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Organocatalytic Carbonyl-Olefin Metathesis

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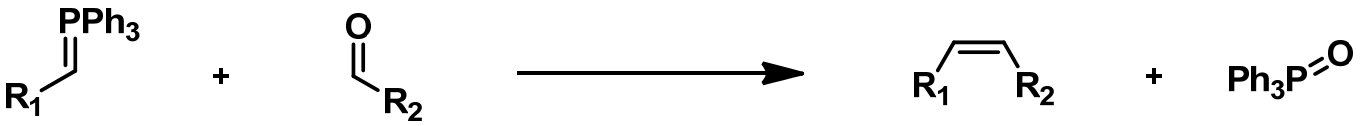
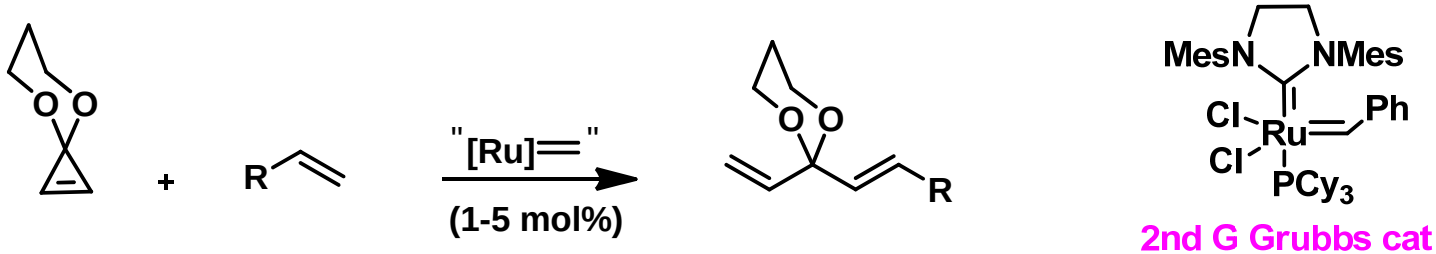
The most widely used olefination

✓ Wittig olefination

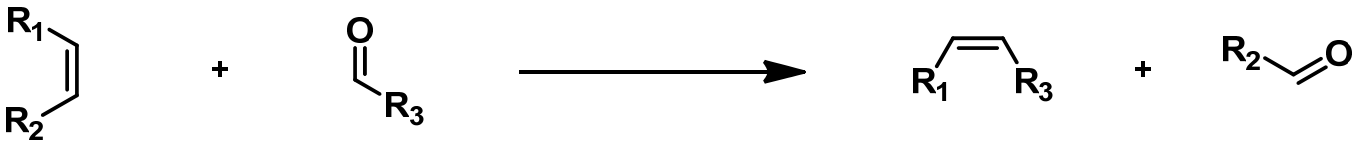


✓ Metathesis olefination



2nd G Grubbs cat

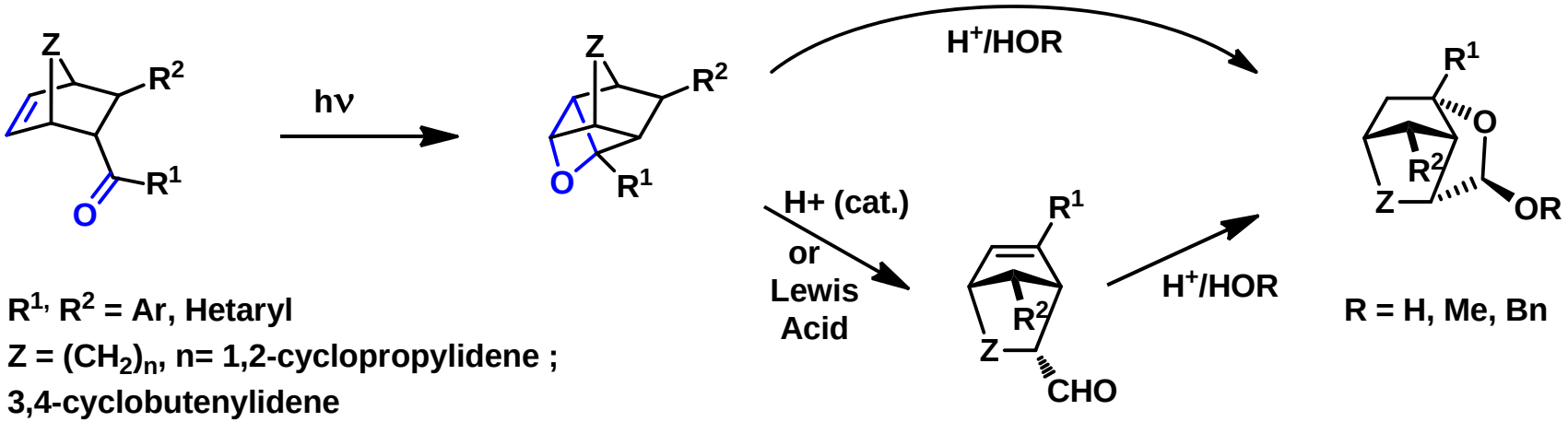
✓ Carbonyl-olefin metathesis



Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863−927.
Michaut, M.; Parrain, J-.L.; Santelli, M. *Chem. Commun.* **1998**, 2567–2568.
Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243−251.

