Aromatic Ion Platform and Its Application

Group Seminar of LSPN

*Laboratory of Synthesis and Natural Products (**LSPN**)*
*Ecole Polytechnique Fédérale de Lausanne (**EPFL**)*

Hua Wu

24.04.2019

Outline

1. Introduction

2. Aromatic cation

3. Aromatic anion

4. Summary and Outlook

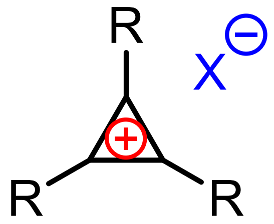
Introduction

Hückel's rule

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons.

$4n + 2 \quad \pi$ electrons

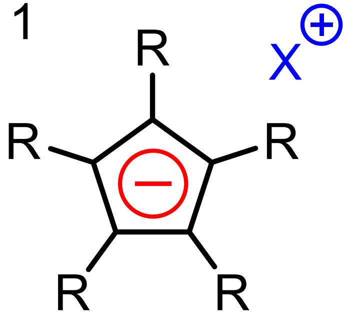
n = 0



Cyclopropenyl cation

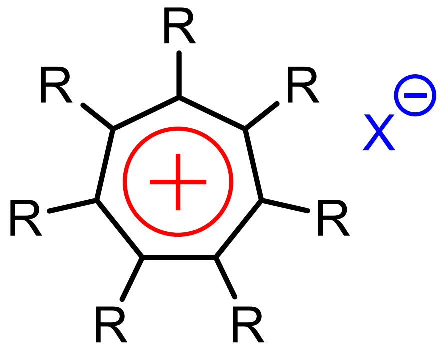
Smallest of the Hückel ring systems

n = 1



Cyclopentadienyl anion
(Cyclopentadienide ion)

n = 1

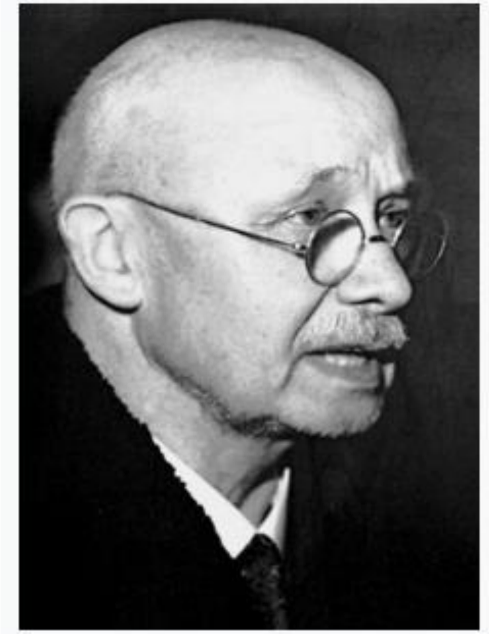


Cycloheptatrienyl cation
(Tropylium ion)

Ronald Breslow

吉田善一 Zen-ichi Yoshida

Otto Diels



S.L. Mitchill Professor of Chemistry and University Professor

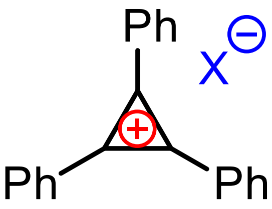
Ronald Breslow was born in Rahway, New Jersey on March 14, 1931.

Kyoto University

Yoshida was born in 1925

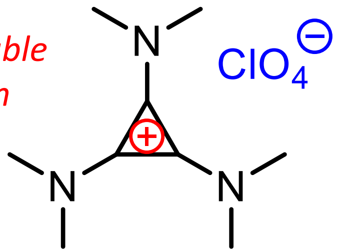
Born	23 January 1876 Hamburg, German Empire

1,2,3,4,5-pentacarbomethoxycyclopentadiene



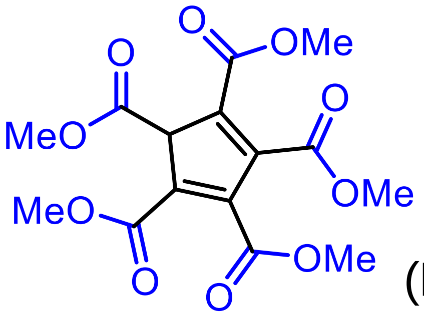
Cyclopropenyl cation

One of the most stable carbocations known



TDAC

Aminocyclopropenium ion



(PCCP)

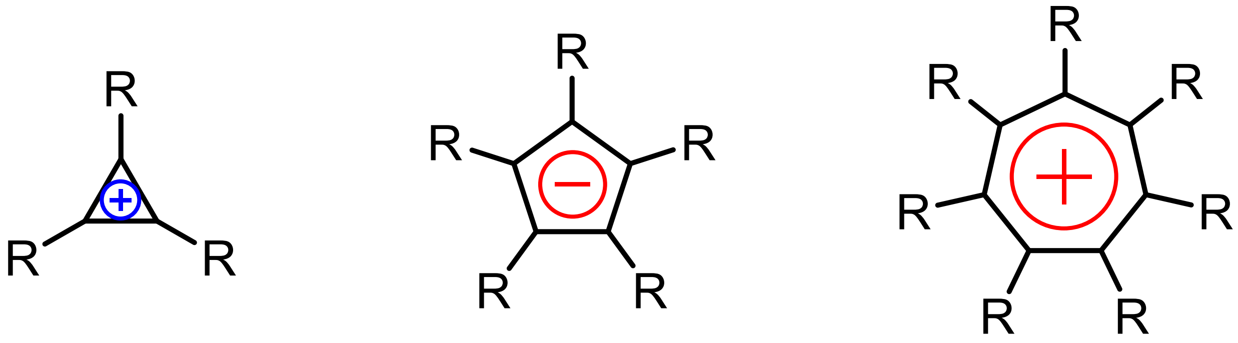
Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318

J. Am. Chem. Soc. **1971**, *93*, 2573.

Diels, O. *Ber. Dtsch. Chem. Ges*. **1942**, *75*, 1452.

Introduction

Aromatic ions



Aromatic ions have been brought into organic synthesis.

Tristan Lambert was born in Madison, WI, in 1976. In 1998, he began graduate studies at UC-Berkeley as one of Dave MacMillan's first students.
In 2000, Tristan moved with the MacMillan group to Caltech where he earned his Ph.D. for the development and application of novel Claisen rearrangements.
In 2004, he began postdoctoral studies with Sam Danishefsky.
In 2006, Tristan accepted a faculty position in the Department of Chemistry at Columbia University.
In 2011 he was promoted to Associate Professor and in 2016 to Full Professor.
In January 2018, he moved to the Department of Chemistry and Chemical Biology at Cornell University. His research group focuses on the study of intriguing chemical building blocks such as aromatic ions and their application to problems in the areas of catalysis, reaction design, and polymers.

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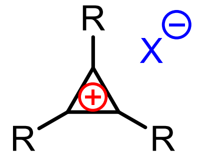
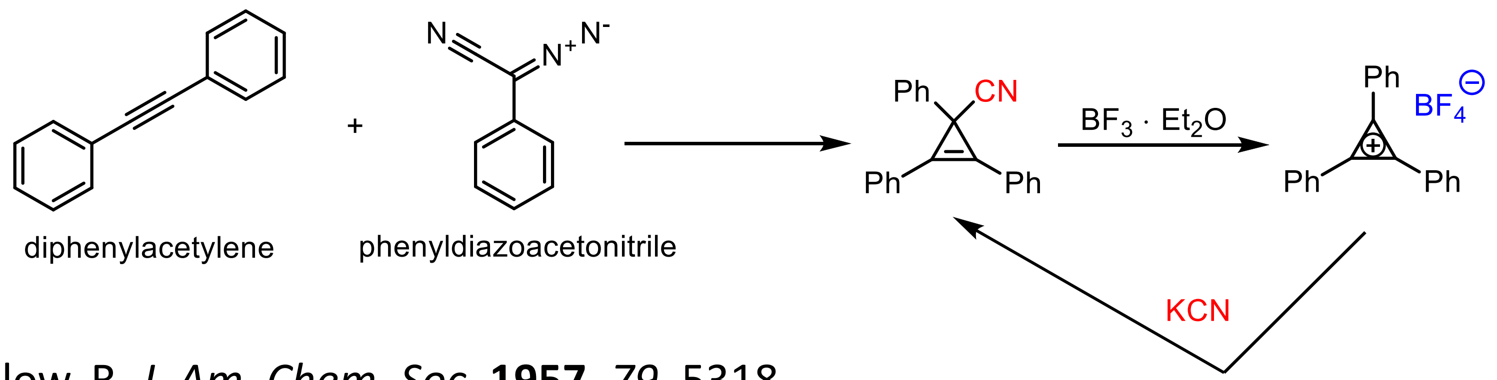
3. Aromatic anion

4. Summary and Outlook

Synthesis of Cyclopropenyl Cation

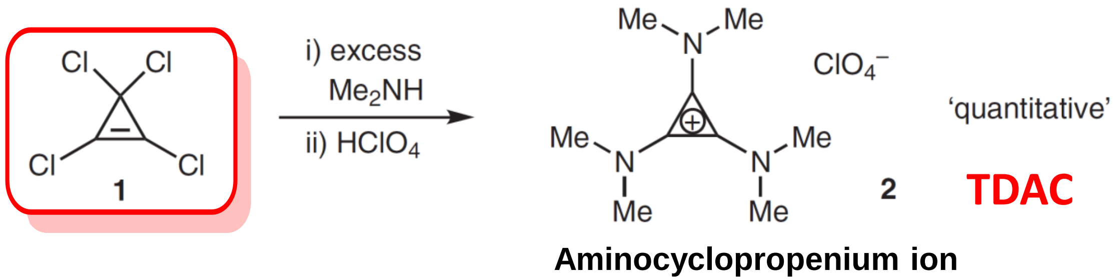


Cyclopropenyl cation



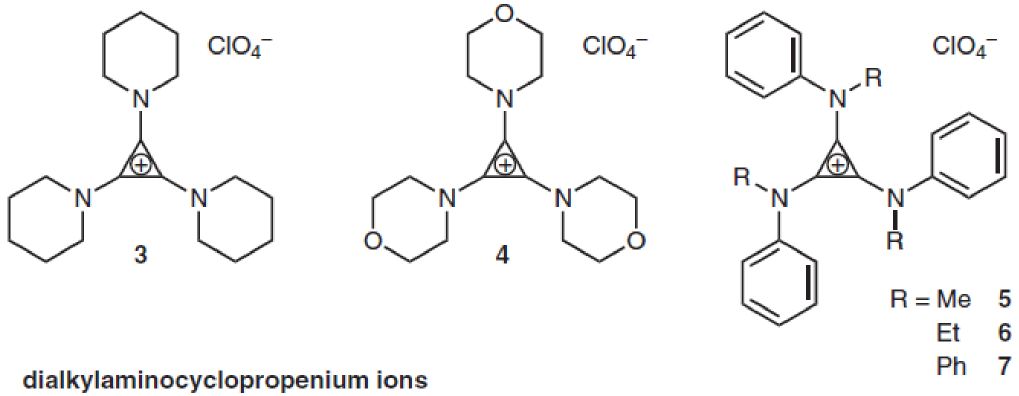
Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318

Yoshida 1971

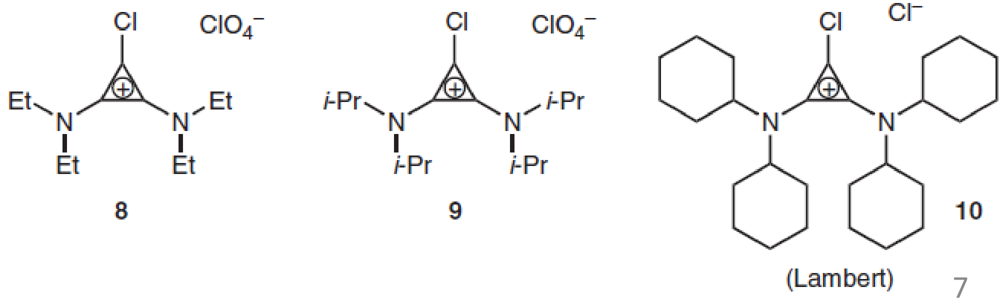


J. Am. Chem. Soc. **1971**, *93,* 2573.

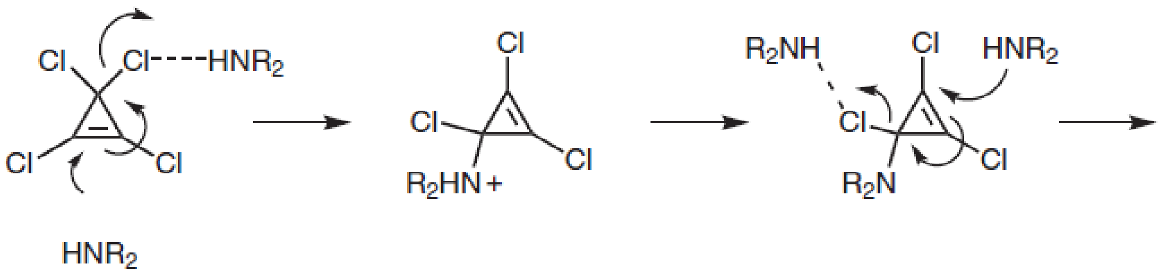
other TDACs prepared



dialkylaminocyclopropenium ions

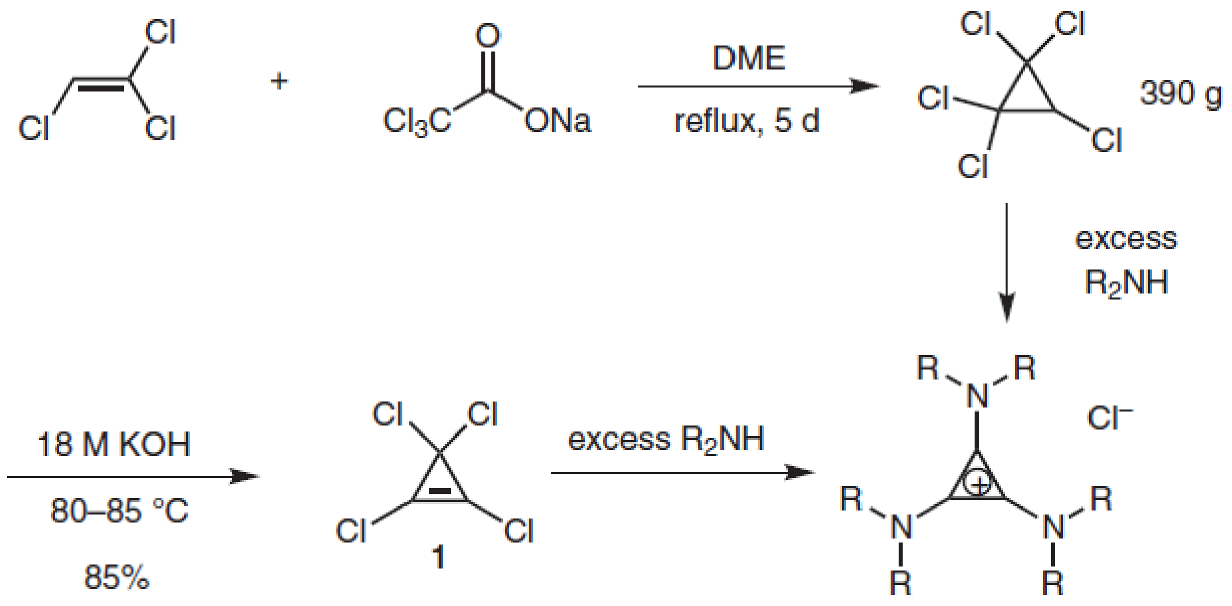


SN2' Mechanism



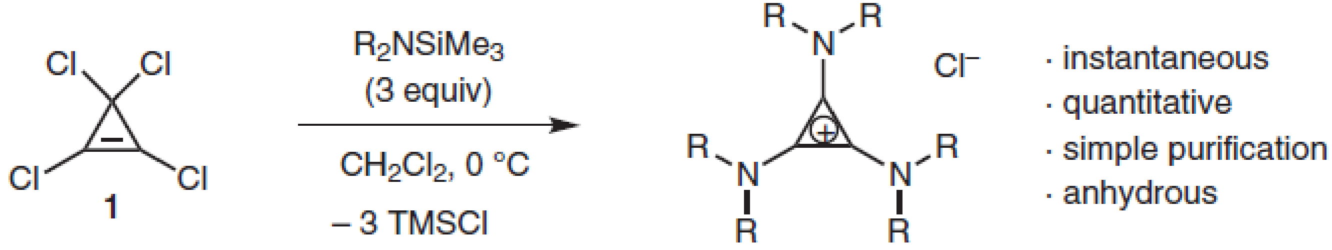
Synthesis of Cyclopropenyl Cation

Taylor 1994



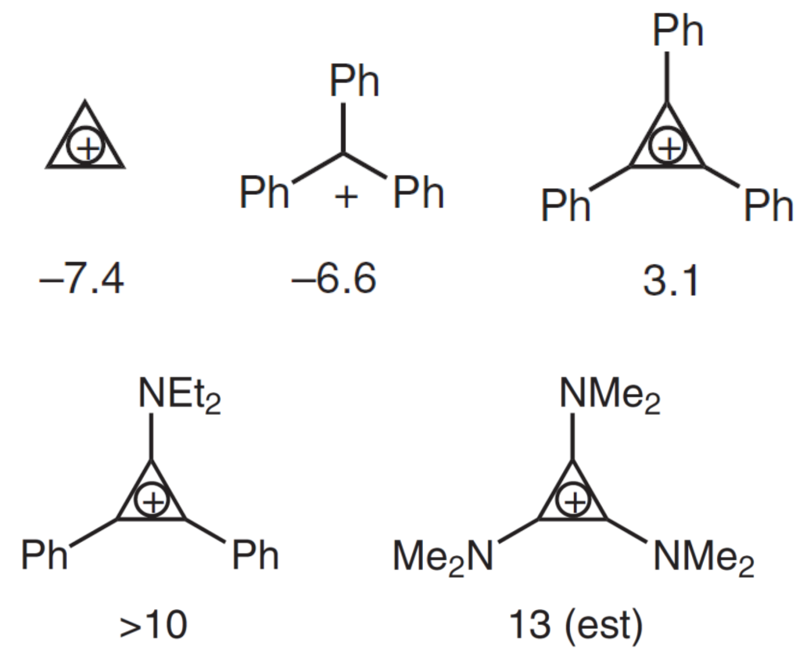
Taylor, M. J. *et al. J. Chem. Soc. Chem. Commun*. **1994**, 2517.

Weiss 1975



Weiss, R. *et al*. *Tetrahedron Lett*. **1975**, 3491

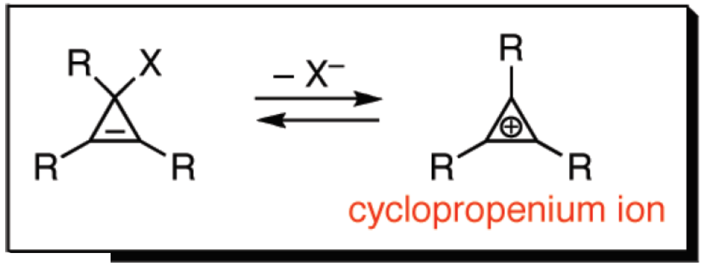
pK_{R+} values



One measure of this stability is given by their pK_{R+} value, which is numerically equivalent to the pH of an aqueous solution in which a given cation is 50% converted into corresponding carbinol.

