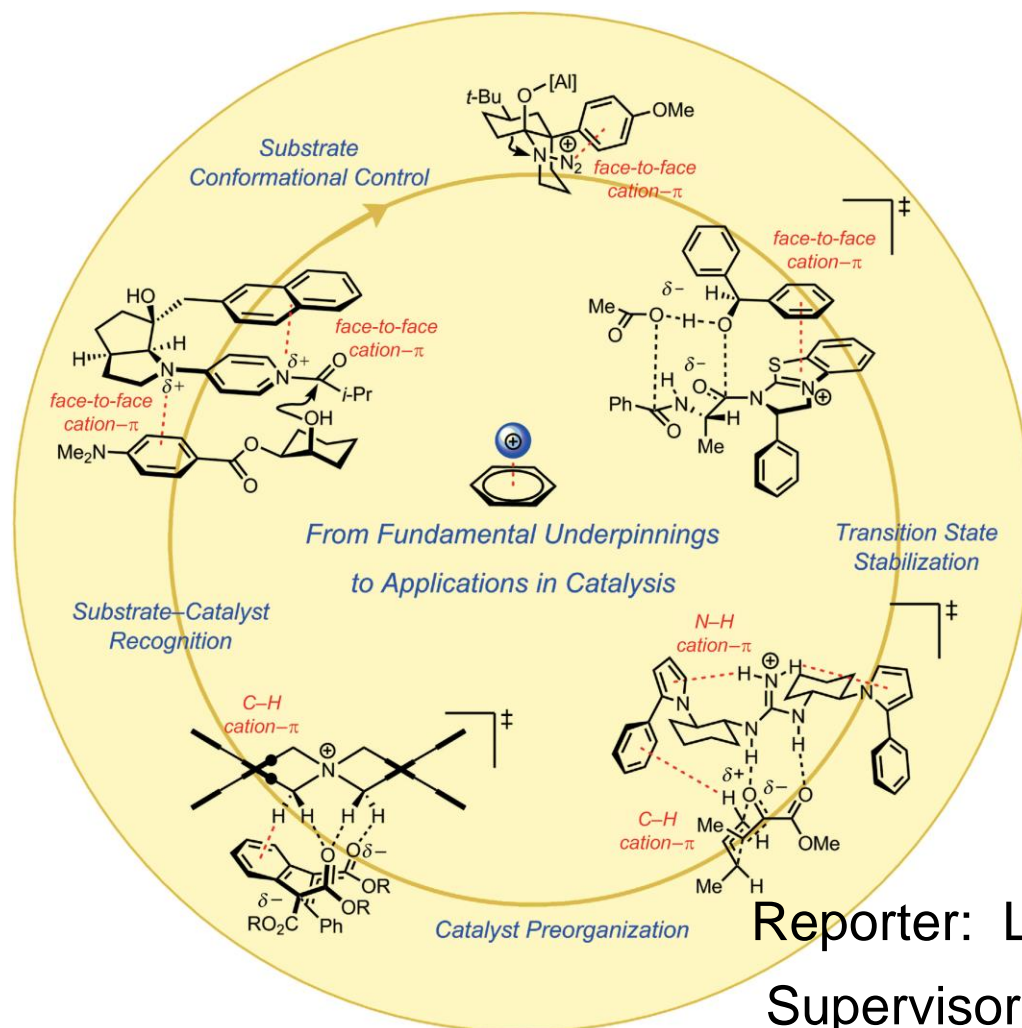


# The Cation- $\pi$ Interaction in Small-Molecule Catalysis

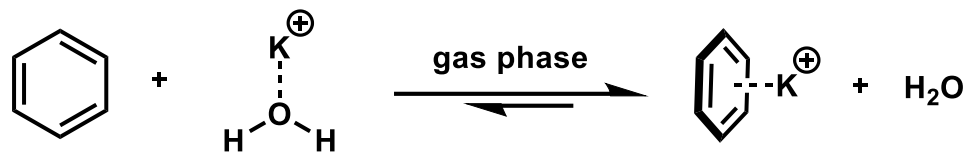


Reporter: Leming Wang

Supervisor: Prof. Yong Huang

2017.03.13

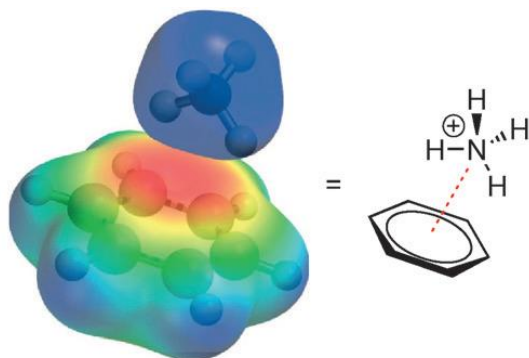
# Introduction



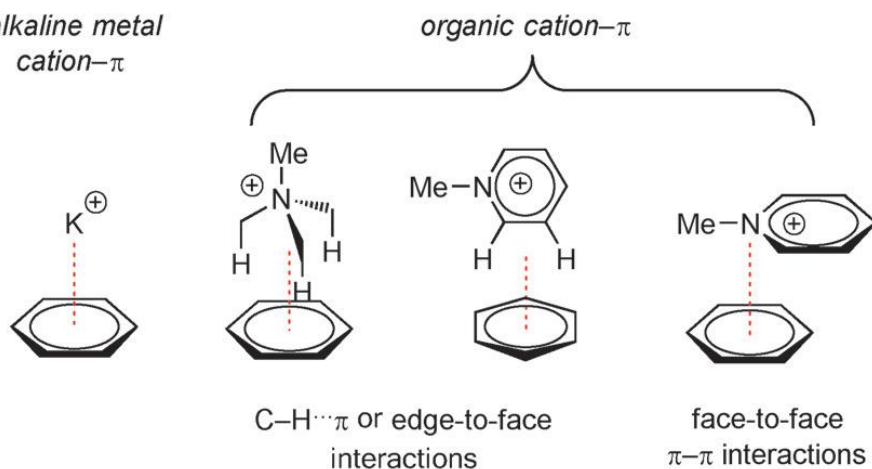
$$\Delta H_{(\text{association})} = 18 \text{ kcal/mol}$$

$$\Delta H_{(\text{association})} = 19 \text{ kcal/mol}$$

(A)



