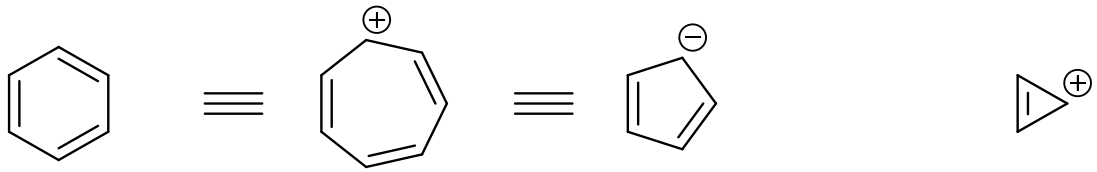
THREE CARBONS, TWO ELECTRONS, ONE RING: RECENT CHEMISTRY OF CYCLOPROPENIUM IONS

Group Meeting

David Kornfilt

4/24/2012

Hückel Aromaticity



•4n + 2 electrons lead to stable, delocalized systems.

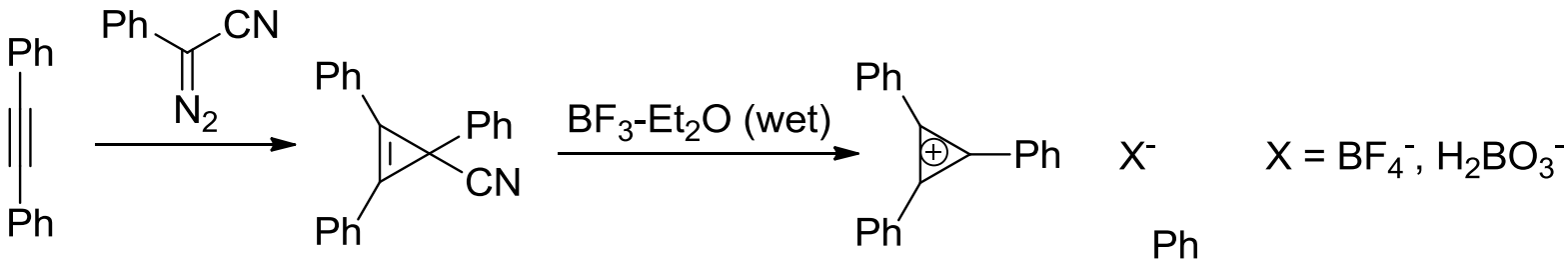
•Tropylium and cyclopentadienide are isoelectronic with benzene, and show aromatic stabilization effects.

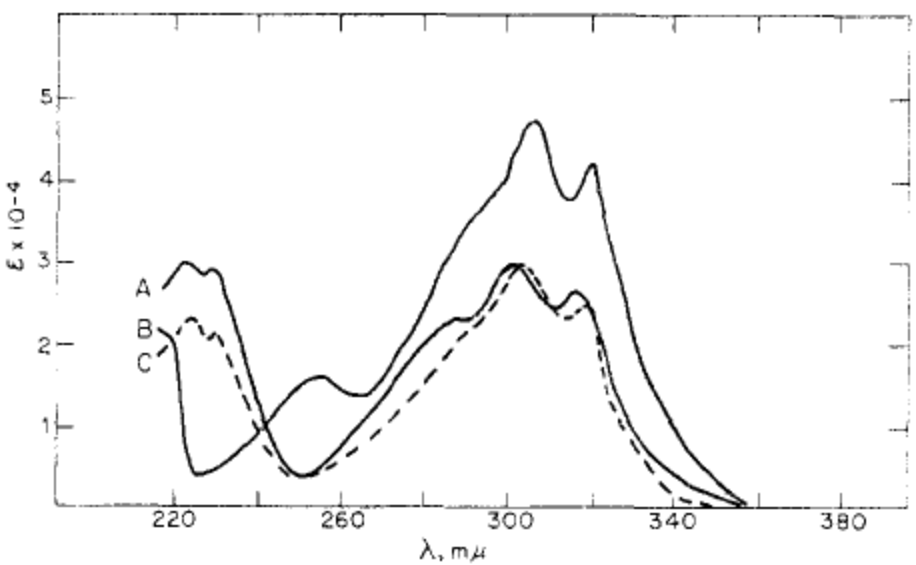
•Cyclopropenium ions are highly geometrically strained. However, they are stabilized due to aromaticity.

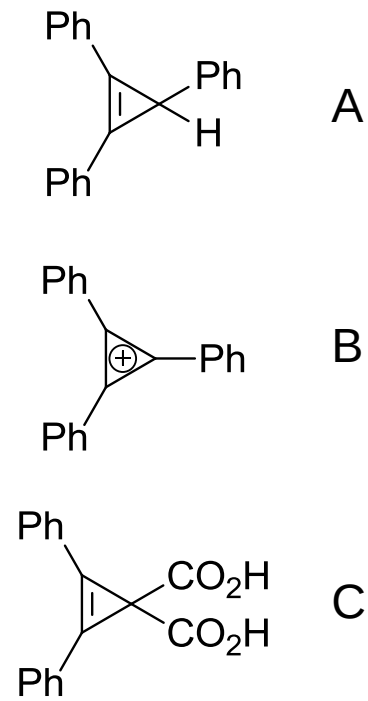
•Synthesis and characterization remained a longstanding challenge until 1957 (Breslow)

Komatsu et. al. *Chem. Rev.* **2003**, *103,* 1371-1427
Breslow et. al. *J. Am. Chem. Soc.*, **1958**, *80*, 5991- 5994

First Synthesis of Cyclopropene

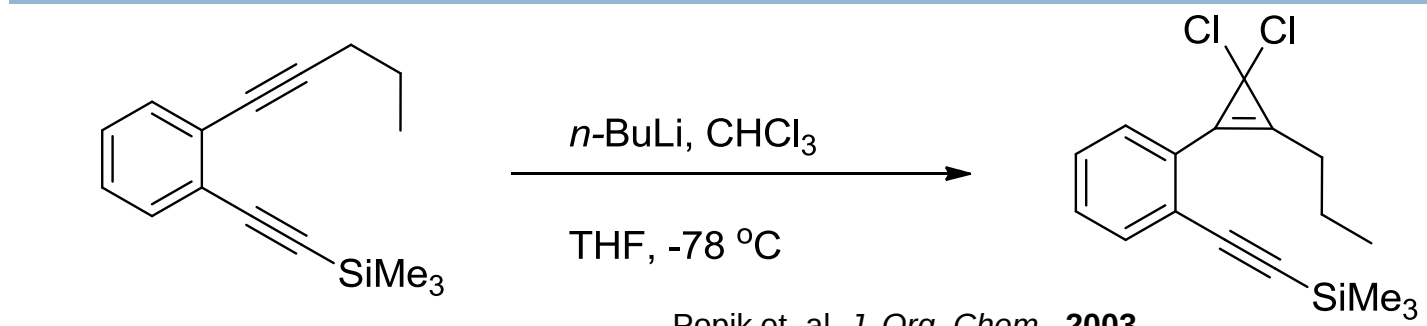






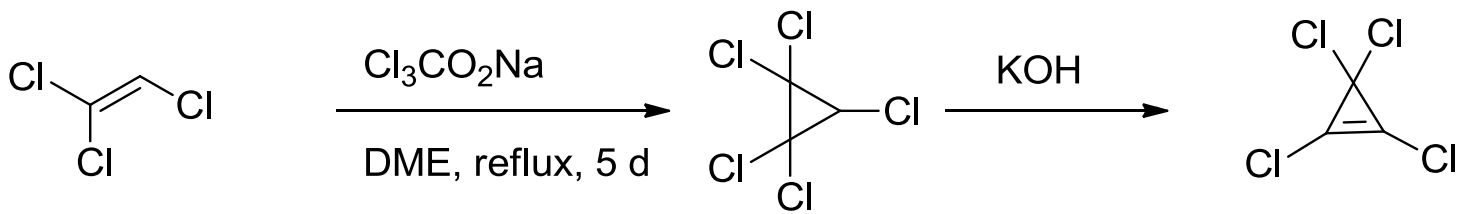
Breslow et. al. *J. Am. Chem. Soc.*, **1958**, *80*, 5991- 5994

Synthesis of Cyclopropenium Ions



Popik et. al. *J. Org. Chem.*, **2003**, *68*, 7833- 7840

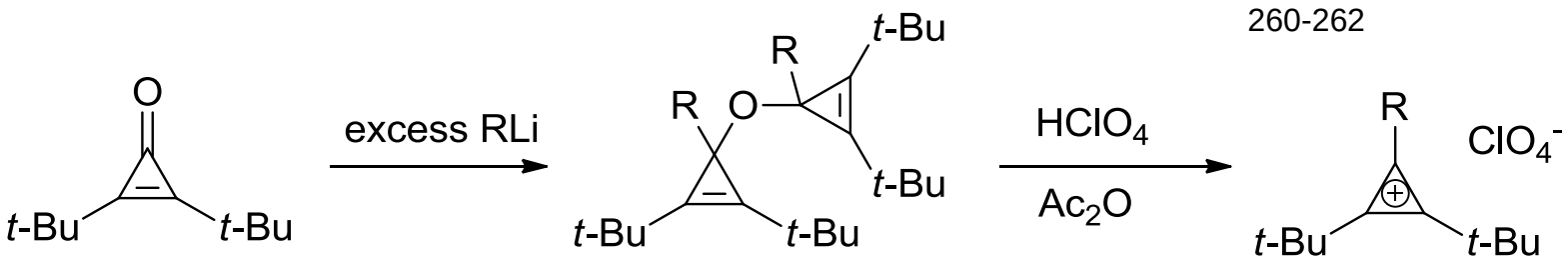
9 %



45%

85%

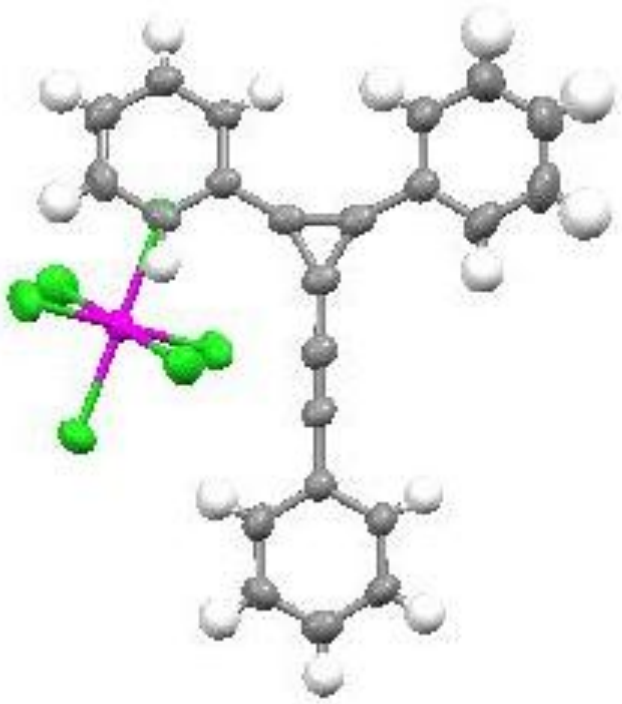
Schwager et. al. *Synth.*, **1987**, *3*, 260-262

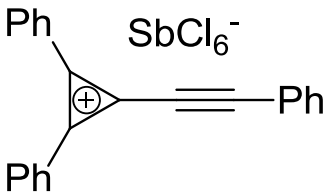


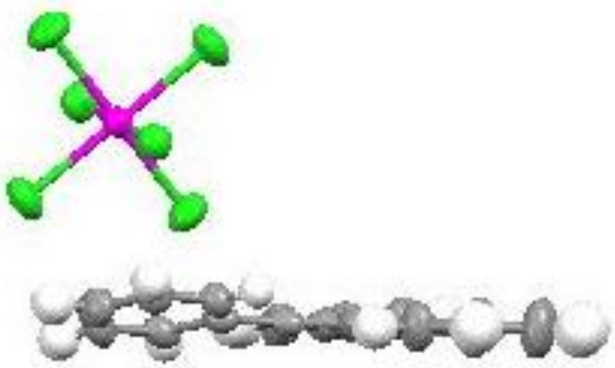
34-58 %

Nathan et. al. *J. Am. Chem. Soc.*, **1969**, *91*, 4766-4771

Crystal Structure of a Cyclopropenium Ion



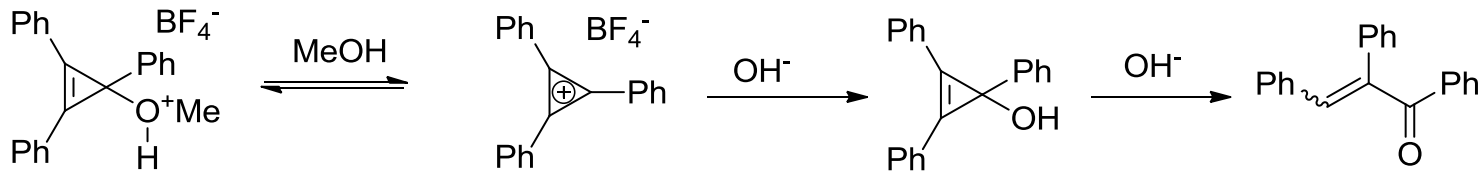


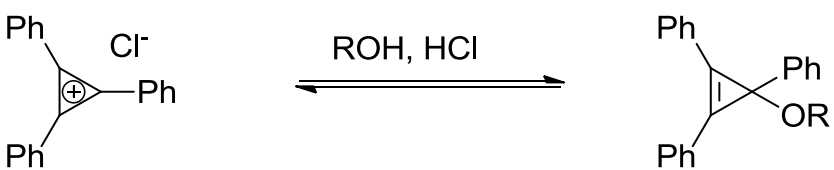


Cyclopropenium ring is planarized.
Substituents can be twisted out of the plane (and out of conjugation).
Overall aromatic stabilization is about 30 kcal/mol (32-35 for benzene)

