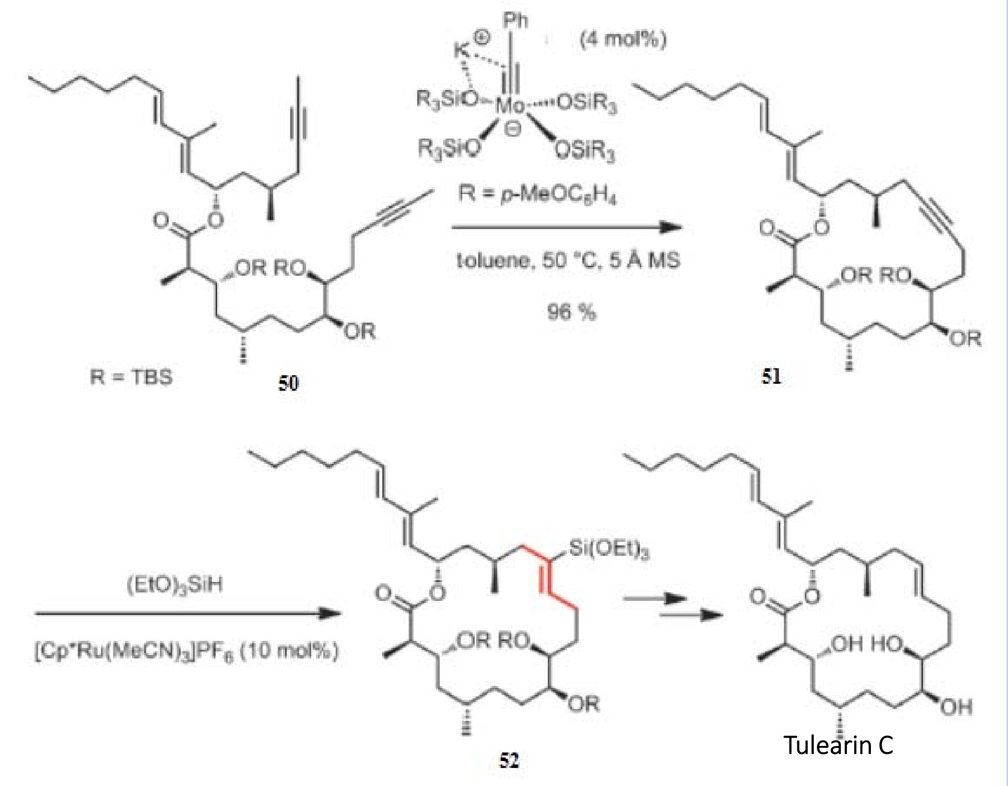
3. RCAM for the Preparation of E-Alkenes - Tulearin C by RCAM

- **Excellent yield** (96%)
- **Excellent diastereoselectity** (> 20:1) with Trost's hydrosilylation
- **RCAM** at the **end** the synthesis
  - **Impossible** with RCM
  - Highly convergent synthesis
- **Tolerates** MOM-protected alcohol, esters and alkenes
- **Orthogonality** RCAM/RCM