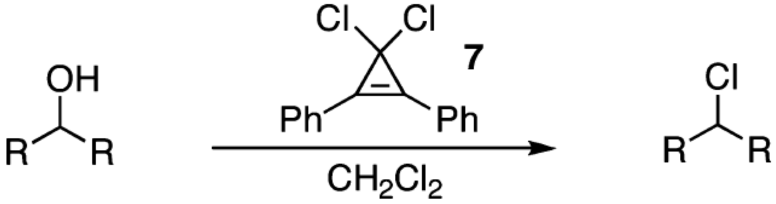
Reaction Promoted by Cyclopropenyl Cation

Aromatic Cation Activation of Alcohols: Conversion to Alkyl Chlorides Using Dichlorodiphenylcyclopropene

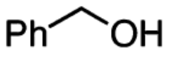
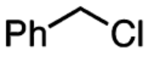
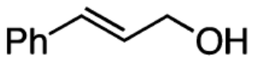
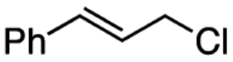
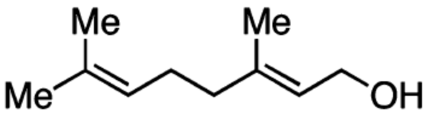
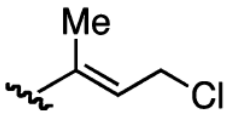
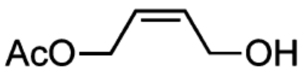
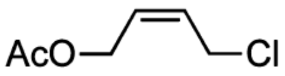
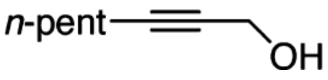
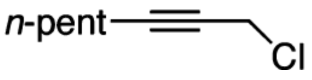
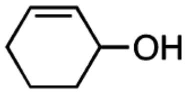
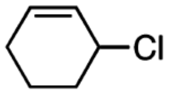
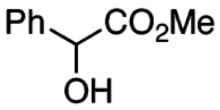
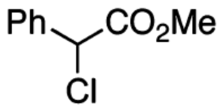
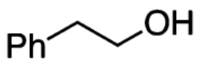
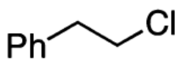
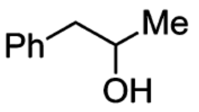
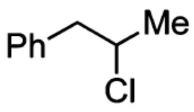
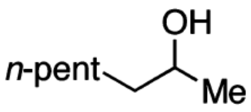
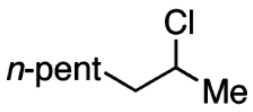
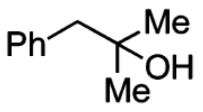
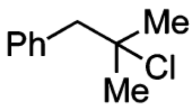


- 2π-electron aromatic system
- discovered by Breslow (1957)
- highly stabilized carbocations
- electronically, sterically tunable
- potential for new reaction design

stoichiometric



T. H. Lambert, *et al. J. Am. Chem. Soc.* **2009**, *131*, 13930.

Entry	Substrate	Product	temp. (°C)	time (min.)	% yield
1			23	10	81
2			23	3	92
3			23	5	95
4			23	5	84
5			23	5	92
6			23	10	88[c]
7			23	65	93
8			23	15	89
9			80[d]	20	95
10			80[d]	30	93[c]
11			23	40	45[c,e]

Reaction Promoted by Cyclopropenyl Cation

Aromatic Cation Activation of Alcohols

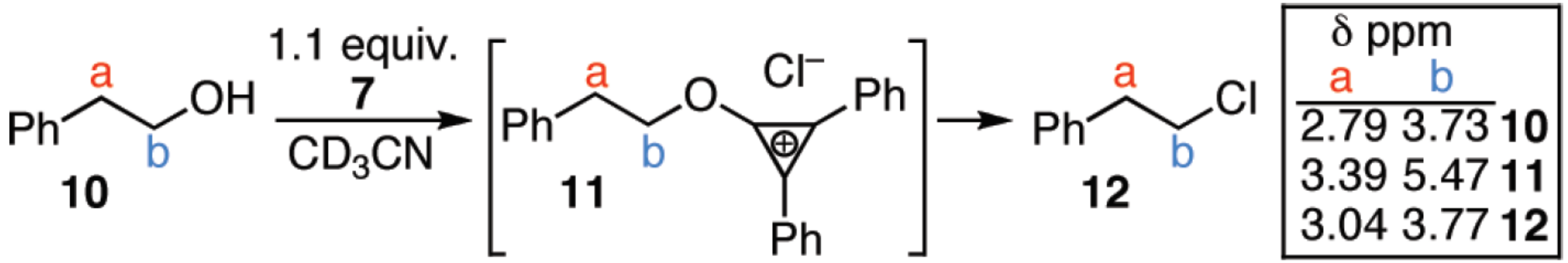
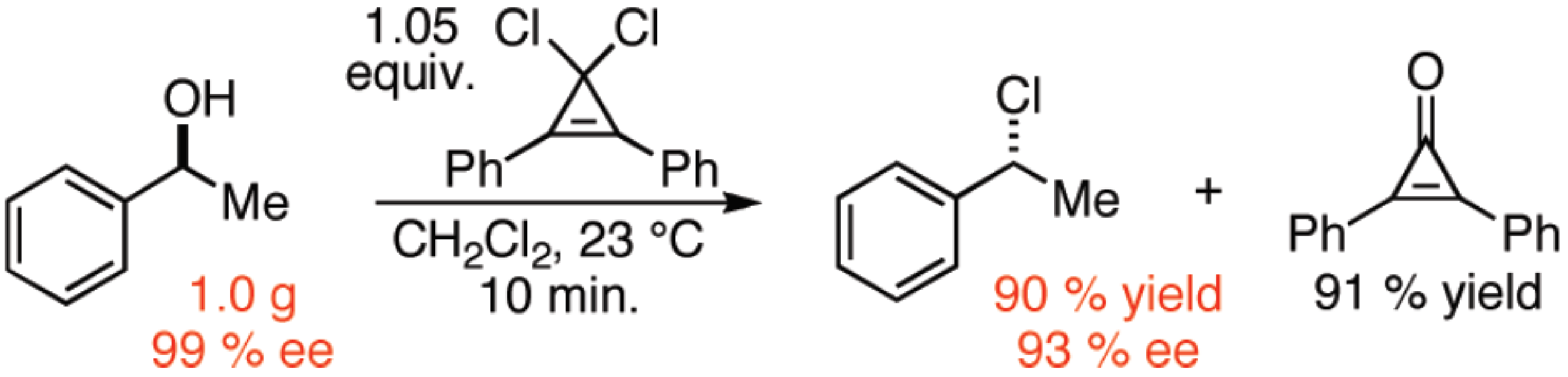


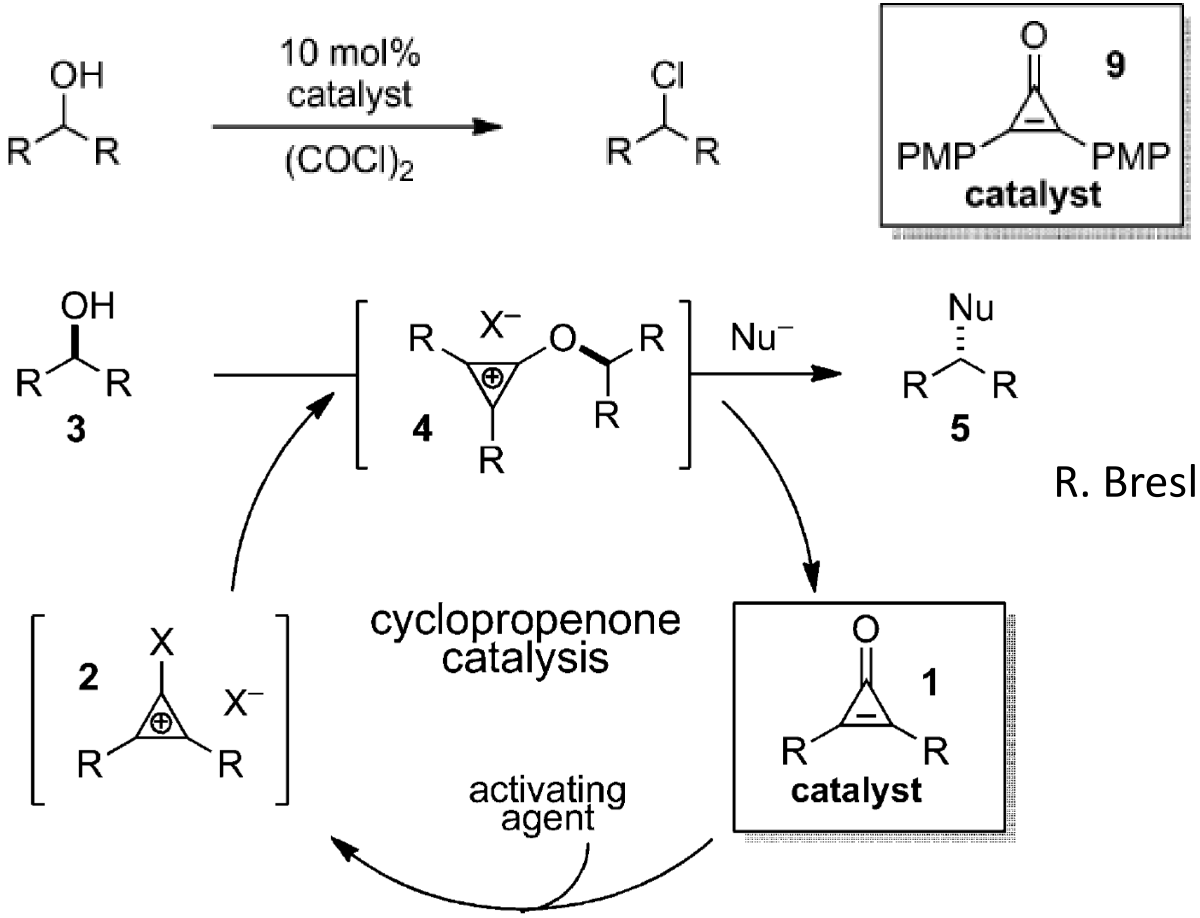
Figure 3. Chemical shifts of the alkoxycyclopropenium intermediate.

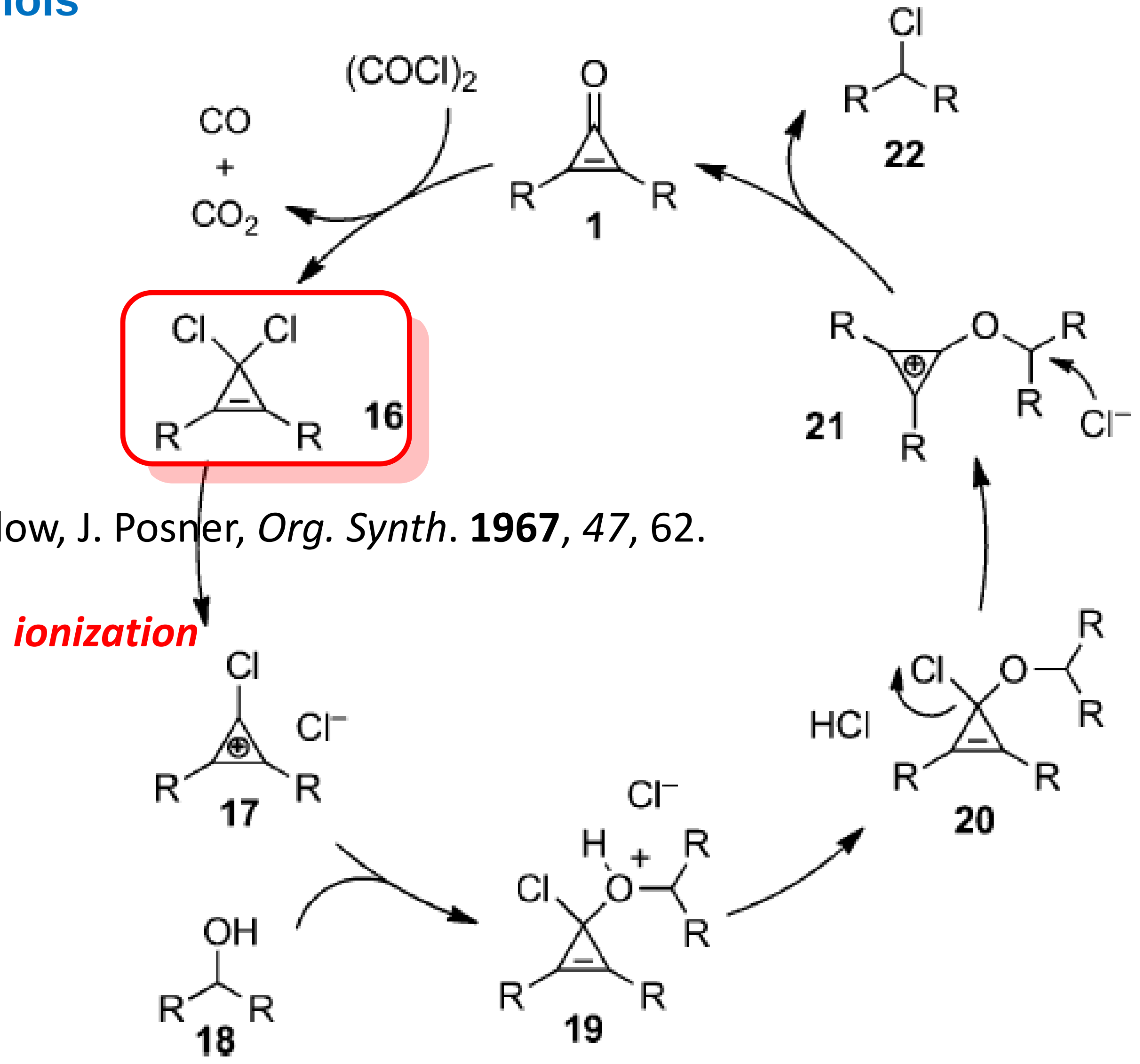


T. H. Lambert, *et al*. *J. Am. Chem. Soc*. **2009**, *131*, 13930.

Reaction Promoted by Cyclopropenyl Cation

Cyclopropenone-Catalyzed Chlorodehydration of Alcohols



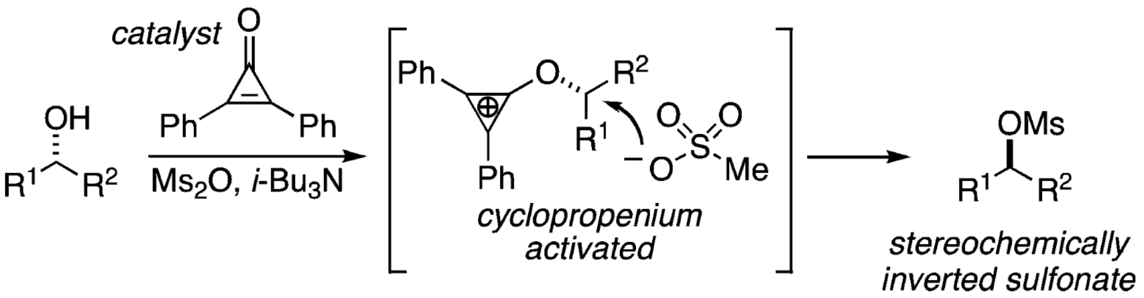


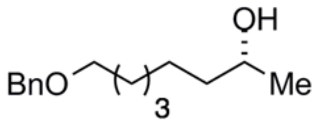
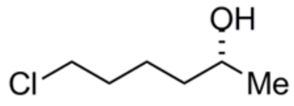
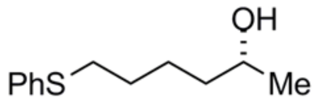
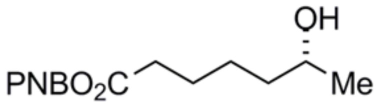
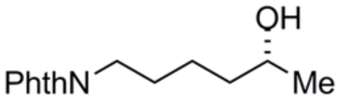
R. Breslow, J. Posner, *Org. Synth*. **1967**, *47*, 62.

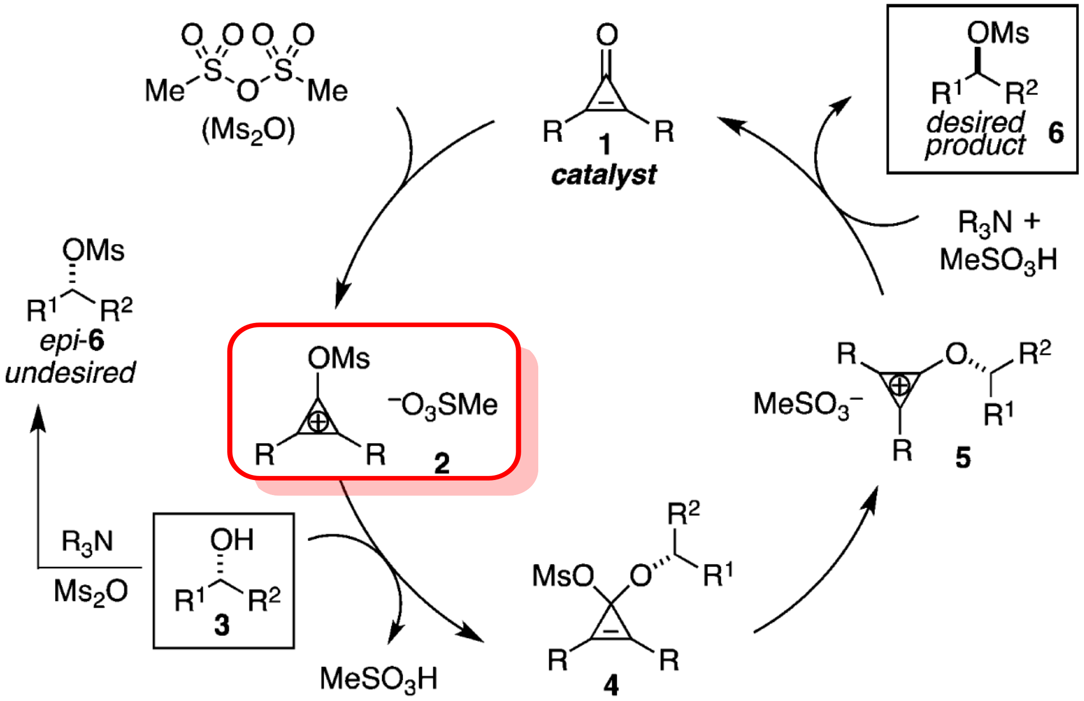
T. H. Lambert, *et al*. *Angew. Chem. Int. Ed*. **2011**, *50*, 12222.

Reaction Promoted by Cyclopropenyl Cation

Cyclopropenone Catalyzed Substitution of Alcohols with Mesylate Ion



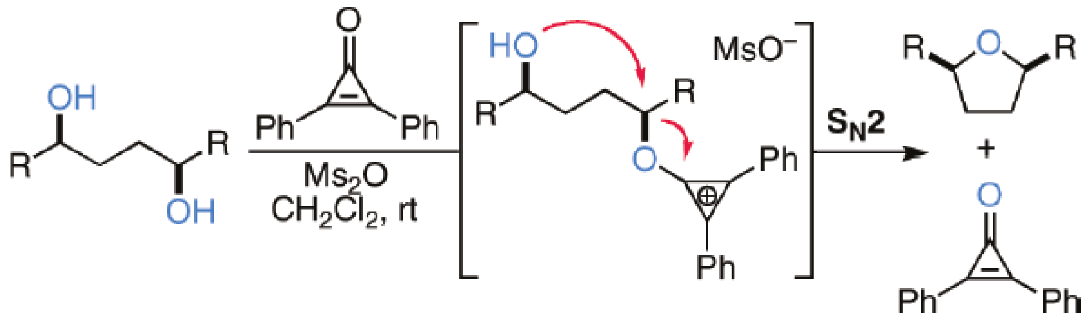
entry	substrate	15 mol% 8 [b] yield (%)	15 mol% 8 [b] er	100 mol% 8 [c] yield (%)	100 mol% 8 [c] er
1		75	97:3	91	95:5
2		77	95:5	92	96:4
3		72	96:4	83	94:6
4 [d]		81	95:5	98	97:3
5		74	96:4	77	95:5

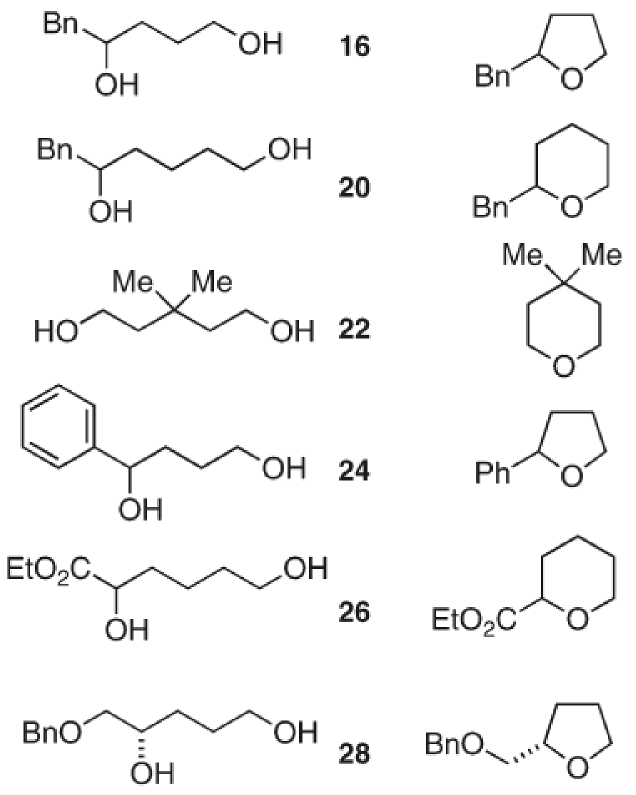


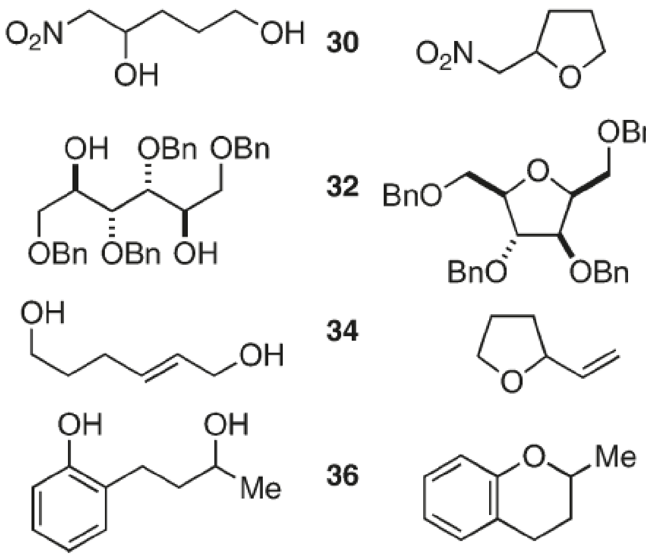
T. H. Lambert, *et al. Org. Lett.* **2013**, *15*, 38.