Haley et. al. *J. Org. Chem.* **2000**, *65*, 1422-1430

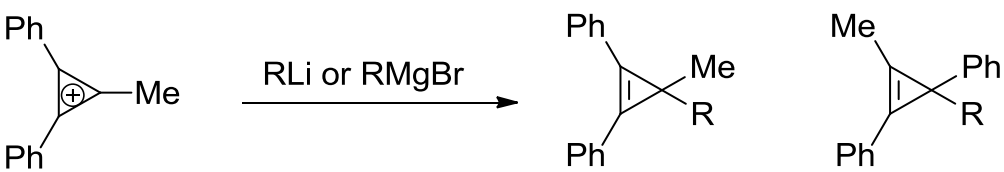
Reactions of Cyclopropenium Ions





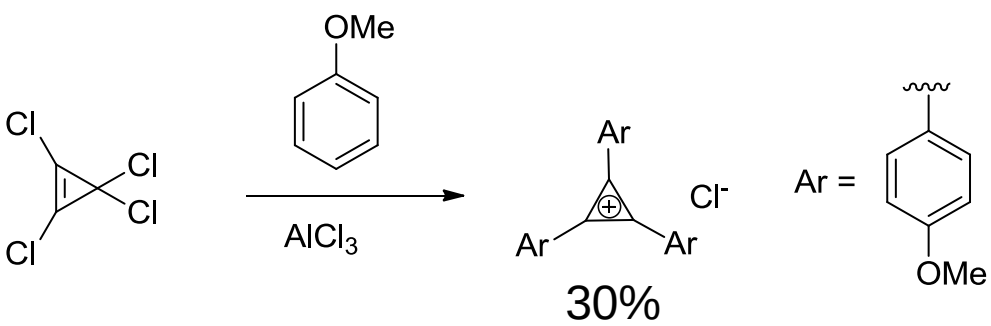
K_{eq} ~1 for 1N acid in EtOH
K_{eq} ~1 for 10^{-4} N acid in 9:1 MeCN:EtOH
pK_a of cation estimated to be about 1.

Breslow et. al. *J. Am. Chem. Soc.*, **1958**, *80*, 5991- 5994



Isomer ratio 1:1 to 5:1
Highly nucleophile dependent

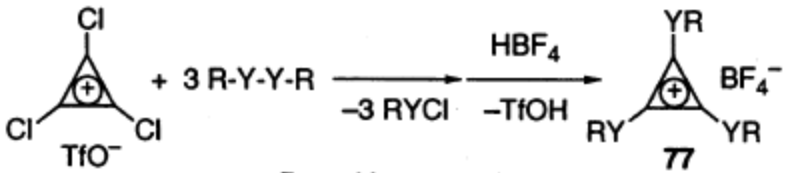
Komatsu et. al. *Chem. Rev.* **2003**, *103*, 1371-1427



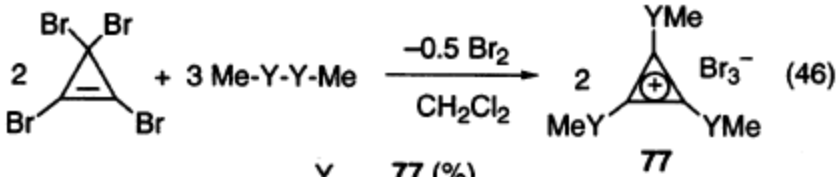
Friedel-Crafts type reactions

West et. al. *J. Am. Chem. Soc.* **1970**, *92*, 149-154

Stabilized Cyclopropenium Ions

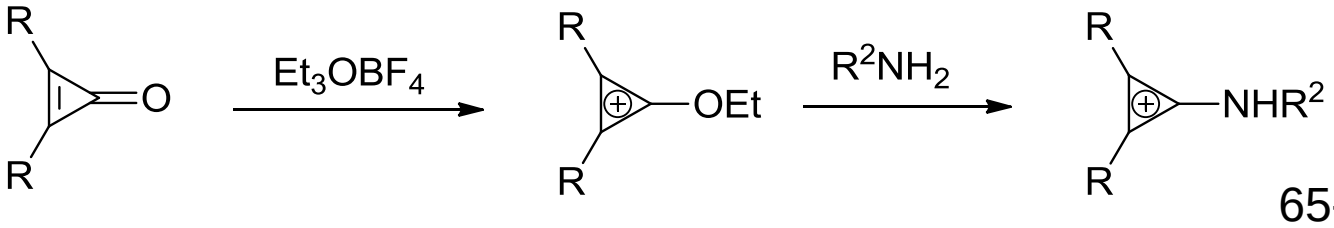


R	Y	77 (%)
Me	S	40
Me	Se	40
Me	Te	40
Ph	S	60-80
Ph	Se	60-80



Y	77 (%)
S	95
Se	92
Te	94

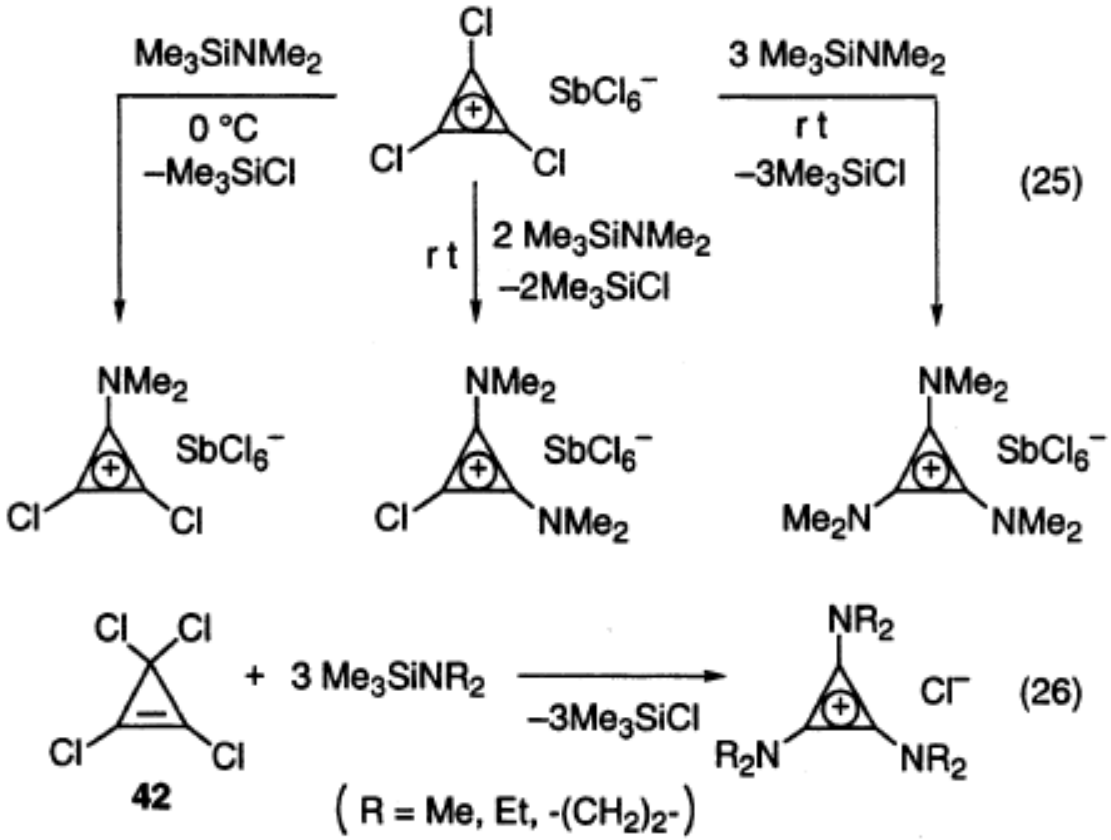
Weiss et. al. *J. Am. Chem. Soc.* ***1976,*** *98,* 4668-4669
Weiss et. al. *Synthesis* ***1980,*** 225-226***.***



Pick et. al. *Synthesis* ***1987,*** 887

Thio- and amino stabilized cyclopropenium ions can be synthesized from easily accessible starting materials.

Aminocyclopropenium Ions



Komatsu et. al. *Chem. Rev.* **2003**, *103*, 1371-1427

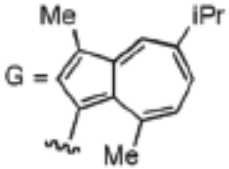
Stabilization Trends Cyclopropenium Ions

Table 1. pK_{R^+} Values of Cyclopropyl- and Phenyl-Substituted Cyclopropenylium Cations[a]

R^1	R^2	R^3	anion	pK_{R^+}	Ref
Ph	Ph	Ph	Br^-	3.1	26
Ph	Ph	Ph	BF_4^-	3.4	25
▷	Ph	Ph	BF_4^-	5.04	25
▷	▷	Ph	BF_4^-	7.09	24
▷	▷	▷	Cl^-	9.4	23,24
▷	▷	▷	BF_4^-	10.0	22

Cyclopropyl to phenyl substution increases stability by 2 log units.

Komatsu et. al. *Chem. Rev.* **2003**, *103*, 1371-1427
Munjal, R. C. *J. Am. Chem. Soc.* **1986,** *108***,** 134-140
Breslow, R. *J. Am. Chem. Soc.* **1962,** *84*, 3168-3174



R	H [a]	Ph	p-c-Pr-Ph [b]	t-Bu [c]	n-Pr [d]	c-Pr	GAz [e]
pK_{R^+}	-7.4	2.60 [b] (2.8 [d])	3.23	6.5	7.2	10.0	>10
Solvent	H_2SO_4-EtOH	23% aq. EtOH		50% aq. MeCN			

Okajima et. al. *Tetrahedron Lett.*, **1980**, 947-950
Kerber, R. C.; *Am. Chem. Soc.* **1973,** *95***,** 3239

Stabilization is Conjugative

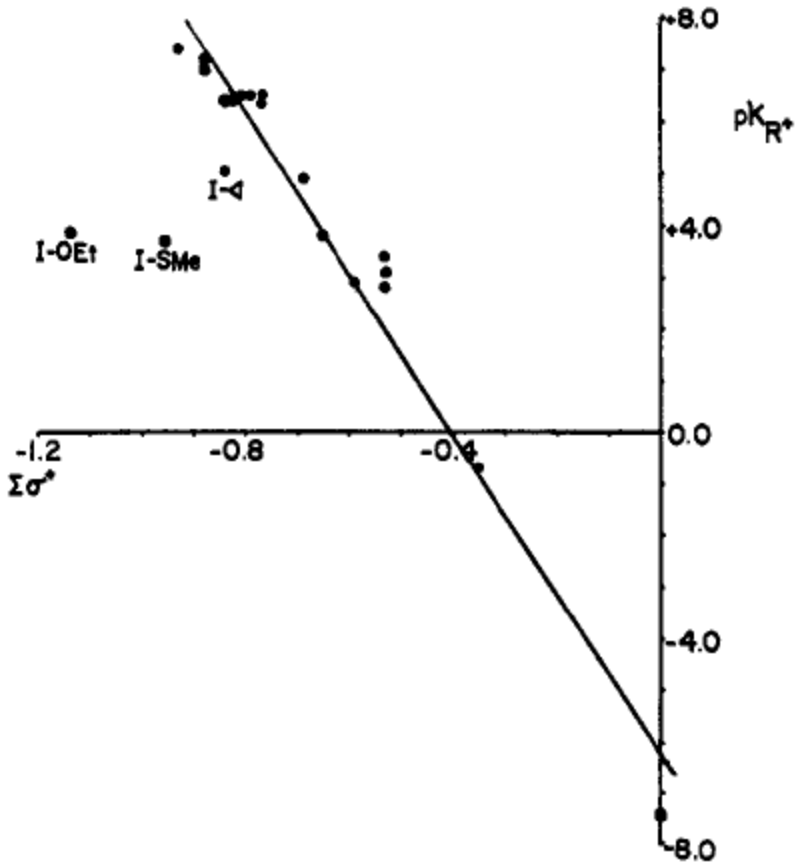


Figure 2. pK_{R^+} of cyclopropenium ions *vs.* the sum of the σ^+ parameters of the three substituents. The correlation line has a slope (σ) of -15.71. The points for I (X = c-C_3H_5, OEt, and SCH_3) were omitted from the correlation.

Order of stabilization:

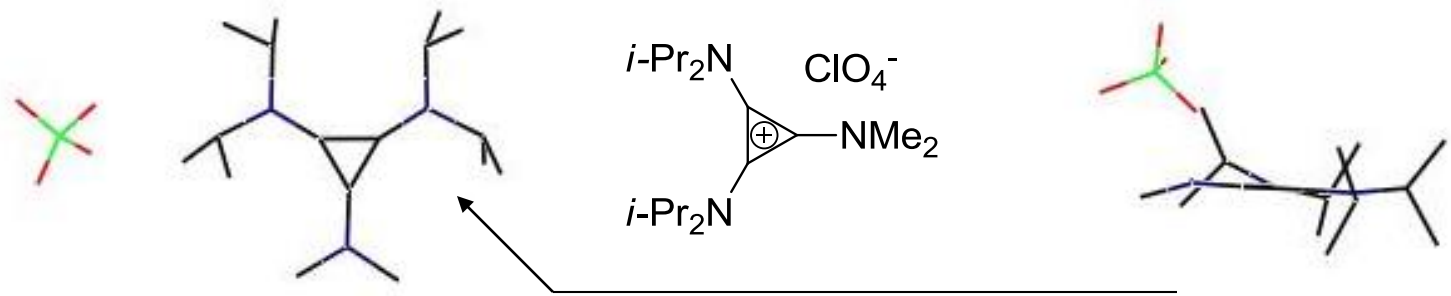
R_2N>> c-C_3H_5 > SR > Me > Et > *i*-Pr > *t*-Bu > Ph > H

Stabilization is mainly a conjugative effect.