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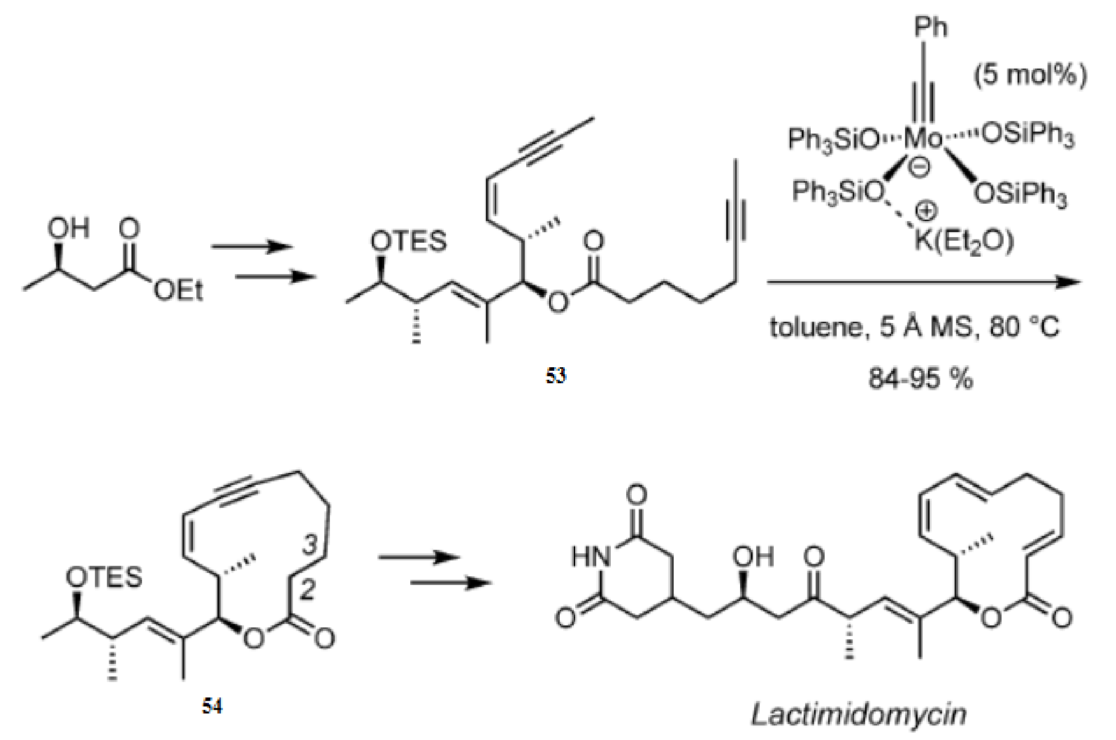
4. Enyne-Yne Metathesis - Preparation of Stereodefined 1,3-Dienes - Lactimidomycin

- Problematic with RCM
  - Internal alkene of 1,3-dienes often preferred



K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* 2010, *132*, 14064 - 14066.
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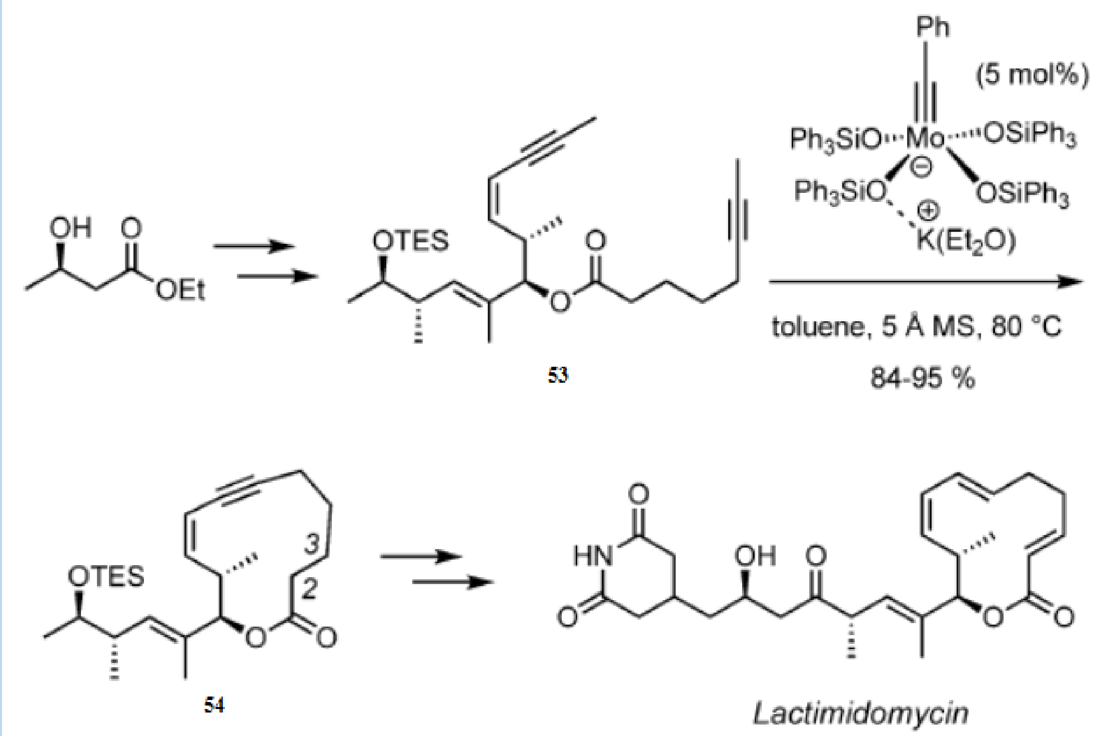

