An Interrupted Vinylogous Iso-Nazarov Reaction: Cycloisomerization of Conjugated Trienones to Cyclopenta[*b*]furan Derivatives

1

Martín J. Riveira and Mirta P. Mischne.

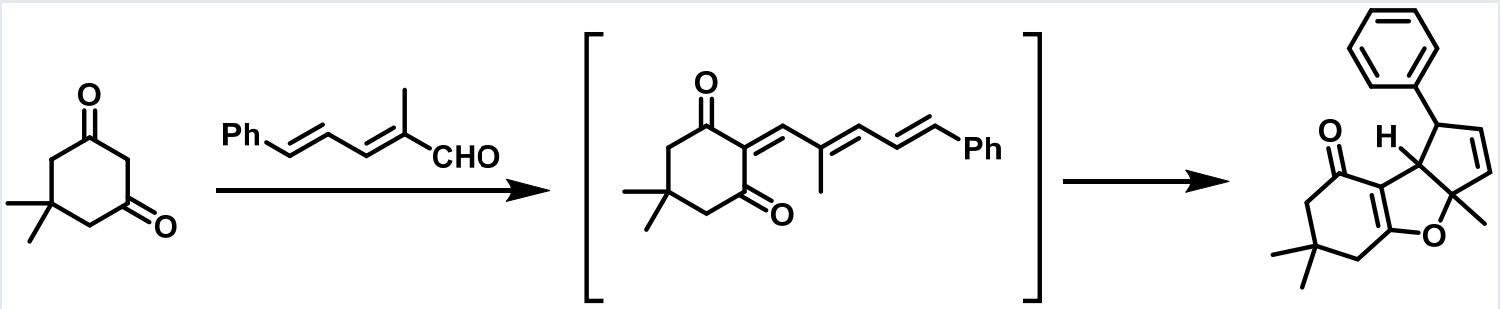
J. Org. Chem., 2014, 79(17), pp. 8244-8254

(National University of Rosario, Sante Fe, Argentina)

A. Manos-Turvey,
Wipf Group Current Literature
October 11th, 2014

New Scaffolds via Cycloisomerisation

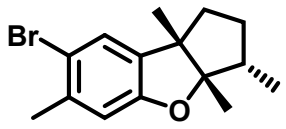
- The Mischne group is interested in synthesis of new carbo- and heteropolycyclic molecular scaffolds, through the use of efficient and innovative methodology
- This work resulted from an unexpected cyclopenta[*b*]furan product obtained from a Knoevenagel-type condensation, leading to a stereoselective annulation cascade
  - reaction of 1,3-dicarbonyl substrate, dimedone, with an α,β,ϒ,δ-unsaturated aldehyde



M.J. Riveira, C. Gayathri, A. Navarro-Vázquez, N.V. Tsarevsky, R.R. Gil, M.P. Mischne, *Org. Biomol. Chem.*, **2011**, *9*, 3170-3175
M.J. Riveira, M.P. Mischne, *Chem. Eur. J.*, **2012**, *18*, 2382-2388

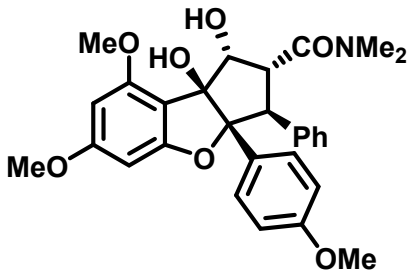
New Biologically Active Scaffolds

- Cyclopenta[*b*]tetrahydrobenzofurans are of interest as they can have antileukemic, insecticidal and cytostatic biological properties



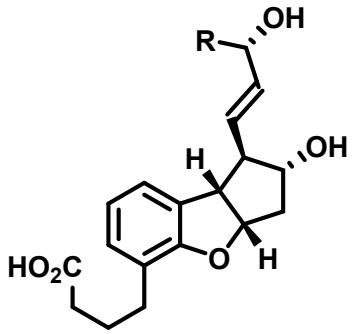
Aplysin

-hepatoprotective effect
-anti-tumour activity,
resensitising agent



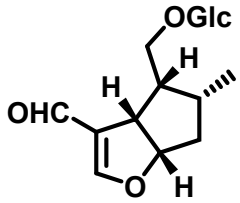
Rocaglamide

-insecticidal activity
-anti-proliferative
cancer activity



Benzoprostacyclins

-active against pulmonary
vascular and diseases



Iridoid glucosides

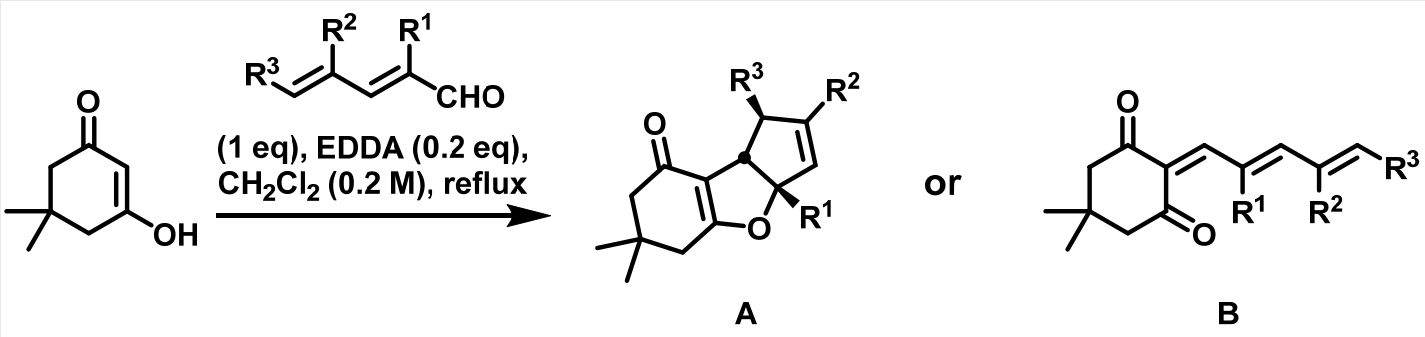
-cytotoxicity against cervical
and gastric carcinomas