Carbonyl-olefin metathesis precedents

✓ Photochemical carbonyl-olefin metathesis reaction :



$R^{1,}$ R^2 = Ar, Hetaryl
Z = $(CH_2)_n$, n= 1,2-cyclopropylidene ;
3,4-cyclobutenylidene

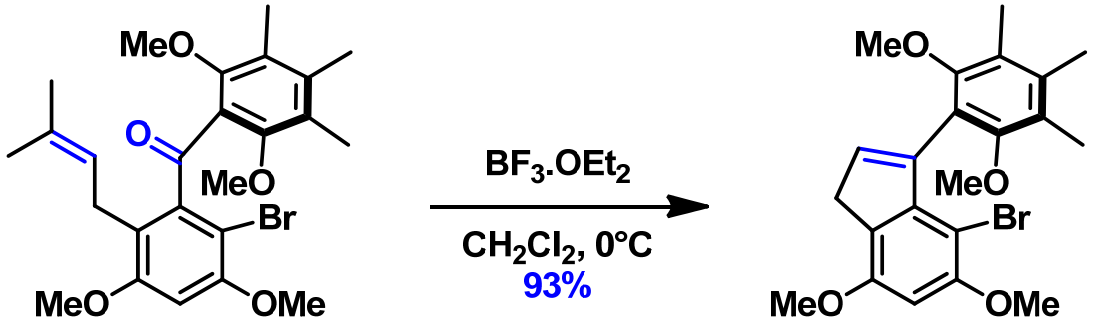
R = H, Me, Bn

- high-yielding two-step sequence

Valualin, R. A.; Kutateladze, A. G. *Org. Lett.* **2009**, *11*, 3886-3889.

Carbonyl-olefin metathesis precedents

✓ Lewis acid promoted carbonyl-olefin metathesis reaction :



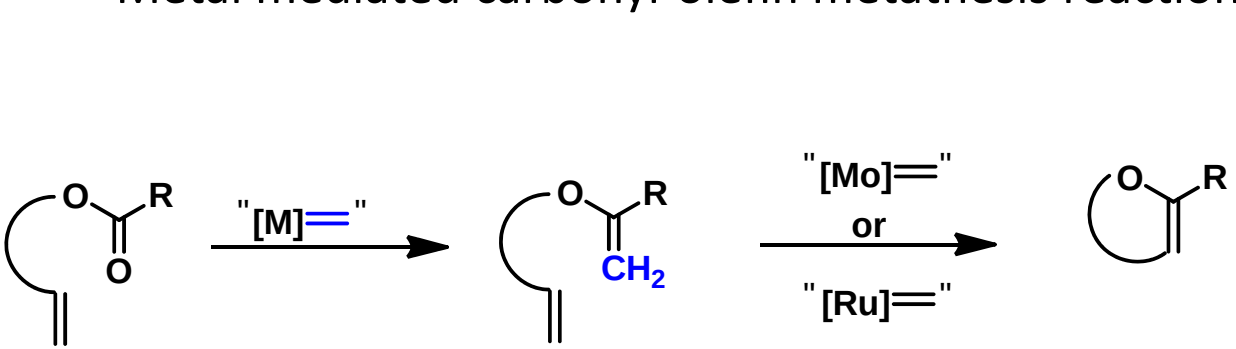
- Cationic cyclization process => formation of an oxetane intermediate followed by a fragmentation reaction

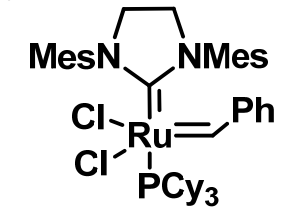
- Several substrates were shown to afford the metathesis products with up to 93% yield.

Soicke, A.; Slavov, N.; Neudörfl, J.-M.; Schmalz, H.-G. *Synlett.* **2011,** 2487-2490.

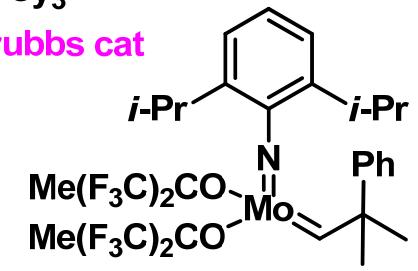
Carbonyl-olefin metathesis precedents

✓ Metal mediated carbonyl-olefin metathesis reaction :





2nd G Grubbs cat



Schrock's cat

- **Tebbe reagent : $Cp_2TiCH_2(Cl)AlMe_2$**
  - *disavantages :* sentive to moisture and air / Lewis acidic character / limited to methylenation

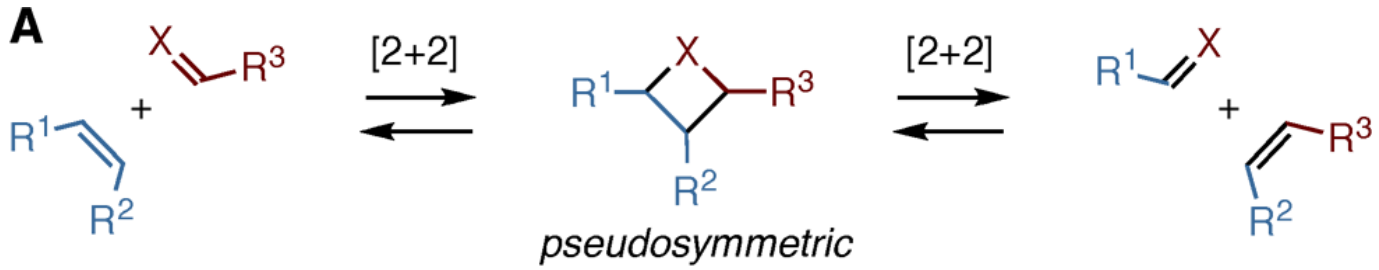
- **Petasis reagent : $Cp_2Ti(CH_3)_2$**
  - *disavantages :* high temperature needed to induce α-elimination