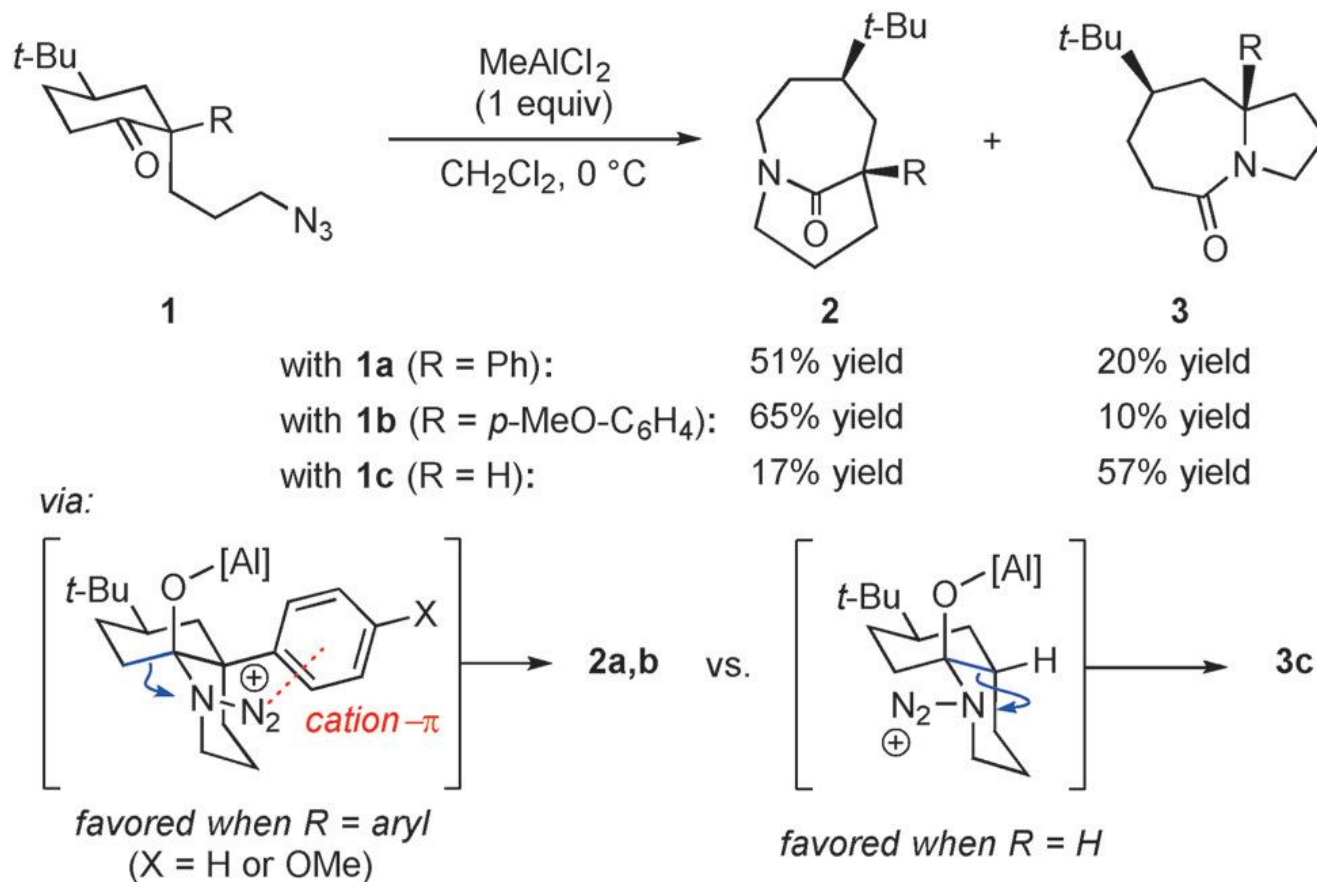
(B) *alkaline metal cation- $\pi$*



A) electrostatic attraction, Dispersion, charge-transfer;  
 B) Directionality: the cations rest directly over the centroid of the  $\pi$ -system.

# Substrate–Substrate Cation– $\pi$ Interactions

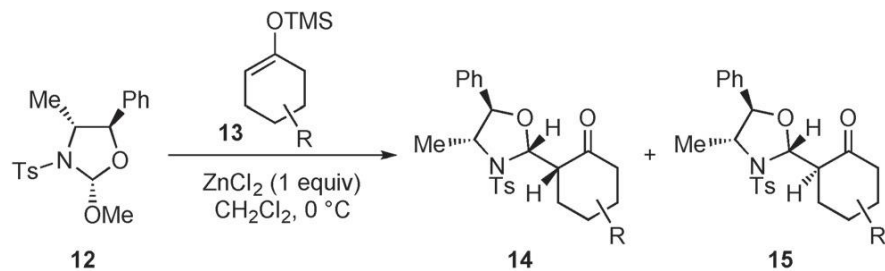