Heteroatoms may have an inductive contribution

Kerber, R. C.; *Am. Chem. Soc.* **1973,** *95,* 3239

Aminocyclopropenium Ions



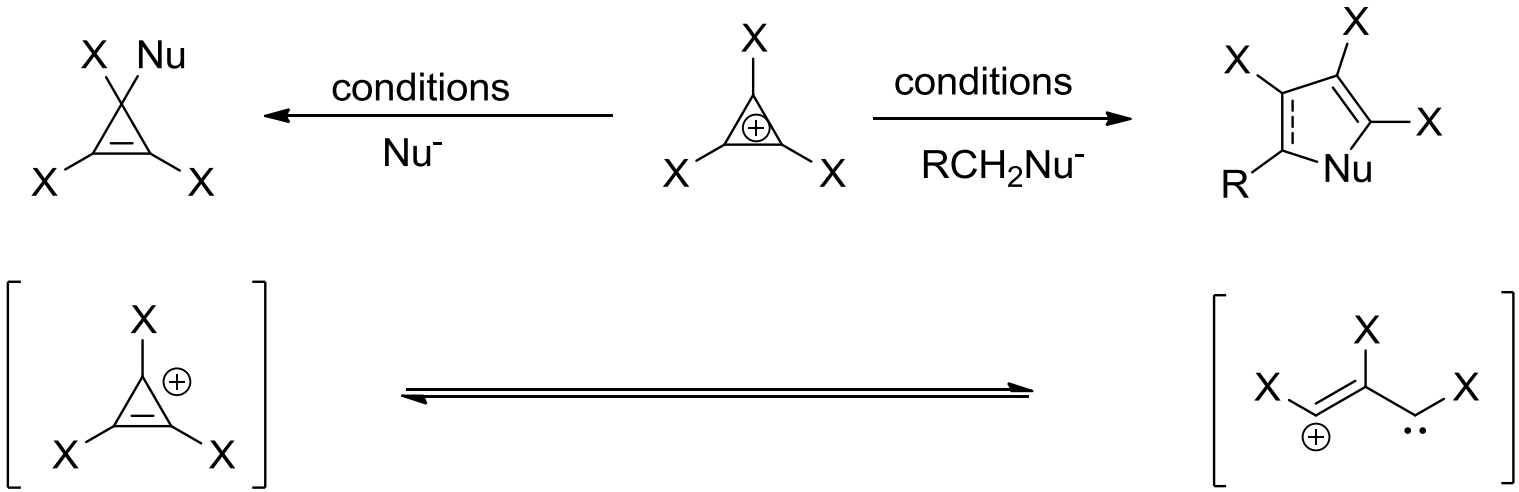
Strong torsional strain due to steric effects of *i*-Pr substituents.

Nitrogens remain planarized. Dihedral angle of ~20° for out of plane substituent.

Free rotation around N-C(*i*-Pr) bonds (No coalescence down to -55 ^{o}C)

Curnow et. al. *J. Phys. Org. Chem.* **2008**, *21,* 127–135

Bimodal Reactivity



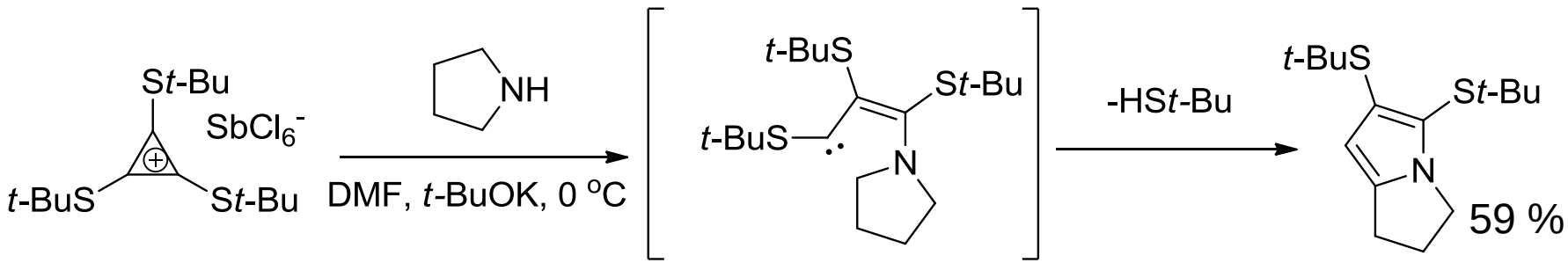
Common cyclopropene intermediate.

Substituent and solvent effects determine propensity for allylcarbene-type reactivity.

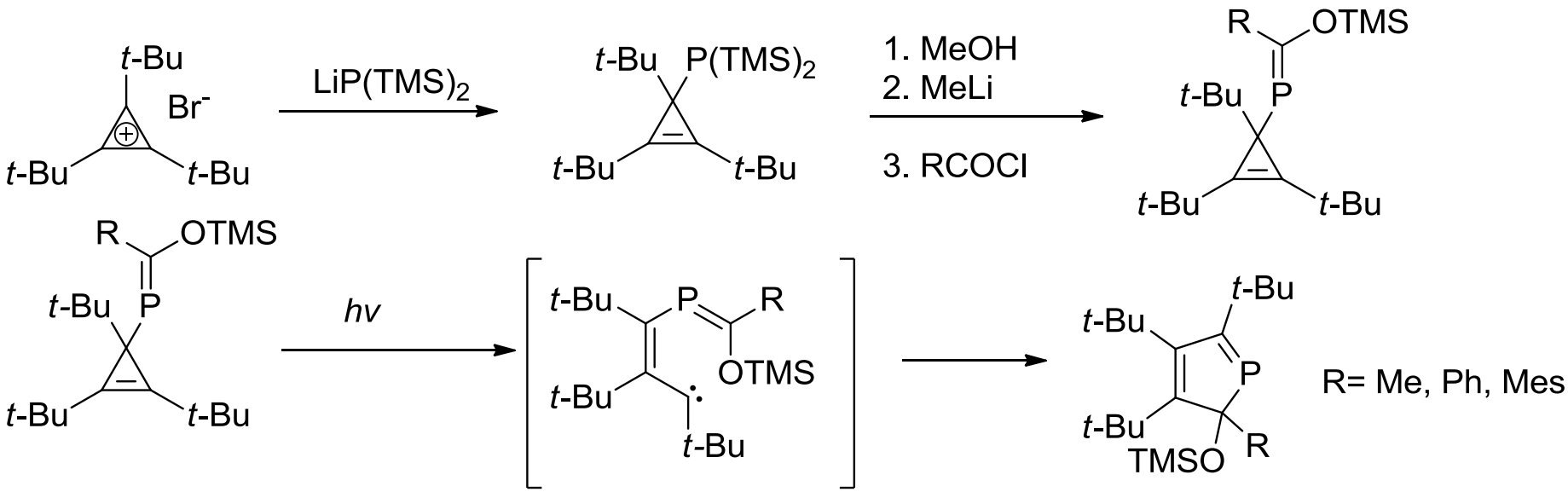
Shi et. al., *Chem. Soc. Rev.*, **2011,** *40***,** 5534–5563

Komatsu et. al. *Chem. Rev.* **2003***, 103,* 1371-1427

An Allylcarbene Synthon



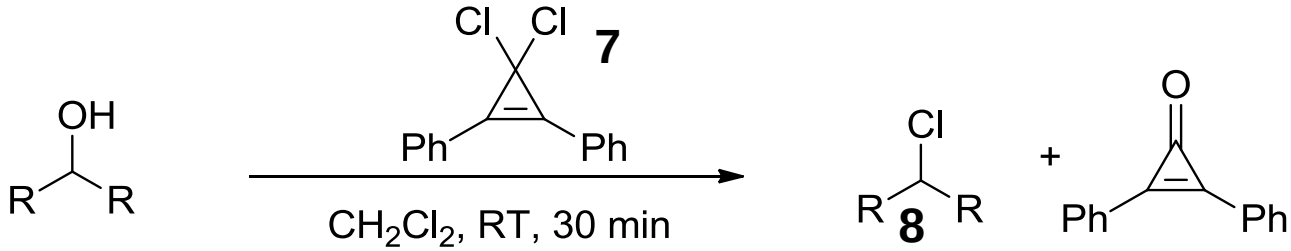
Yoshida et. al. *Heterocycles* **1981**,*15,* 865-869



76-91% yield from P-cyclopropene

Regitz et. al. *J. Organomet. Chem.* **1987**, *332,* C1-C5

In-situ Generated Cyclopropenium Ions as Dehydrating Reagents

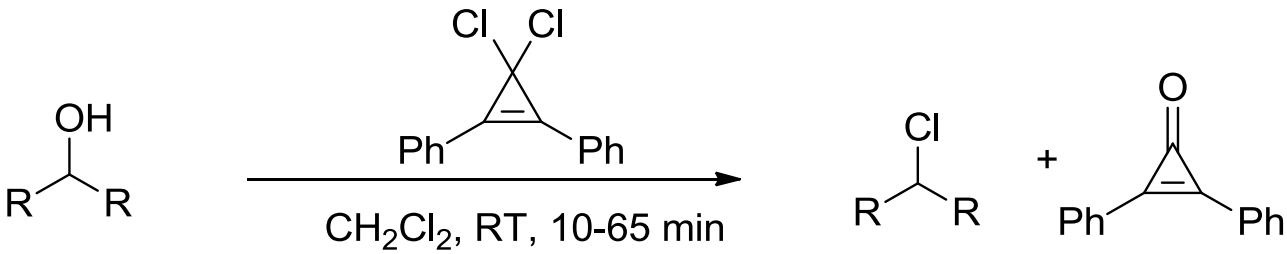


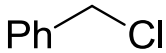
entry	solvent	equiv of **7**	additive (equiv)		% yield of **8**
1	CH_3CN	1.5	–		73
2	DMSO	1.5	–		49
3	acetone	1.5	–		30
4	THF	1.5	–		51
5	toluene	1.5	–		52
6	DCE	1.5	–		71
7	CH_2Cl_2	1.5	–		91
8	**CH_2Cl_2**	**1.1**	–	***10 min***	**91**
9	CH_2Cl_2	–	HCl (1.5)		~5

Apolar CH_2Cl_2 is the best solvent. No catalysis was observed by HCl.

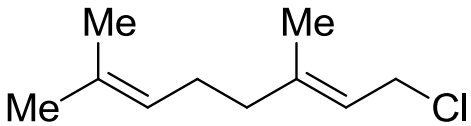
Lambert et. al. *J. Am. Chem. Soc*. **2009**, *131,* 13930-13931