- **Takai reagent : [$TiCl_4$, Zn, $PbCl_2$, $AlkX_2$, TMEDA]**

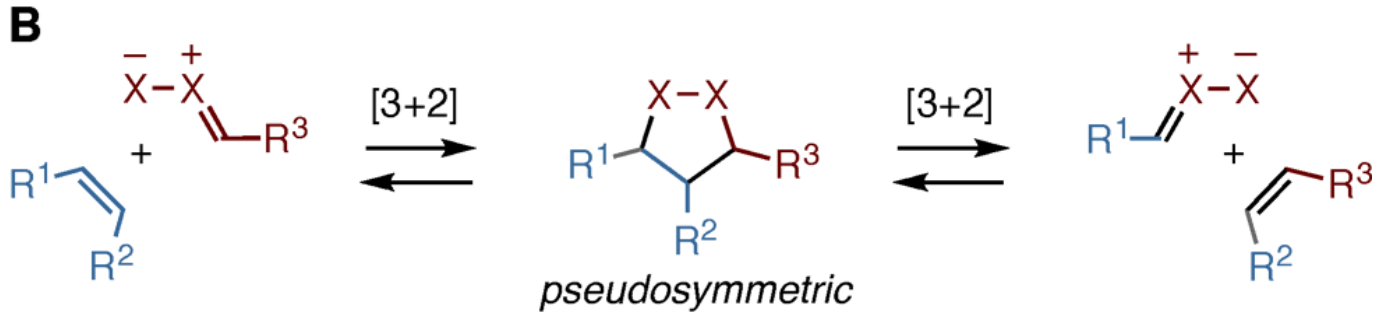
Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc*. **2007**, *129*, 12604−12605
Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc*. **1996**, *118*, 1565−1566

Metathesis paradigm

A - Traditional [2 + 2] metathesis paradigm :

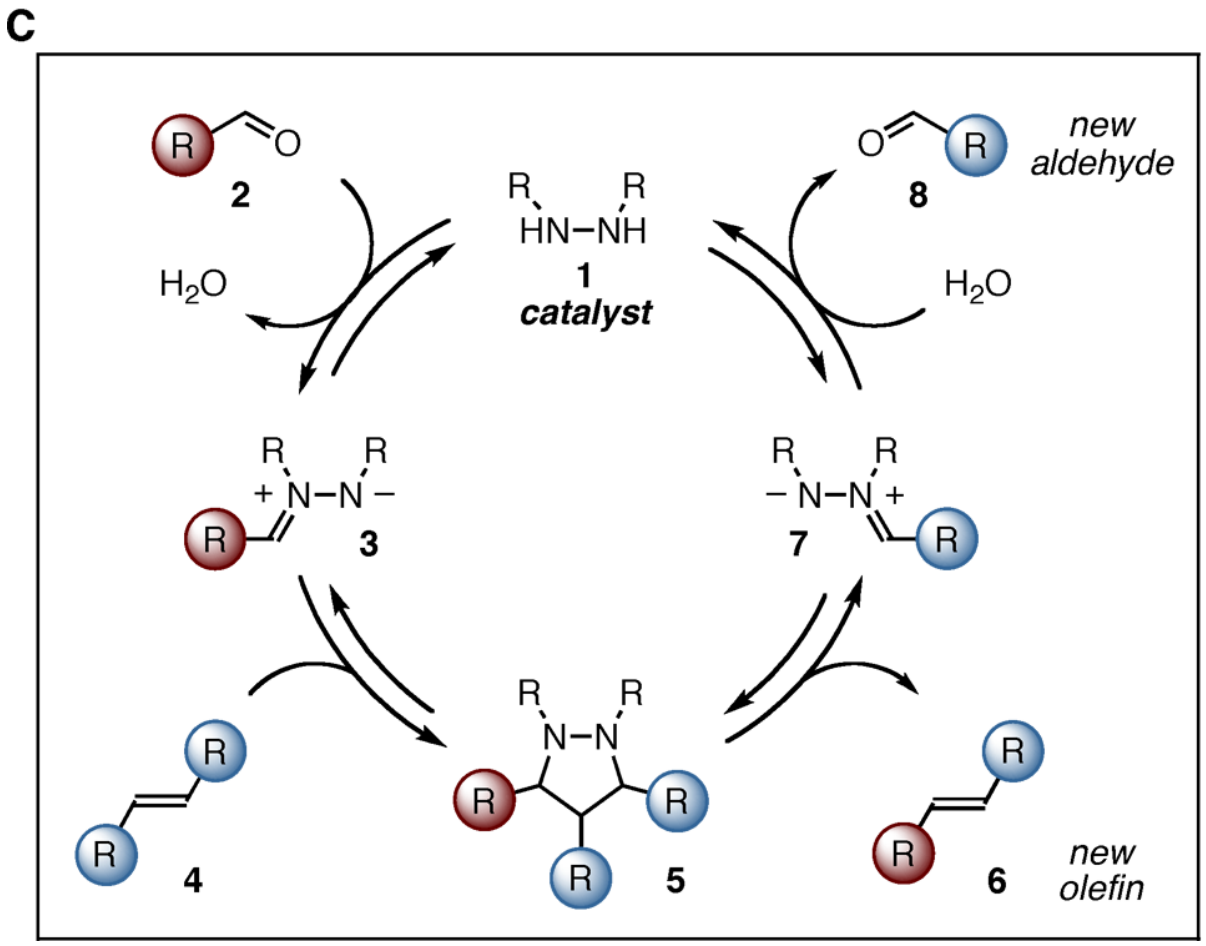


B - [3 + 2] metathesis paradigm.

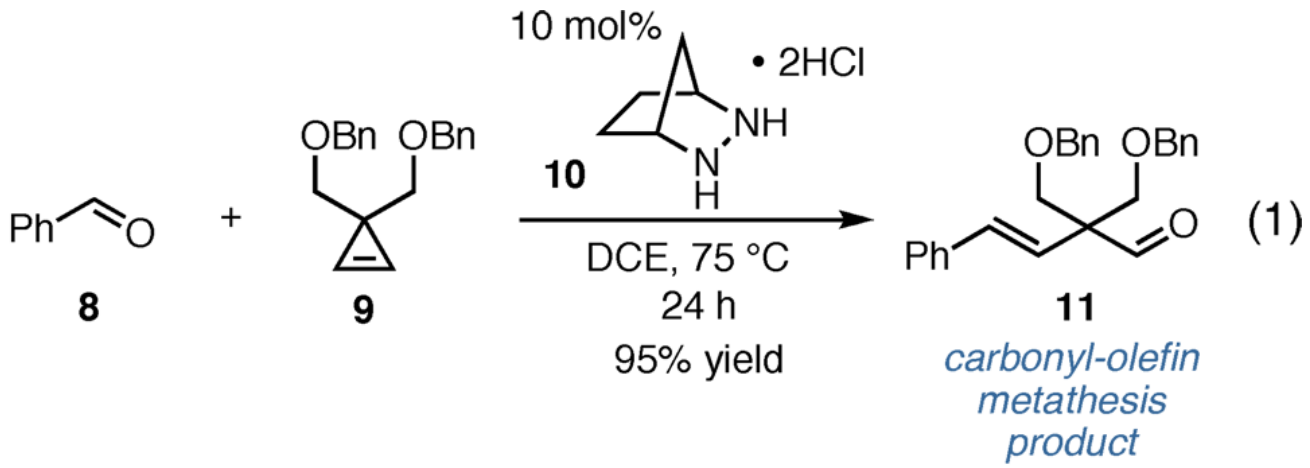


Metathesis paradigm

C- Carbonyl-olefin metathesis reaction based on azomethine imine 1,3-dipolar cycloadditions.