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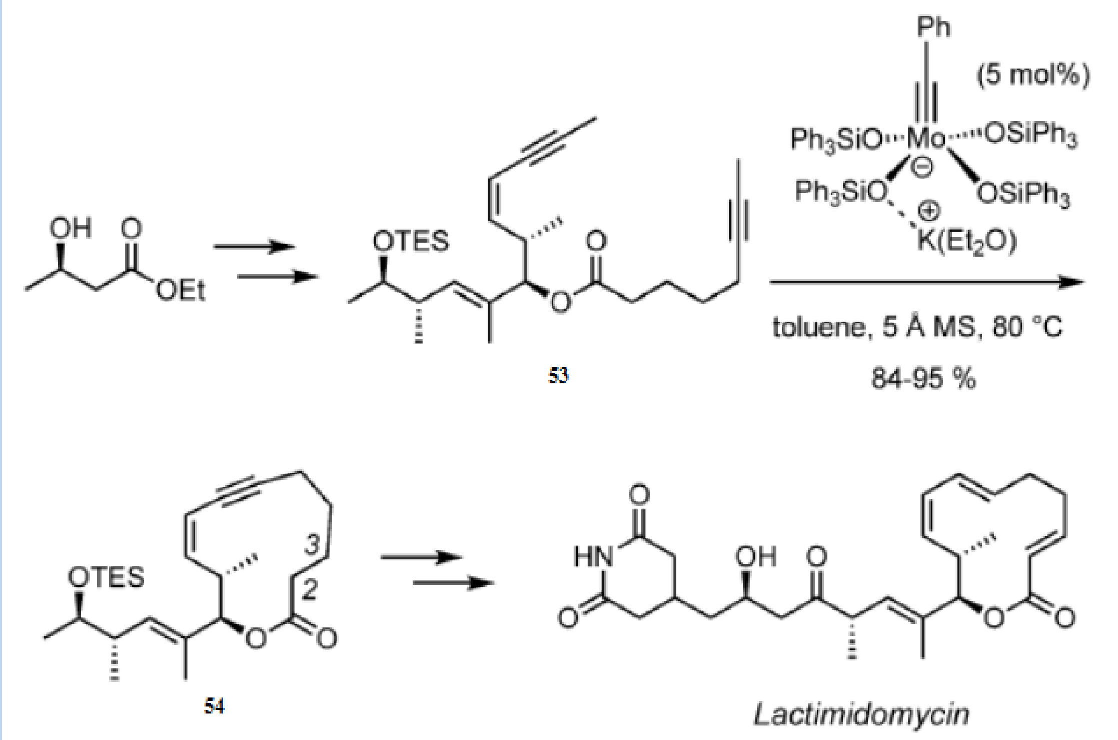