## Lewis Acid Promoted Regioselective Schmidt Annulation Reactions



L. Yao, J. Aubé, *J. Am. Chem. Soc.* **2007**, *129*, 2766–2767;

# Substrate–Substrate Cation– $\pi$ Interactions

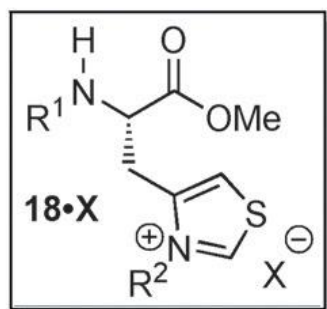
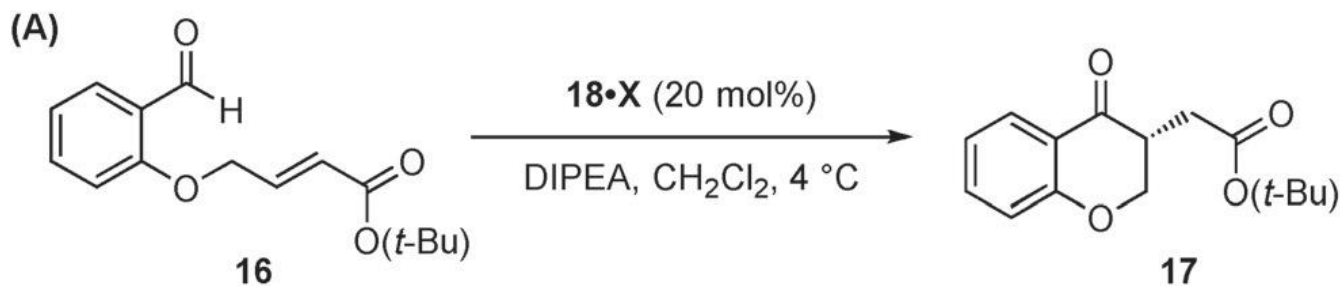
Lewis Acid Catalyzed Diastereoselective Additions of Silyl Enol Ethers to a Chiral Oxazolinium Ion