Hydrazine catalyzed carbonyl-olefin metathesis reaction



- No reaction was observed between 8 and 9 without catalyst 10

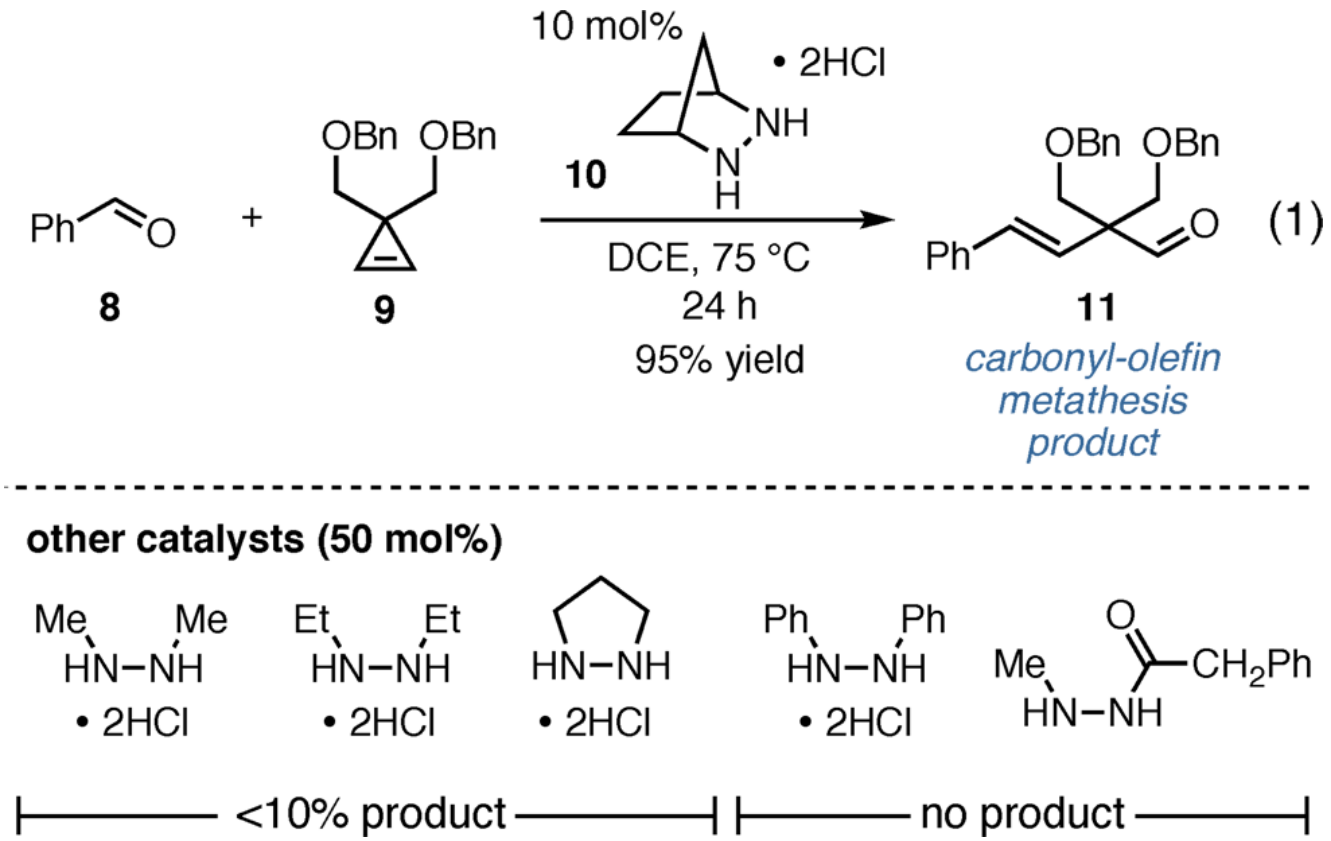
- With 50 mol % of catalyst :