Reaction Promoted by Cyclopropenyl Cation

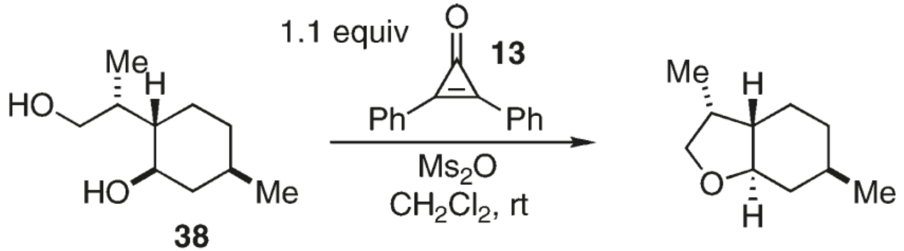
Cyclopropenium-Activated Cyclodehydration of Diols







entry	substrate	product	time (h)	% yield
1	16	17	4	91
2	20	21	10	89
3	22	23	1	91[c]
4	24	25	1	94
5	26	27	3.5	87
6	28	29	7	92
7	30	31	6	81
8	32	33	11	82
9	34	35	3	95[c]
10	36	37	22	83[d]



38
7:1 dr

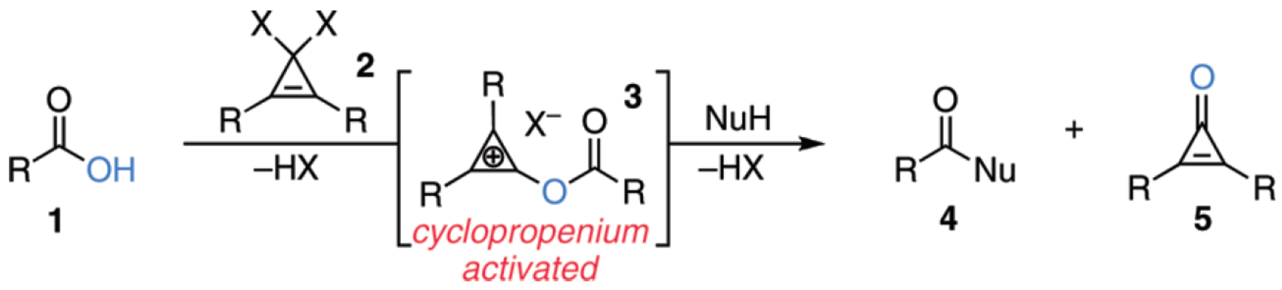
39
7:1 dr

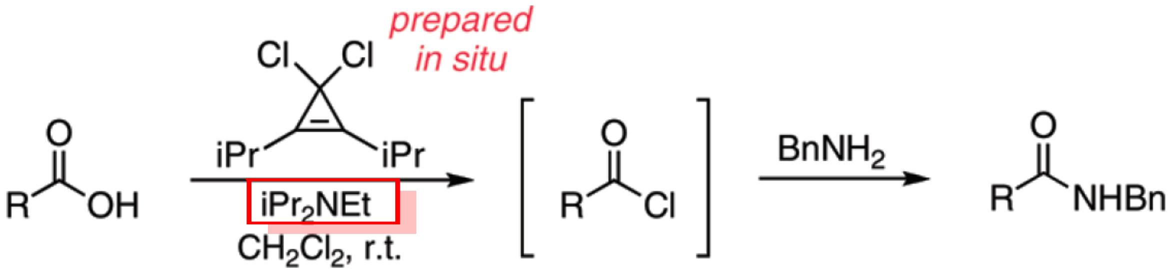
w/ cyclopropenone + Ms_2O	**8 h, 95% yield gram scale**
Ms_2O	no reaction
Ms_2O, Et_3N	12 h, 18% yield

T. H. Lambert, *et al*. *Org. Lett*. **2011**, *13*, 740.

Reaction Promoted by Cyclopropenyl Cation

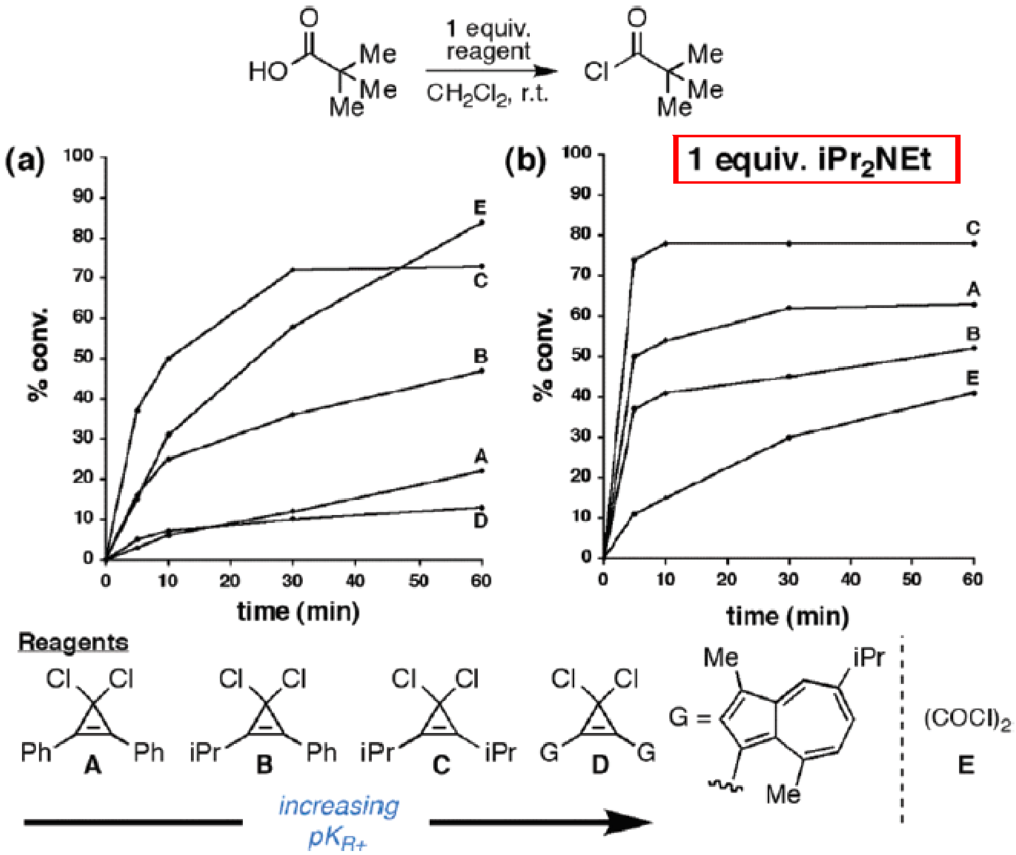
Nucleophilic Acyl Substitution via Aromatic Cation Activation of Carboxylic Acids: Rapid Generation of Acid Chlorides under Mild Conditions





T. H. Lambert, *et al*. *J. Am. Chem. Soc*. **2010**, *132*, 5002.

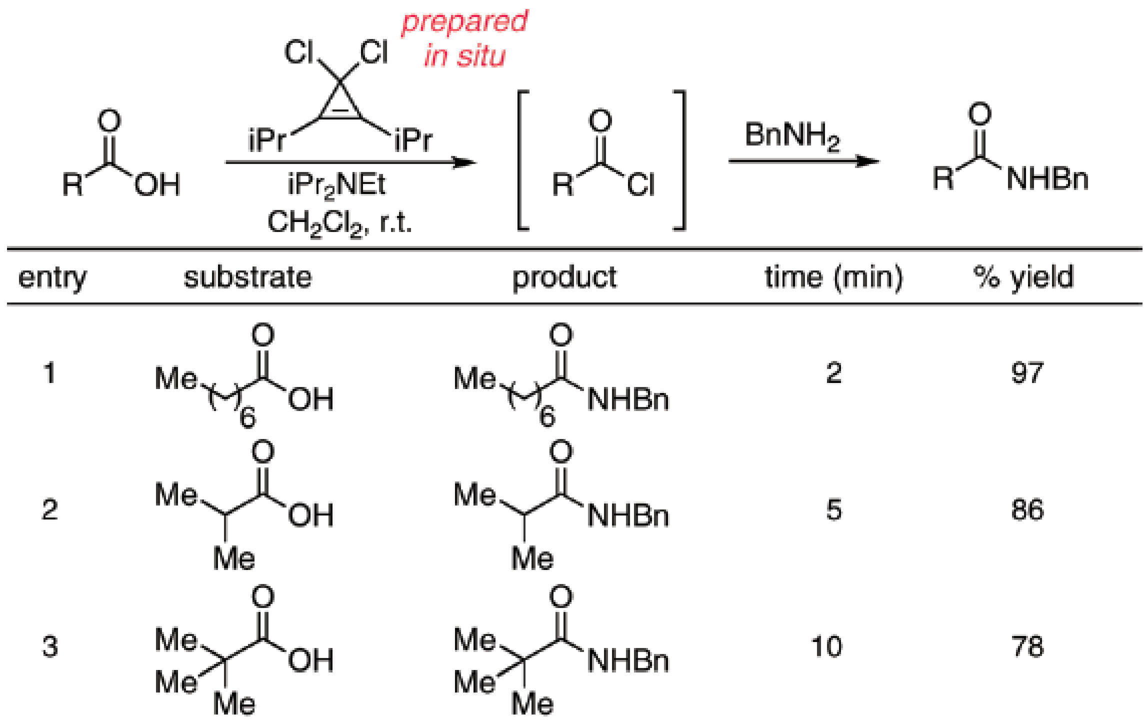
Chart 1. Rate Comparison for Acid Chloride Formation[a]



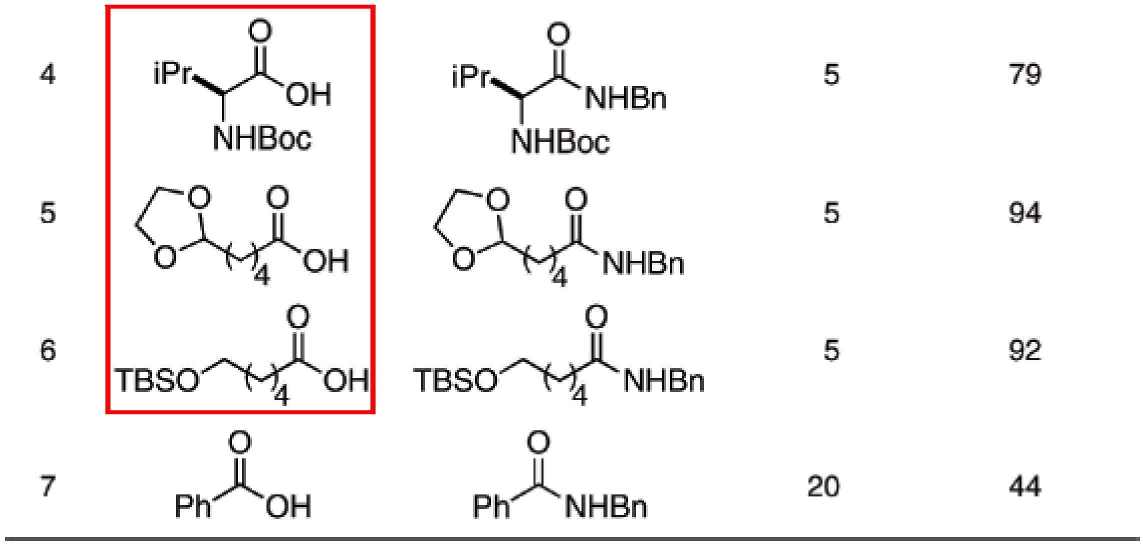
[a] Reactions were run by the addition of a solution of pivalic acid without (a) or with (b) $i\mathrm{Pr_2NEt}$ to a solution of 3,3-dichlorocyclopropenes **A**–**D** in CH_2Cl_2. Timed aliquots were quenched with excess (5 equiv) benzylamine, and % conversions were determined by ^{1}H NMR analysis of *N*-benzylpivalamide compared to Bn_2O as an internal standard.

Reaction Promoted by Cyclopropenyl Cation

Nucleophilic Acyl Substitution via Aromatic Cation Activation of Carboxylic Acids: Rapid Generation of Acid Chlorides under Mild Conditions



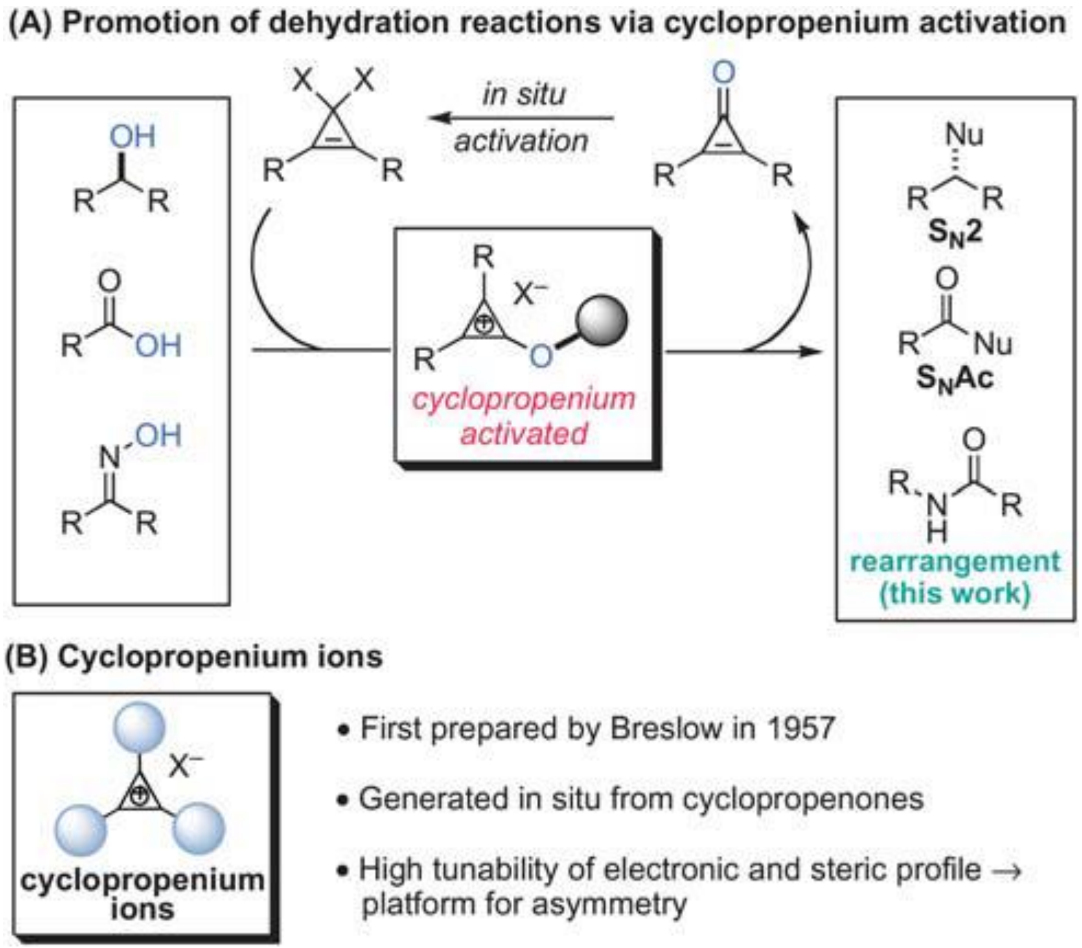
Acid sensitive substrates were also well tolerated!

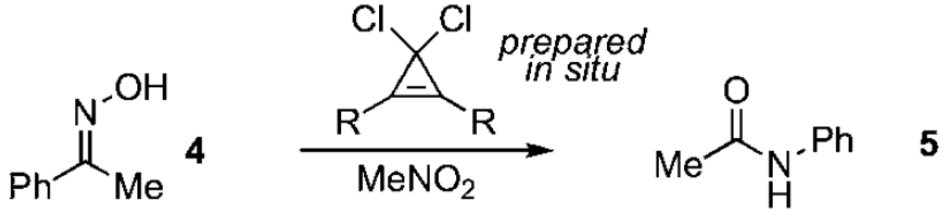


T. H. Lambert, *et al. J. Am. Chem. Soc.* **2010**, *132*, 5002.

Reaction Promoted by Cyclopropenyl Cation

Cyclopropenium-activated Beckmann rearrangement. Catalysis versus self-propagation in reported organocatalytic Beckmann rearrangements



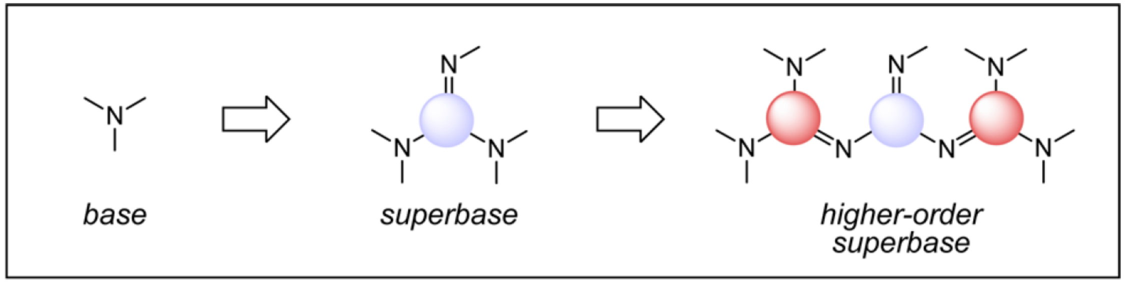


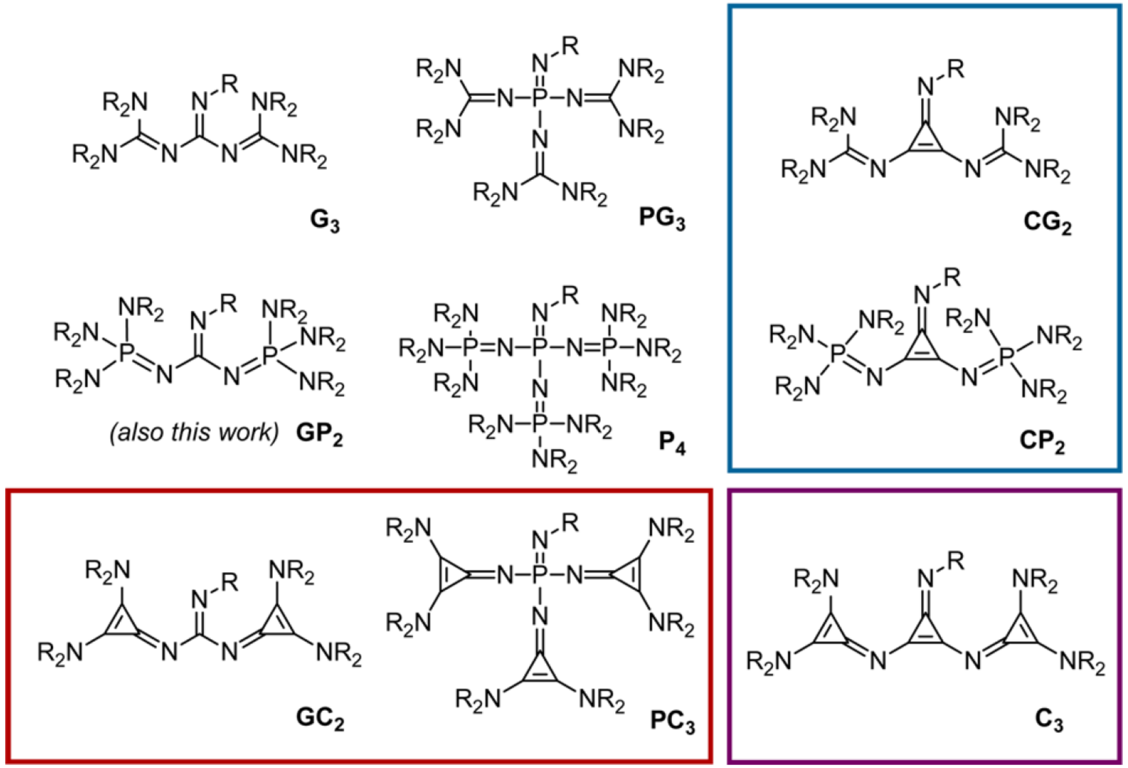
entry	R[c]		mol (%)	T/°C	time/min	% yield
1	Ph	**2**	105	21	90	70
2	*i*Pr	**6**	105	21	75	77
3	4-OMe-Ph	**7**	105	21	45	77
4	Xyl	**8**	105	21	20	98
5	Mes	**9**	105	21	30	92[d]
6	Mes	**9**	10	21	30	10
7	Mes	**9**	10	60	30	100
8	Mes	**9**	5	60	90	100
9	Mes	**9**	2	60	8 h	24

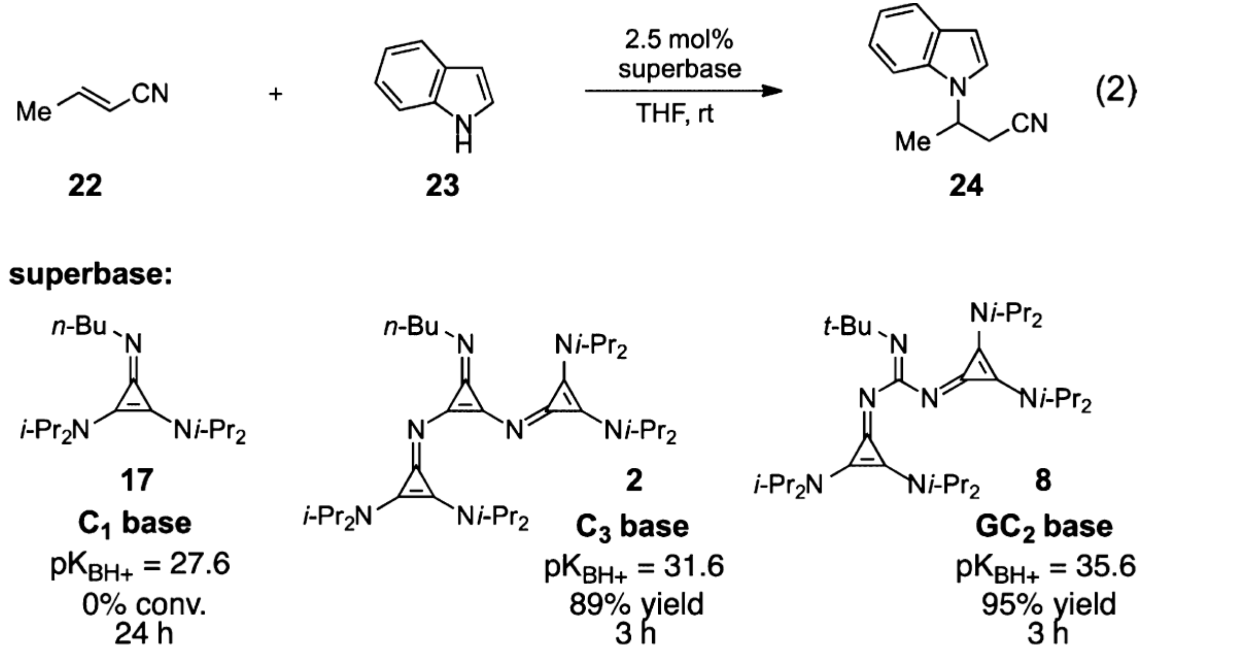
T. H. Lambert, *et al*. *Chem. Sci*. **2010**, *1*, 705.