nucleophile	d.r. ( <b>14</b> / <b>15</b> )	computed transition structures ( $\Delta\Delta E^\ddagger$ , kcal/mol)	
		TS-14	TS-15
<p><b>13a</b></p>	> 95:5	<p>(0.0)</p>	<p>(2.2)</p> <p><i>partially eclipsed dihedral</i></p>
<p><b>13b</b></p>	20:80	<p>(0.0)</p>	<p>(-0.8)</p> <p><i>C-H cation-<math>\pi</math></i></p>
<p><b>13c</b></p>	20:80	<p>(0.0)</p>	<p>(-3.1)</p> <p><i>C-H cation-<math>\pi</math></i></p>

# Catalyst–Catalyst Cation– $\pi$ Interactions

## Peptidic Thiazolium Ion Catalysts for Stetter Reactions

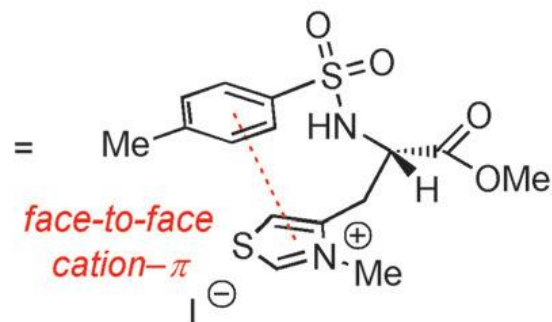
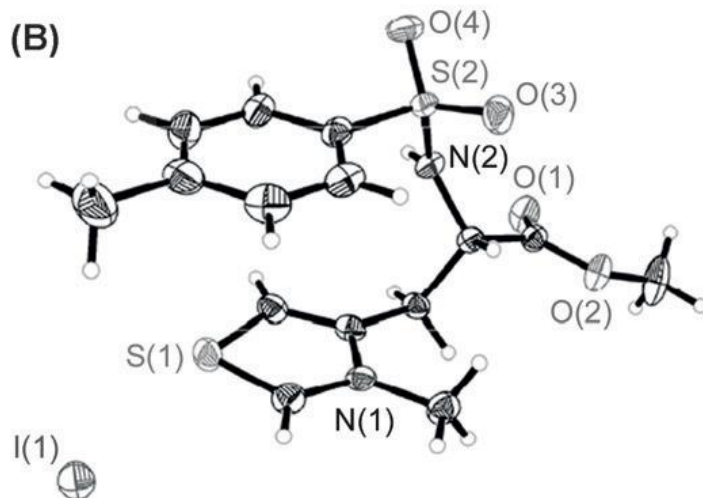