- The cyclopenta[*b*]furan motif alone has also been shown to be of clinical significance

N. Ribeiro, F. Thuaud, C. Nebigil, L. Désaubry, *Bioorg. Med. Chem.*, **2012**, *20*, 1857-1864
N. Li, L. Di, W.-C. Gao, K.-J. Wang, L.-B. Zu, *J. Nat. Chem.*, **2012**, *75*, 1723-1728

New Scaffolds via Cycloisomerisation

- Further experimental investigations revealed:



  - substituted dienals at the α- and ϒ-position (R^1 and R^2 resp.) result in cyclopenta[*b*]furan derivatives
  - unbranched dienals (R^1 and R^2 = H) give trienedione products, stable in solid form
  - alternate dicarbonyl substrates are tolerated
- Suggested that steric effects may contribute to destabilisation of the expected Knoevenagel condensation open form product

M.J. Riveira, M.P. Mischne, *Chem. Eur. J.*, **2012**, *18*, 2382-2388

Stalled Cycloisomerisation Products

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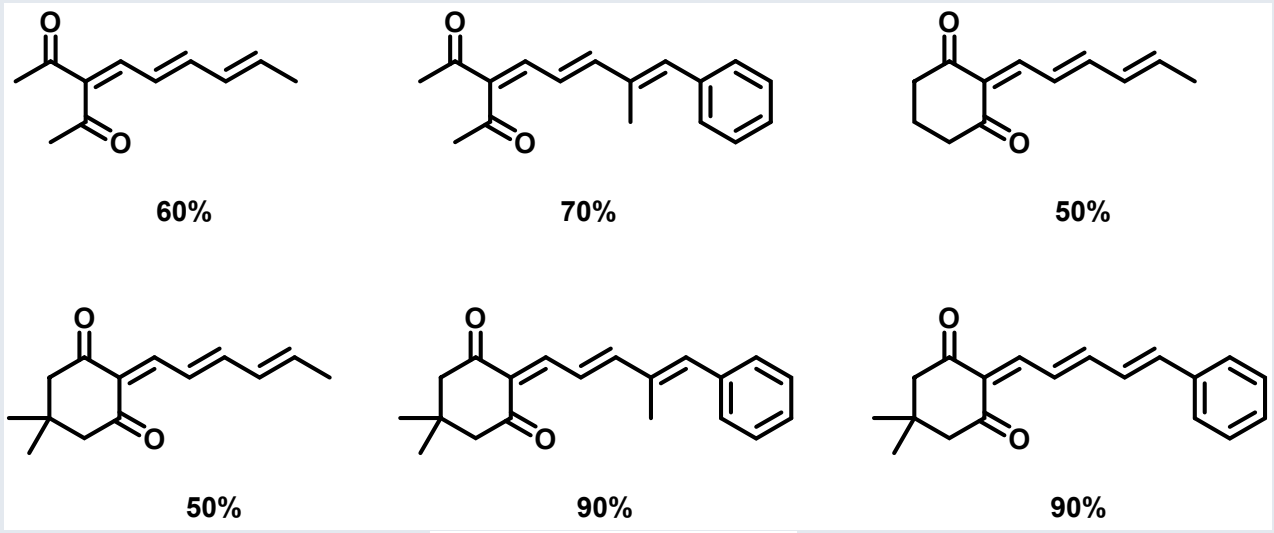
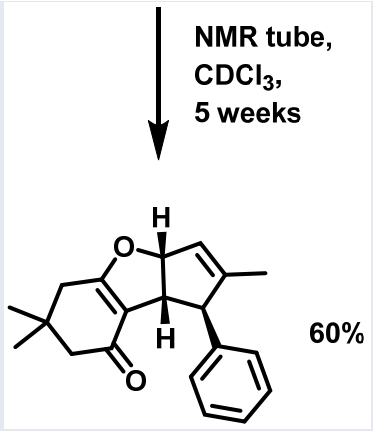
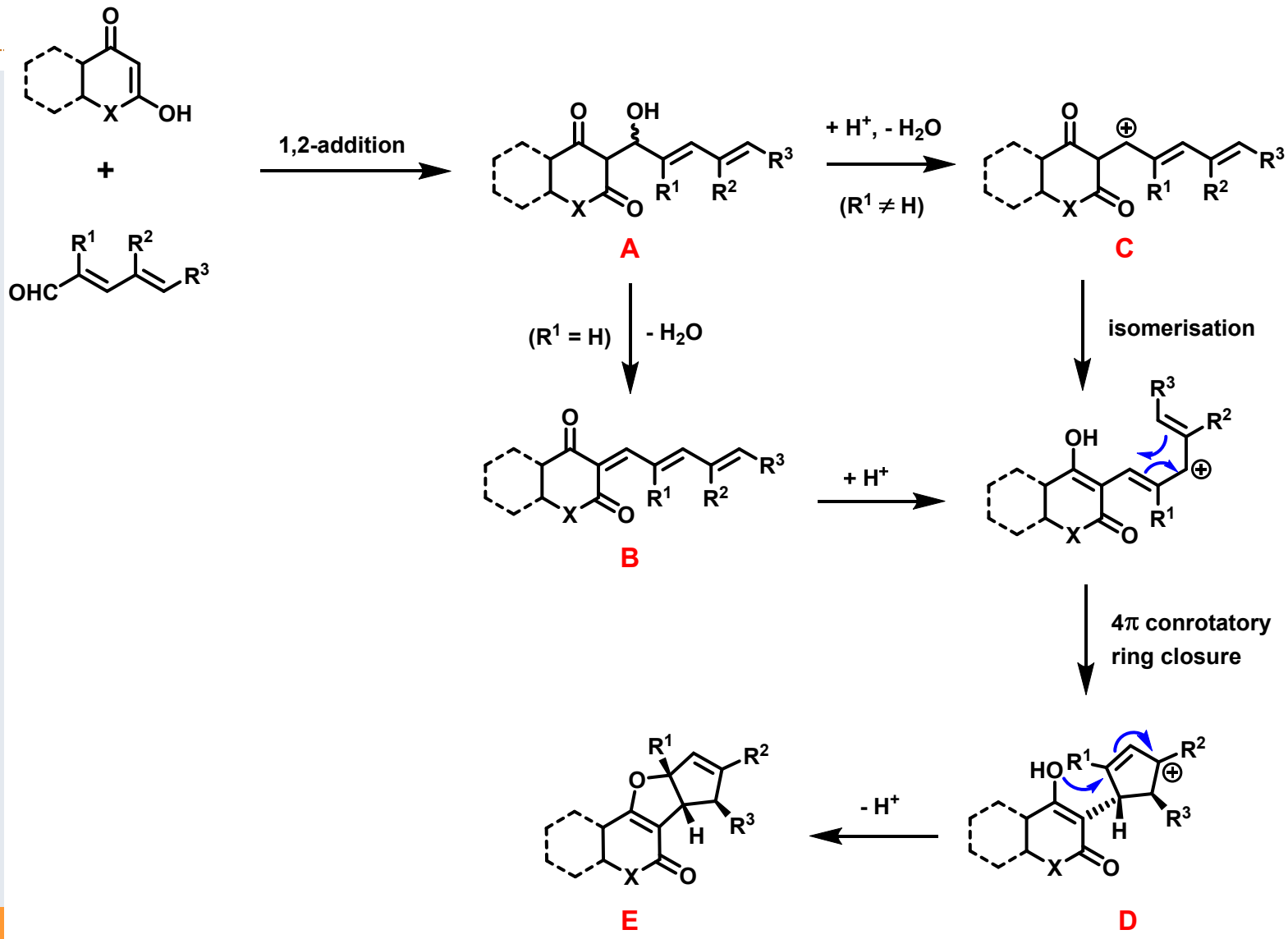