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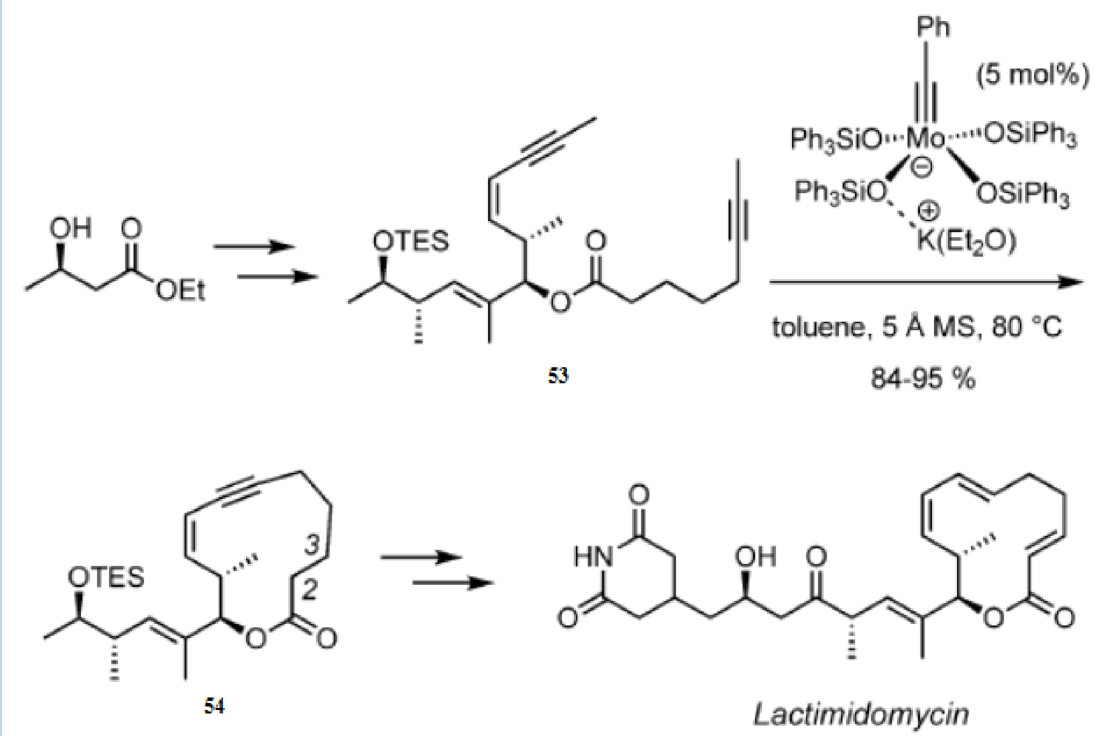

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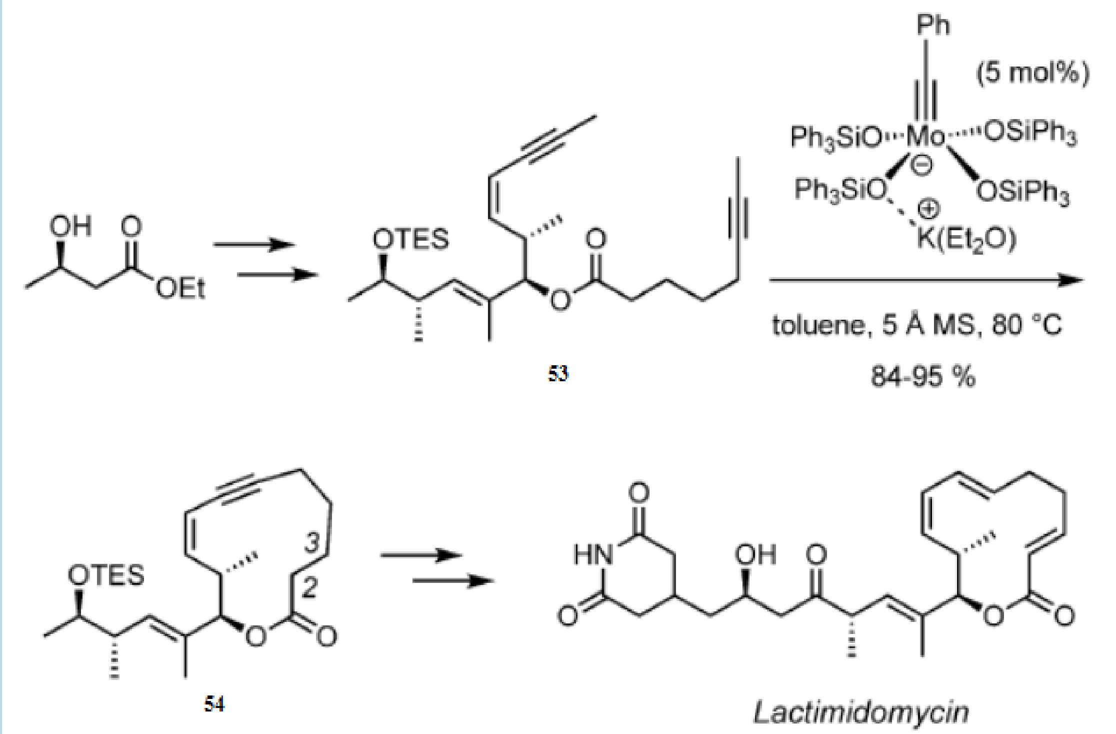
  - ➢ Preparation of **analogues** for biological testing
- Access to (E,Z)-dienes



