New formal (4+3) annulation strategy by taking advantage of cyclopropanes reactivity

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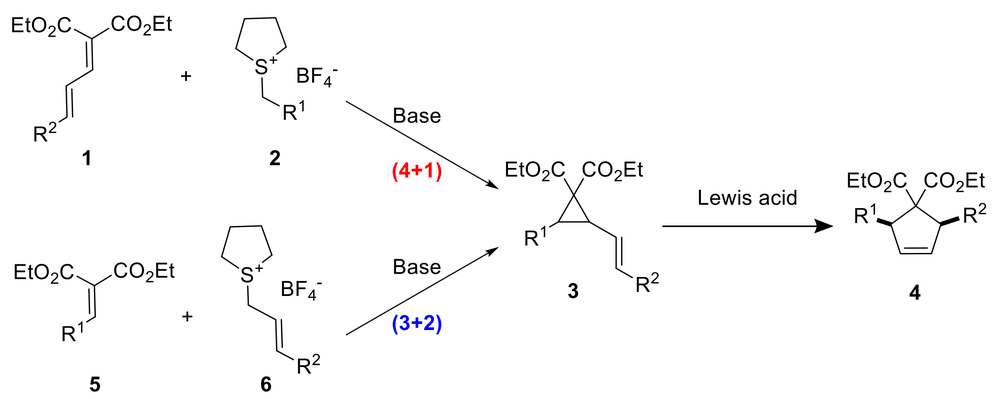
- Background -

Our research group has been working these last years on the development of annulation strategies using sulfonium ylides.
We have successfully developed effective methodologies for synthesizing five-membered carbocycles **4**, through formal (4+1) and (3+2) annulation strategies.[1,2] In both pathways, we initiate the process by forming a vinylcyclopropane intermediate **3**. This intermediate is then rearranged into **4**, facilitated by a Lewis acid catalysis.

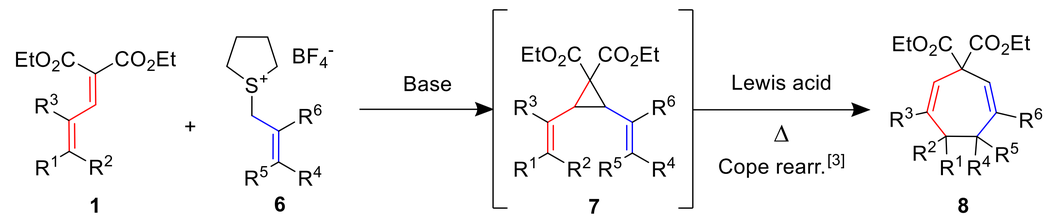


- Introduction and objectives -

We would like to continue the exploitation of cyclopropane's reactivity to develop new annulation methodologies. The aim of this project is to obtain a series of seven-membered carbocycles **8** through a new formal (4+3) annulation strategy. To achieve this, we propose using activated olefins **1** from the (4+1) strategy and allylic sulfonium salts **6** from the (3+2) annulation.

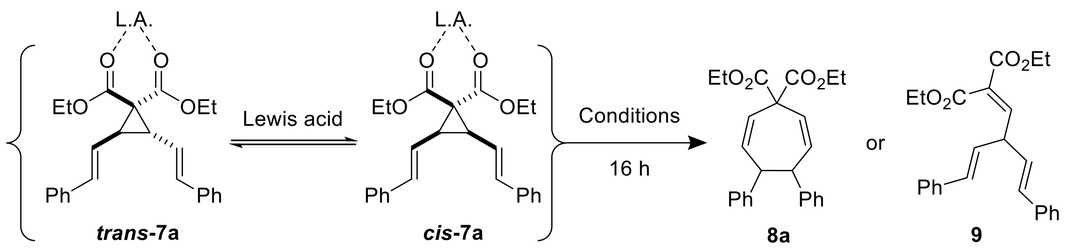
In practice, this work is leaded by two main objectives :

1. Develop and optimise the conditions of the Cope rearrangement (2nd step)
2. Determine the scope of this formal (4+3) strategy



- Results (1) : Cope optimisation -

Addition of Lewis acid helps for the *cis* ⇌ *trans* isomerization ⇒ better conversion and decreases working T°