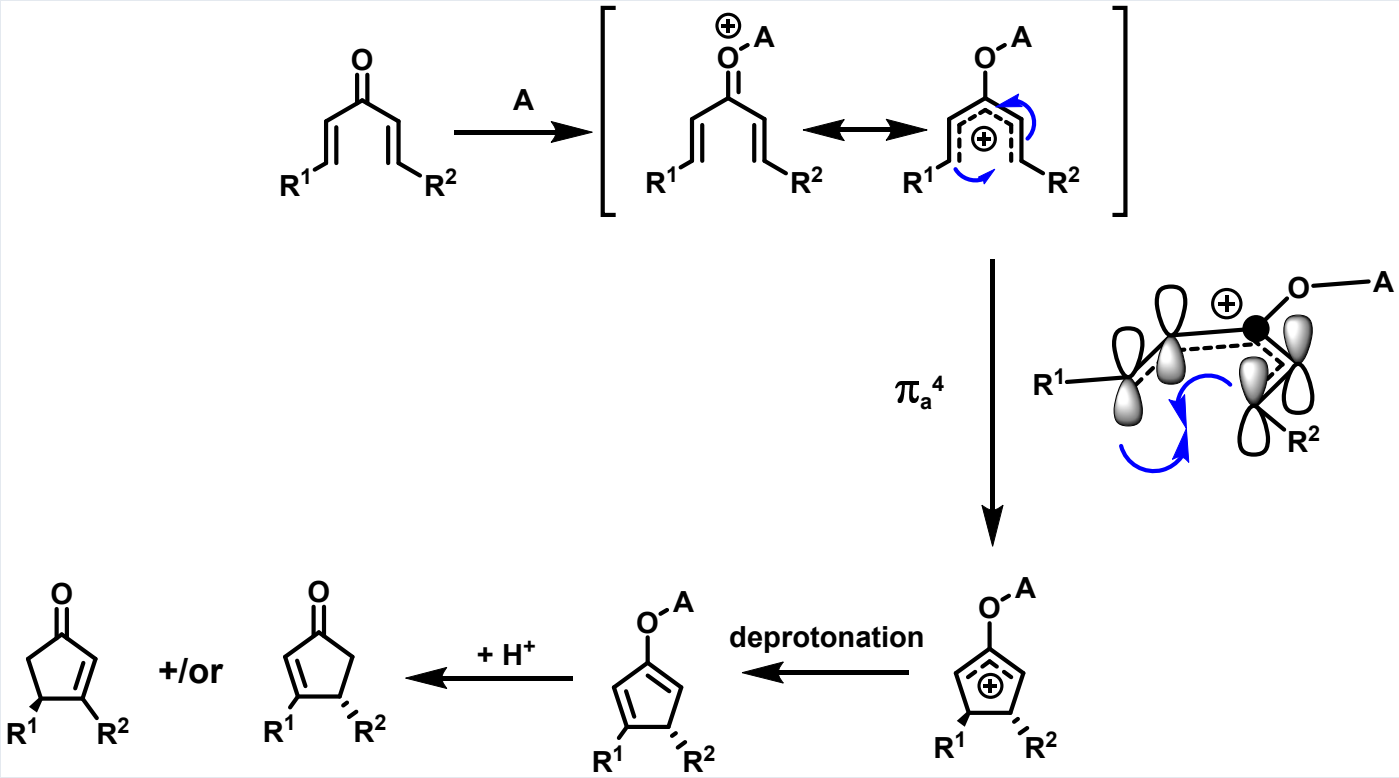
M.J. Riveira, M.P. Mischne, *Chem. Eur. J.*, **2012**, *18*, 2382-2388