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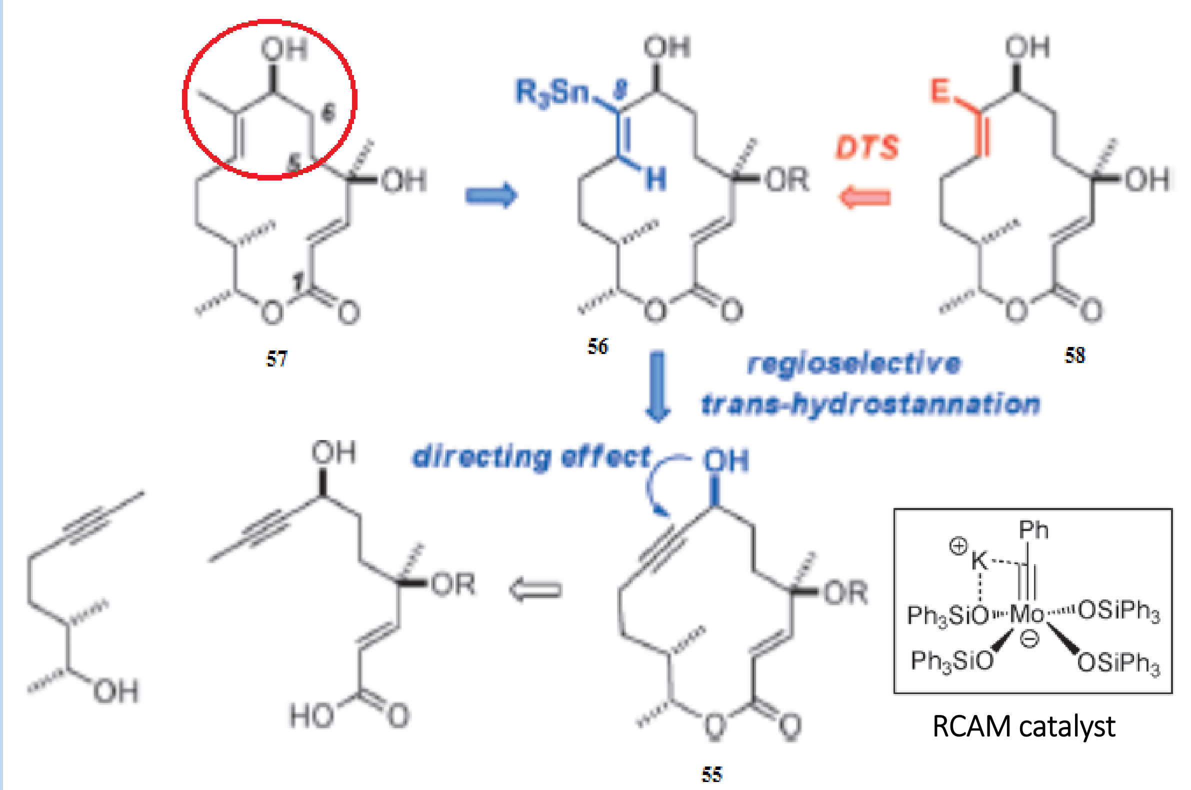
5. Trisubstituted alkene synthesis - 5,6-Dihydrocineromycin B

- *E*-configured 2-methyl-but-2-en-1-ol substructure
  - ➢ Present in countless natural products