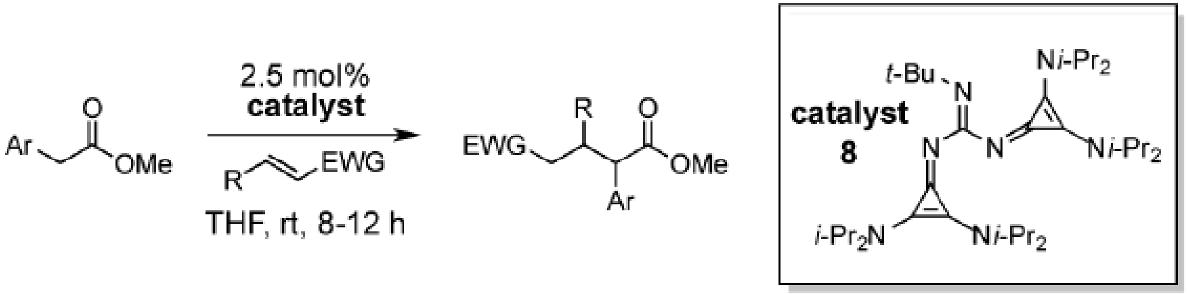
Cyclopropenyl Cation: Superbase

Higher-Order Cyclopropenimine Superbases: Direct Neutral Brønsted Base Catalyzed Michael Reactions with α-Aryl Esters







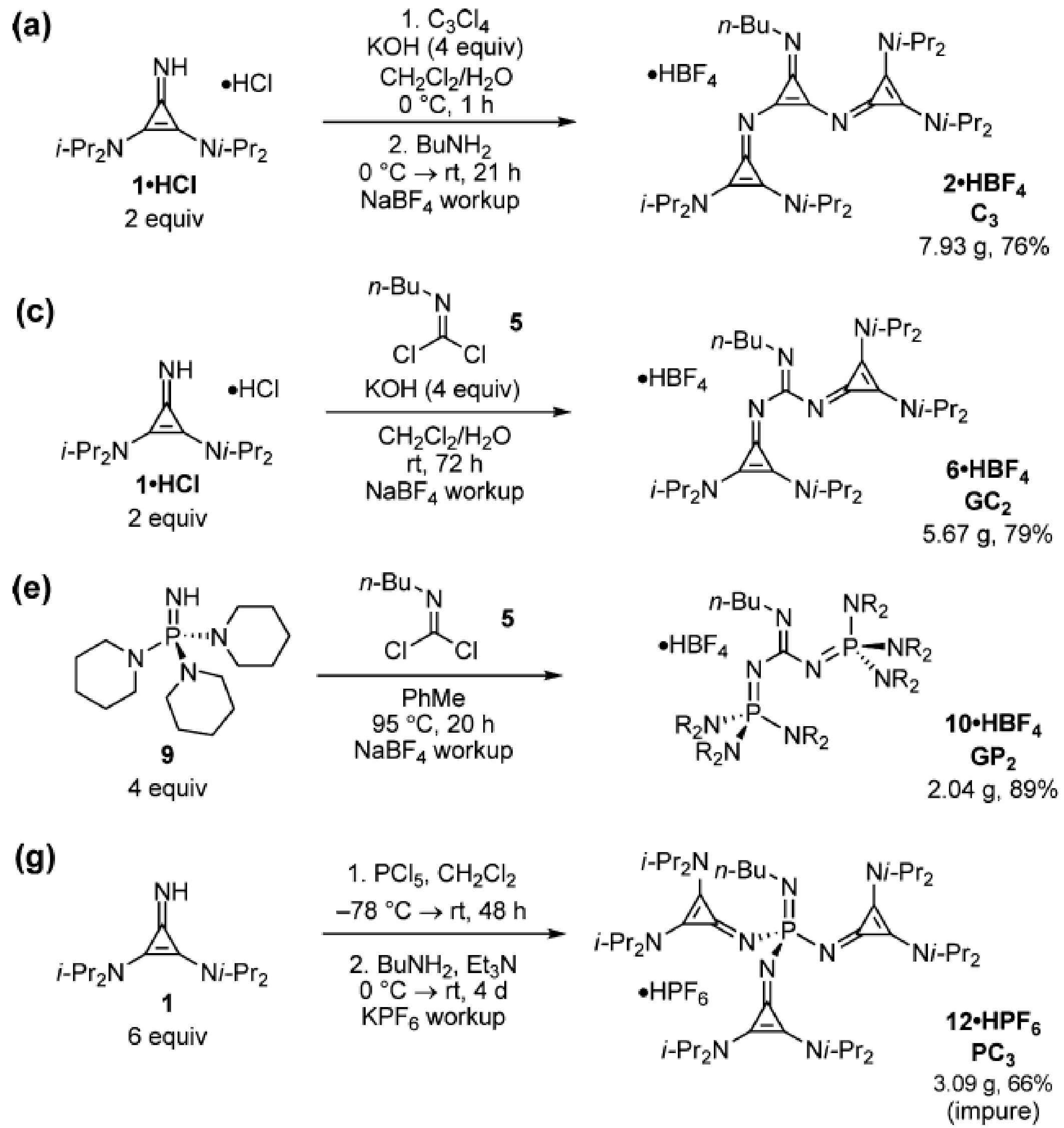


T. H. Lambert, *et al. J. Am. Chem. Soc.* **2015**, *137*, 10246.

"G" for guanidinyl, "P" for phosphazenyl, and "C" for cyclopropeniminyl.

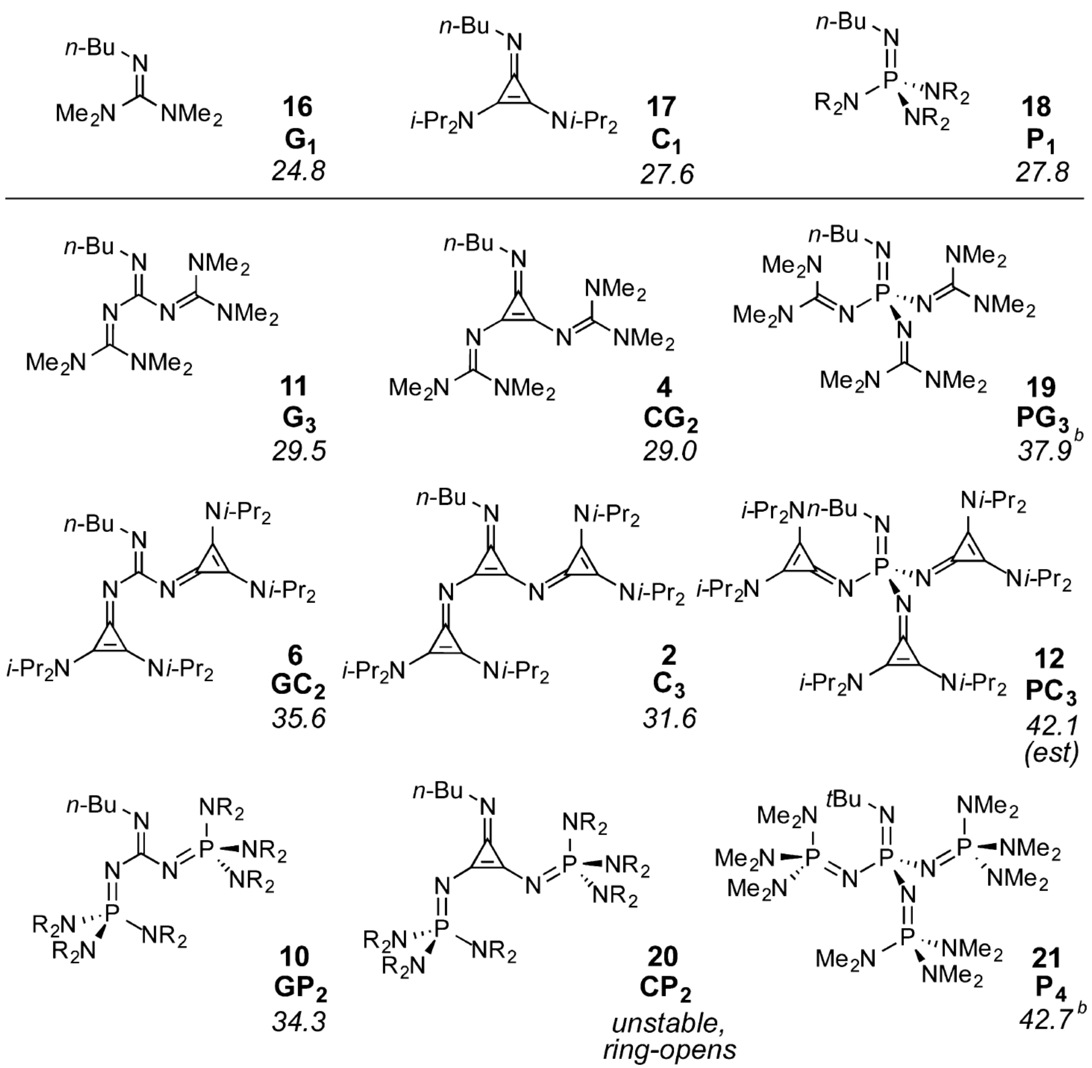
Cyclopropenyl Cation: Superbase

Synthesis method



Basicities of different higher-order superbases

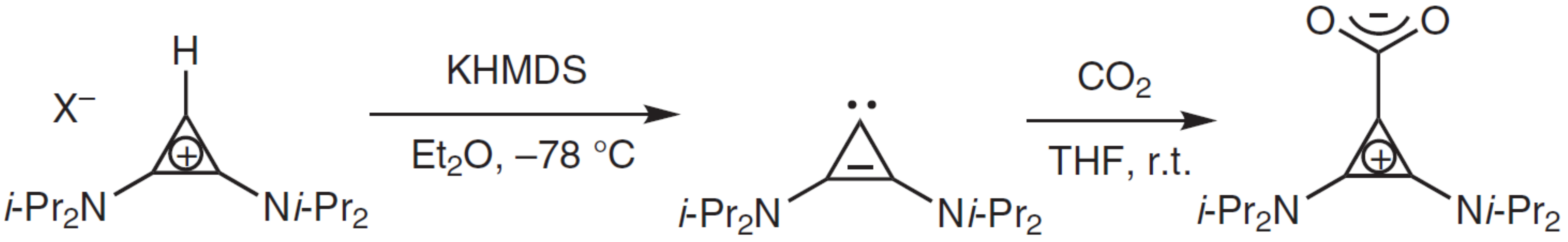
Table 1. Basicities of Higher-Order Superbases[a]



T. H. Lambert, *et al. J. Am. Chem. Soc.* **2015**, *137*, 10246.

Reaction Promoted by Cyclopropenyl Cation

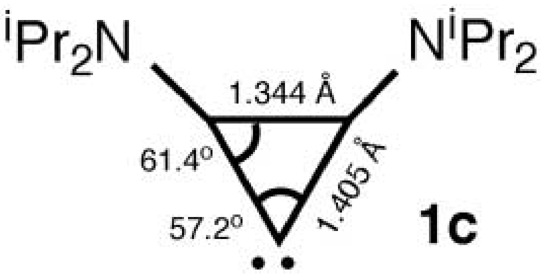
Cyclopropenylidenes: From Interstellar Space to an Isolated Derivative in the Laboratory



X = BPh_4; 20%
X = BF_4; 53%

(X-ray)

Betaine, quantitative yield



1c

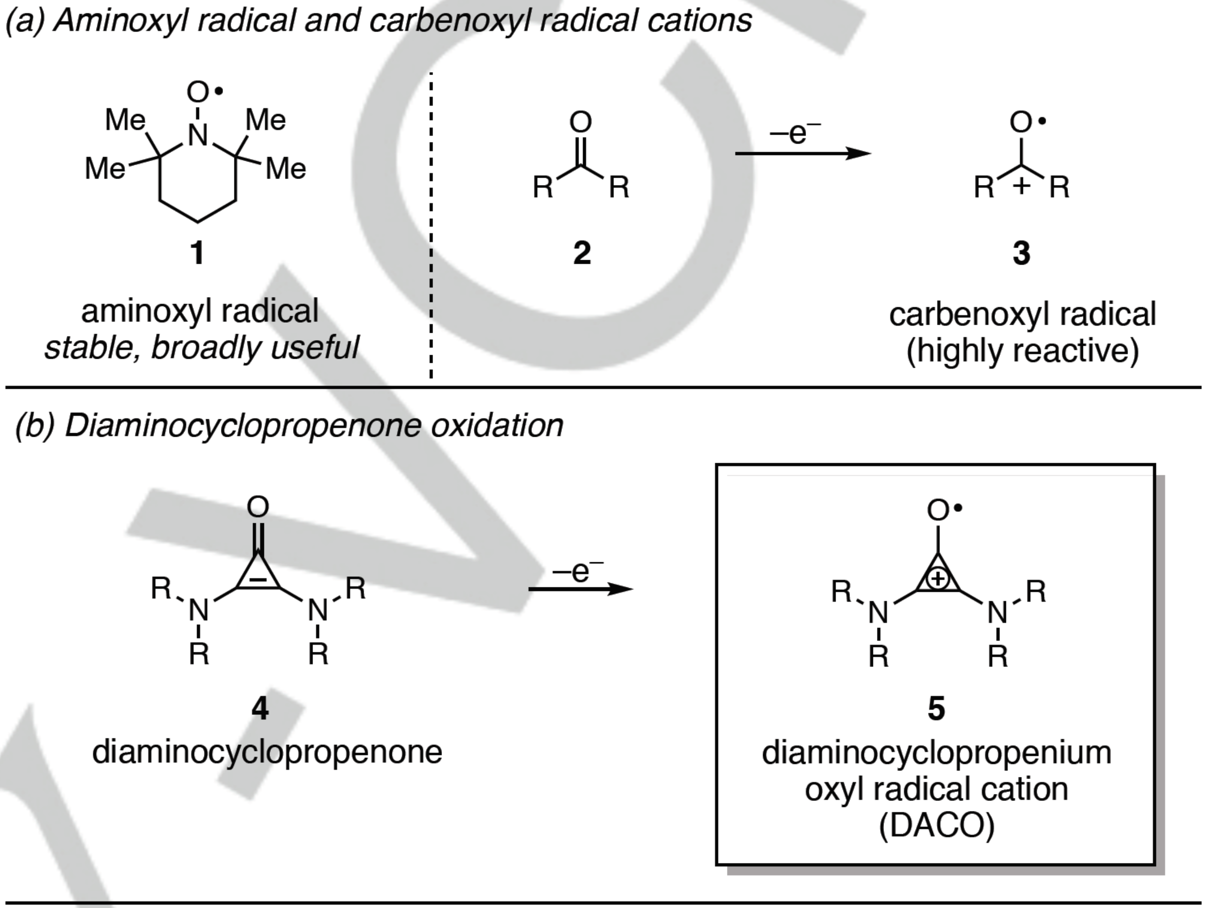
a) It was found that only certain combinations of counteranions of the precursor and bases led to the generation of free, uncomplexed carbine.

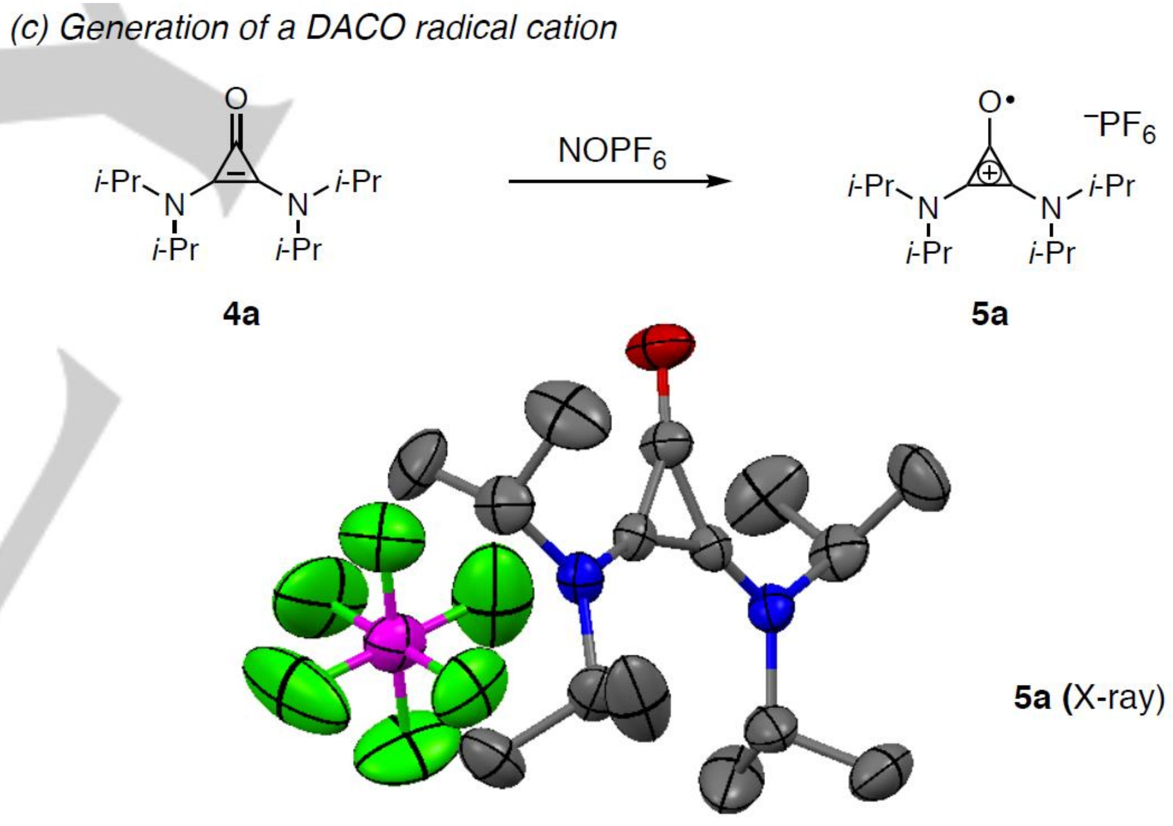
b) Although not air stable, the carbine proved to be relatively thermally stable, only decomposing 10% when heated to 80 degree in toluene for two hours.

Bertrand, G. *et al*. *Science* **2006**, *312*, 722.

Reaction Promoted by Cyclopropenyl Cation

Oxidizable Ketones: Persistent Radical Cations from the Single Electron Oxidation of 2,3-Diaminocyclopropenones



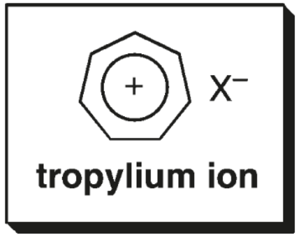


single electron oxidation to produce persistent radical cations

T. H. Lambert, *et al*. **2019**. *Doi: 10.1002/anie.201902265*

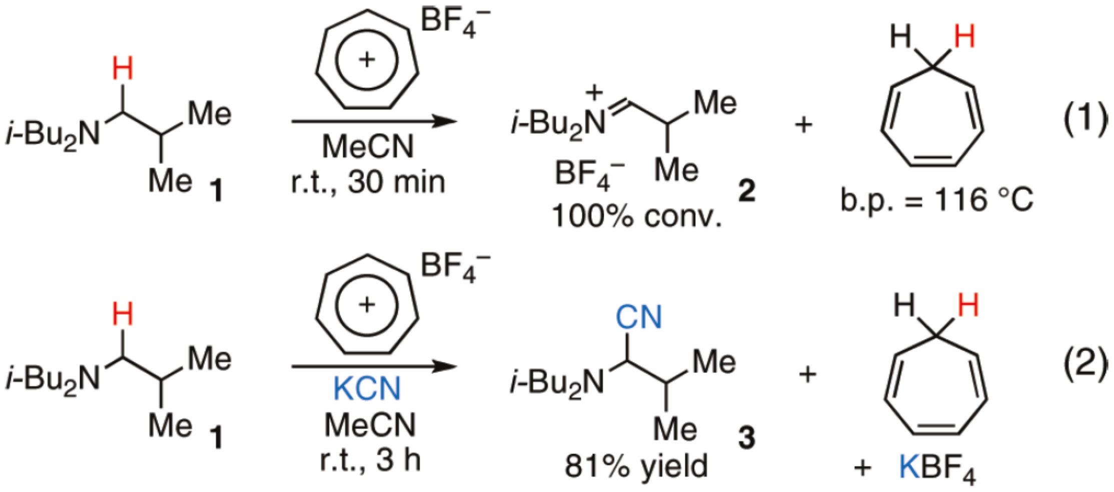
Reaction Promoted by Tropylium Ion

Tropylium Ion Mediated α-Cyanation of Amines

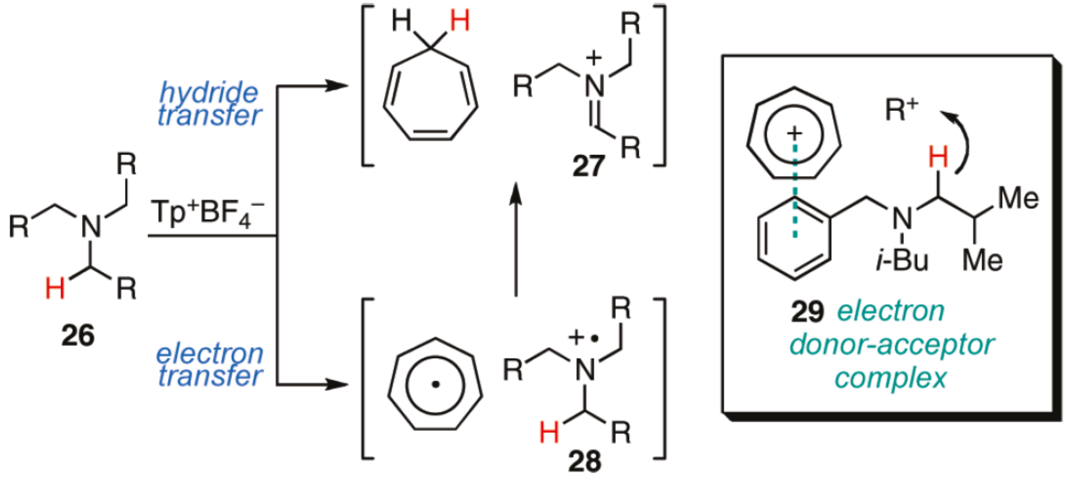


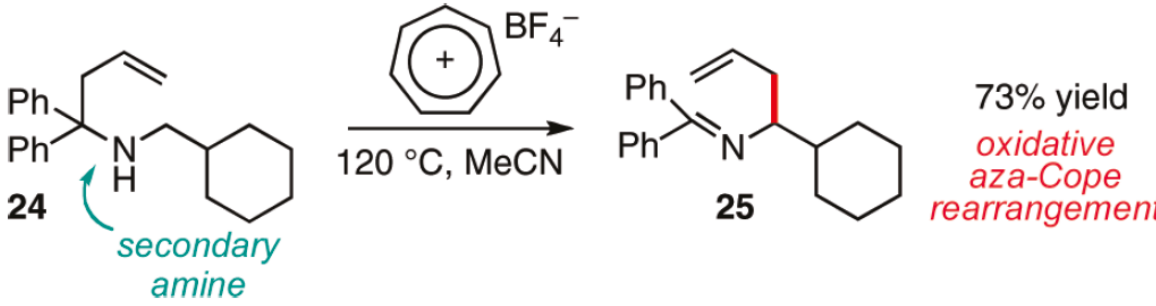
- 6π-electron aromatic system
- first prepared by Doering and Knox in 1954
- aromatic carbocation

Knox, L. H. *et al. J. Am. Chem. Soc.* **1954**, *76*, 3203.