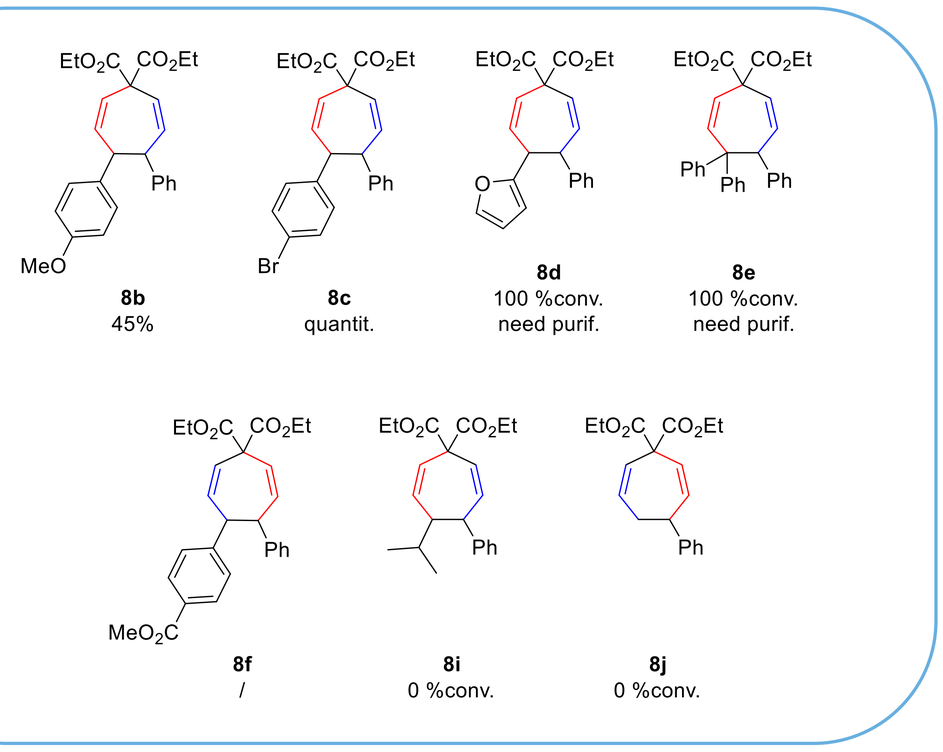
Entry	Lewis ac. (eq.)	T° (°C)	Solvent	trans-7a : cis-7a : 8a ratio
1	/	130	Xylene	0 : 0 : 100
2 [4]	/	110	Toluene	30 : 0 : 70
3 [4]	$ZnCl_2$ (0.1)	110	Toluene	< 1 : < 1 : 99
4	$Fe(OTf)_3$ (0.1)	110	Toluene	Degradation
5	$Sc(OTf)_3$ (0.1)	110	Toluene	Degradation
6	$TiCl_4$ (0.1)	110	Toluene	**9** only
6	MgI_2 (0,1)	80	MeCN	30 : 0 : 70
7*	MgI_2 (0,3)	80	MeCN	< 5 : < 1 : > 95
8	MgI_2 (0,1)	r.t.	MeCN	100 : 0 : 0

* 24 h instead of 16 h

Interestingly, the rearrangement was successfully performed with unpurified **7a**, which will increase the global yield of this strategy.

- Results (2) : scope -

A series of cycloheptadienes with both electro-donating or electro-withdrawing aryl substituents (**8b** to **8d**) was obtained with a total conversion of the divinylcyclopropane (regardless of the initial *cis*:*trans* ratio).



- Compatible with heteroaromatic substituent (**8d**)
- Formation of a sterically hindered quaternary carbon (**8e**)
- Electron deficient aryl substituents prevent the cyclopropanation (**8f**)
- Alkyl substituents and terminal alkene prevent the rearrangement (**8i** and **8j**)

- Conclusions -

We successfully develop an efficient new formal (4+3) annulation strategy using sulfonium ylides through the rearrangement of divinylcyclopropane derivative. We observed that a thermal activation is mandatory to perform the rearrangement of *cis*-divinylcyclopropane and the *cis* ⇌ *trans* isomerization. As the rearrangement takes place at lower temperature than the isomerization, we have discovered that it is possible to decreased the working temperature with the addition of a Lewis acid (MgI_2) in a catalytic amount to obtain a total conversion.

In addition, a series of cycloheptadienes was already obtained with electro-donating or electro-withdrawing group, even heteroaromatic (2-furyl) but, at this time, we are not able to obtain the divinylcyclopropane intermediate with an electron-depleted aryl and the rearrangement seems to be prevented with alkyl substituents or terminal alkene (no substituent on one reagent). Other examples are planned, such as a second heteroaromatic group (2-pyridine) or *m*-MeO-C_6H_5.

References:

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