Broad Scope for Chlorodehydration

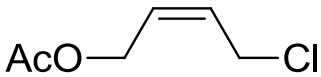




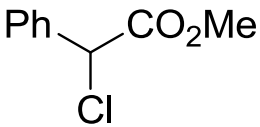
81 %



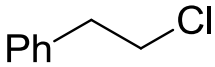
92 %



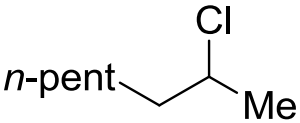
84 %



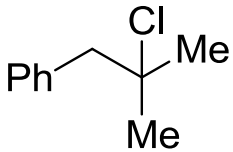
93 %



89 %



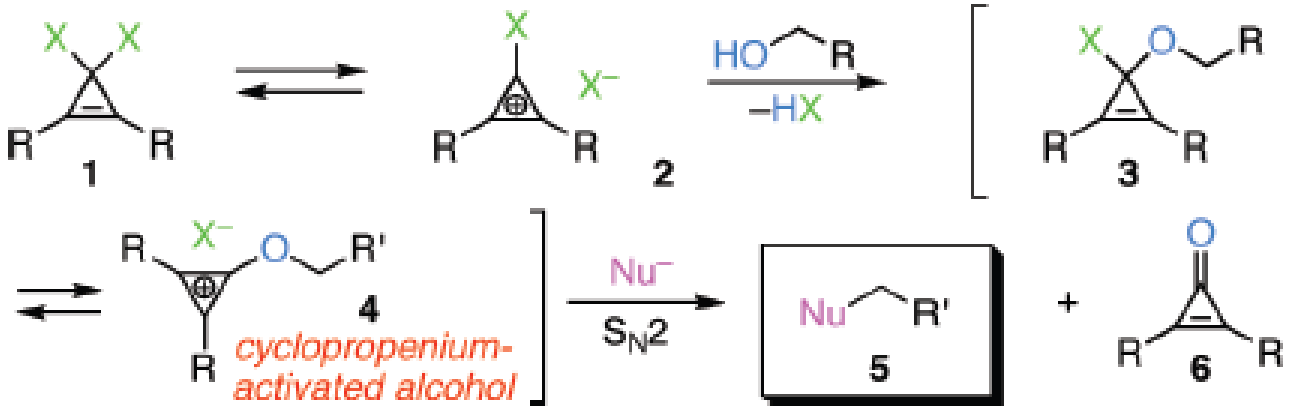
93 % (NMR)
80 °C



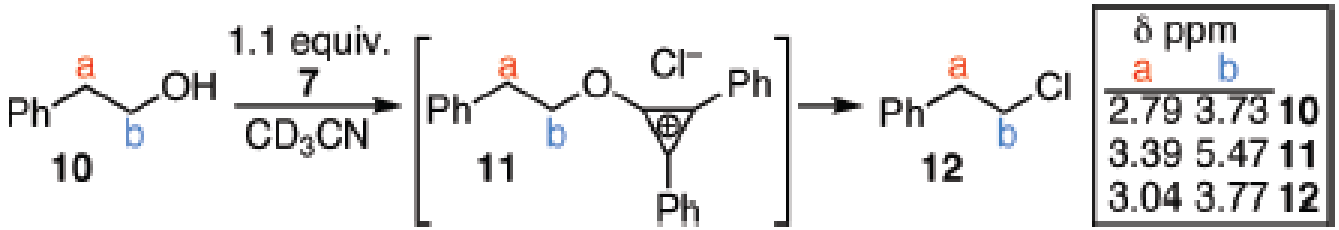
45 %
33 % styrene

Lambert et. al. *J. Am. Chem. Soc*. **2009**, *131,* 13930-13931

Mechanistic Hypothesis



Electrophilic Activation of the Alcohol

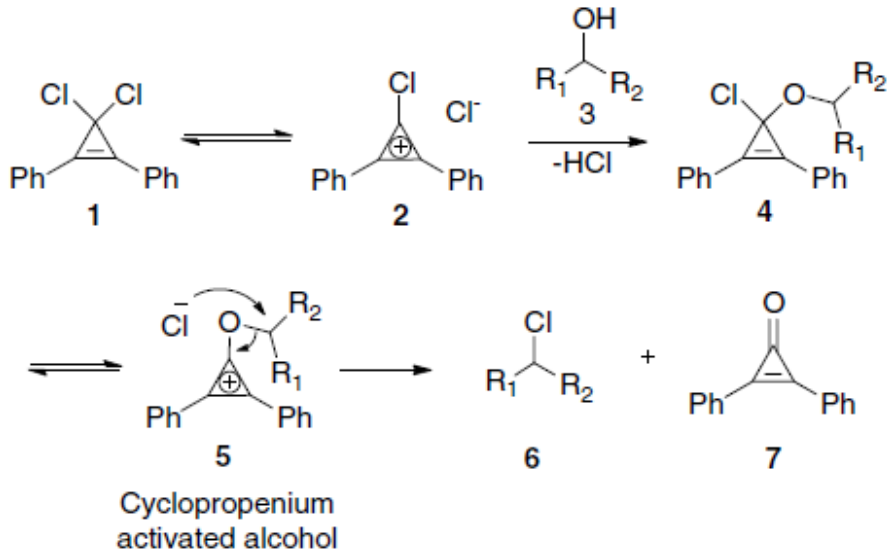


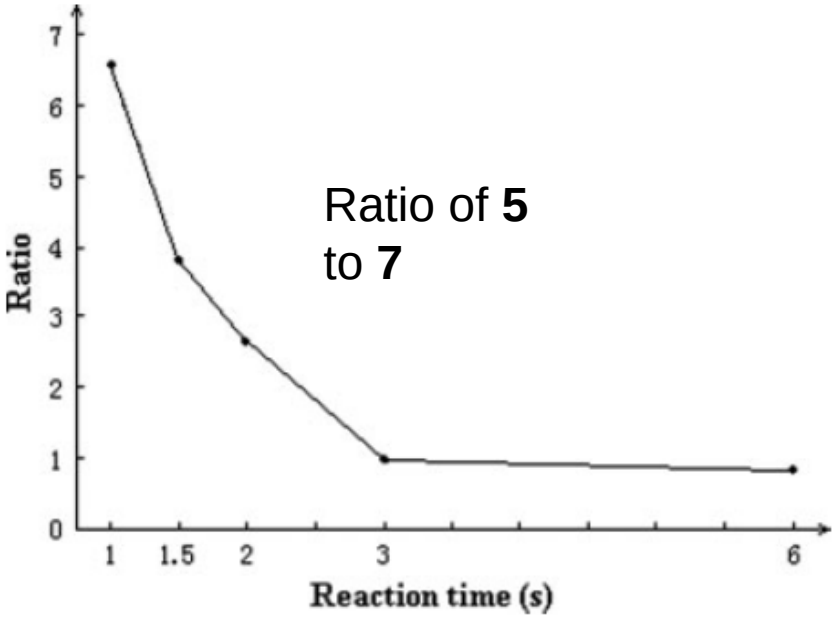
δ ppm a	δ ppm b	
2.79	3.73	**10**
3.39	5.47	**11**
3.04	3.77	**12**

NMR data consistent with formation of a charged intermediate

Lambert et. al. *J. Am. Chem. Soc*. **2009**, *131*, 13930-13931

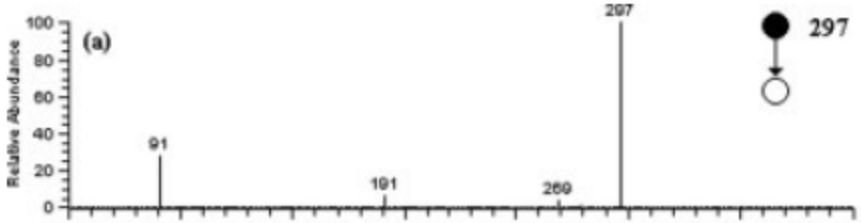
Characterization via ESI-MS/MS





Ratio of **5** to **7**

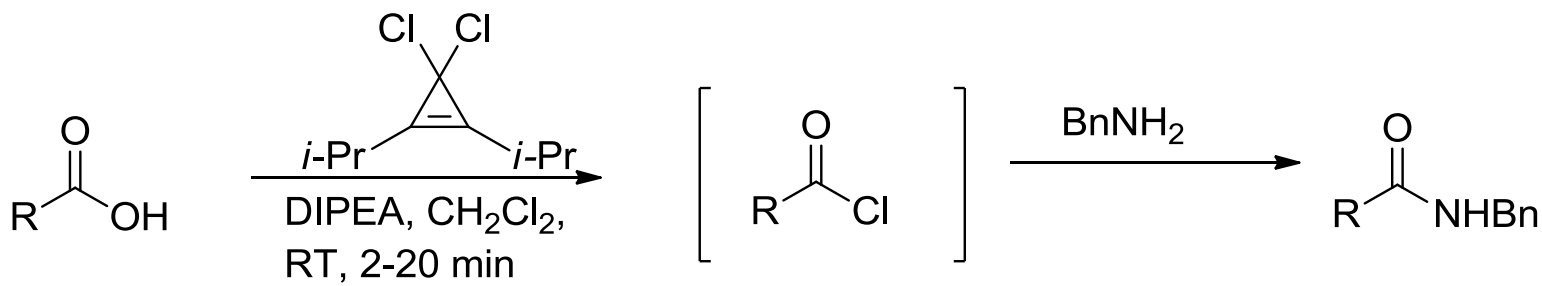
5 not detected after 1 min. reaction time

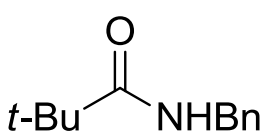


Peak at m/z = 297 corresponds to **5** (R1= Bn, R2= H)
Peak at m/z = 91 corresponds to loss of neutral **7**

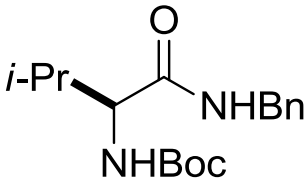
Guo et. al. *J. Mass. Spectrom.* **2011**, *46,* 856–858

Application to Acid Chlorides

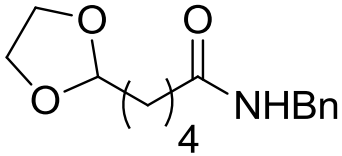




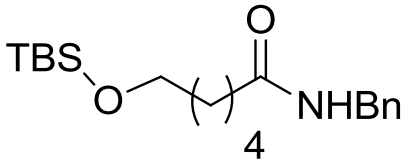
78 %



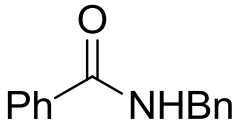
79 %



94 %



92 %

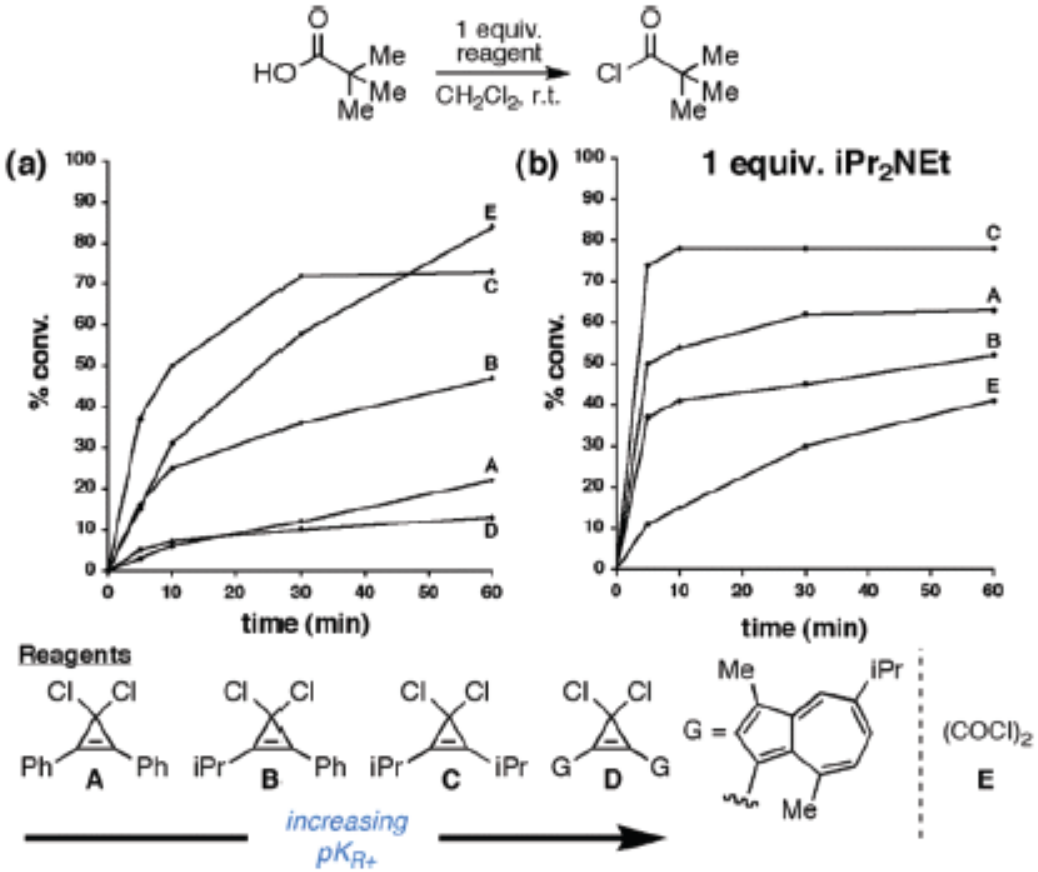


44 %

Lambert et. al. *J. Am. Chem. Soc*. **2010**, *132,* 5002–5003

Formation of acid chlorides in the presence of acid sensitive functional groups can be accomplished.

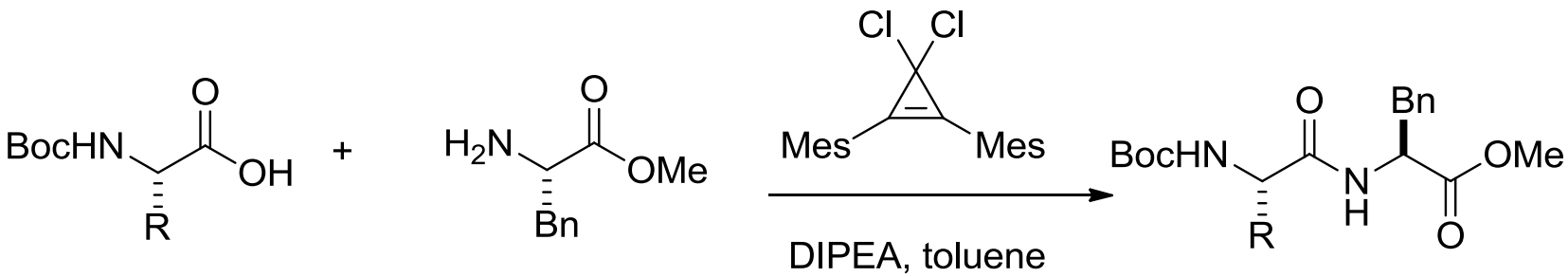
Striking a Balance for Cyclopropenium Ion Stability



i-Pr-cyclopropene provided best results. The catalyst needs to balance rate of ionization with rate of nucleophilic attack by the neutral acid.

Lambert et. al. *J. Am. Chem. Soc*. **2010**, *132,* 5002–5003

Amide Coupling of a Peptide



R = Me, RT, 5 min, 77%, >20:1 d.r.

R = Ph, -78 ^{o}C, 20 min, 80%, >20:1 d.r.