    - 10.2HCl gave the product 11 in 60% yield

    - 10.HCl gave the product 11 in 35% yield

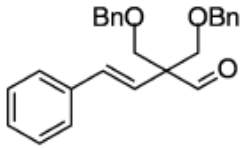
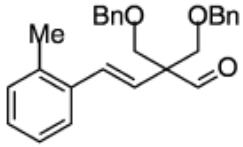
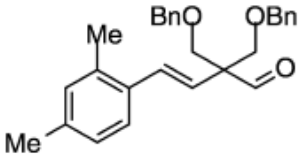
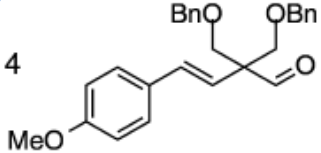
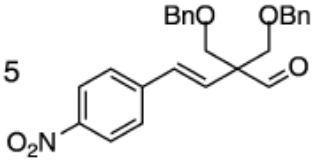
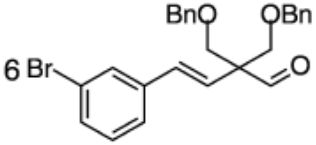
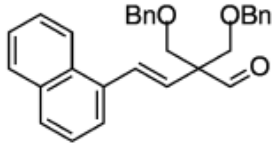
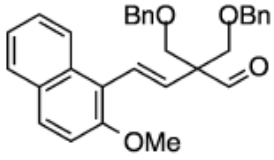
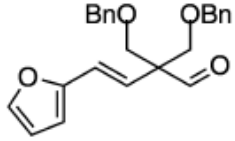
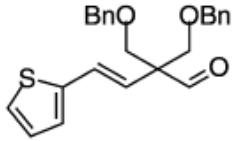
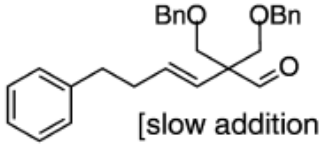
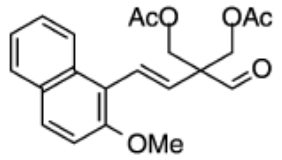
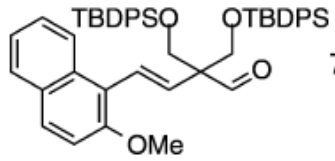
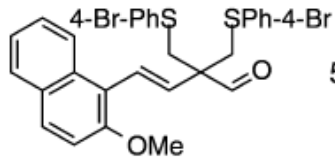
    - free base gave the product 11 in 15% yield

Hydrazine catalyzed carbonyl-olefin metathesis reaction



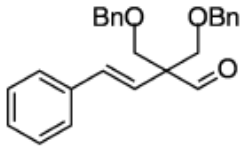
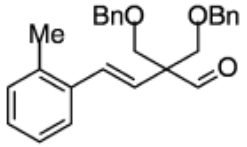
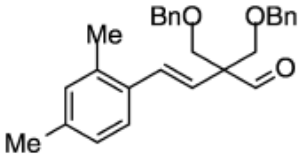
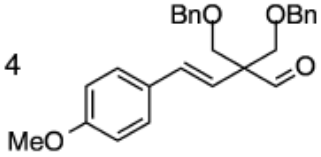
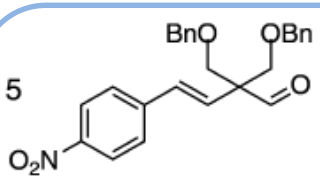
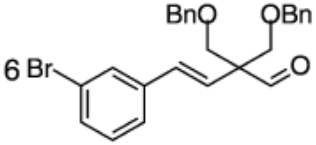
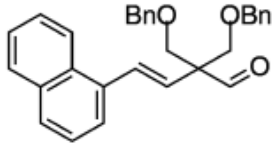
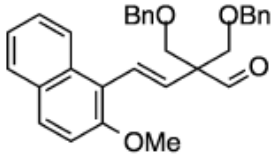
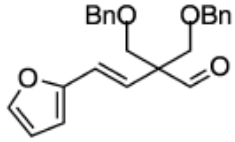
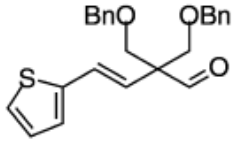
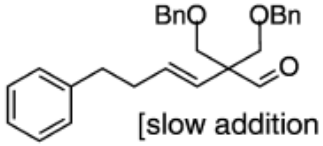
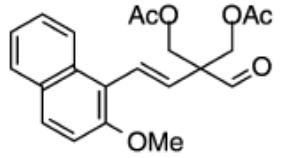
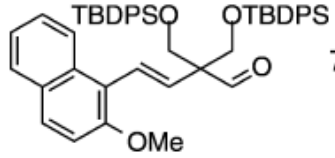
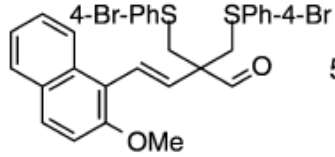
- Bicyclic structure => plays a key role in the high performance of this hydrazine catalyst.

Scope hydrazine catalyzed carbonyl-olefin metathesis reaction

entry	product	% yield
1		95 (80)
2		85
3		66
4		50
5		60 [48 h]
6		75 (60) [48 h]
7		67
8		68 [6 h]
9		80
10		35
11	 [slow addition 48 h]	35
12		68
13		79
14		50

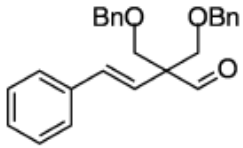
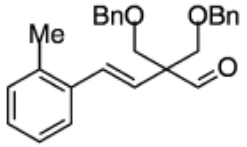
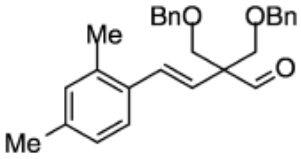
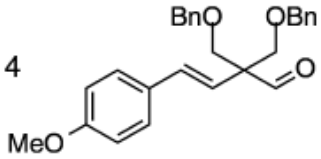
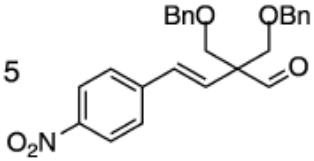
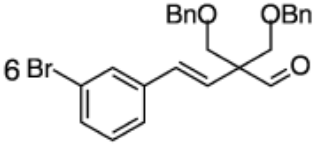
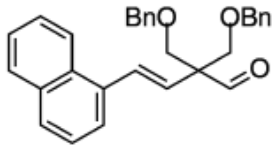
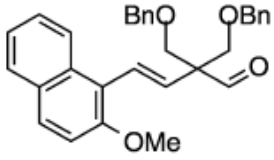
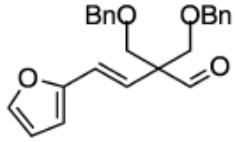
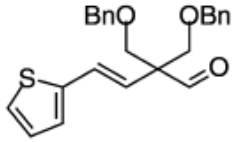
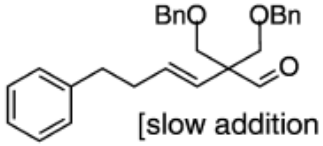
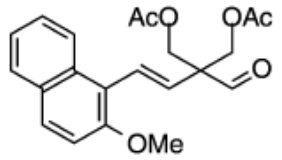
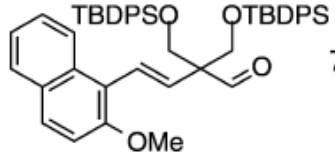
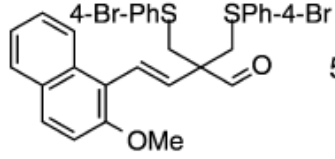
Inverse correlation between the electron-rich character of the aldehyde and the yield of isolated metathesis product.