with **18a•Br** ( $R^1 = \text{Ts}$ ,  $R^2 = \text{Bn}$ ): 80% ee

with **18b•I** ( $R^1 = \text{Ts}$ ,  $R^2 = \text{Et}$ ): 70% ee

with **18c•I** ( $R^1 = \text{Ac}$ ,  $R^2 = \text{Et}$ ): 63% ee

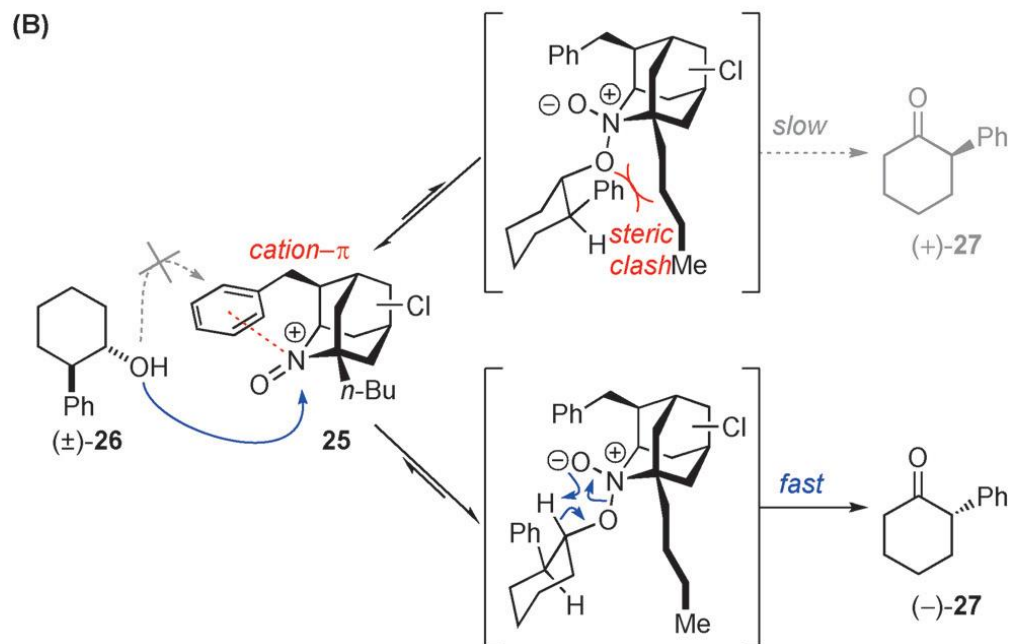
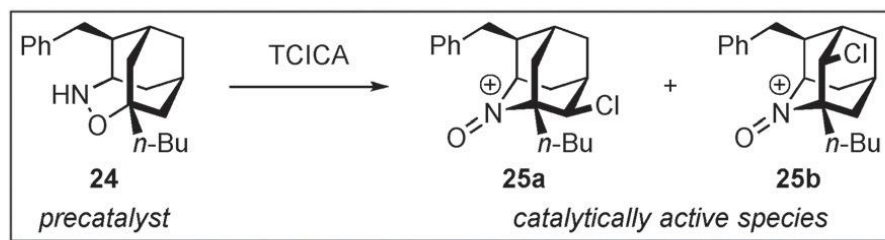
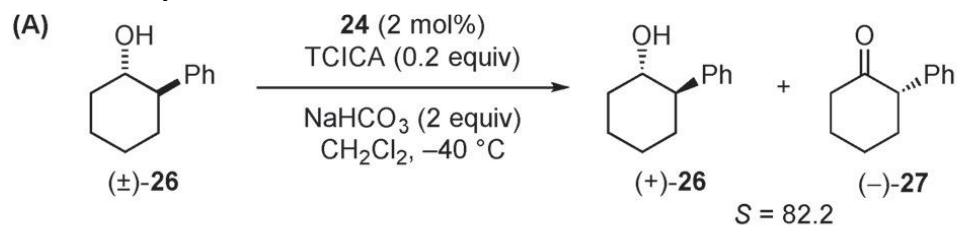
with **18d•I** ( $R^1 = \text{Boc}$ ,  $R^2 = \text{Et}$ ): 42% ee