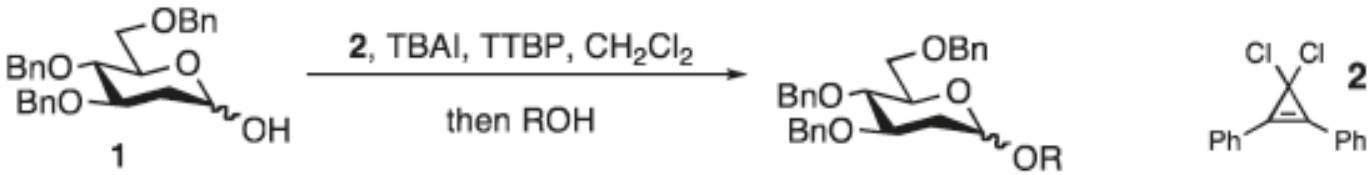
No racemization observed at enolizable positions

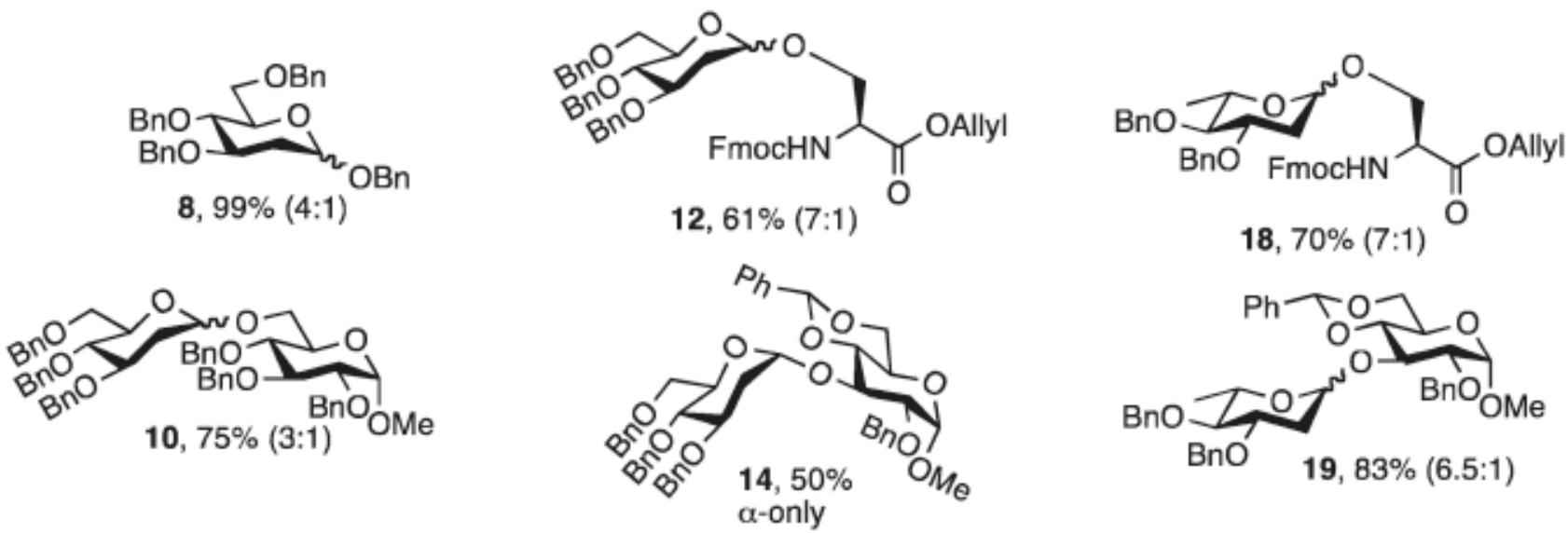
Boc protecting group remains intact.

Very mild method of generating acid chlorides. Has not been applied in complicated syntheses yet.

Lambert et. al. *J. Am. Chem. Soc*. **2010**, *132,* 5002–5003

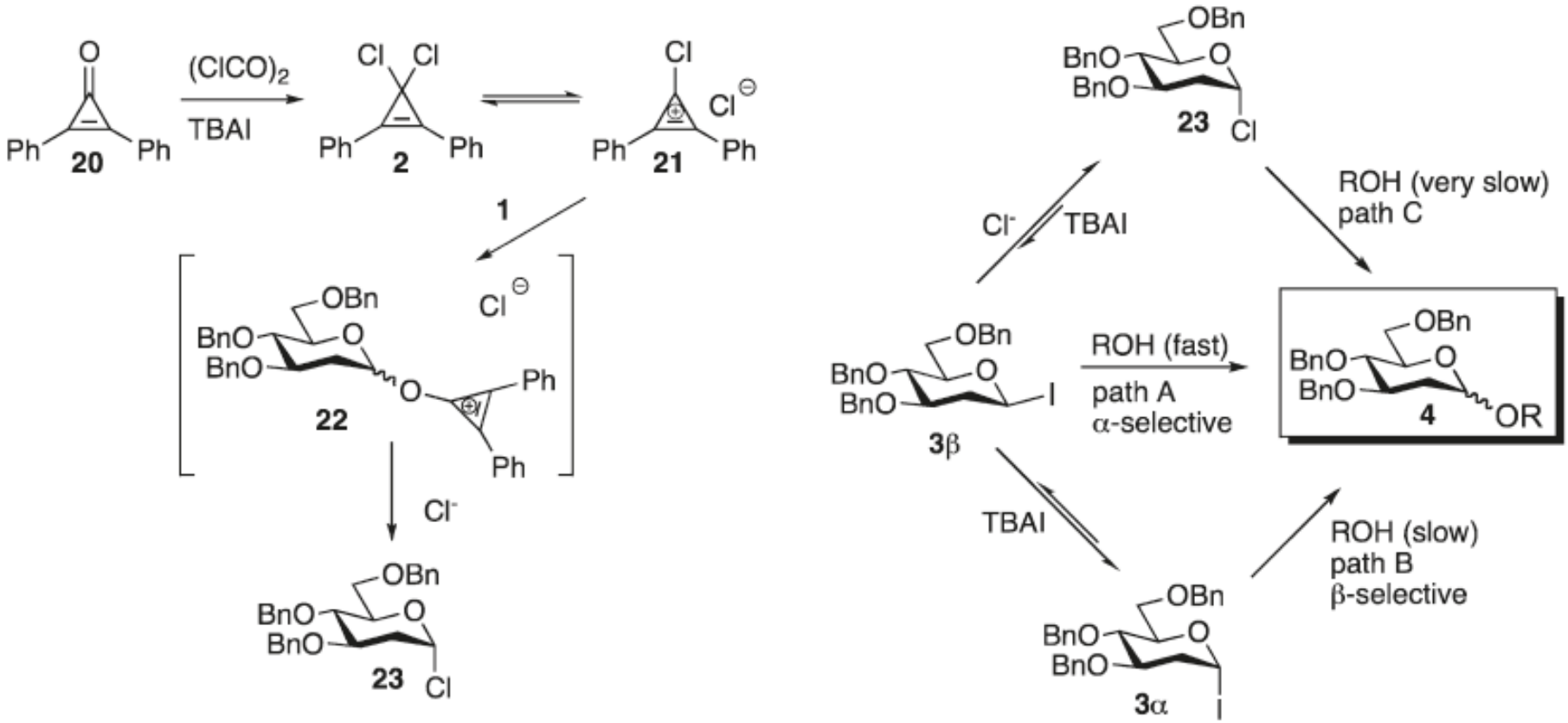
Application of the Chlorodehydration Reaction





Bennett et. al. *Org. Lett.*, **2011**, *13*, 2814-2817

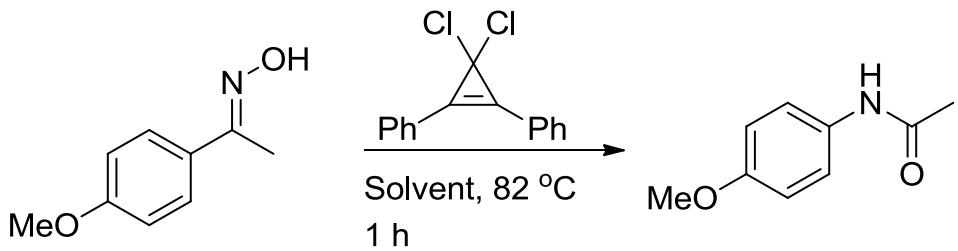
α-Anomeric Sugars



Formation of chloride, followed by double displacement

Bennett et. al. *Org. Lett.*, **2011**, *13*, 2814-2817

Cyclopropenium Catalyzed Beckmann Rearrangement

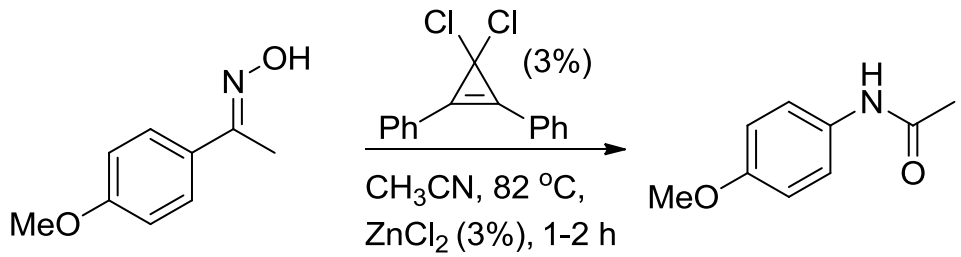


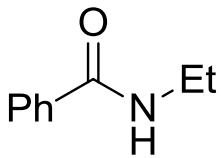
Entry	Solvent	Catalyst (mol %)	Cocatalyst	Conv., %
1	CH_3CN	3	-	90
2	CH_3CN	0	$ZnCl_2$ (3%)	0
3	CH_3CN	3	$ZnCl_2$ (3%)	100
4	Toluene	3	$ZnCl_2$ (3%)	30
5	CH_3CN	0	HCl + $ZnCl_2$ (3%)	30
6	[bmim]PF_6	0	$ZnCl_2$ (3%)	20

Other Lewis acidic chlorides did not work as well.
Apolar solvents generally gave inferior results. CH_2Cl_2 was not tested

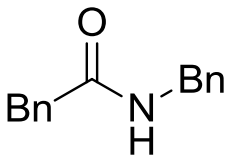
Yadav et. al. *Chem. Commun.*, **2010**, *46*, 5808–5810

A Versatile Organocatalytic Beckmann Rearrangement?

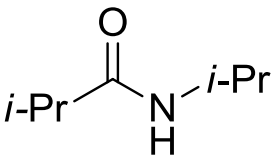




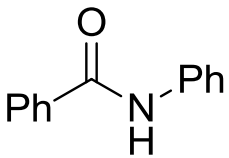
94 %



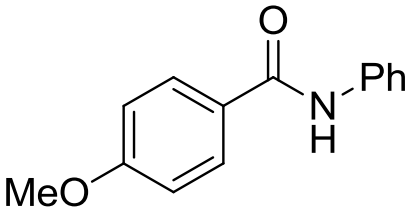
91 %



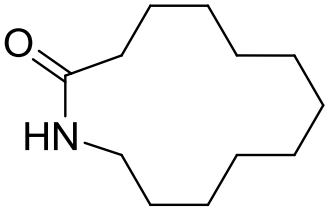
94 %



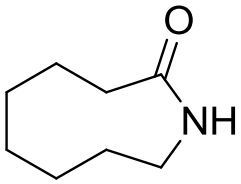
94 %



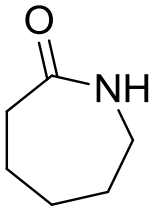
89 %
1:0.7 oxime
1:0.7 ratio in product



94 %



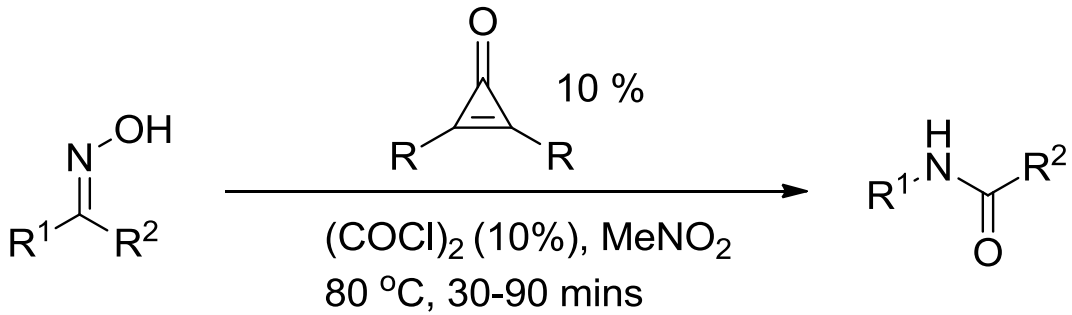
29 %



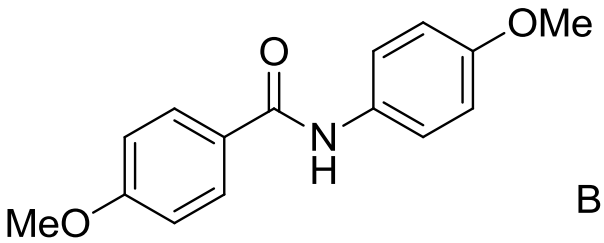
18 %

Yadav et. al. *Chem. Commun.*, **2010**, *46*, 5808–5810

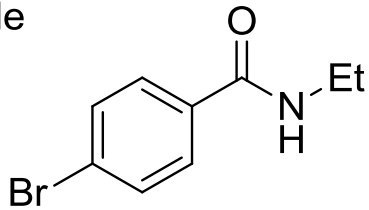
Lambert's Competing Rearrangement



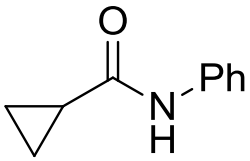
R= Ph, Mes



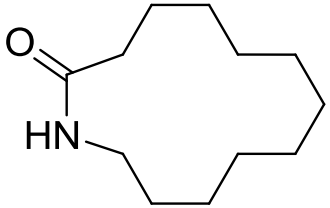
95 %



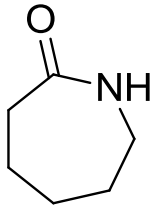
99 %



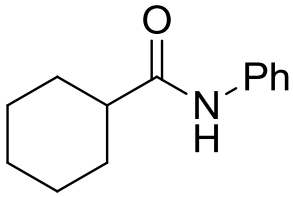
89 %



24 h, 93 %



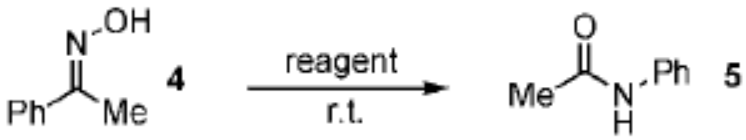
96 %
(NMR)