Scope hydrazine catalyzed carbonyl-olefin metathesis reaction

entry	product	% yield
1		95 (80)
2		85
3		66
4		50
5		60 [48 h]
6		75 (60) [48 h]
7		67
8		68 [6 h]
9		80
10		35
11		35 [slow addition 48 h]
12		68
13		79
14		50

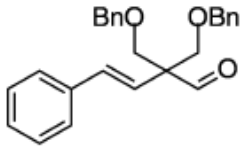
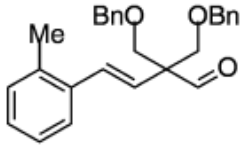
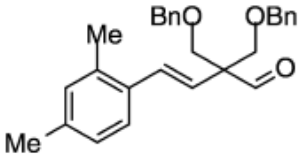
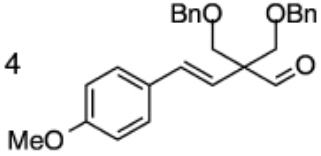
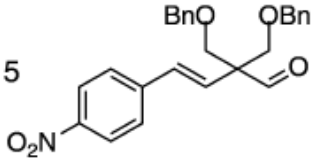
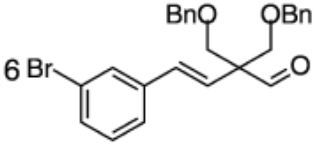
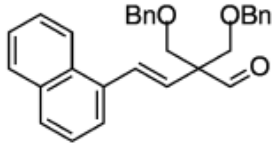
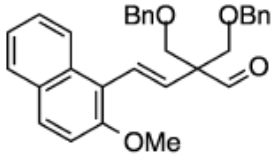
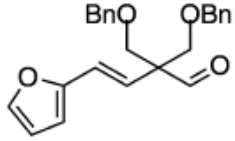
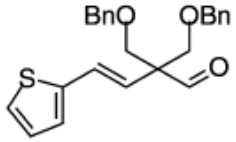
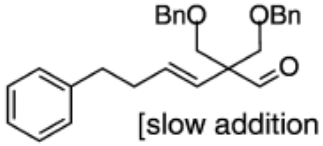
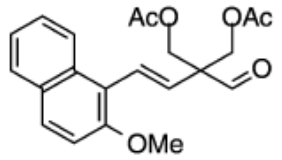
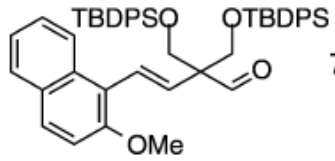
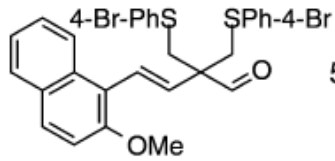
With substrates bearing EWG the conversion rate is slower => HOMO of the dipole
=> typical demand 1,3-dipolar cycloadditions.

Scope hydrazine catalyzed carbonyl-olefin metathesis reaction

entry	product	% yield
1		95 (80)
2		85
3		66
4		50
5		60 [48 h]
6		75 (60) [48 h]
7		67
8		68 [6 h]
9		80
10		35
11		35 [slow addition 48 h]
12		68
13		79
14		50

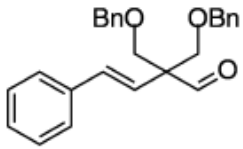
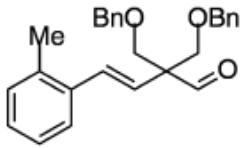
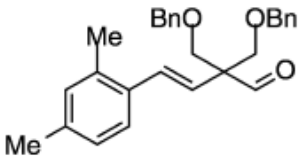
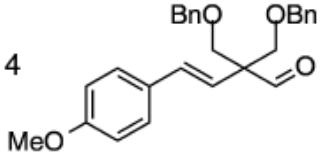
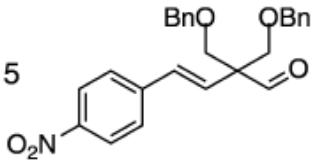
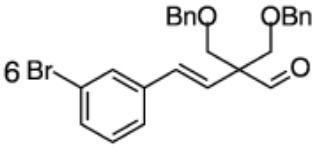
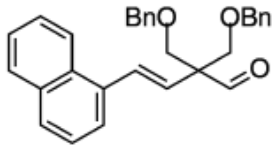
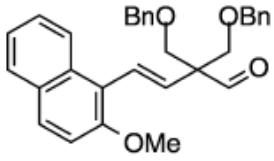
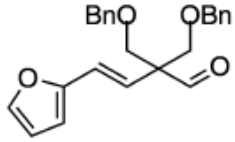
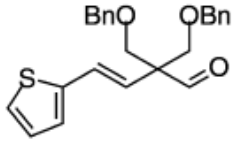
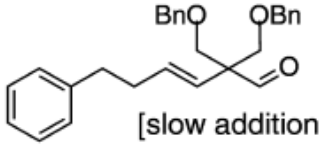
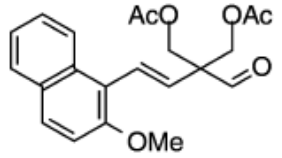
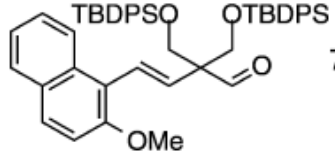
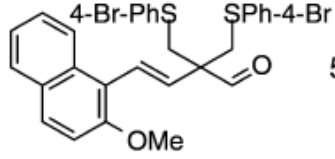
Entry 10 : modest yield due to the sensitive nature of the vinylthiophene functionality