**18e•I** ( $R^1 = \text{Ts}$ ,  $R^2 = \text{Me}$ ):

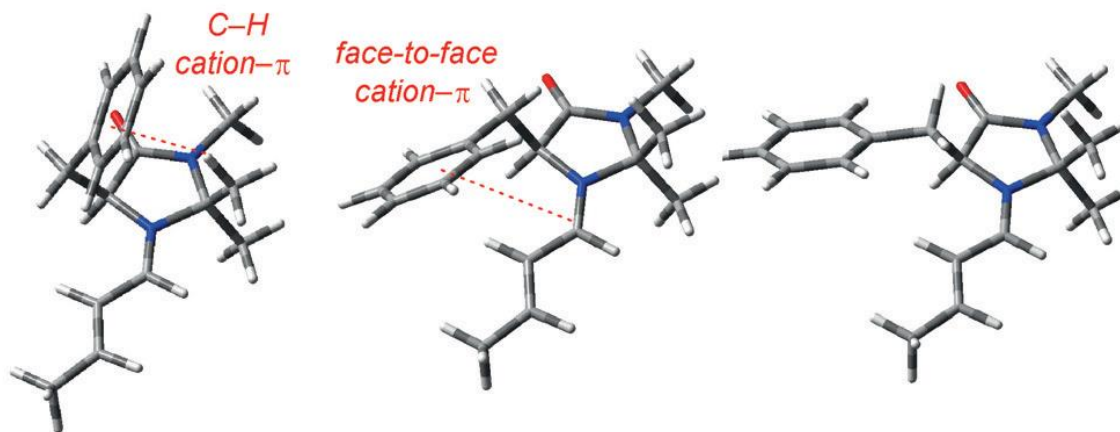
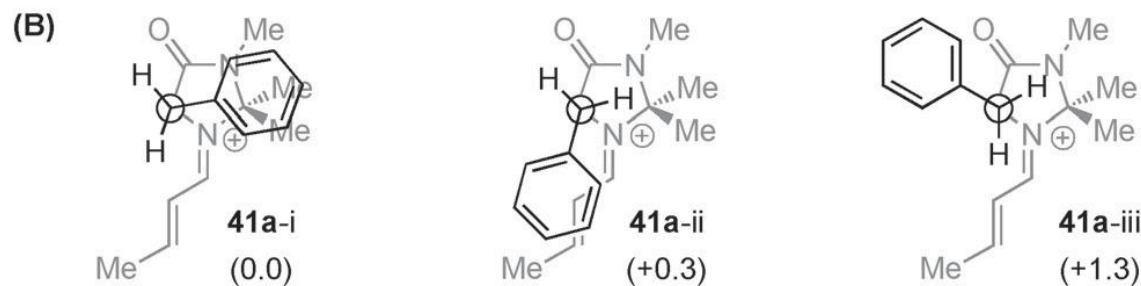
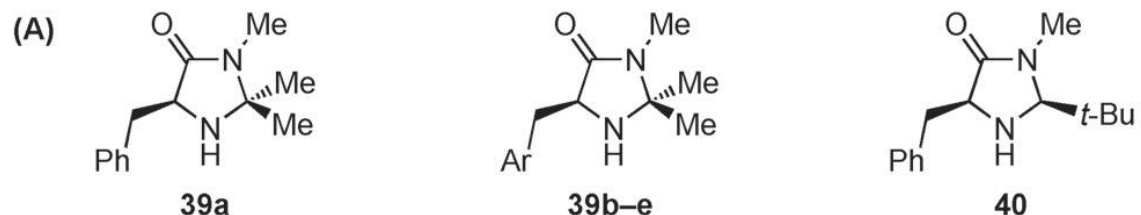
# Catalyst–Catalyst Cation– $\pi$ Interactions

## Oxoammonium Ion Catalysts for Alcohol Oxidations



# Catalyst–Catalyst Cation– $\pi$ Interactions

## Secondary Amine Catalysts for the Activation of Enals



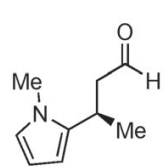
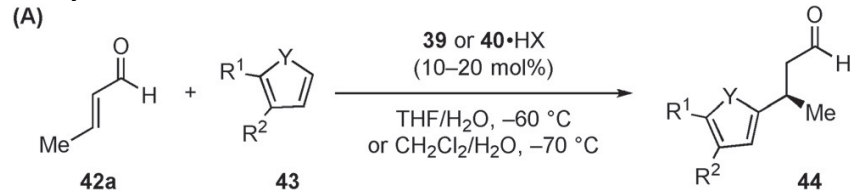
J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172.

R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543.

Y. Mori, S. Yamada, *Molecules* **2012**, *17*, 2161

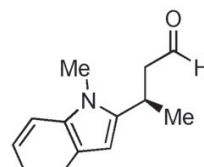
# Catalyst–Catalyst Cation– $\pi$ Interactions

## Secondary Amine Catalysts for the Activation of Enals



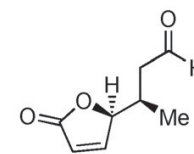
**44a**

with **39a**•TFA:  
83% yield, 91% ee



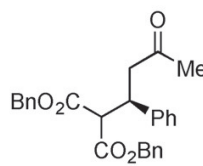
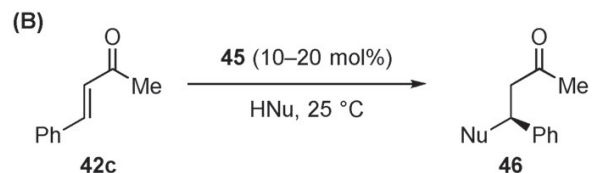
**44b**