Proposed Mechanism for Alternate Products



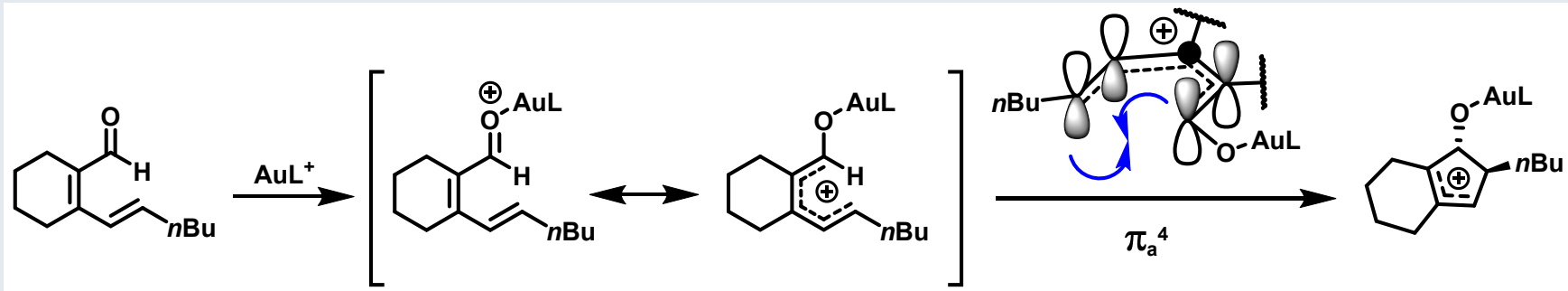
M.J. Riveira, M.P. Mischne, *Chem. Eur. J.*, **2012**, *18*, 2382-2388
A.F. Kluge, C.P. Lillya, *J. Org. Chem.*, **1977**, *36*, 1971-1988

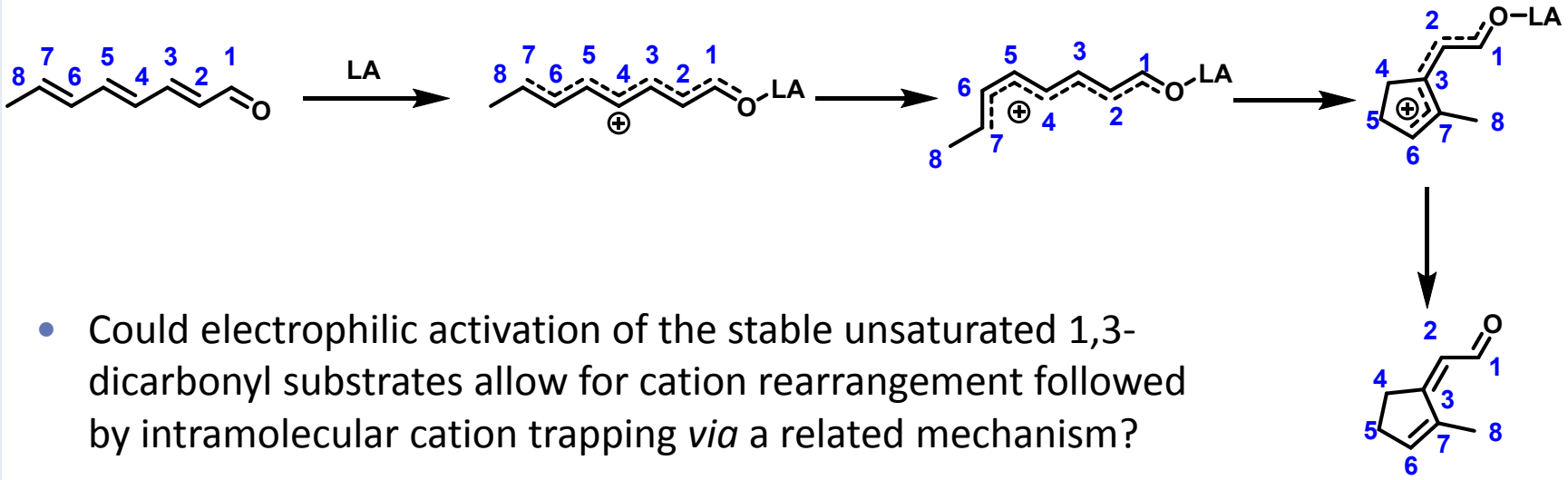
The Nazarov Cyclisation



C. Santelli-Rouvier, M. Santelli, *Synthesis*, **1983**, 429-442
E.A. Braude, J.A. Coles, J. Chem. Soc., Abstracts, **1952**, 1430-143
D.N. Kursanov, Z.N. Parnes, I.I. Zaretskaya, I.N. Nazarov, *Chem. Sci*, **1953**, 103-107

The Iso-Nazarov Cyclisation

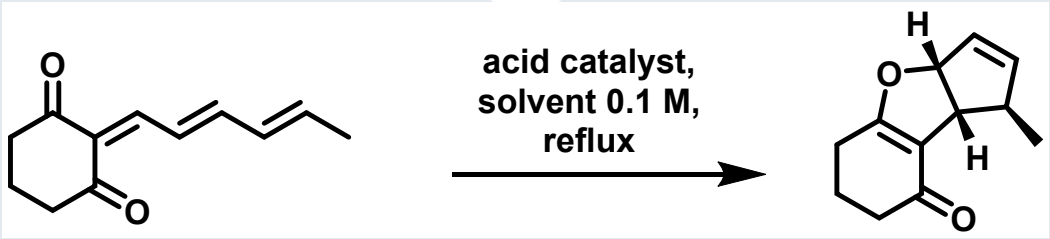




- Could electrophilic activation of the stable unsaturated 1,3-dicarbonyl substrates allow for cation rearrangement followed by intramolecular cation trapping *via* a related mechanism?