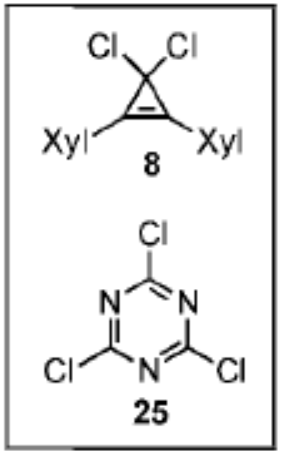
99 %
2:1 isomer ratio
from 2:1 E:Z oxime

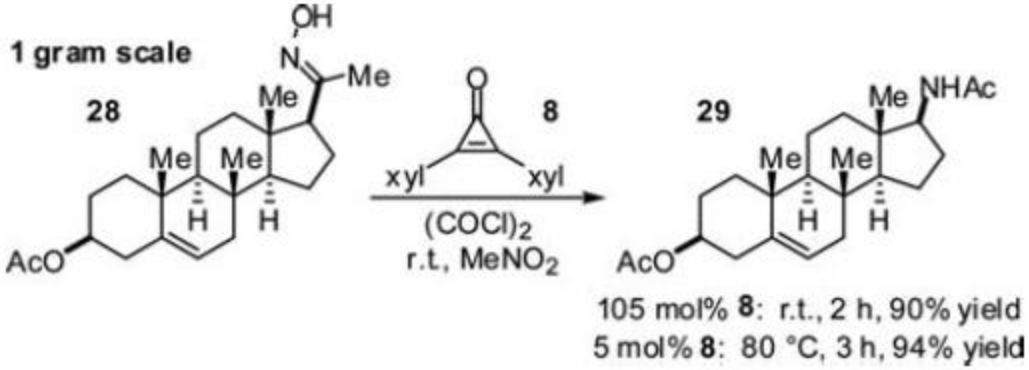
Lambert et. al. *Chem. Sci.*, **2010**, *1*, 705–708

Comparison of Reagents



reagent	solvent	time	% yield
8	MeCN	20 min	98
25	MeCN	N.R.	--
25	DMF	6 h	100[b]

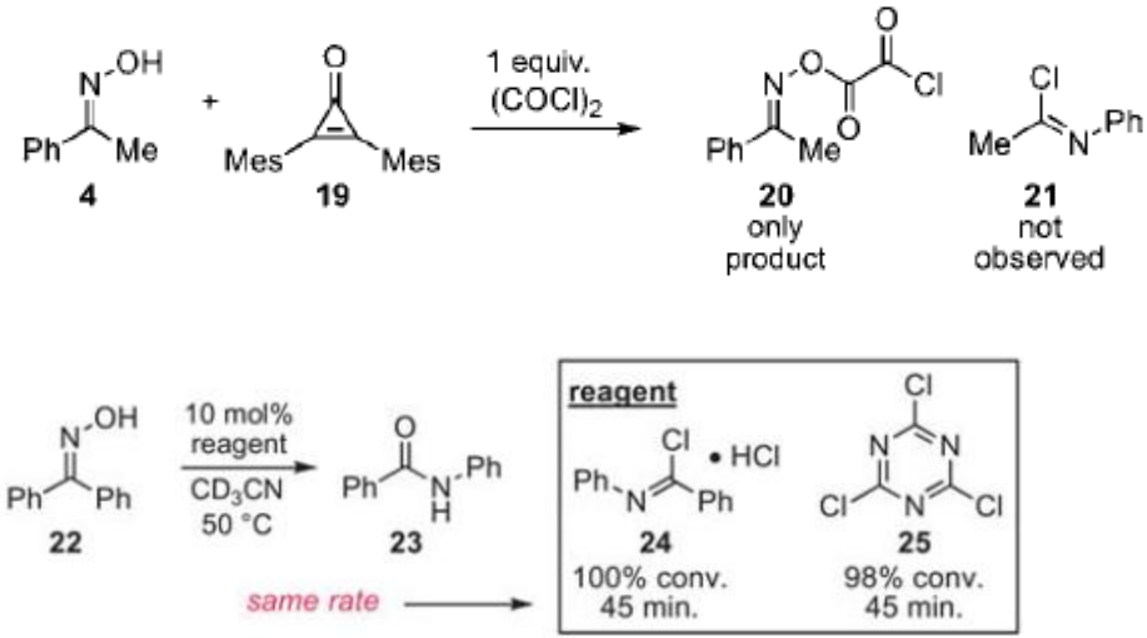




8 is significantly more active than cyanuric chloride, the reagent commonly employed to effect the Beckmann rearrangement.
8 can be employed in a complex molecular setting.

Lambert et. al. *Chem. Sci.*, **2010**, *1*, 705–708

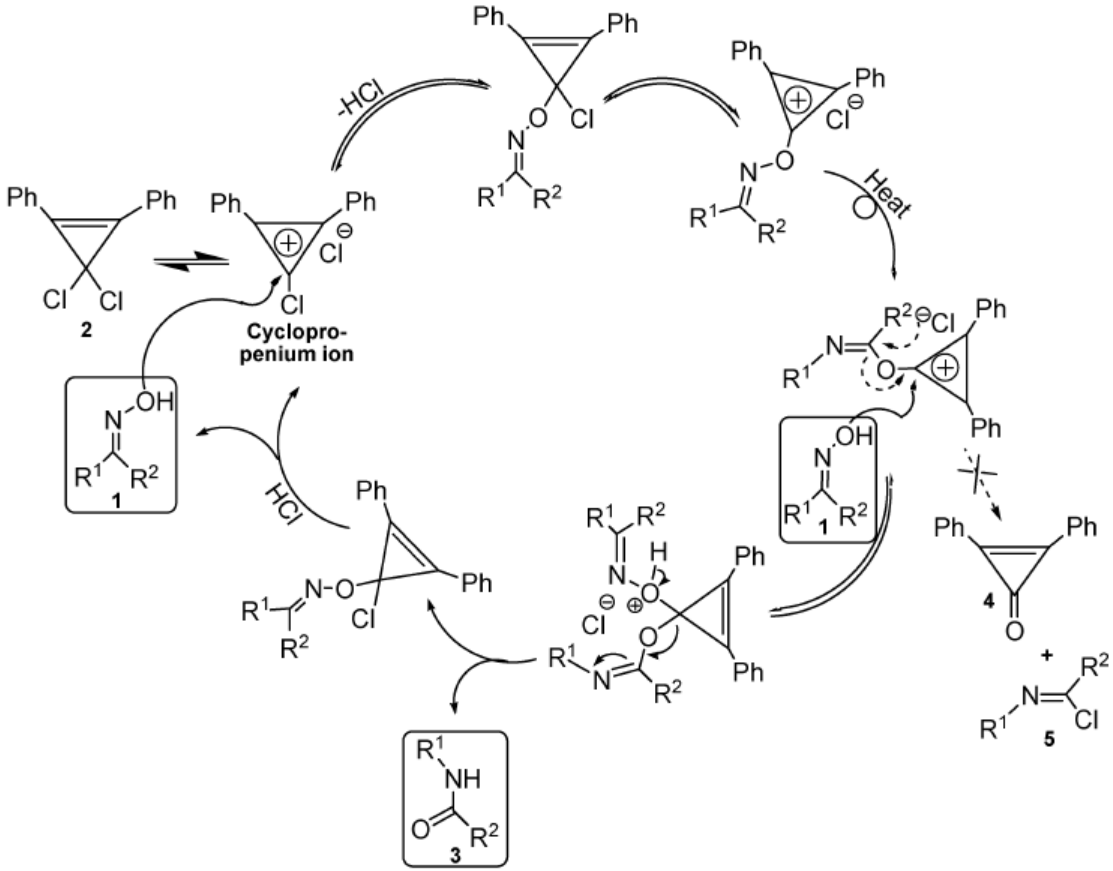
Mechanistic Experiments



Based on these results, propose two different mechanistic cycles for the catalytic Beckmann rearrangement.

Lambert et. al. *Chem. Sci.*, **2010**, *1*, 705–708

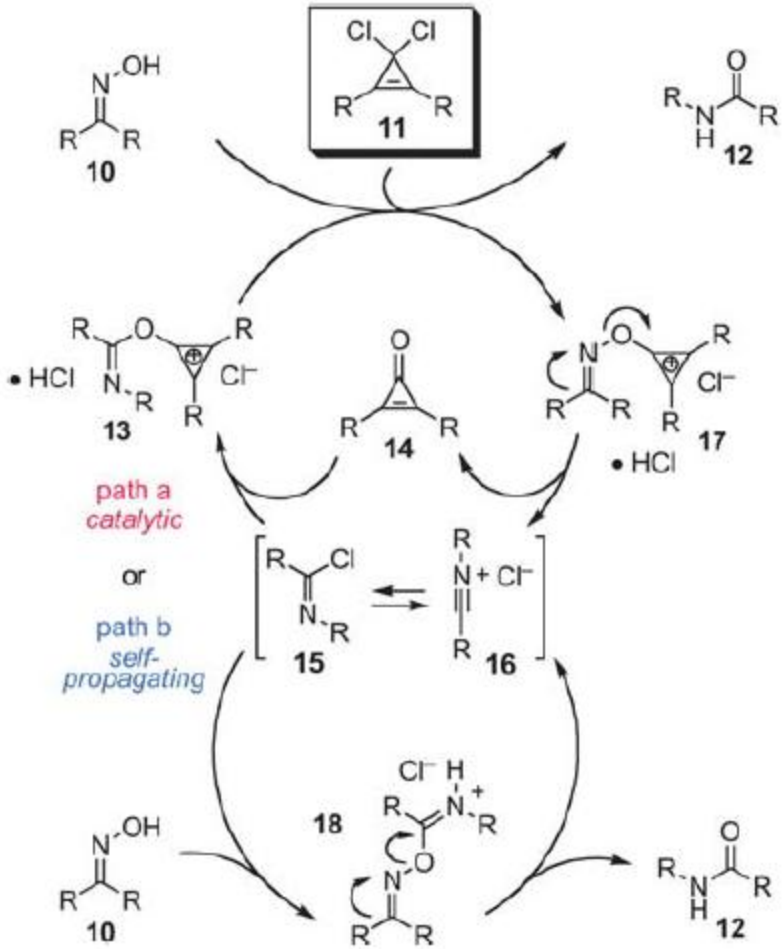
An Organocatalytic Pathway



Key step is the N-to-C migration of alcohol with concomitant migration of R^1

Yadav et. al. *Chem. Commun.*, **2010**, *46*, 5808–5810

An Autocatalytic Pathway



Conditions which form the Vilsmeier reagent may promote autocatalysis.

The evidence is against an organocatalytic mechanism:

-Cyclopropenone is not a competitive nucleophile in comparison to oximes.

-Imidoyl chloride **15** is an effective initiator of the Beckmann rearrangement

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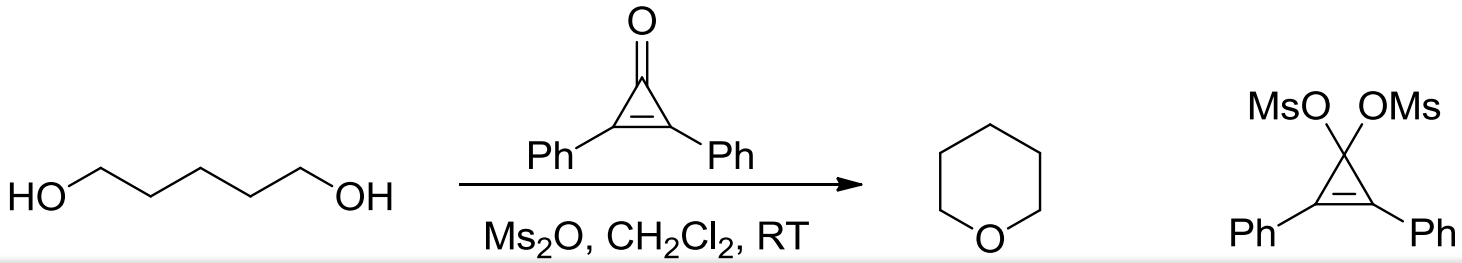
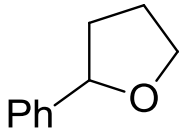
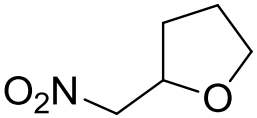
Dehydrative Cyclizations

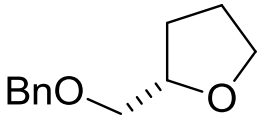




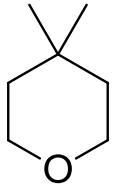
1 h , 94%



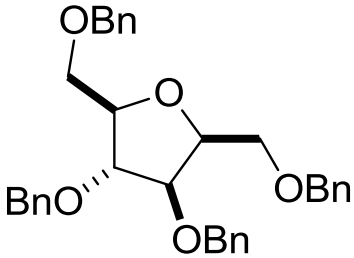
6 h , 81%



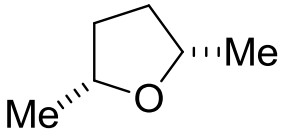
7 h , 92%, 100% e.s.