T. H. Lambert, *et al. J. Am. Chem. Soc.* **2011**, *133*, 1260.





Chiral Cyclopropenyl Cation

Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines

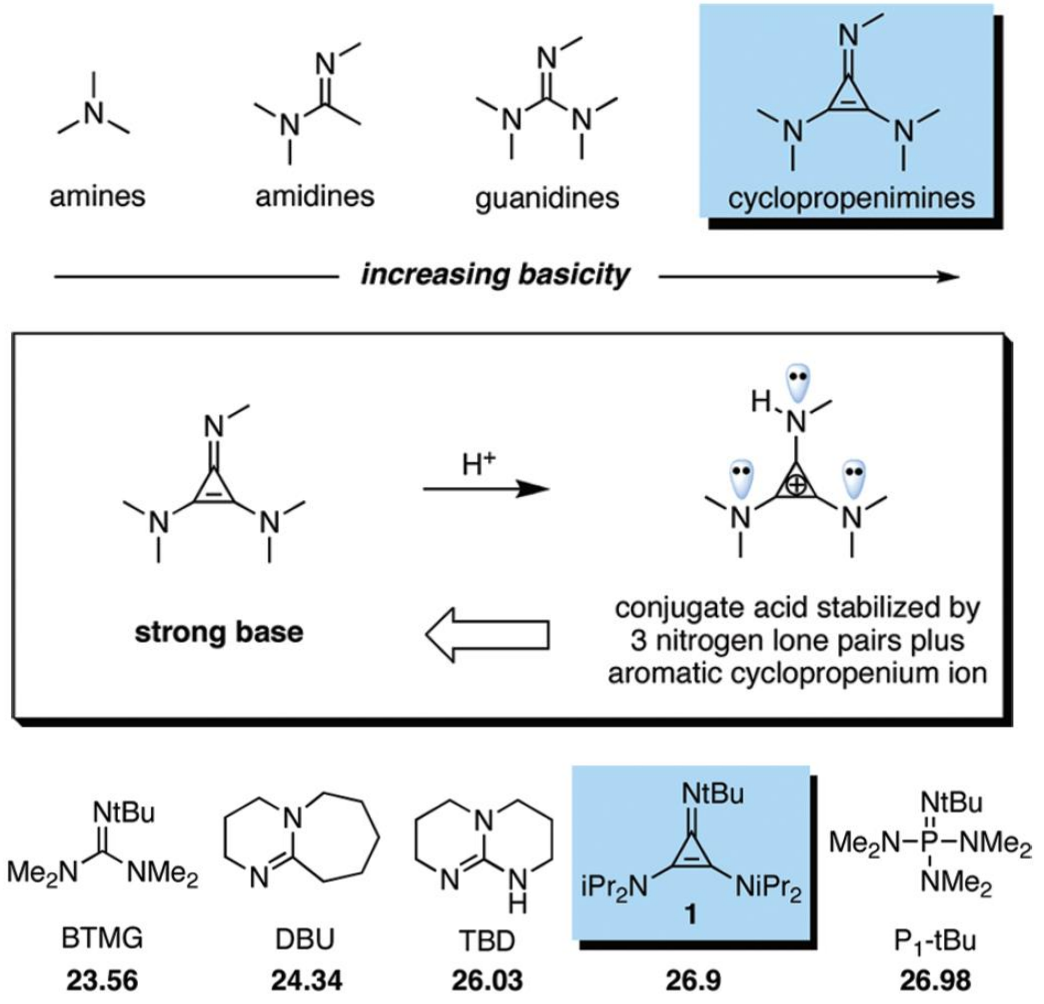
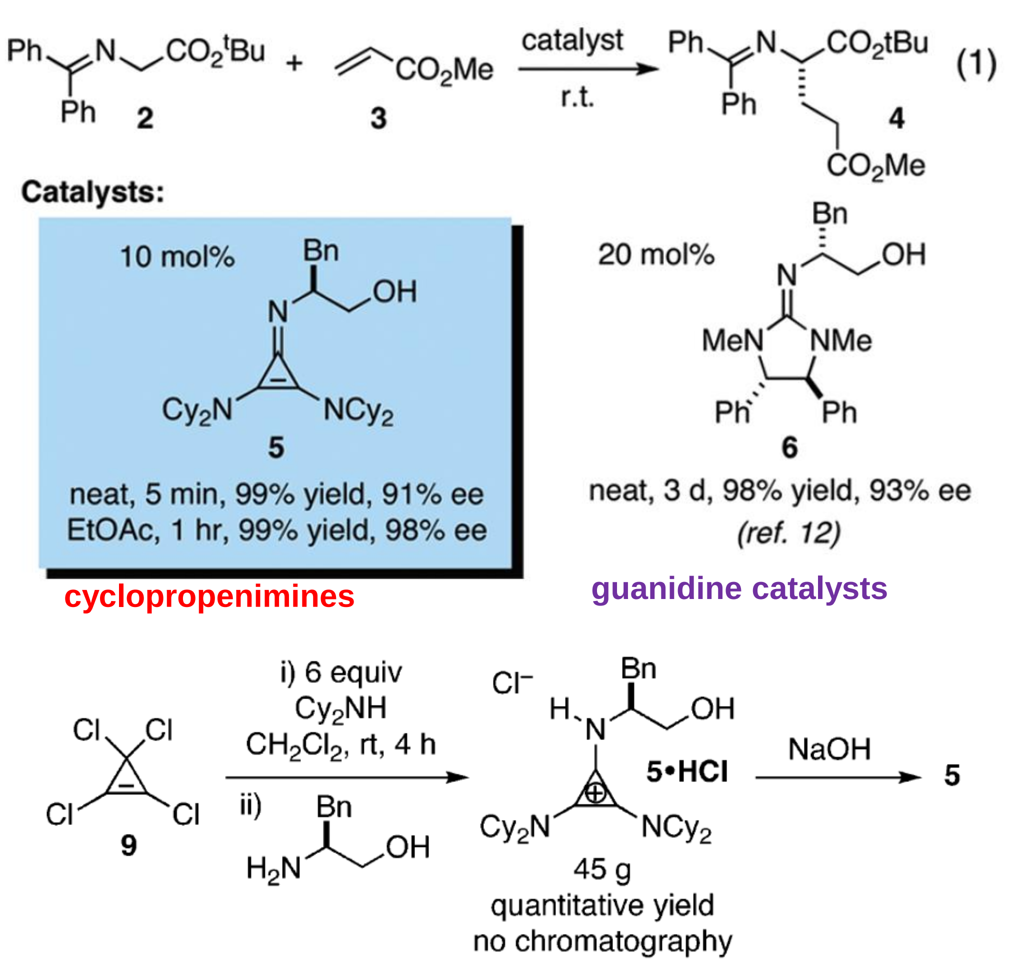


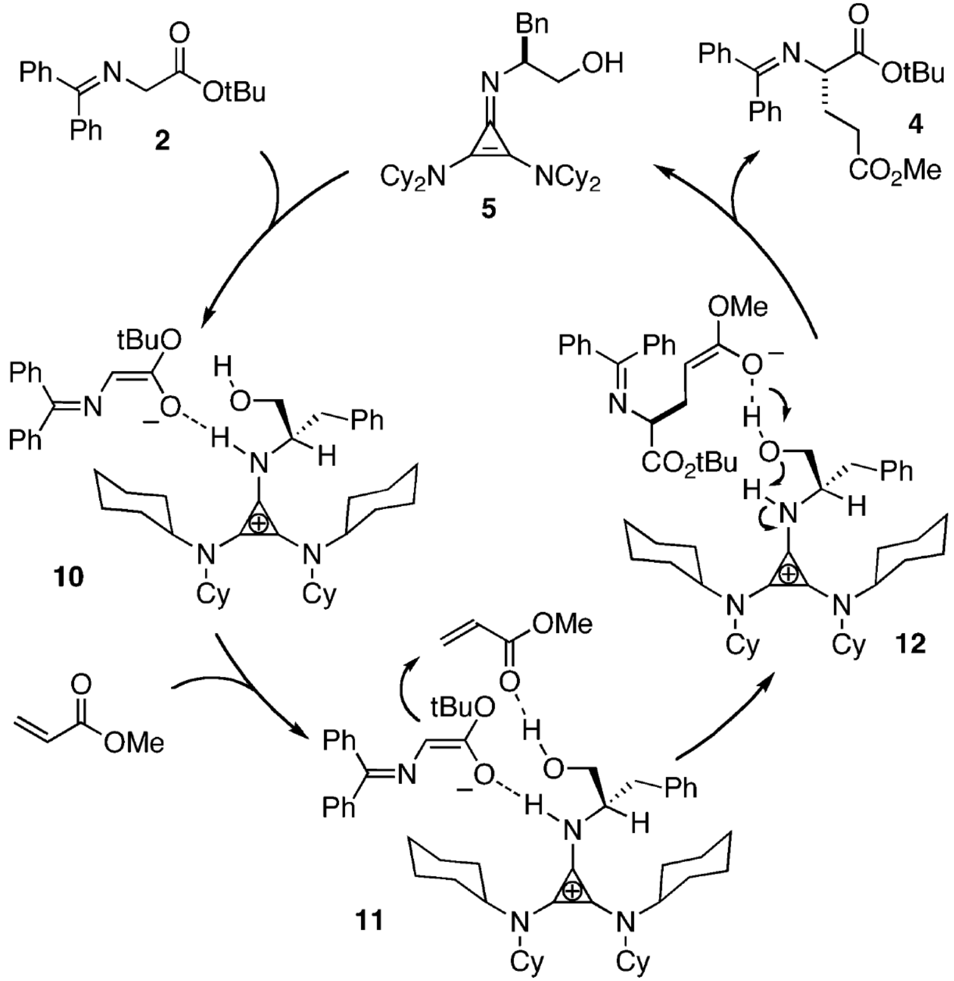
Figure 2. Basicity of cyclopropenimine **1** and several common strong organic bases. Bold numbers are pK_{BH+} values in acetonitrile.



T. H. Lambert, *et al. J. Am. Chem. Soc.* **2012**, *134*, 5552.

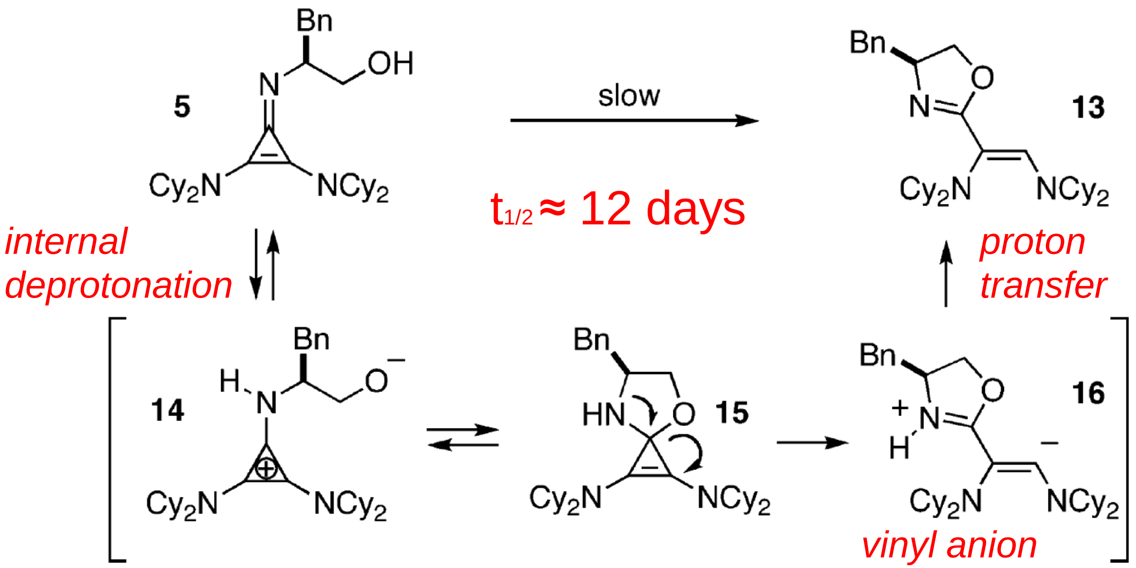
Chiral Cyclopropenyl Cation

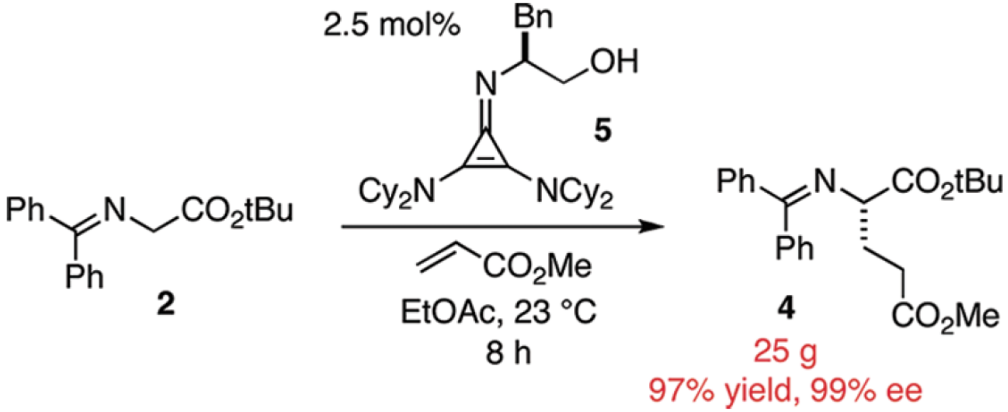
Mechanism and Scale-up Reaction



T. H. Lambert, *et al*. *J. Am. Chem. Soc*. **2012**, *134*, 5552.

Scheme 2. Decomposition Pathway of Cyclopropenimine 5





Chiral Cyclopropenyl Cation

Structure-activity Relationship Studies of Cyclopropenimines

several catalyst scaffolds

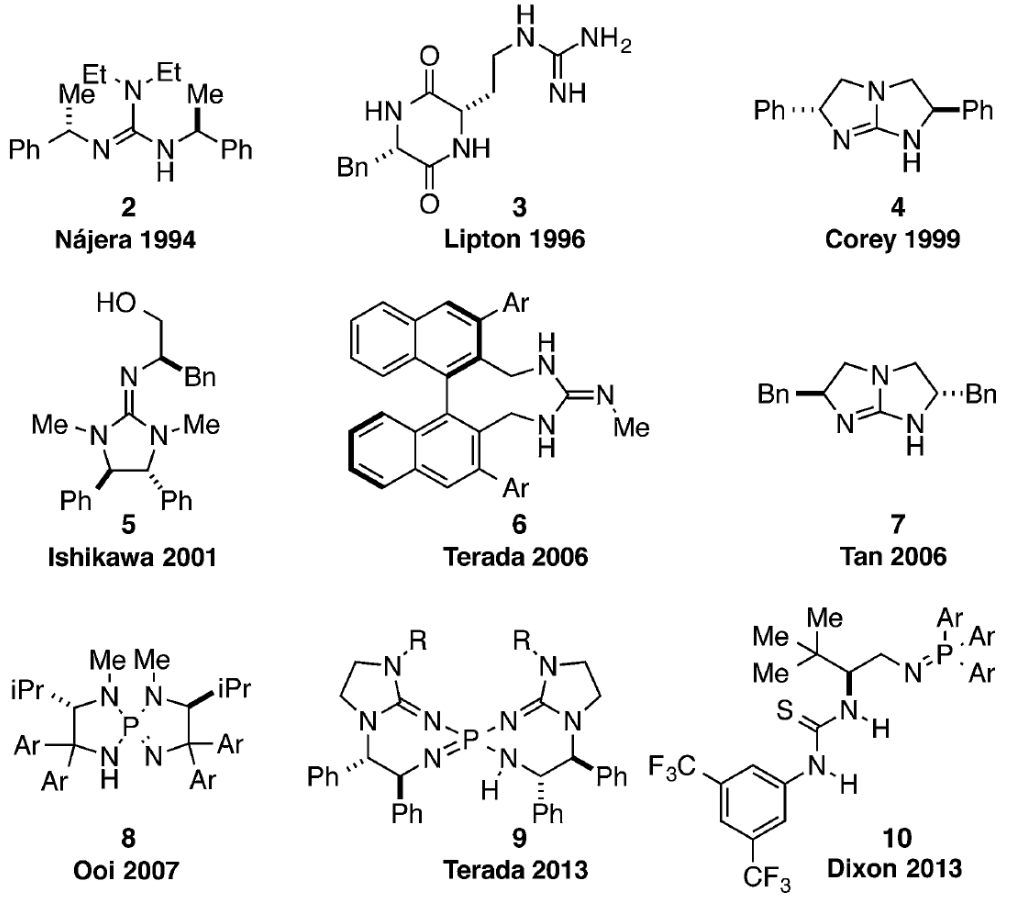
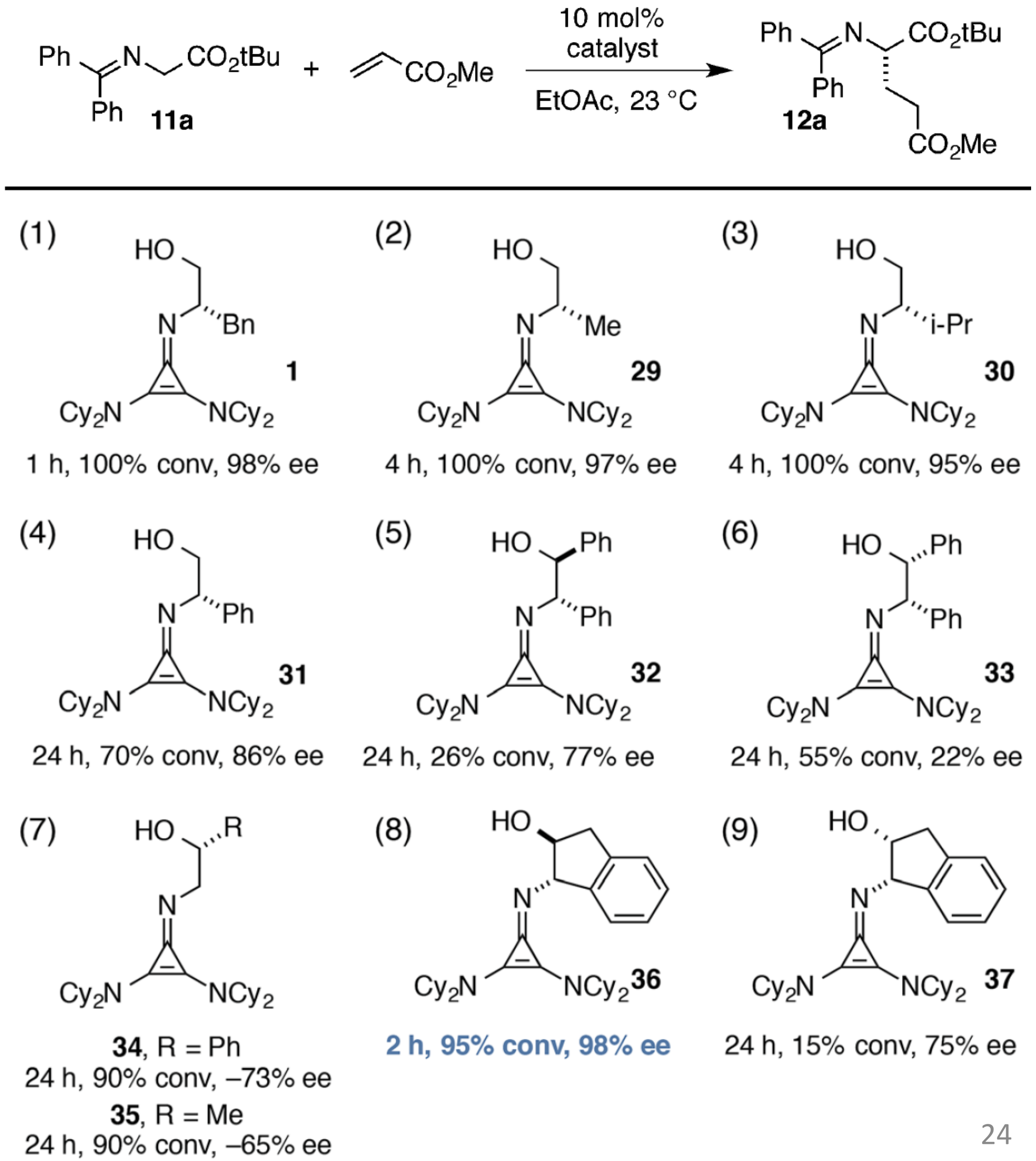


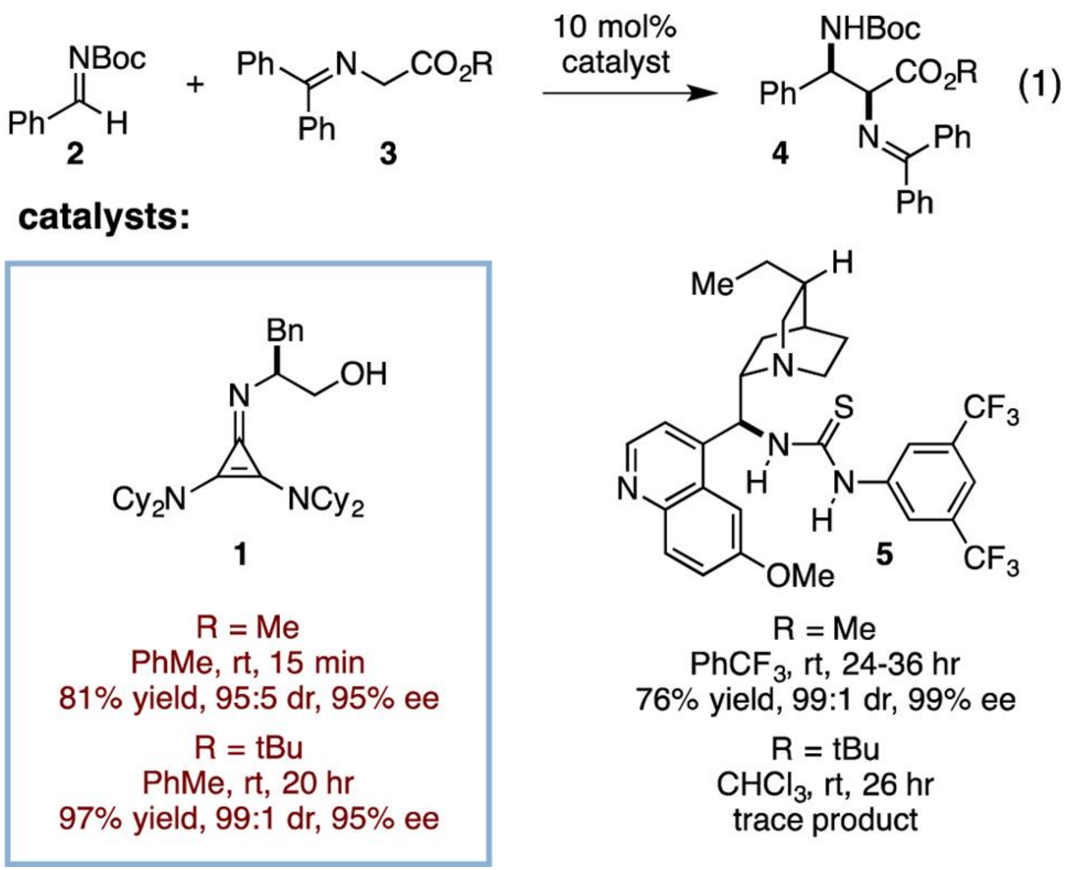
Fig. 2 Examples of chiral Brønsted base catalysts with strong basicities.