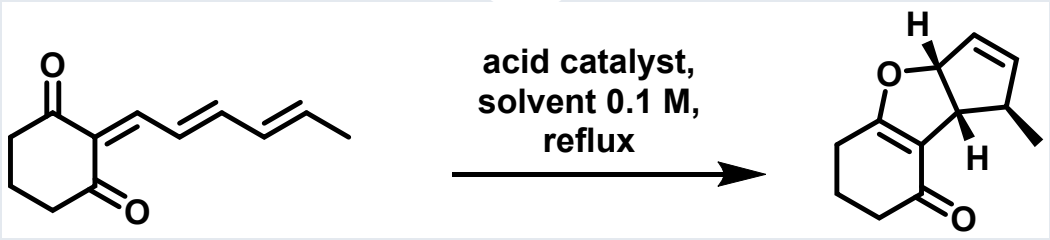
W.T. Spencer III, T. Vaidya, A.J. Frontier, *Eur. J. Org. Chem.*, **2013**, 3621-3633
G.R. Elia, R.F. Childs, G.S. Shaw, *Can. J. Chem.*, **1992**, 2065-2069
N.C. Baird, *Tetrahedron*, **1972**, 2355-2360

Reaction Condition Screening



catalyst (equiv)	solvent	t [h]	conv.[b]	yield
CSA (0.5)	CH_2Cl_2	8	95%	30%
TFA (0.5)	CH_2Cl_2	4	100%	56%
$BF_3{\cdot}OEt_2$ (2)	CH_2Cl_2[c]	2	100%	80%
$PtCl_2$ (0.5)	CH_2Cl_2	6	30%	6%
$CuCl_2$ (0.5)	CH_2Cl_2	>6	30%	traces
$ZnCl_2$ (0.5)	CH_2Cl_2	4	100%	83%
$Ti(O^iPr)_4$ (0.5)	CH_2Cl_2	6	20%	traces
$AuCl_3$ (0.5)	CH_2Cl_2	3	100%	65%
$AlCl_3$ (0.5)	CH_2Cl_2	1	91%	67%
$FeCl_3$ (0.5)	CH_2Cl_2	4	100%	88%

Screening of $FeCl_3$ as Catalyst

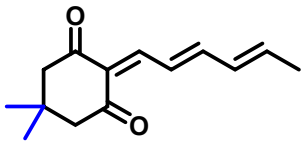
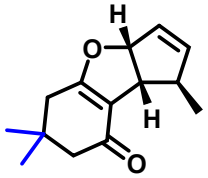
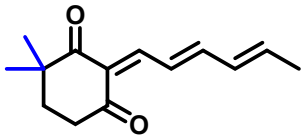
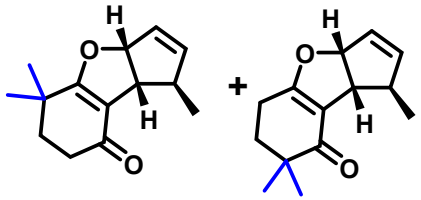
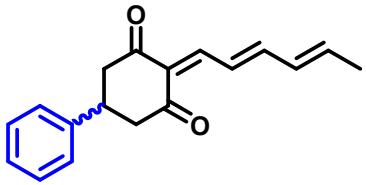
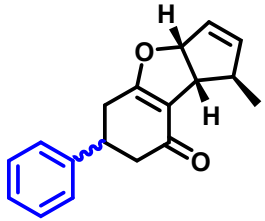
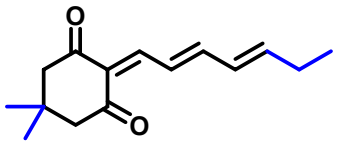
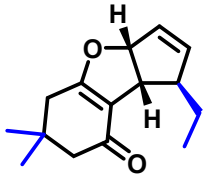
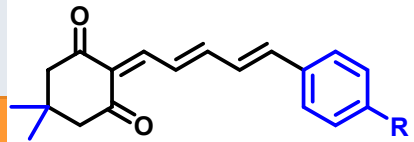
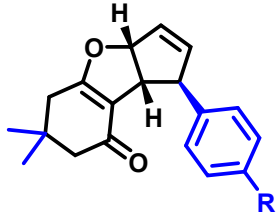


catalyst (equiv)	solvent	t [h]	conv.[b]	yield
$FeCl_3$ (0.5)	CH_2Cl_2	4	100%	88%
$FeCl_3$ (3)	CH_2Cl_2[c]	0.25	100%	85%
$FeCl_3$ (0.25)	CH_2Cl_2	6	82%	50%
$FeCl_3$ (0.25)	CH_2Cl_2[d]	6	72%	39%
$FeCl_3$ (0.05)	CH_2Cl_2	>50	77%	36%
$FeCl_3$ (0.5)	THF	1	100%	60%
$FeCl_3$ (0.5)	toluene	1	100%	73%
$FeCl_3.6H_2O$ (0.5)	CH_2Cl_2	6	95%	70%

- c = reaction carried out at rt
- d = only distilled, not dried, CH_2Cl_2 was used

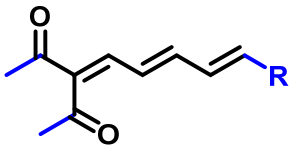
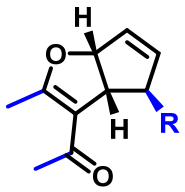
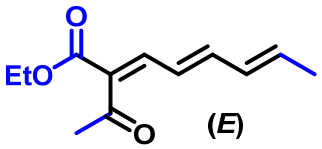
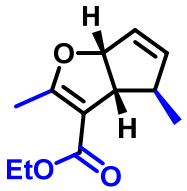
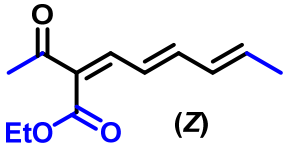
Substrate Scope

0.5 mmol substrate in CH_2Cl_2 (0.1 M) at reflux with $FeCl_3$ (0.5 eq)

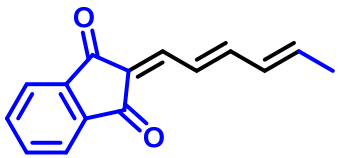
substrate	time (h)	product	yield
	3		80%
	4		85% (0.6:1)
	4		80% (insep dias.)
	4		80%
	R = H, 7 R = OMe, 4 R = F, 3		R = H, 85% R = OMe, 85% R = F, 75%

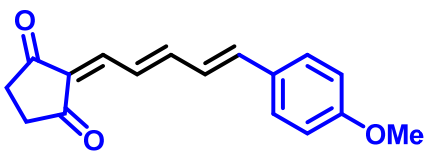
Substrate Scope and Limitations

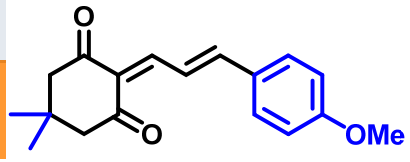
0.5 mmol substrate in CH_2Cl_2 (0.1 M) at reflux with $FeCl_3$ (0.5 eq)