with **39a**•TFA: 83% yield, 56% ee  
with **40**•TFA: 82% yield, 92% ee



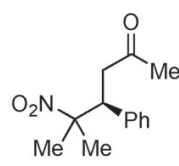
**44c**

with **40**•DNBA:  
87% yield, 90% ee



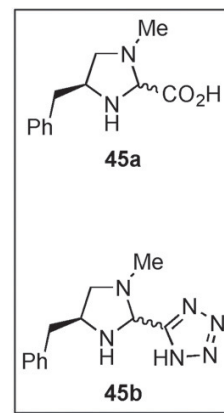
**46a**

with **45a**:  
93% yield, >99% ee



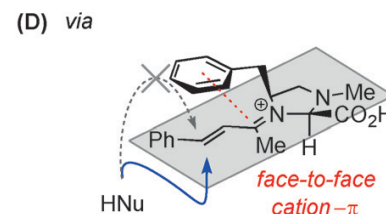
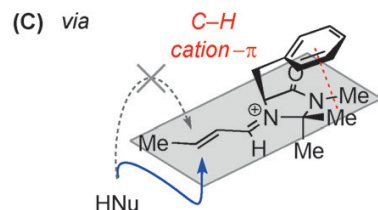
**46a**

with **45a**: 95% yield, 79% ee  
with **45b**: 97% yield, 87% ee



**45a**

**45b**

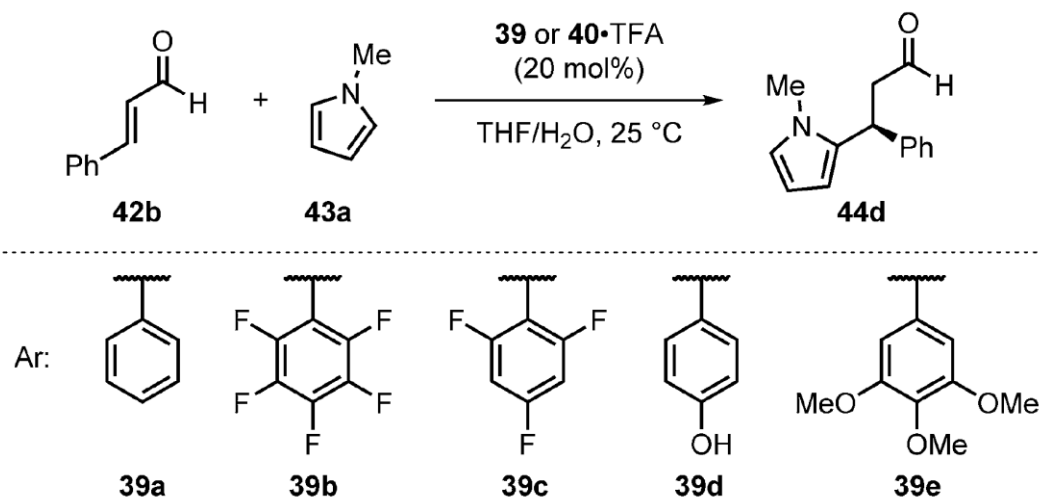


D. W. C. MacMillan, *Nature* **2008**, *455*, 304.



# Catalyst–Catalyst Cation– $\pi$ Interactions

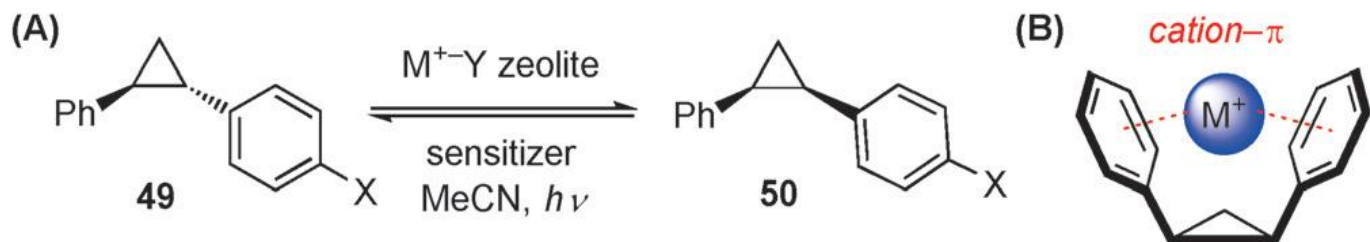
## Secondary Amine Catalysts for the Activation of Enals



Entry	Catalyst <sup>[a]</sup>	$Q_{ZZ}$	Iminium ion mole fraction			$ee^{[b]}$ [%]
			41 x-i	41 x-ii	41 x-iii	
1	39b	+3.01	0.37	0.16	0.47	65
2	39c	+0.28	0.39	0.21	0.40	70
3	39a	-3.46	0.75	0.03	0.23	84
4	39d	-3.71	0.76	0.04	0.20	90
5	39e	-5.68	0.65	0.17	0.18	94
6	40	-3.46	–	–	–	85