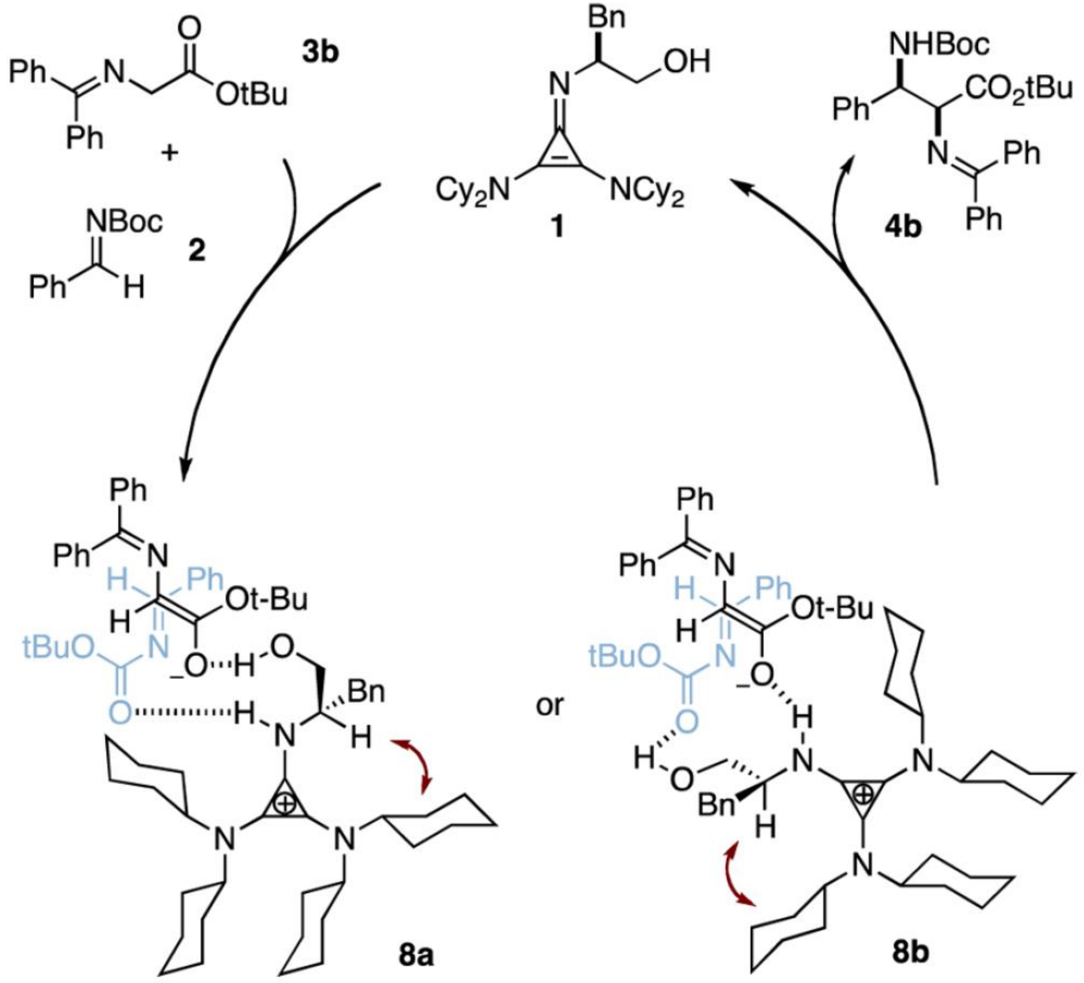


T. H. Lambert, *et al*. *Chem. Sci*. **2015**, *6*, 1537.

Chiral Cyclopropenyl Cation

Cyclopropenimine-Catalyzed Enantioselective Mannich Reactions of tert-Butyl Glycinates with N-Boc-Imines





T. H. Lambert, *et al*. *J. Am. Chem. Soc*. **2013**, *135*, 11799.

Outline

1. Introduction

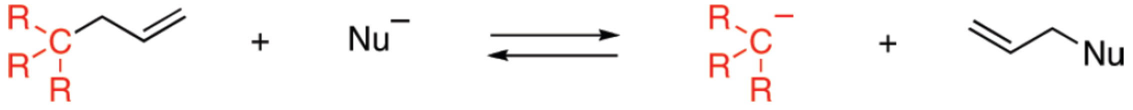
2. Aromatic cation

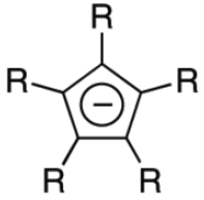
3. Aromatic anion

4. Summary and Outlook

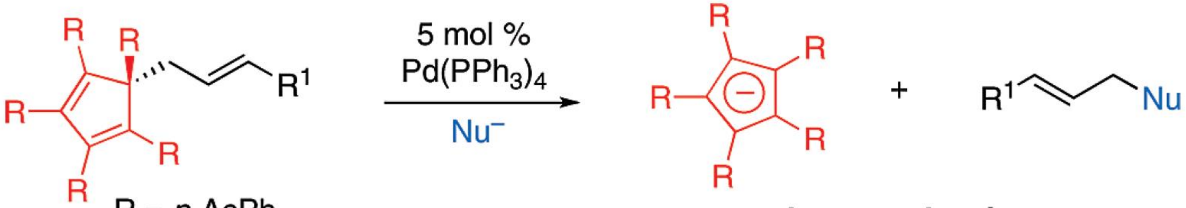
Aromatic anion

Leaving Group Potential of a Substituted Cyclopentadienyl Anion Toward Oxidative Addition





- Highly stabilized carbanions
- pKa of conjugate acids as low as –10
- Readily synthesized
- Electronically and sterically tunable
- General carbon leaving group?

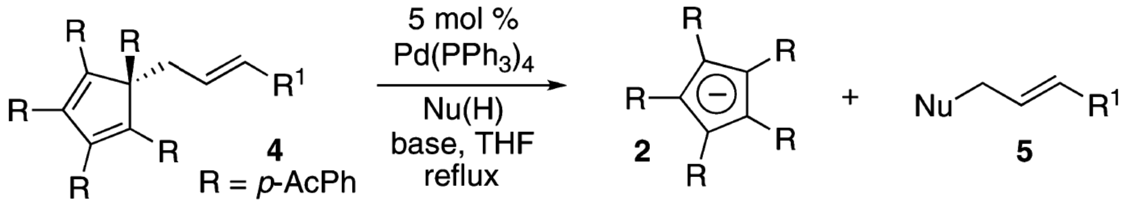


R = *p*-AcPh

carbon as a leaving group

T. H. Lambert, *et al*. *Org. Lett*. **2009**, *11*, 4108.

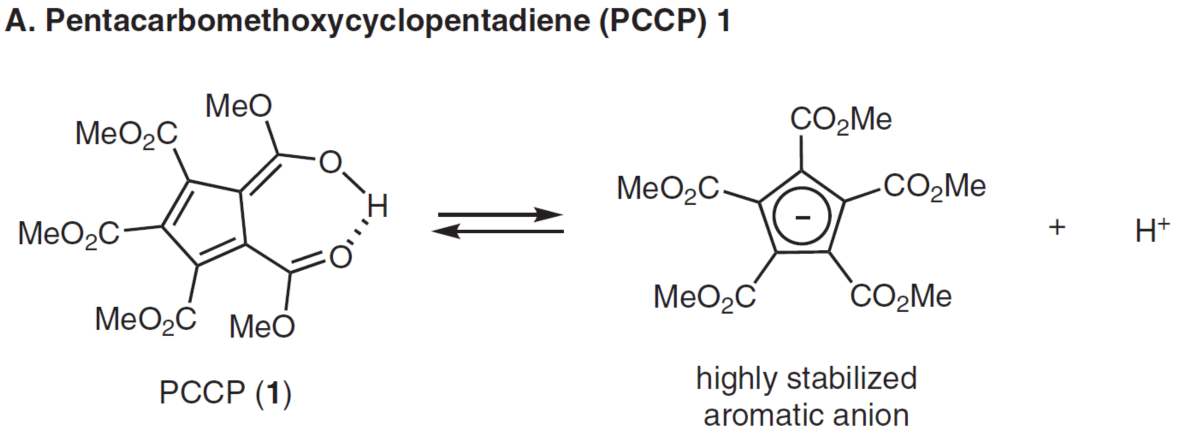
Selected examples



entry	substrate	Nu(H)	base	time (h)	% yield
1	R_5Cp	$(EtO_2C)_2CHMe$	NaH	1.5	80
2	R_5Cp Me	$(EtO_2C)_2CHMe$	NaH	4	71
3	R_5Cp Ph	$(EtO_2C)_2CHMe$	NaH	4	70
4	R_5Cp Me	$(EtO_2C)_2CHMe$	NaH	> 6	0
5	R_5Cp CO_2Me	$(EtO_2C)_2CHMe$	NaH	3	71
6	R_5Cp	EtO_2C C(O)Me Me	NaH	3	78
7	R_5Cp	Ph_5CpH	n-BuLi	3	77
8[b],[c]	R_5Cp	BnNHMe	Cs_2CO_3	3	69

Aromatic anion

PCCP and Its Derivatives

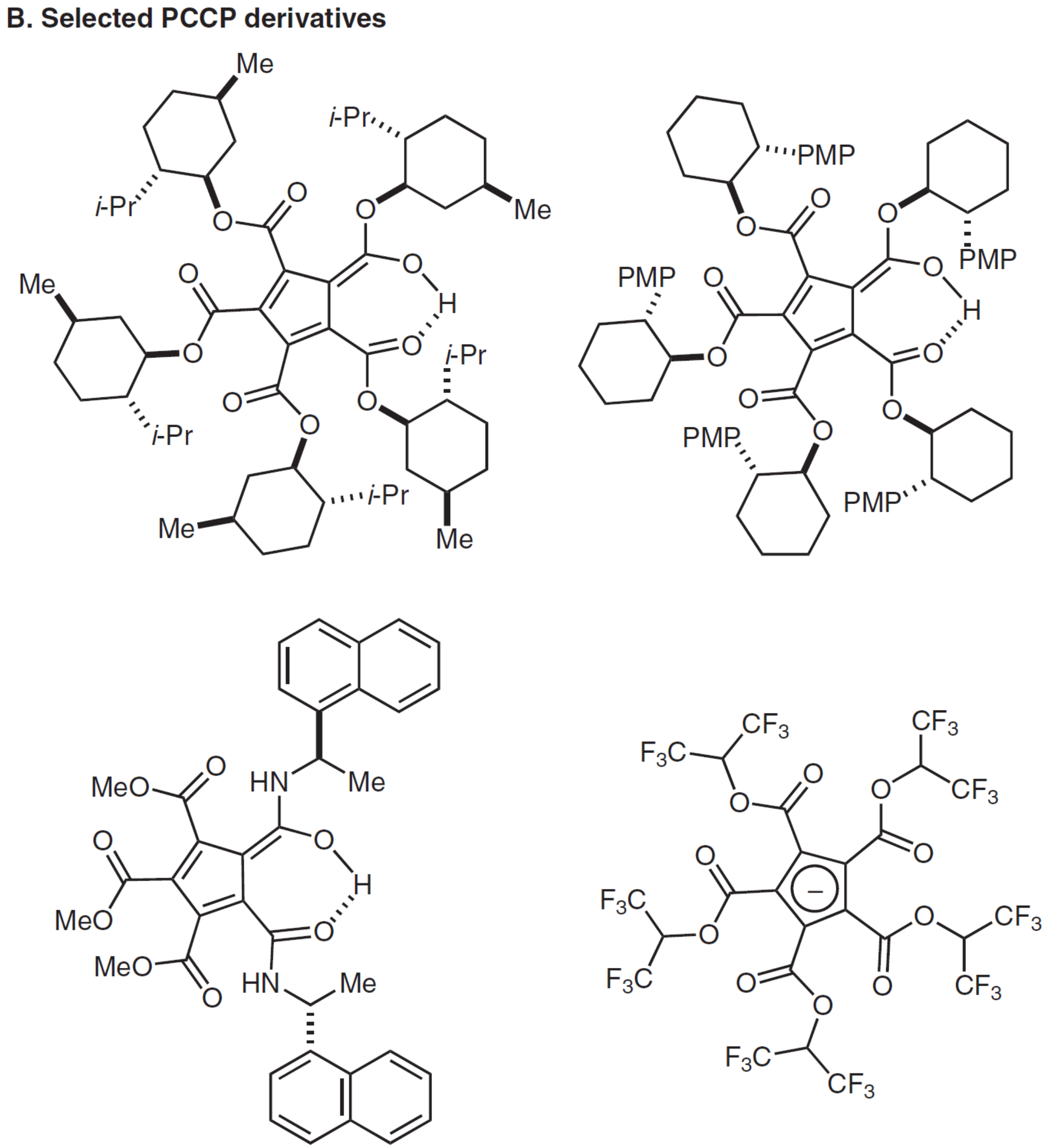


Diels, O. *Ber. Dtsch. Chem. Ges*. **1942**, *75*, 1452.

a) The acidity of the cyclopentadiene can be further increased through introduction of stabilizing groups, such as cyano or carbonyl substituents.

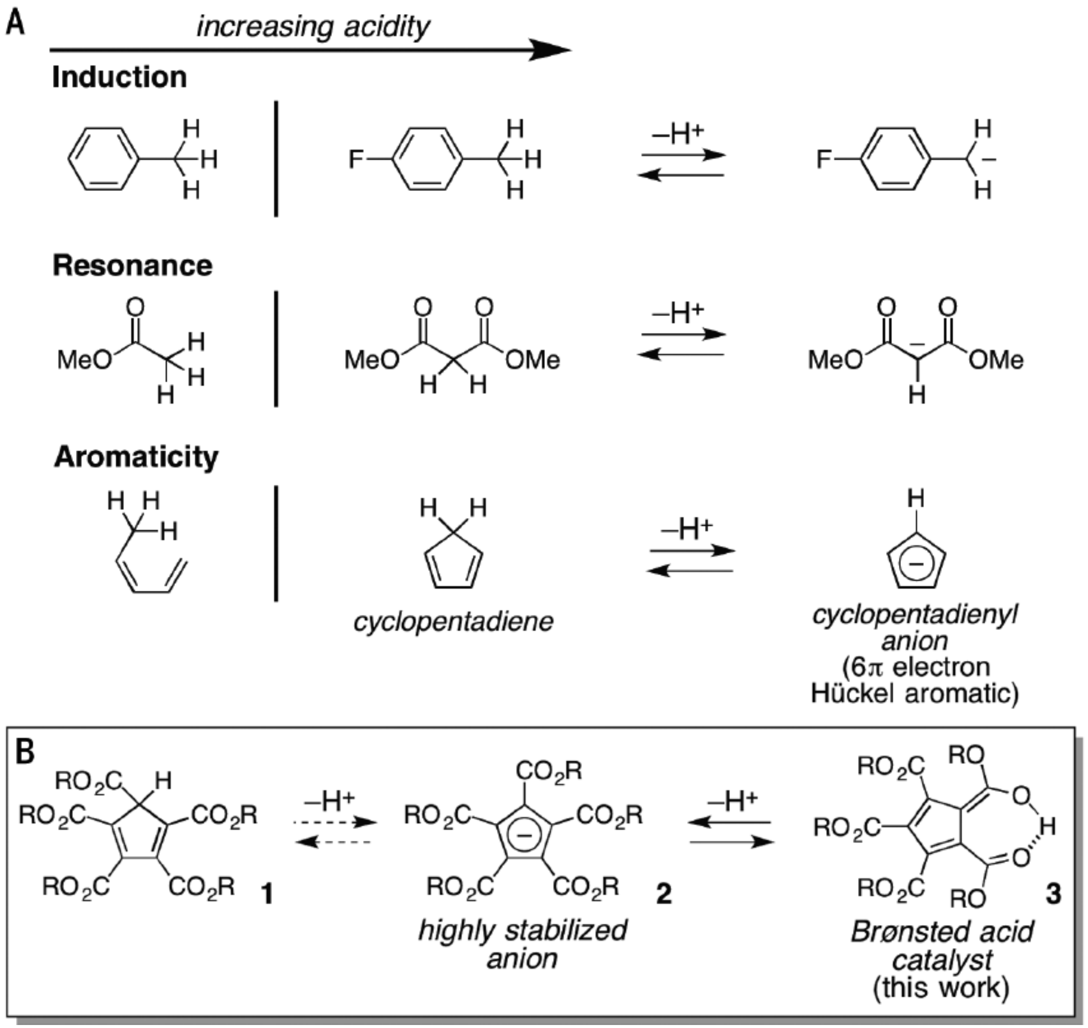
b) The highly eletron-deficient PCCP is approximately as acidic as HCl.

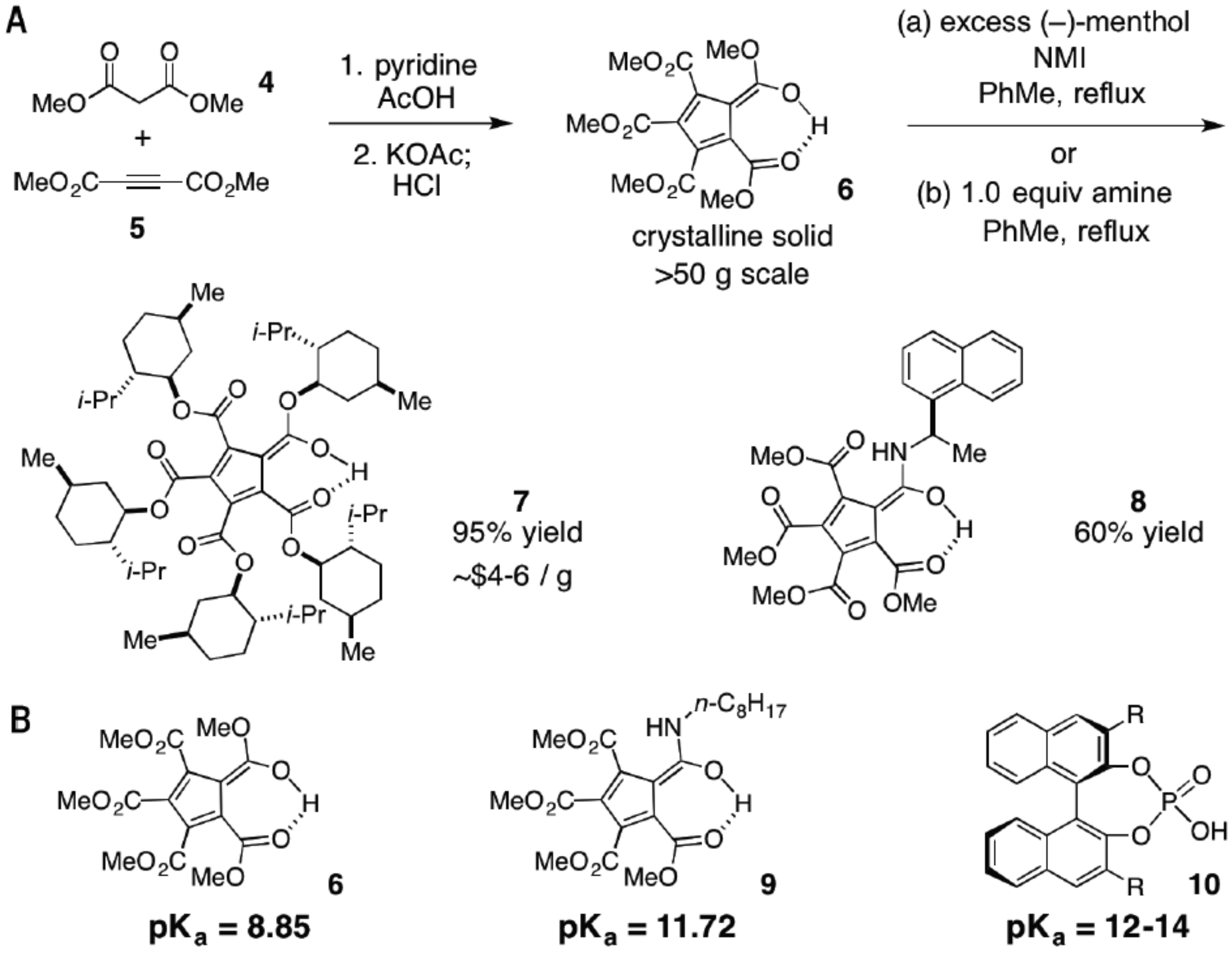
T. H. Lambert, *et al*. *Synthesis* **2019**, *51*, 1135.



Chiral Aromatic anion

An aromatic ion platform for enantioselective Brønsted acid catalysis





Determined in acetonitrile

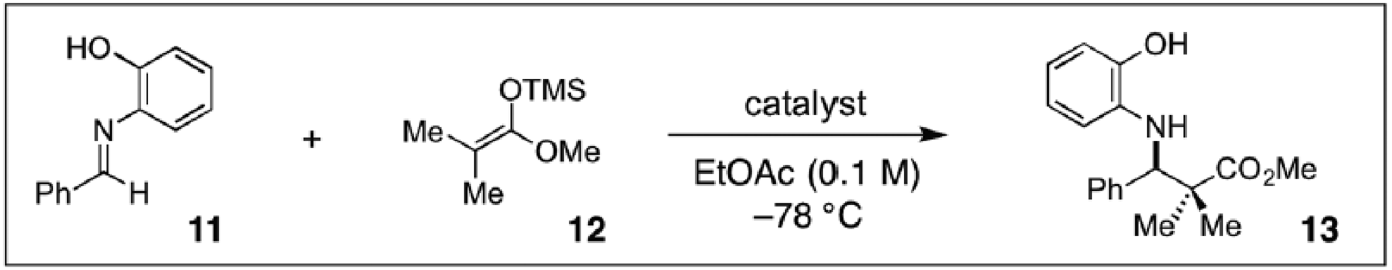
T. H. Lambert, *et al*. *Science* **2016**, *351*, 961.