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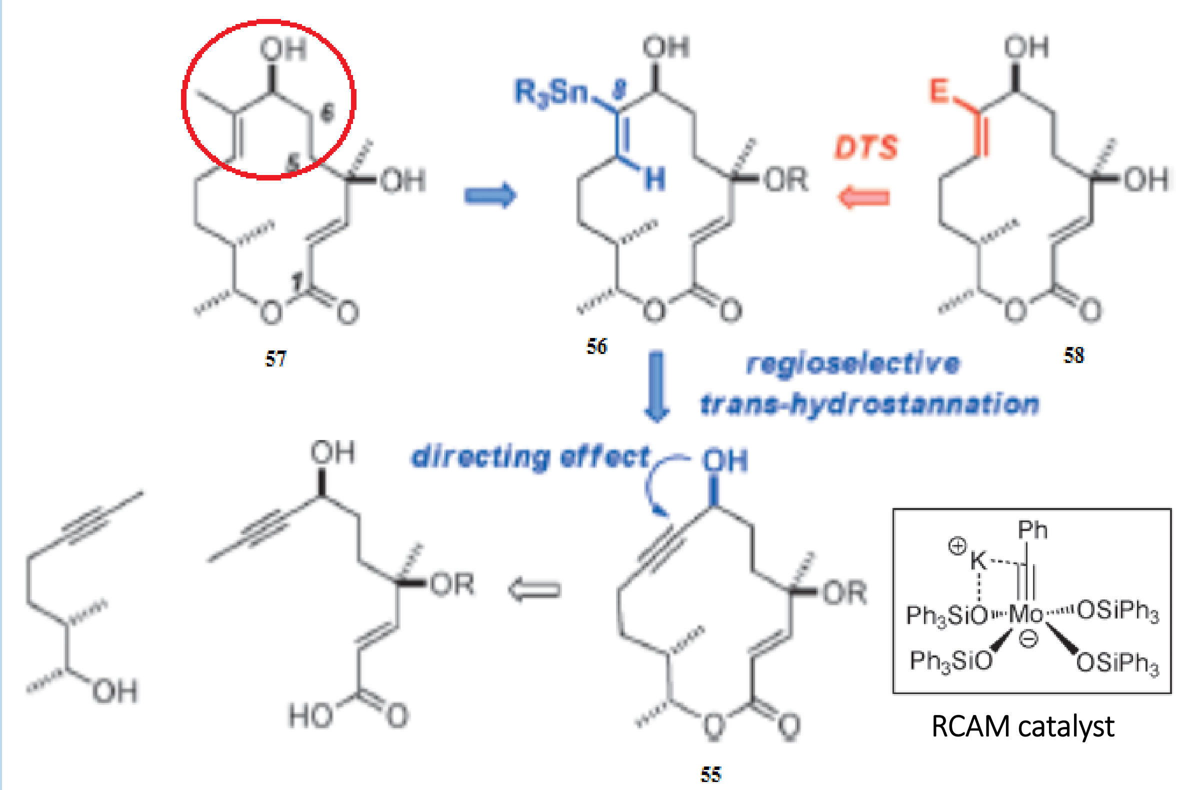
  - ➢ Present in countless natural products
- RCAM + Regioselective trans-hydrostannation
- Tolerates esters, silyl ethers, alkenes
- Possible **D**iverted **T**otal **S**ynthesis by Sn-coupling



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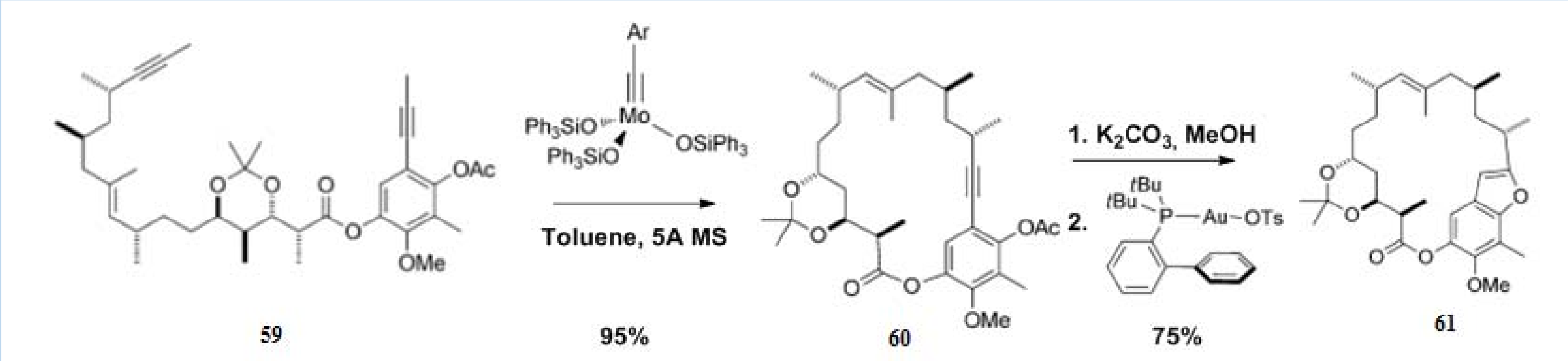
6. How to further use that alkyne ? - Kendomycin



- **RCAM** followed by **Au-cat. Hydroalkoxylation** - Synthesis of **benzofurane**
- **Excellent yield** (95%)
- **Tolerates** esters, ether, alkenes

L. Hoffmeister, P. Persich, A. Fürstner, *Chem. Eur. J.* **2014**, *20*, 4396 - 4402.

- First discovered 48 years ago (1968)

A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794 - 2819; A. D. Lackner, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12814 - 12818.