Scope hydrazine catalyzed carbonyl-olefin metathesis reaction

entry	product	% yield
1		95 (80)
2		85
3		66
4		50
5		60 [48 h]
6		75 (60) [48 h]
7		67
8		68 [6 h]
9		80
10		35
11		35 [slow addition 48 h]
12		68
13		79
14		50

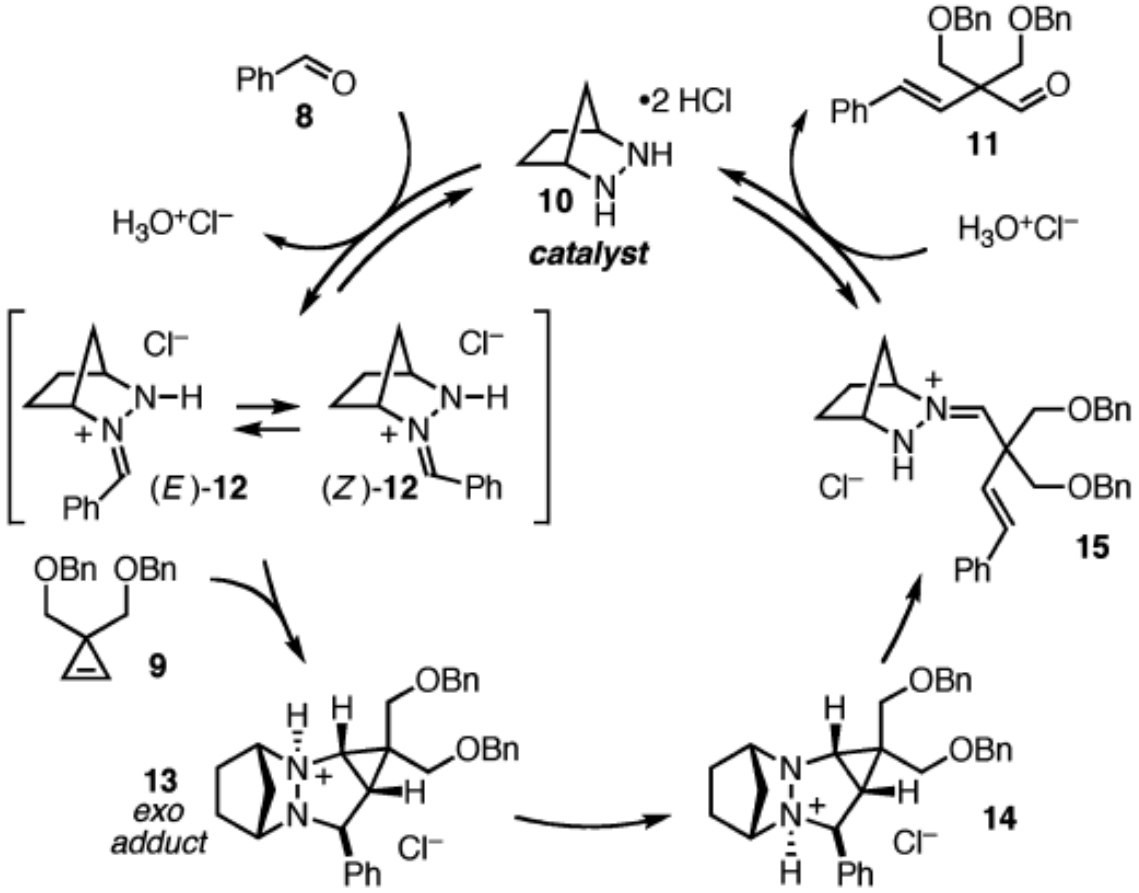
Aliphatic aldehydes participate in a variety of amine-catalyzed transformations.

Scope hydrazine catalyzed carbonyl-olefin metathesis reaction

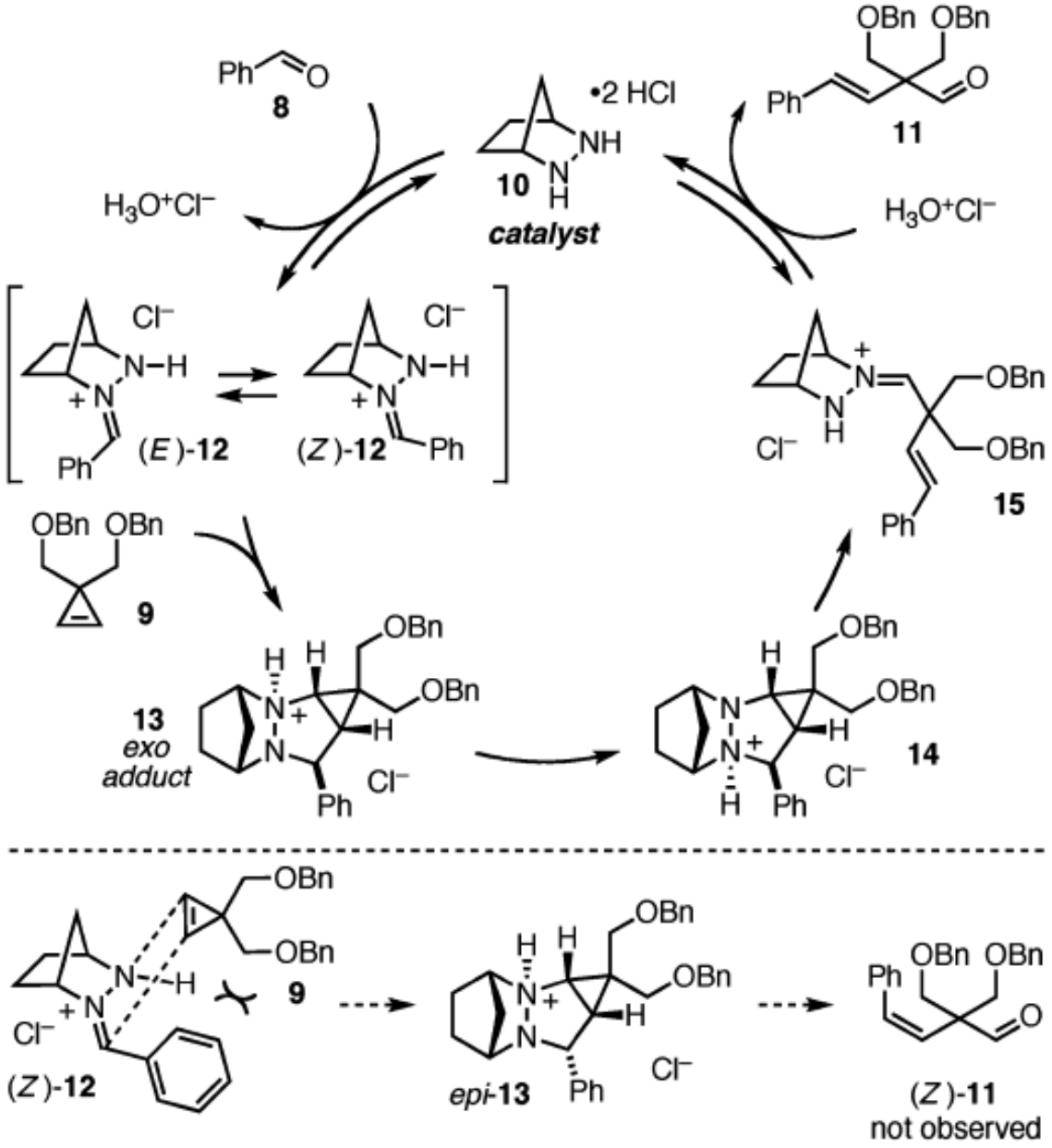
entry	product	% yield
1		95 (80)
2		85
3		66
4		50
5		60 [48 h]
6		75 (60) [48 h]
7		67
8		68 [6 h]
9		80
10		35
11	 [slow addition 48 h]	35
12		68
13		79
14		50