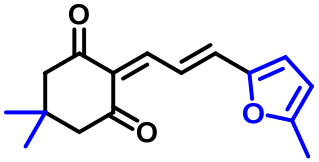
substrate	time (h)	product	yield
	R = Me, 4 R = Ph, 10		R = Me, 55% R = Ph, 40%
	1		25%
			

unreactive:

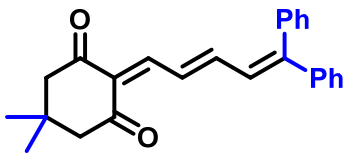


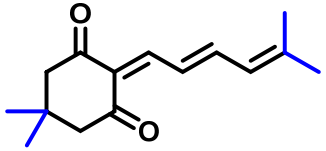




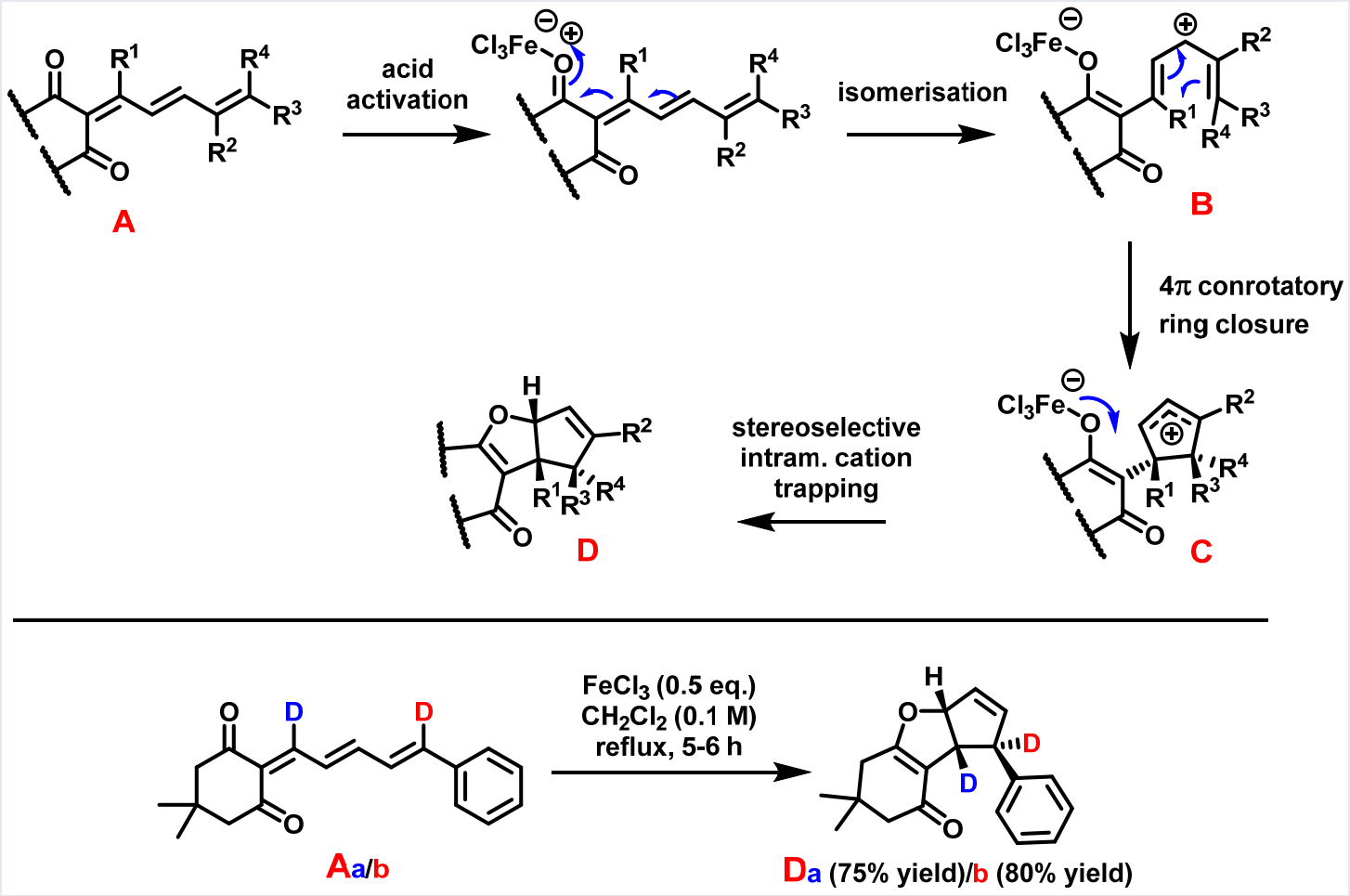


decomposed:



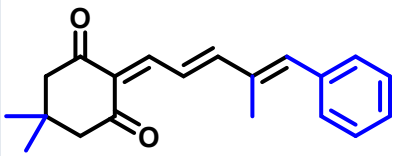
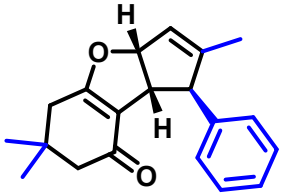
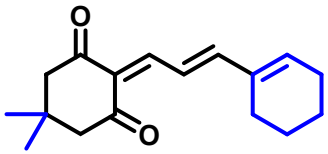
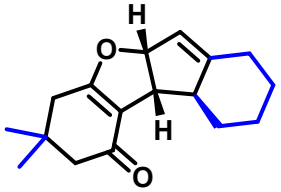
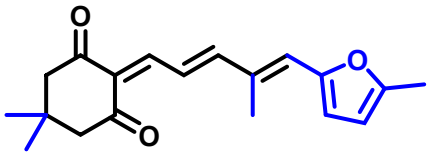
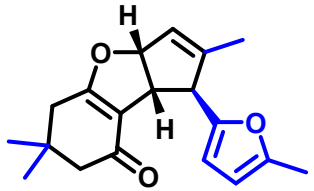