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Introduction → Catalyst Development → Total Synthesis → **Conclusion**

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- Wide variety of **applications** (polymers, supramolecular chemistry, total synthesis)
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- **Quintessential tool** of the preparative chemist

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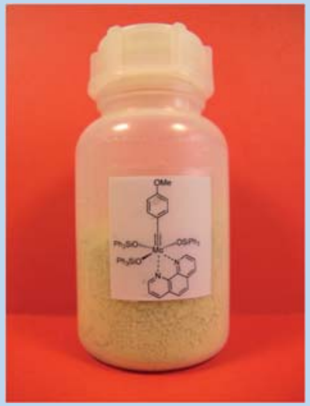

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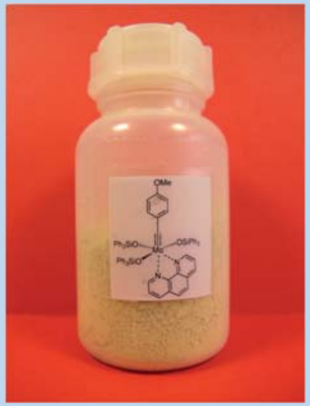

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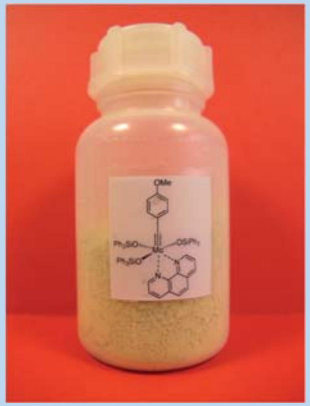

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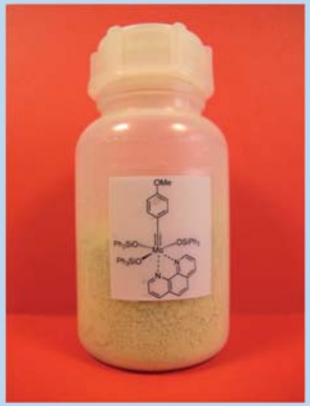

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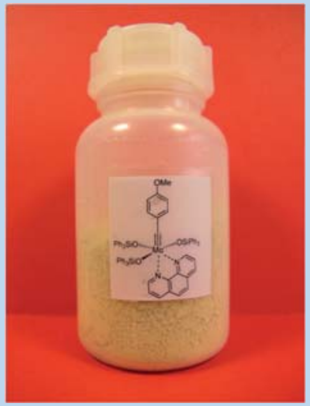
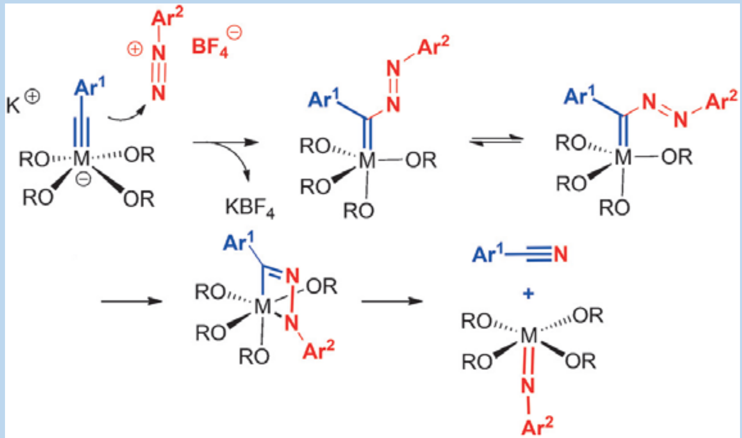
  - ➢ **Cleavage of dinitrogen**





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Let's → Ask → Some → Questions !

Thank you for your attention !