Chiral Aromatic anion

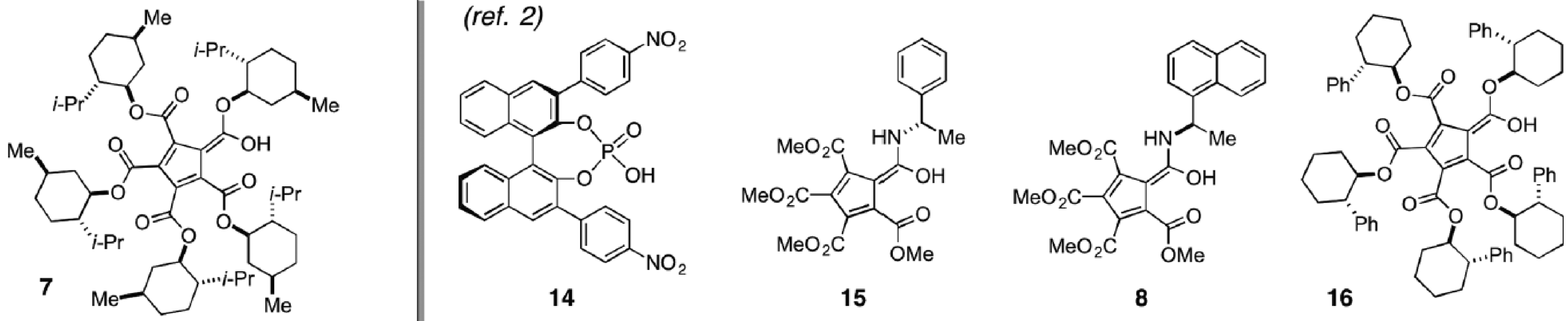
An aromatic ion platform for enantioselective Brønsted acid catalysis

A

Mukaiyama-Mannich

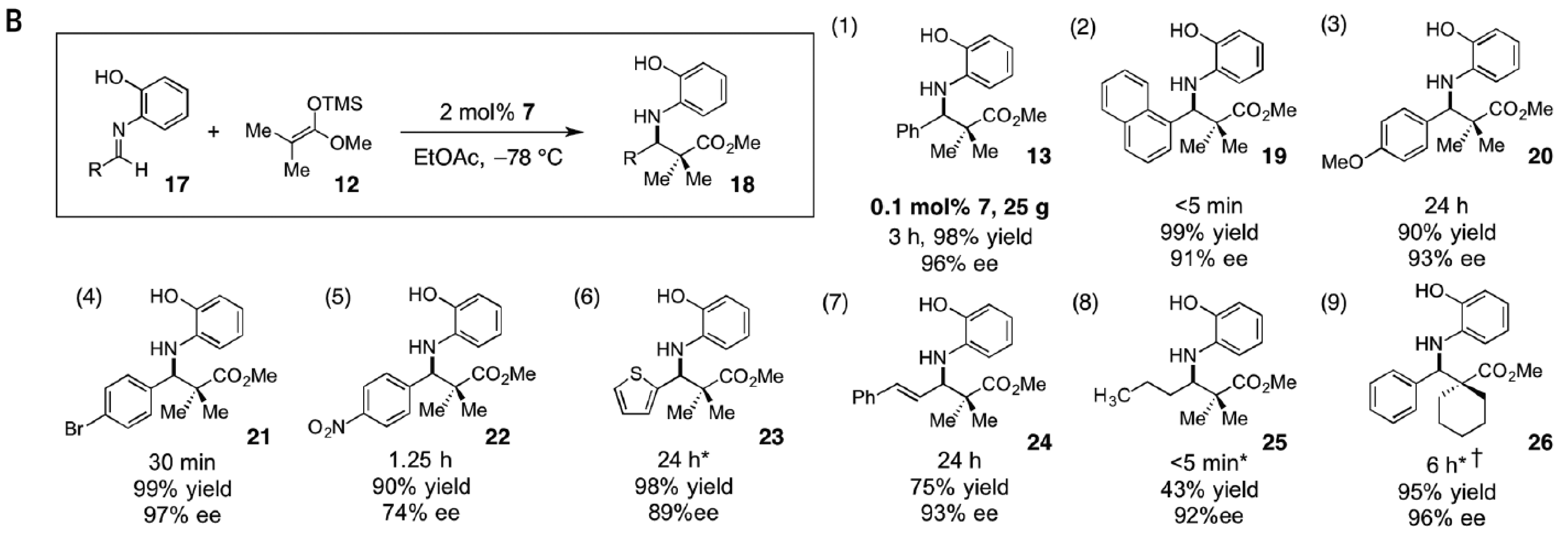


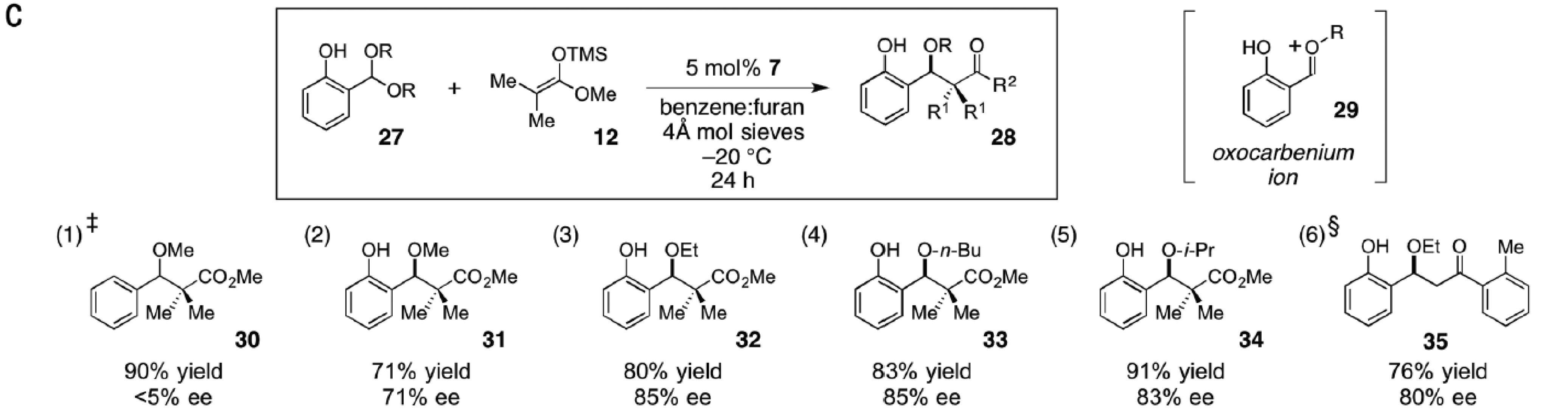
Catalysts



7		14	15	8	16
1 mol% 1 h 97% yield, 97% ee	**0.01 mol% (0.3 M) 48 h 90% yield, 97% ee**	10 mol%, 24 h 98% yield, 89% ee (toluene)	10 mol%, 6 h 88% yield, –30% ee	10 mol%, 8 h 85% yield, 44% ee	5 mol%, 5 min 90% yield, 89% ee

T. H. Lambert, *et al*. *Science* **2016**, *351*, 961.

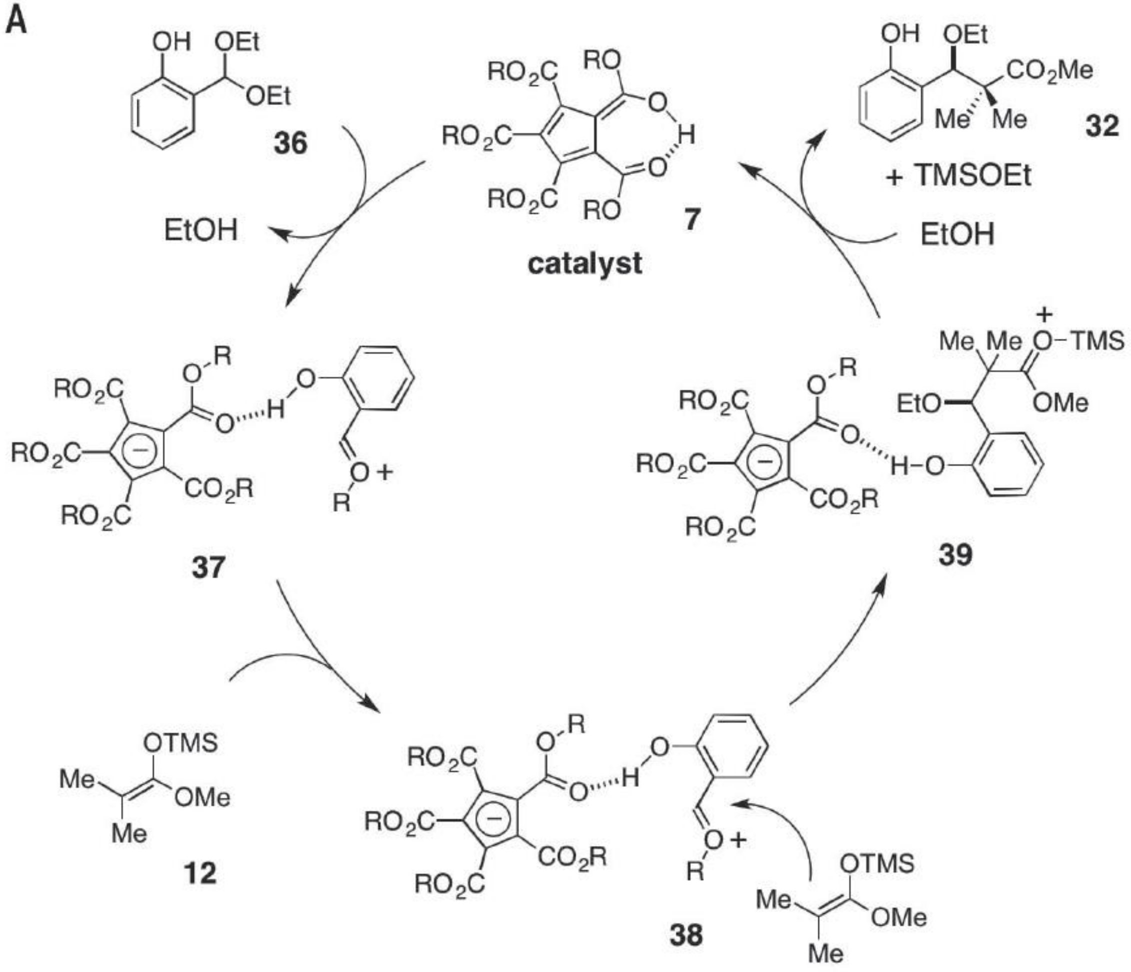


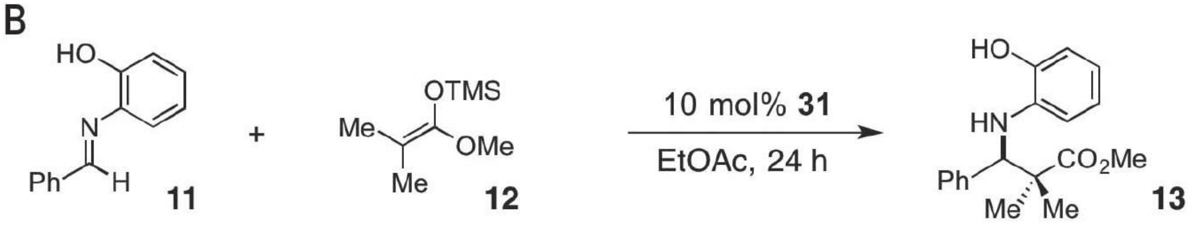


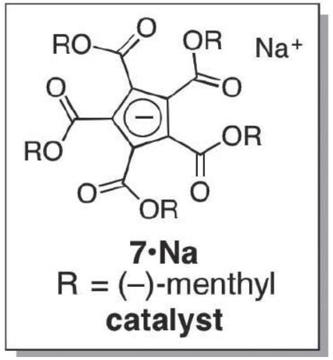
T. H. Lambert, *et al*. *Science* **2016**, *351*, 961.

Chiral Aromatic anion

An aromatic ion platform for enantioselective Brønsted acid catalysis





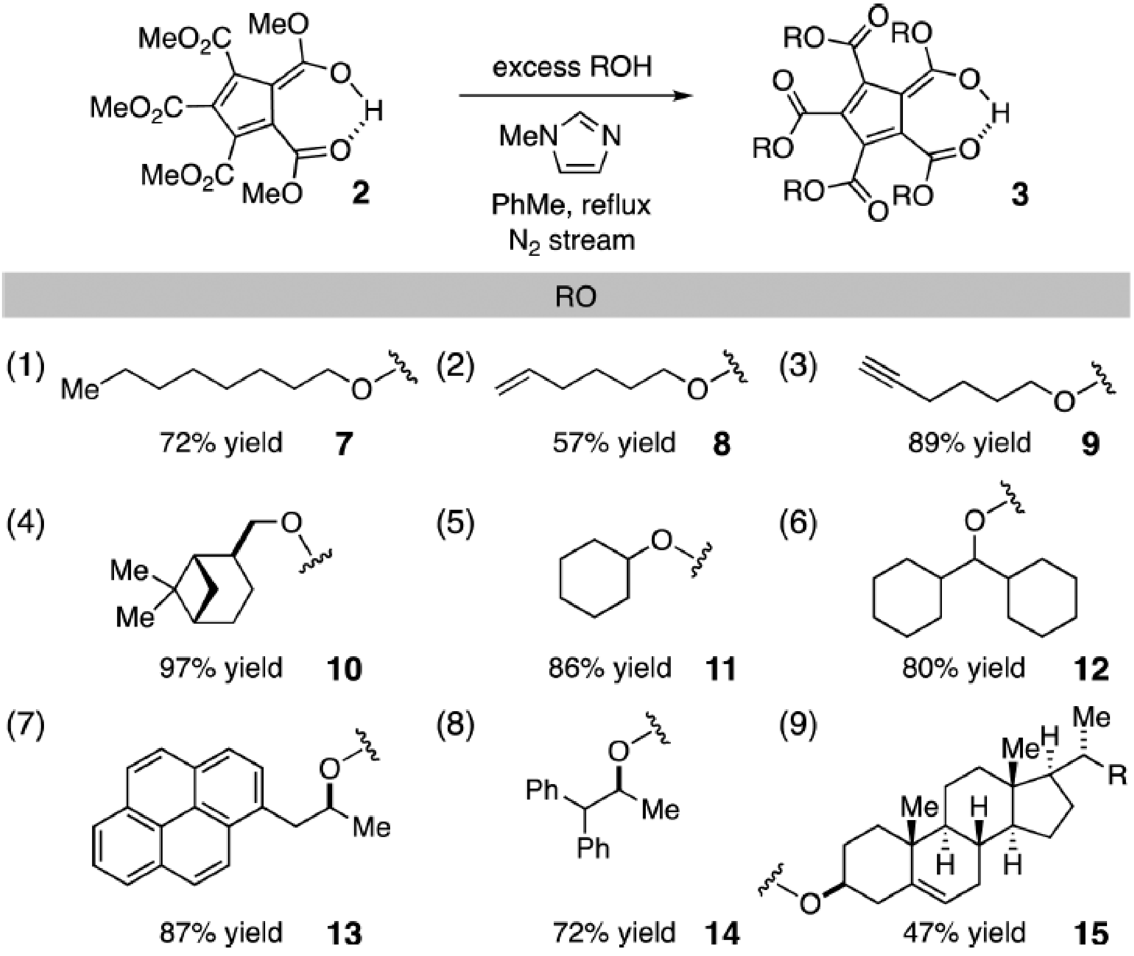


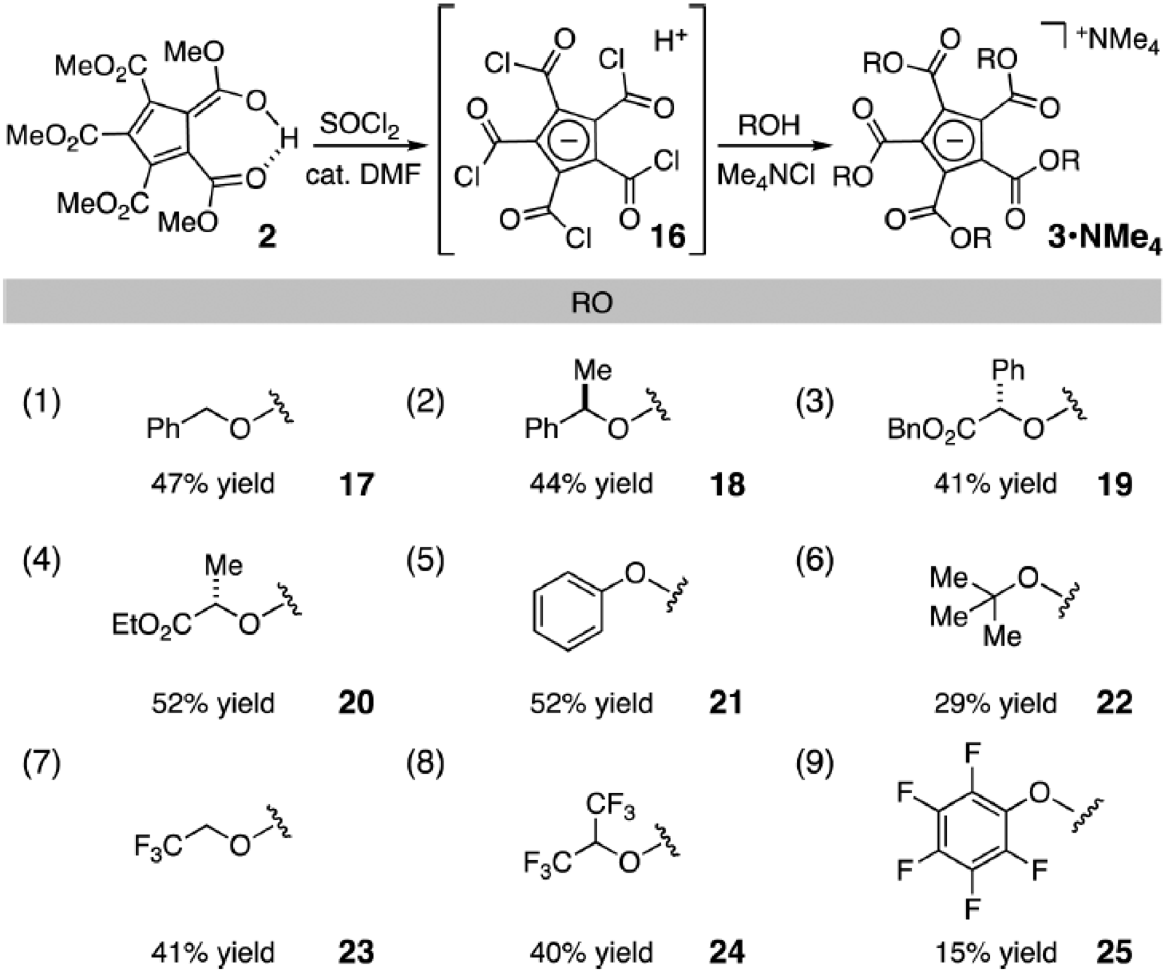
entry	temp (°C)	additive	conv (%)	ee (%)
1	–78	--	0	–
2	rt	--	79	47
3	rt	2,6-*t*-Bu_2-4-Me-pyridine	80	48