Proposed Mechanism



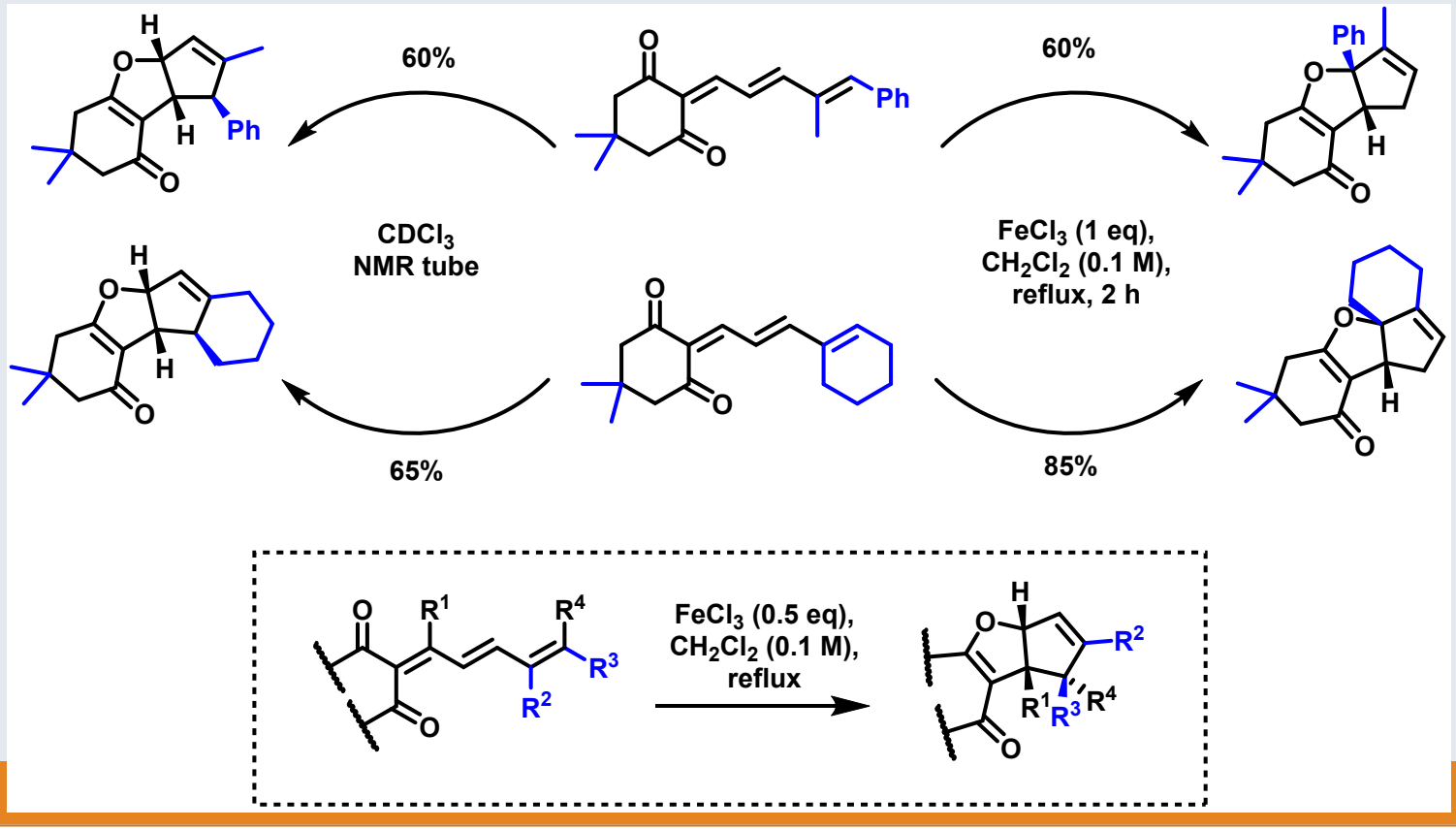
Substrate Limitation?