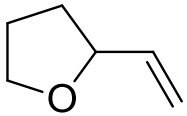
1 h , 91% (NMR)



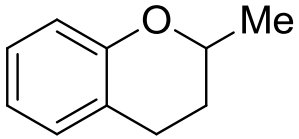
11 h , 82%



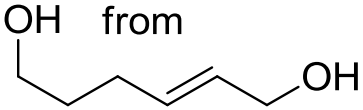
2.5 h , 95%



3 h , 95%

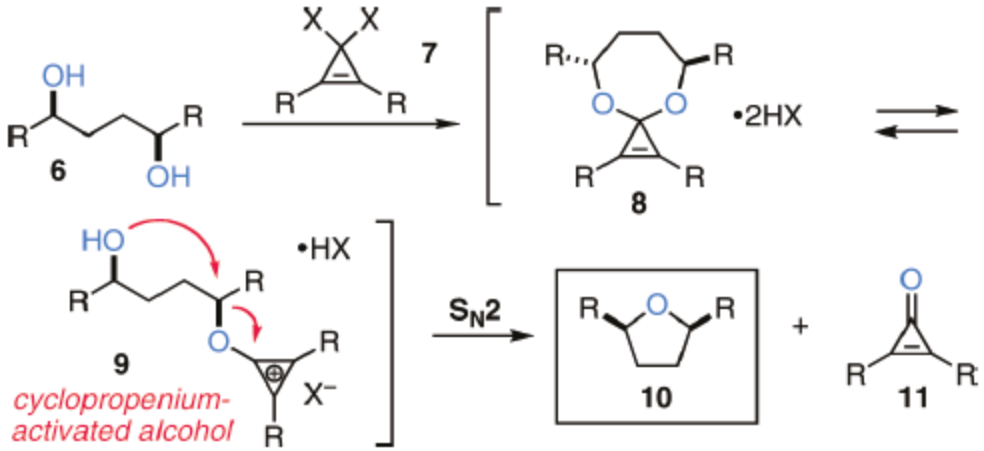


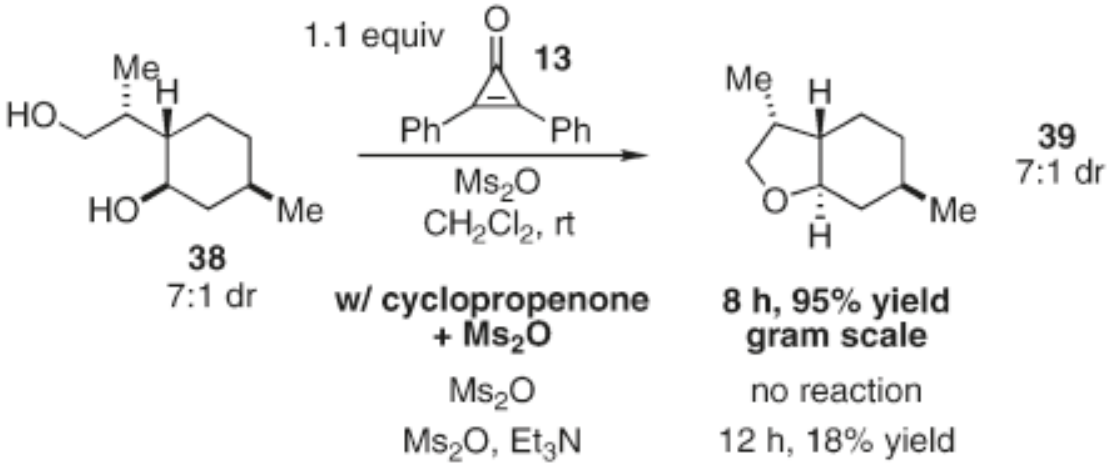
22 h , 83%



Lambert et. al.,*Org. Lett.* **2011**, *13,* 740-743

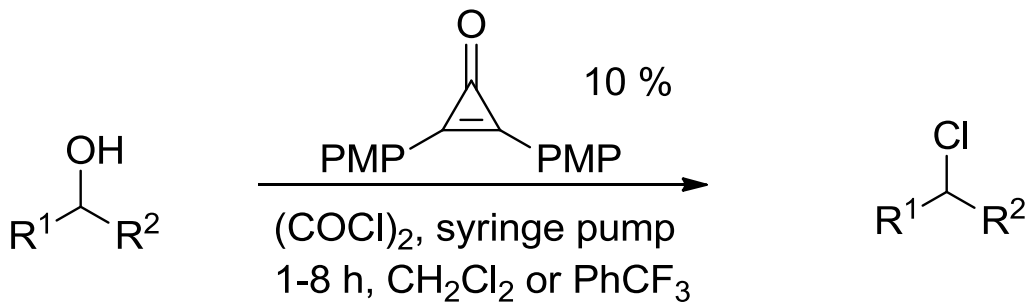
Mechanism and Utility



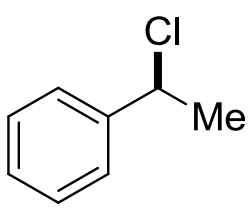


Lambert et. al.,*Org. Lett.* **2011**, *13,* 740-743

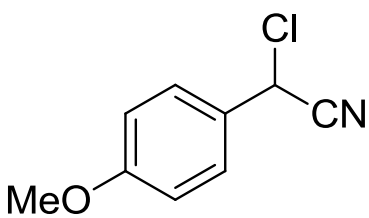
Catalytic Chlorodehydration - Conditions



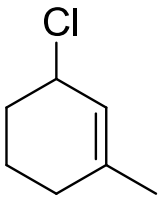
PMP = 4-OMe-C_6H_4-



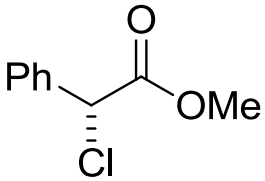
99%, 100% e.s.



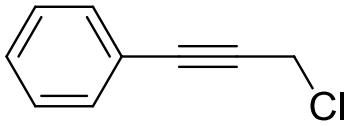
75%



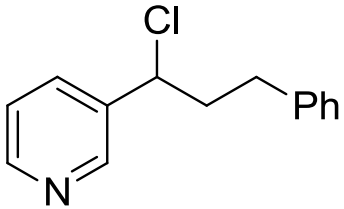
81%



72%, 100% e.s.



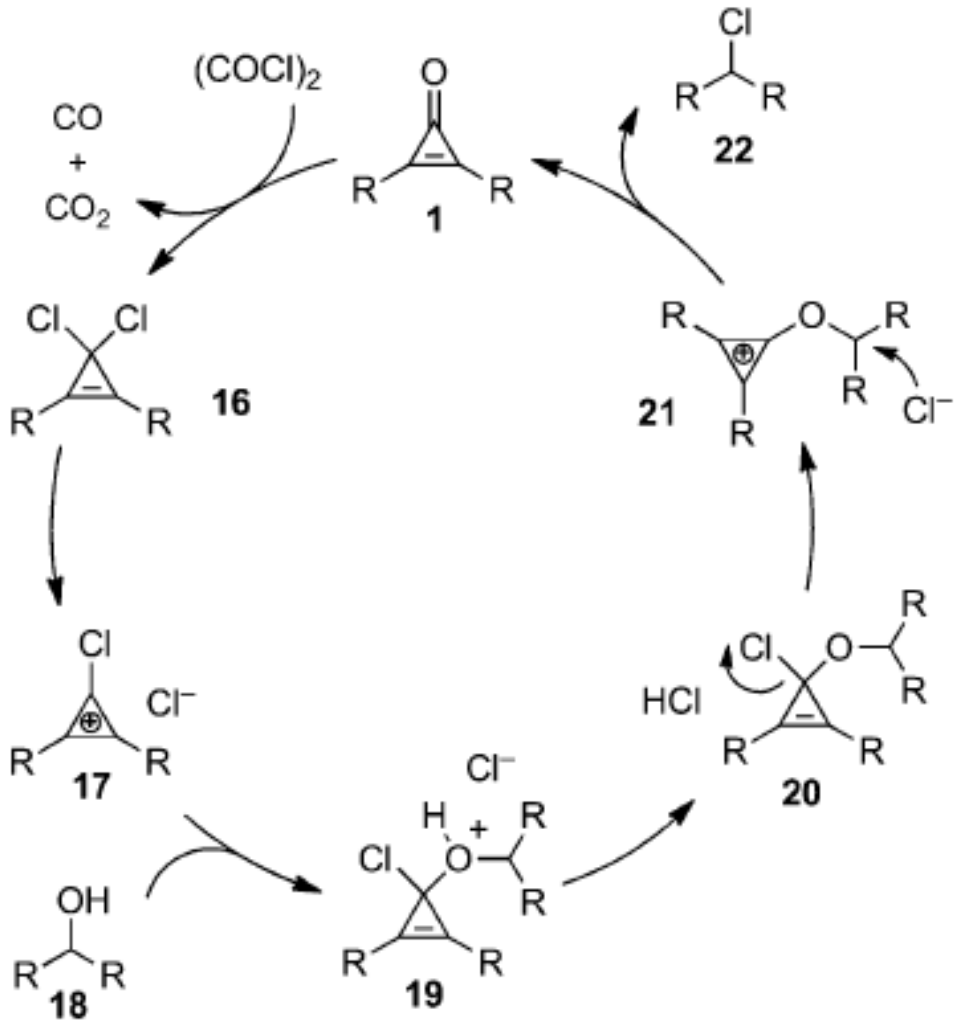
96%



77%

Lambert et. al., *Angew. Chem. Int. Ed.* **2011**, *50,* 12222 –12226

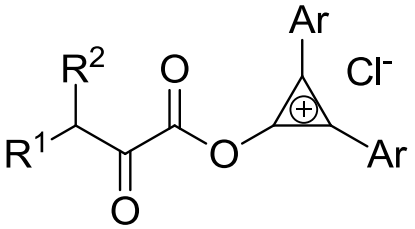
Catalytic Chlorodehydration



Slow addition of oxalyl chloride is beneficial

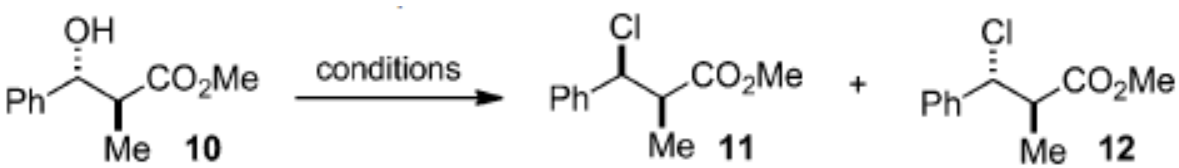
21 detected by NMR

Alternative Intermediate:

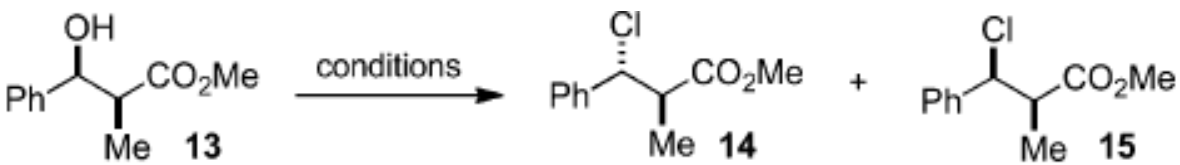


Lambert et. al., *Angew. Chem. Int. Ed.* **2011**, *50,* 12222 –12226

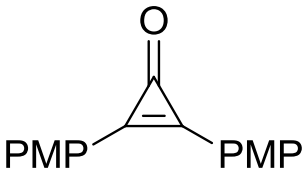
Stereochemical Outcome Of Chlorodehydration



Entry	Conditions[a]	Yield [%][b]	*syn/anti*[c]
1	**9** (10 mol %), $(COCl)_2$	90	> 98:2
2	$SOCl_2$	100	93:7
3	$SOCl_2$, pyridine	90	57:43



Entry	Conditions[a]	Yield [%][b]	*syn/anti*[c]
4	**9** (10 mol %), $(COCl)_2$	79	> 98:2
5	$SOCl_2$	0	–
6	$SOCl_2$, pyridine	55	58:42



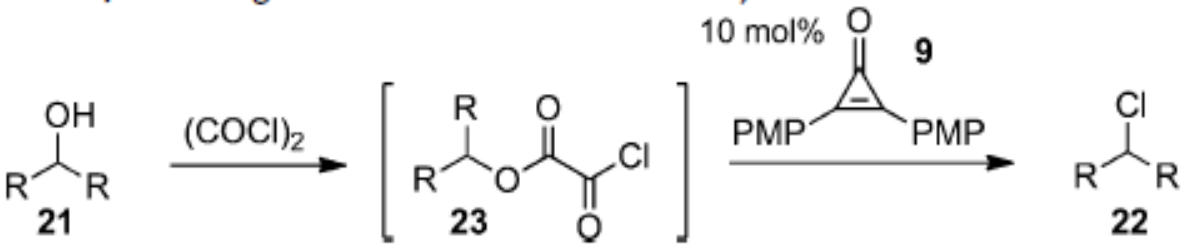
9

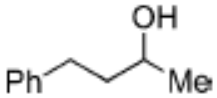
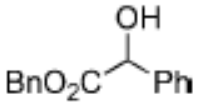
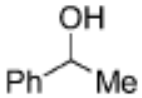
The catalytic cyclodehydration results in significantly improved yields and selectivitiy.

Lambert et. al., *Angew. Chem. Int. Ed.* **2011**, *50,* 12222 –12226

Alternative Pathways

Table 4: Investigation of alternative chlorodehydration mechanism.