T. H. Lambert, *et al*. *Science* **2016**, *351*, 961.

Chiral Aromatic anion

Methods for the Synthesis of Functionalized Pentacarboxycyclopentadienes

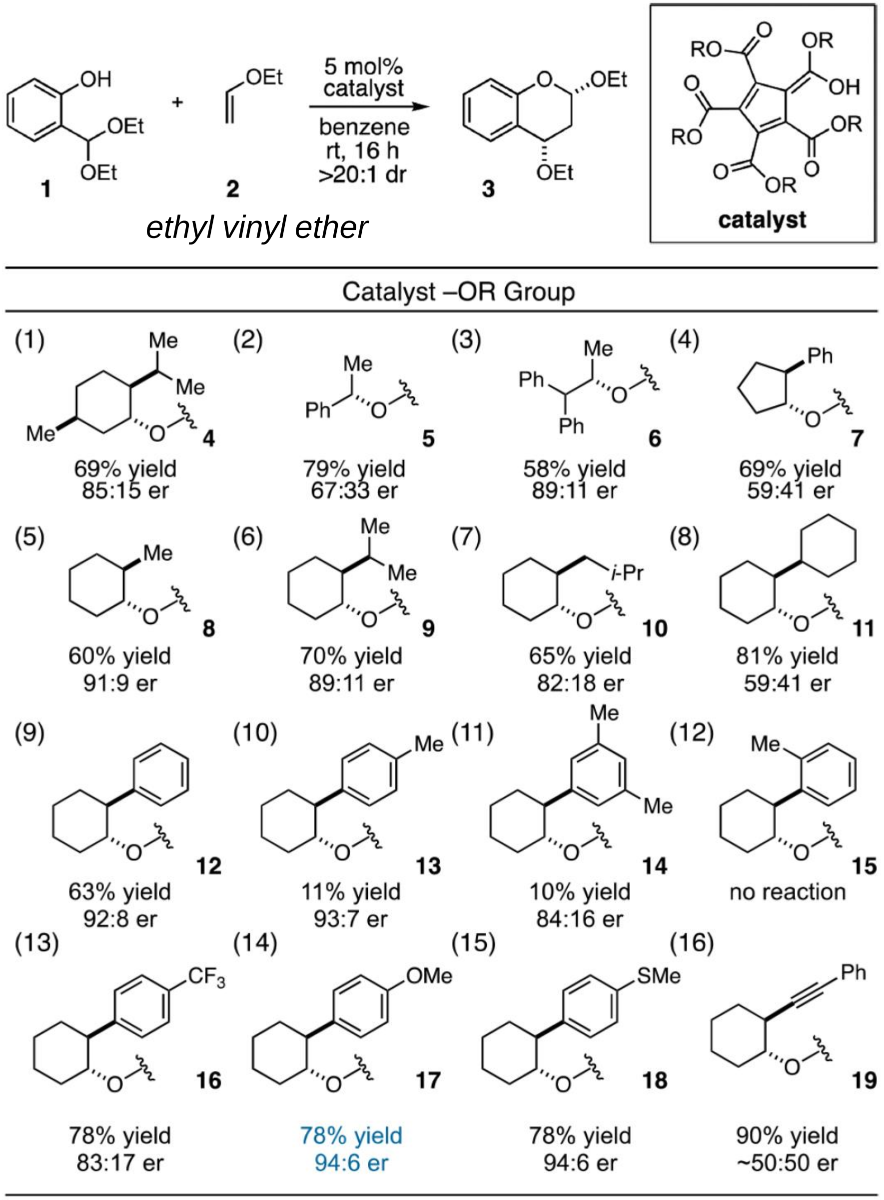


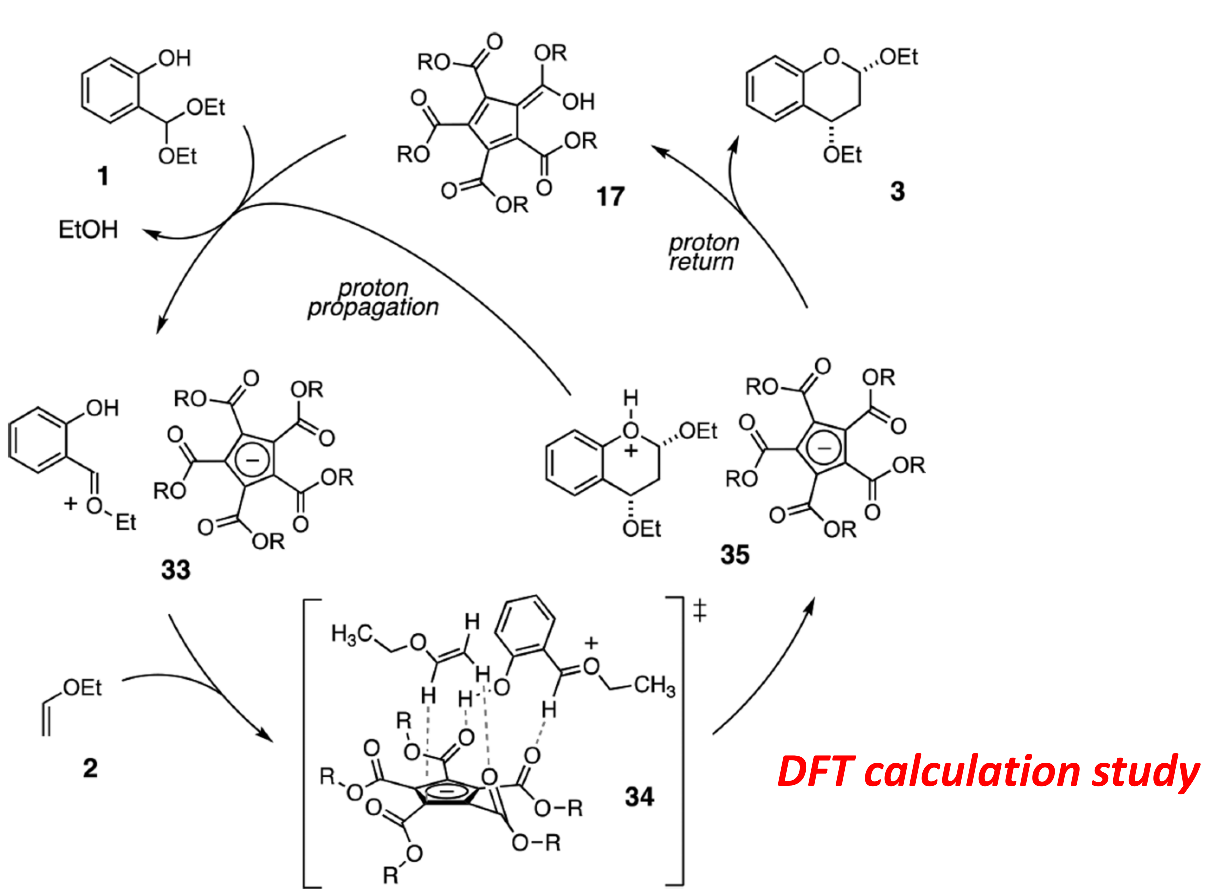


T. H. Lambert, *et al*. *Org. Lett.* **2017**, *19*, 4227.

Chiral Aromatic anion

Enantioselective PCCP-Catalyzed Diels−Alder Cycloaddition of Oxocarbenium Ions



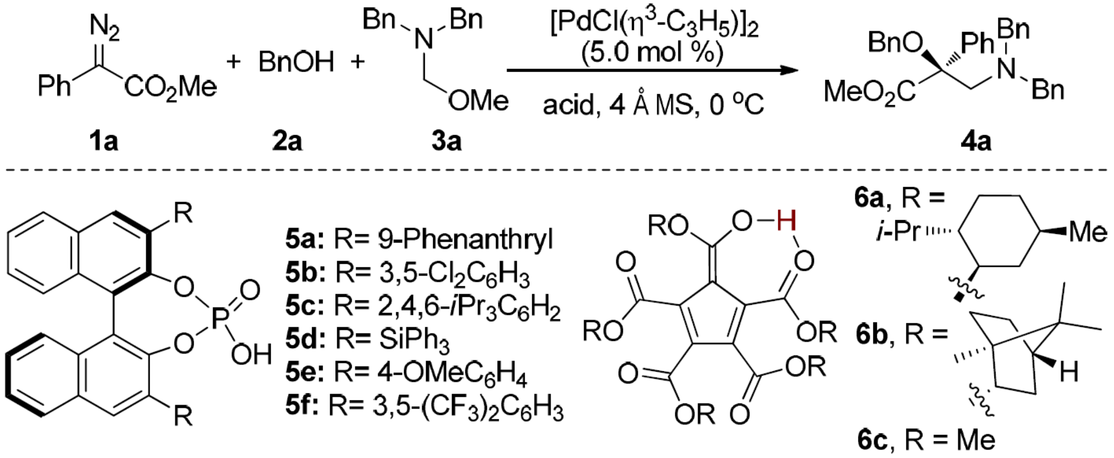


A strong CH−π interaction between the polarized internal vinylic C−H of 2 and the cyclopentadienyl anion was involved.

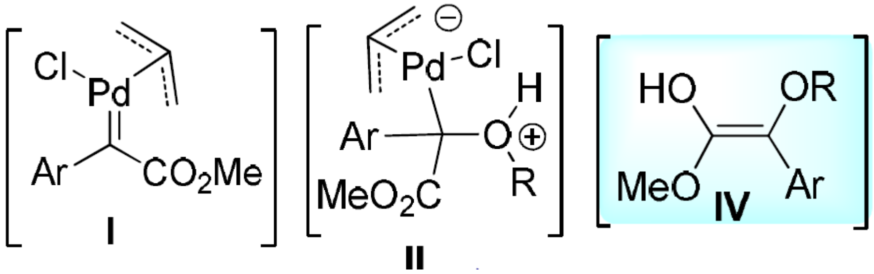
T. H. Lambert, *et al. J. Am. Chem. Soc.* **2018**, *140*, 3523.

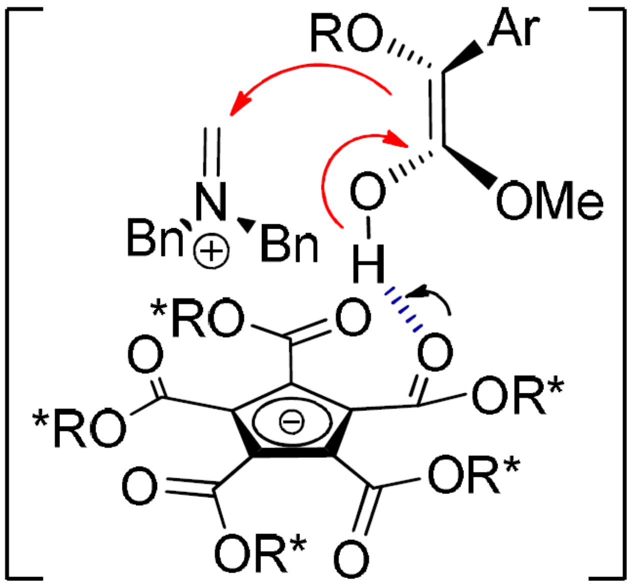
Chiral Aromatic anion

Asymmetric Counter-Anion-Directed Aminomethylation: Synthesis of Chiral β-Amino Acids via Trapping of an Enol Intermediate



entry	solvent	acid	yield (%)[b]	ee (%)[c]
1	DCM	**5a**	93	<5
2	DCM	**5b**	89	5
3	DCM	**5c**	95	51
4	DCM	**5d**	92	27
5	DCM	**5e**	90	<5
6	DCM	**5f**	89	15
7	DCM	**6c**	90	–
8	DCM	**6a**	90	88
9	DCM	**6b**	88	84
10	$CHCl_3$	**6a**	92	96

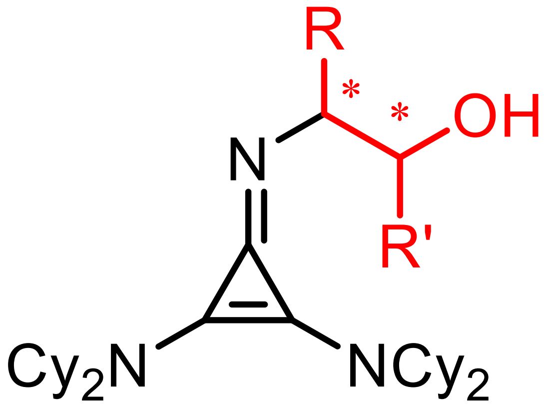




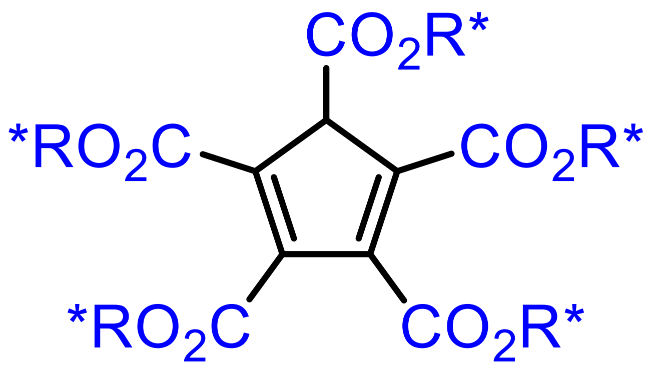
W.-H. Hu, *et al. J. Am. Chem. Soc.* **2019**, *141*, 1473.

Summary and Outlook

Aromatic ions have been attracted more and more attention.



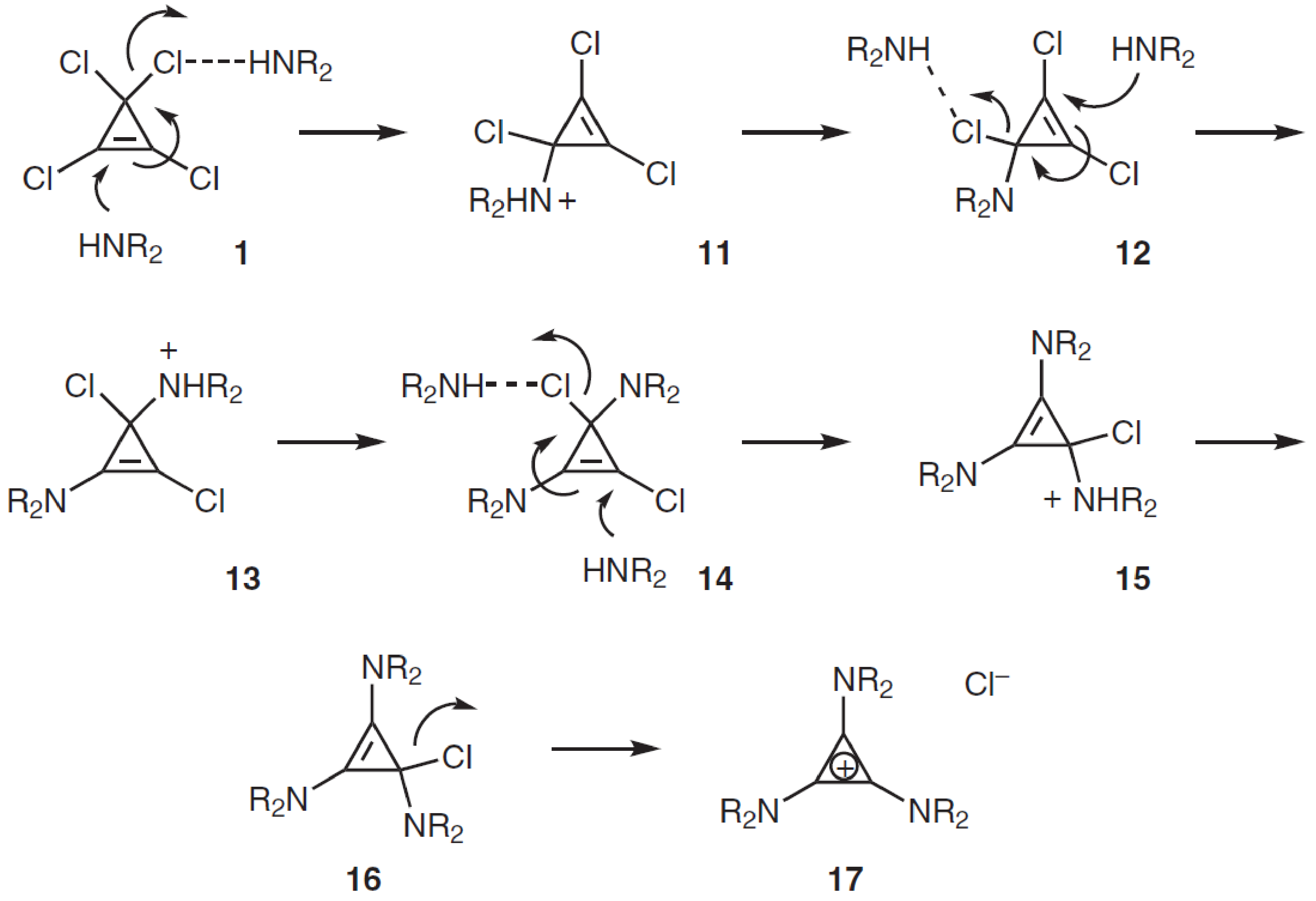
chiral cyclopropenyl cation



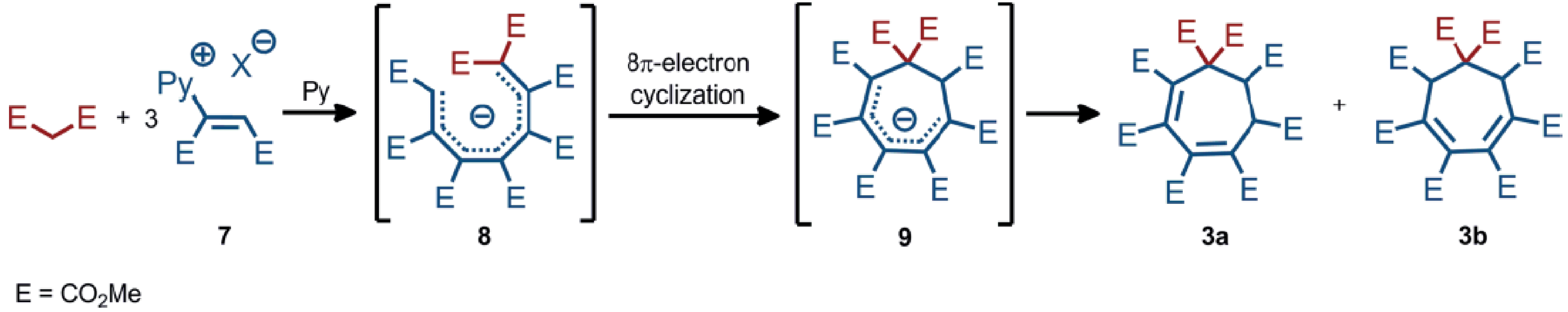
Cyclopentadienyl anion
(PCCP)

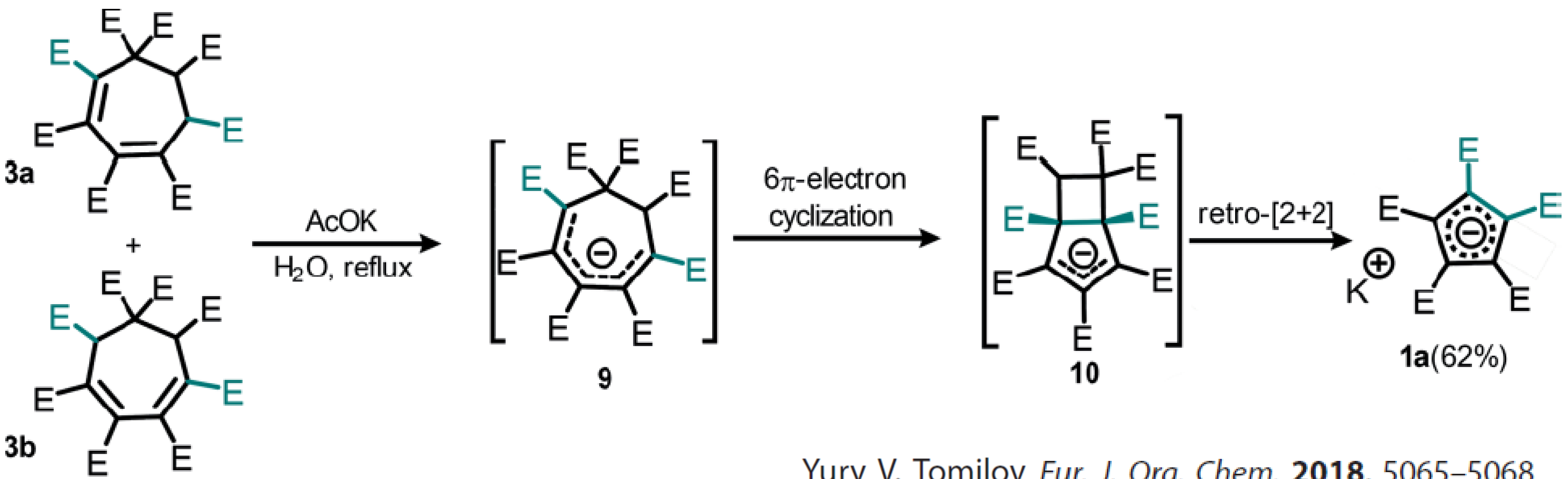
a) Old chemistry but turned out to be a new research area.
b) Novel organic base: TDACs; Novel organic Brønsted acid: PCCPs
c) Exploitation of PCCP-Metal is on the way.
d) Great potential in organic synthesis by chiral aromatic ion catalysis.

Thanks for your attention !
Any questions ?

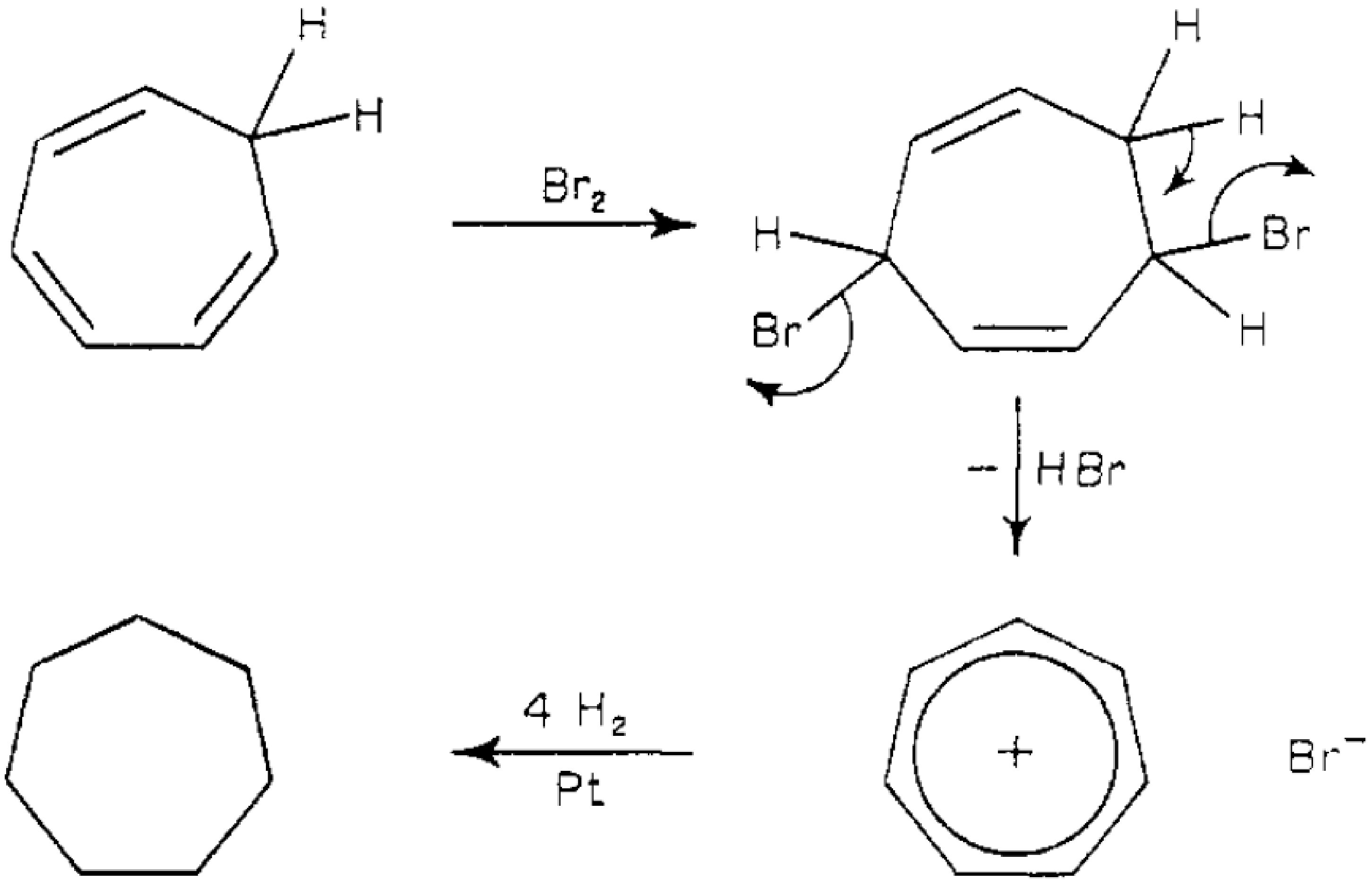

Cl
Cl
HNR2
Cl
Cl
HNR2
1
Cl
Cl
R2HN+
Cl
11
R2NH
Cl
HNR2
Cl
R2N
Cl
12
+
Cl
NHR2
R2N
Cl
13
R2NH
Cl
NR2
R2N
Cl
HNR2
14
NR2
Cl
R2N
+ NHR2
15
NR2
Cl
R2N
NR2
16
NR2
Cl−
R2N
NR2
17

Synthesis of 1,2,3,4,5-Penta(methoxycarbonyl)cyclopentadienides through Electrocyclic Ring Closure and Ring Contraction Reactions





Yury V. Tomilov *Eur. J. Org. Chem.* **2018**, 5065–5068



BY W. VON E. DOERING[1] AND L. H. KNOX

pK_{BH+} Measurements. Stock solutions of the HX salt of the "substrate" superbase being studied (0.0667 M, 0.60 mL, 0.040 mmol) and a reference free base (0.200 M, 0.20 mL, 0.040 mmol) were mixed in NMR tubes under inert atmosphere. CD_3CN was employed for all experiments, which were performed using a dual manifold, except for the GC_2 (**6**) and GP_2 (**10**) bases, which employed d_8-THF and were performed in a glovebox. The mixture was analyzed by ^1H NMR spectroscopy (as well as by ^{13}C NMR for measurements in d_8-THF).

The extents of protonation of both the substrate superbase and the reference base were determined by comparison to the spectra of the HX salt and the free base of each component. These data were used to calculate the relative basicities of the substrate superbase and the reference base, and this value was compared to the known pK_{BH+} value of the reference base to obtain the pK_{BH+} value of the substrate. Measurements were performed in triplicate. Corrections were made for the observed relative NMR integrations and to convert THF data to the acetonitrile scale.

The reference bases used were DBU (pK_{BH+} = 24.34, MeCN)[24] for G_1 (**16**); P_1-*t*Bu(pyrr)$_3$ (pK_{BH+} = 28.35, MeCN)[19] for C_1 (**17**), P_1 (**18**), G_3 (**11**), CG_2 (4), C_3 (**2**), and PC_1 (**14**); and P_2-Et (pK_{BH+} = 32.94, MeCN)[6c] for GC_2 (**6**), and GP_2 (**10**). The remaining superbases