$CDCl_3$ at rt for 2 weeks

substrate	time (h)	product	yield
	spon.		60%
	spon.		65%
	spon.		60%

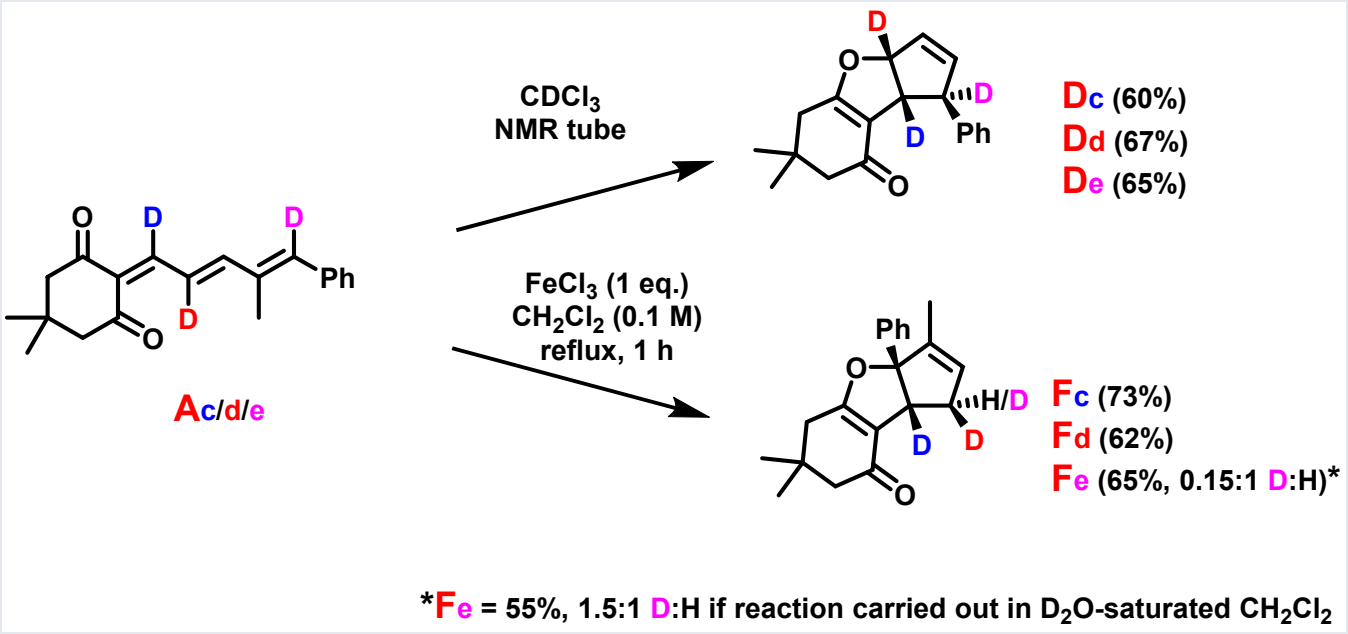
ε-Branched Compound Reactivity

- The compounds that had undergone "spontaneous" cyclisation in initial testing were subjected to the actual reaction conditions, to give different tricyclic products
  - greater efficiency with 1 eq of $FeCl_3$



Further Labeling Studies

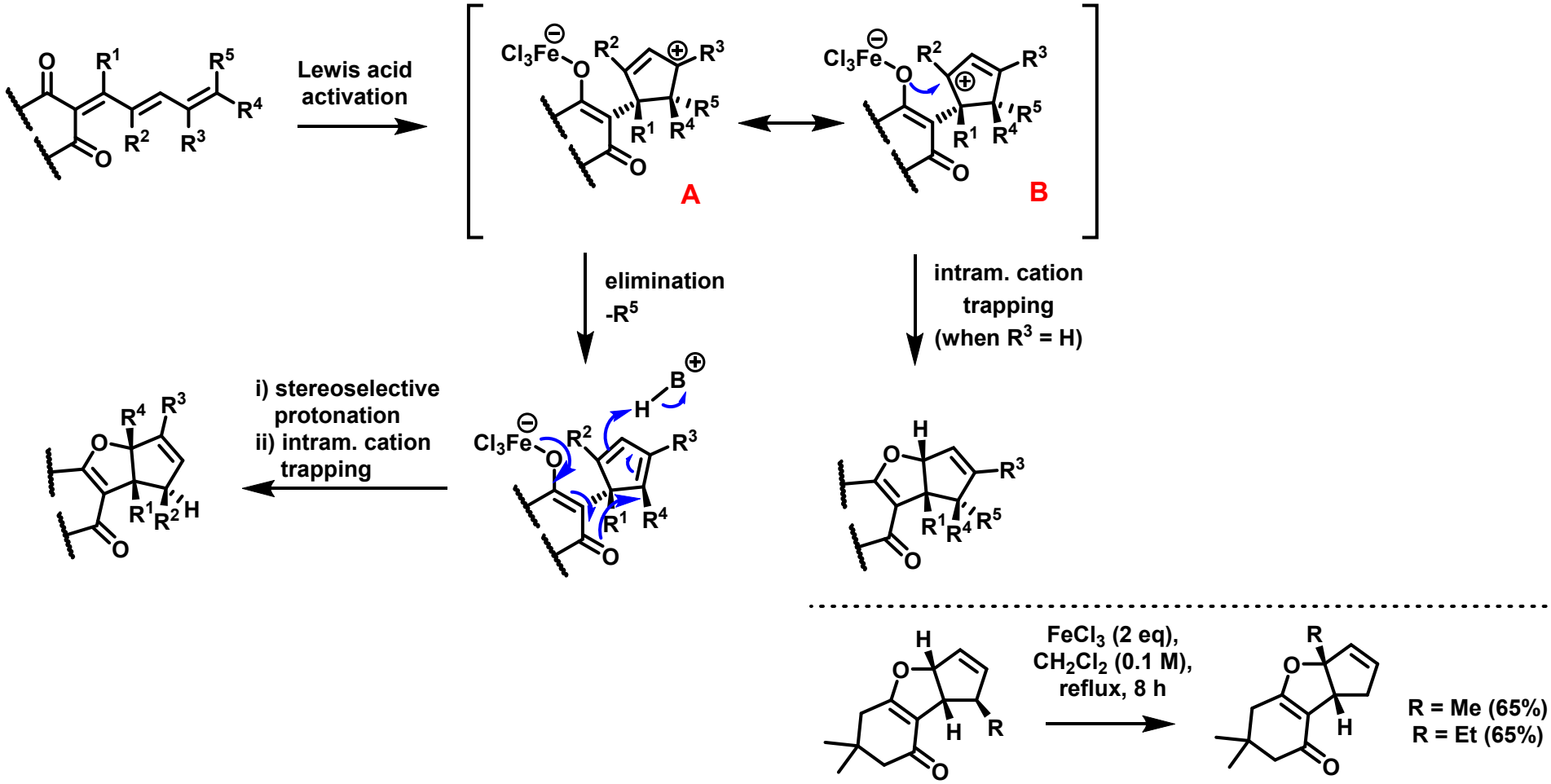
- Three alkyl-branched deuterated substrates were synthesised and products assessed



- ζ-D retention was quite low in the alternate cycloisomerisation, suggesting a new mechanism
  - an elimination step was considered likely

New Mechanistic Insight

- The authors suggest that the ε-branched substrates can lead to a preference for the tertiary cyclopentenyl cation intermediate



Conclusions

- Successfully demonstrated an unusual cascade reaction leading to the formation of cyclopenta[*b*]furan derivatives in one pot
  - good yields, mild conditions
  - restrictions in substrate reactivity
  - potential for further scaffold expansion courtesy of “re-rearranged” product discovery
- The exact utility of this synthetic strategy on non-diketal substrates is of interest
  - reach structures of greater similarity to the cyclopenta[*b*]tetrahydrobenzofurans?
- More detailed mechanistic studies are in the works
- Can these reactions be carried out asymmetrically?