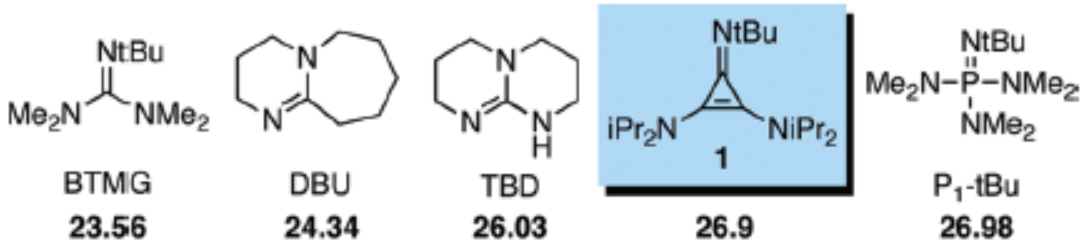


Entry	Alcohol	Conditions[a]	Time [h]	Conv [%][b]
1		$PhCF_3$, 80 °C	4	0 (67)
2		$PhCF_3$, 80 °C	4	0 (88)
3		CH_2Cl_2, 23 °C	1	50 (99)

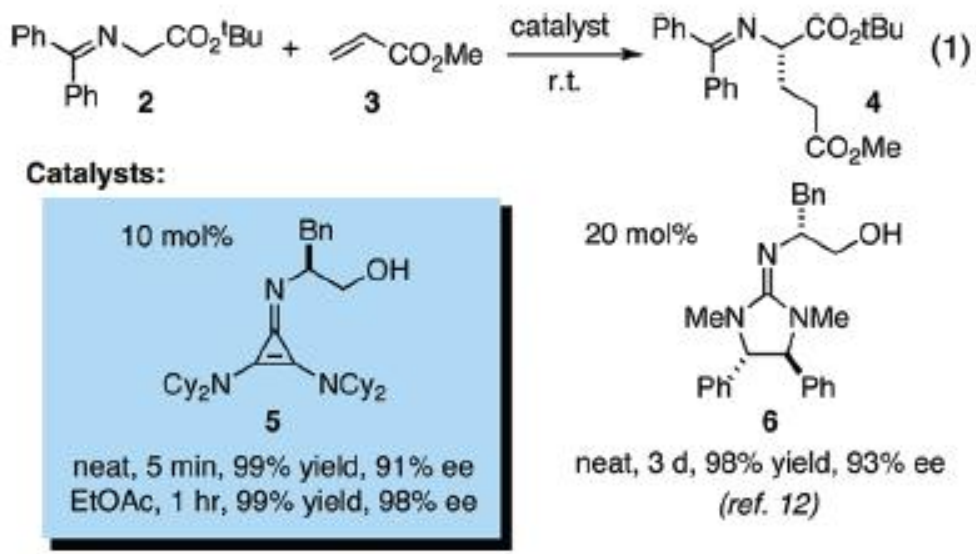
Higher yields are obtained in the catalytic reaction.
For some products, **23** may be a viable intermediate.

Lambert et. al., *Angew. Chem. Int. Ed.* **2011**, *50,* 12222 –12226

Cyclopropeneimines as Superbase Catalysts

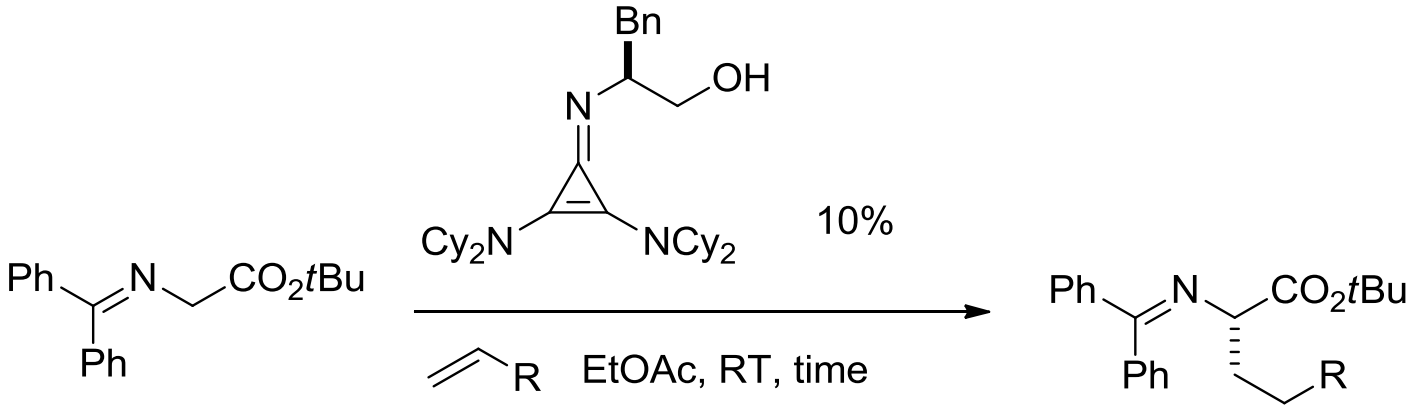


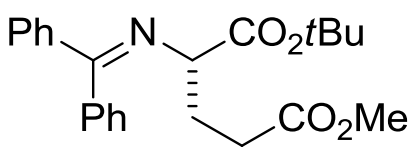
Stabilized cyclopropene imines are exceptional superbases



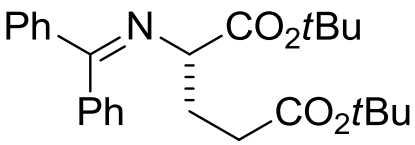
Lambert et. al., *J. Am. Chem. Soc.*, **2012**, *134*, 5552 -5555

Michael Reactions with Cyclopropeneimines

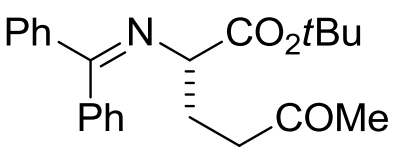




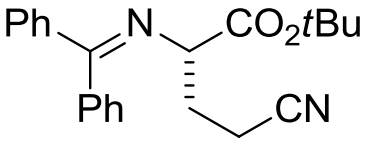
1 h, 99%, 99:1 e.r.



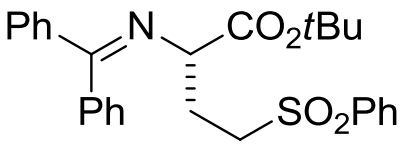
12 h, 98%, >99:1 e.r.



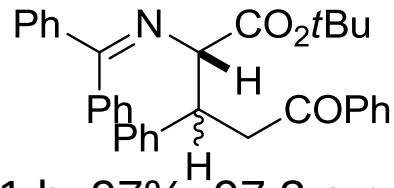
0.25 h, 97%, 97:3 e.r.



30 h, 97%, 89:11 e.r.



30 h, 97%, 70:30 e.r.

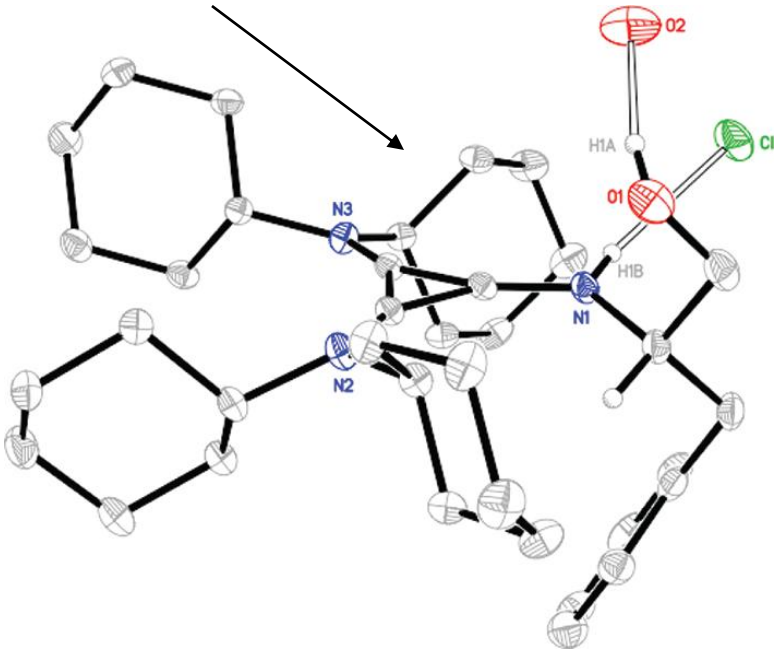


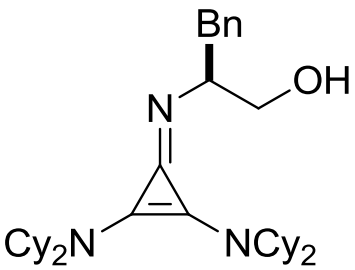
1 h, 97%, 97:3 e.r., 6:1 d.r.

Lambert et. al., *J. Am. Chem. Soc.*, **2012**, *134*, 5552 -5555

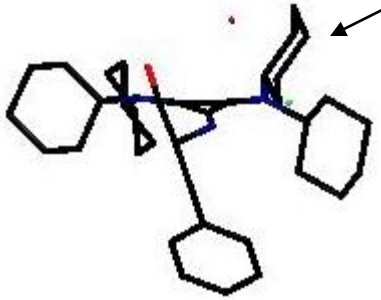
Structural Features of the Catalyst

Cy substituents are bent out of plane



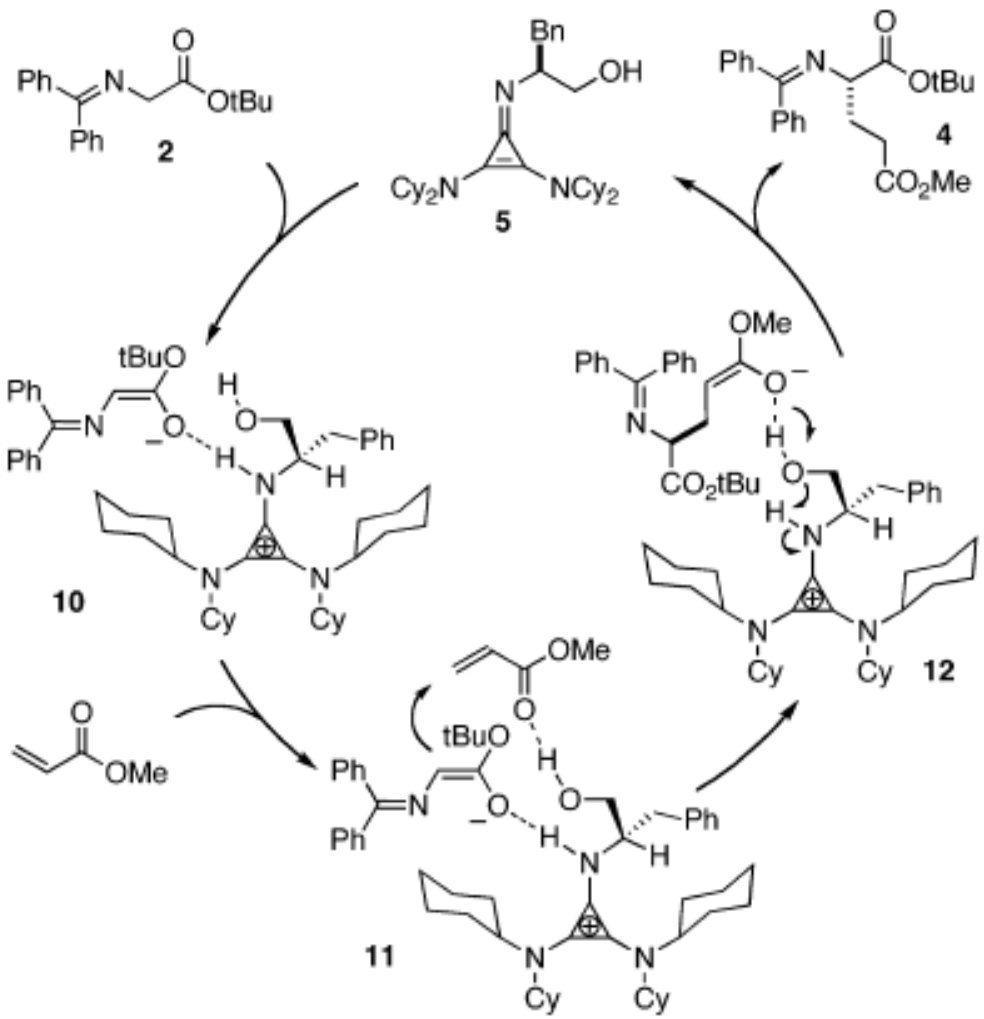


stereodetermining element?



Lambert et. al., *J. Am. Chem. Soc.,* **2012**, *134*, 5552 -5555

Stereoselective Michael Reaction



Stereochemical model posits a hydrogen bonding interaction.

Selectivity observed with acrylonitrile and phenylvinyl sulfone.

Selectivity abolished in the absence of alcohol.

Proposed deprotonation appears unlikely…

Lambert et. al., *J. Am. Chem. Soc.,* **2012**, *134*, 5552 -5555

Outlook

- The use of cyclopropenium ions as catalysts is still developing.
- Novel applications of dehydrative reactions necessary.
- Catalysis, especially enantioselective catalysis is hindered by the reactivity of the reagents required to generate cyclopropenium ions
- Chiral cyclopropenium ions have so far not been intensively investigated.
- Functional group tolerance has only been minimally demonstrated.

Conclusions

- Cyclopropenium ions offer novel reactivity: both as allyl carbenes and as electrophilic activators
- The steric bulk and electronic properties of the system can be easily modified, offering a versatile platform for catalyst development
- Intermediates involved have been isolated and characterized.
- Applicability is limited so far, but allows access to important synthetic building blocks.
- Future work is expected to focus on developing catalytic and enantioselective conditions.