O-linkages are well tolerated.
Thioether were also found to be compatible.

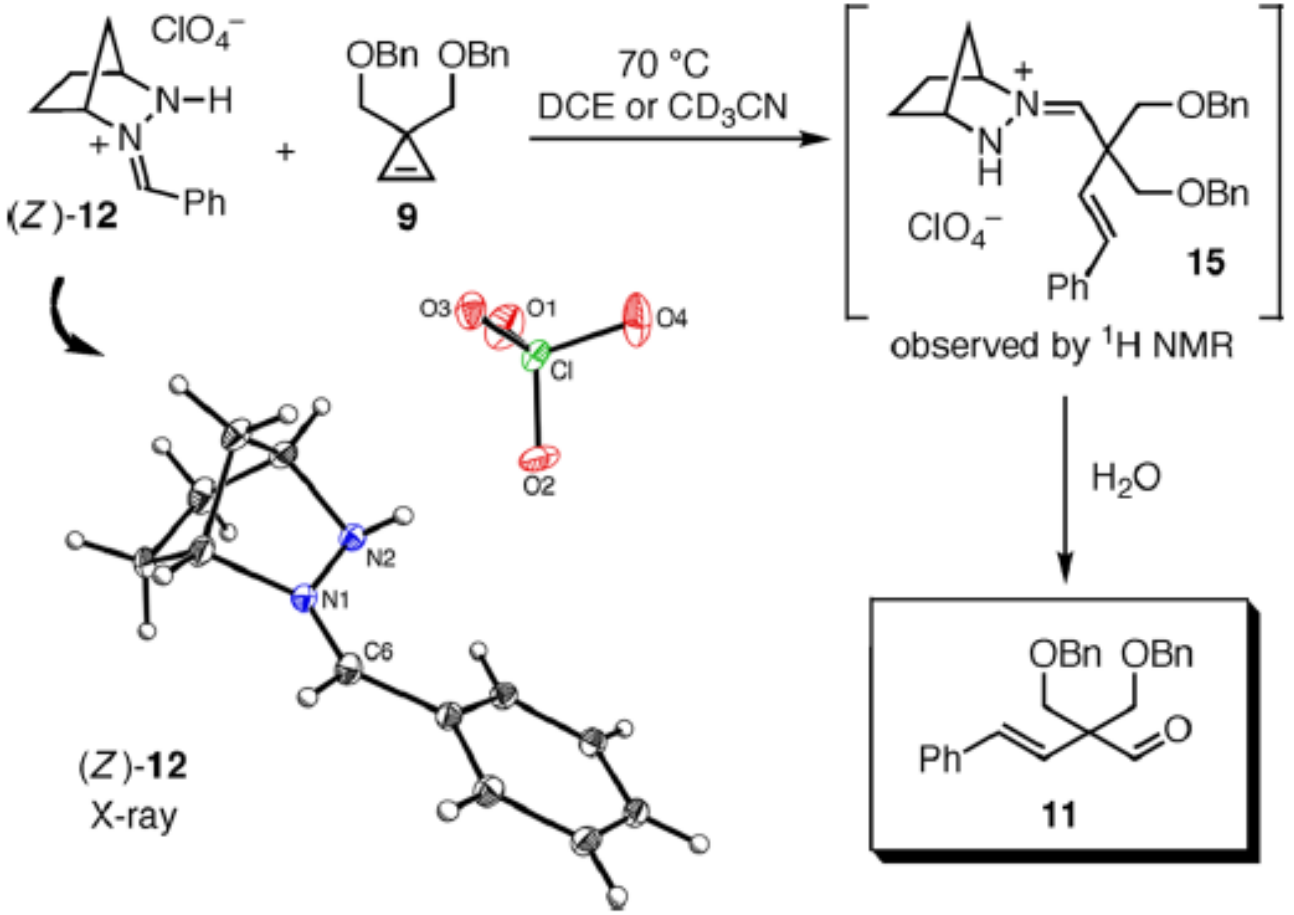
Mechanistic studies



Mechanistic studies



Mechanistic studies



Conclusion

- Carbonyl-olefin metathesis using simple organic catalysts and pericyclic reactions
- Development of catalysts able to perform the cycloreversion step
- Methodology applicable on a variety of subtrates
- No asymmetric version

Thank you for your attention