# Catalyst–Substrate Cation– $\pi$ Interactions

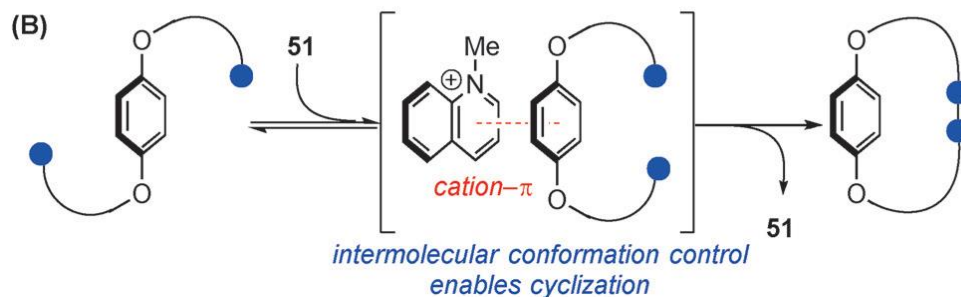
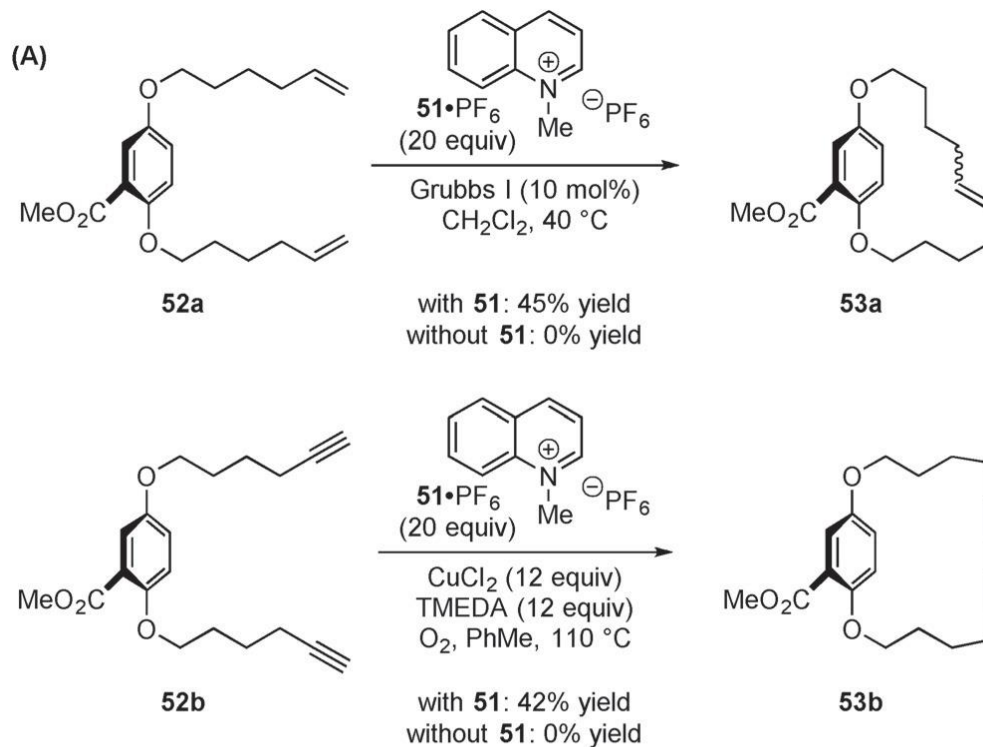
Alkali Metal Ion Controlled Diastereoselective Photoisomerization of Diphenylcyclopropane



Entry	Substrate <sup>[a]</sup>	X	M <sup>+</sup>	$E_{\text{int}}^{\text{[b]}}$ [kcal mol <sup>-1</sup> ]	49/50 <sup>[c]</sup>
1	49/50 a	H	–	n/a	44:55
2			Li <sup>+</sup>	–75.8	91:9
3			Na <sup>+</sup>	–53.9	92:8
4			K <sup>+</sup>	–32.6	88:12
5			Rb <sup>+</sup>	–28.2	85:15
6			Cs <sup>+</sup>	–22.7	65:35
7	49/50 b	OMe	Na <sup>+</sup>	–53.7	n.d.
8	49/50 c	CN	–	n/a	45:55
9			Na <sup>+</sup>	–43	44:46

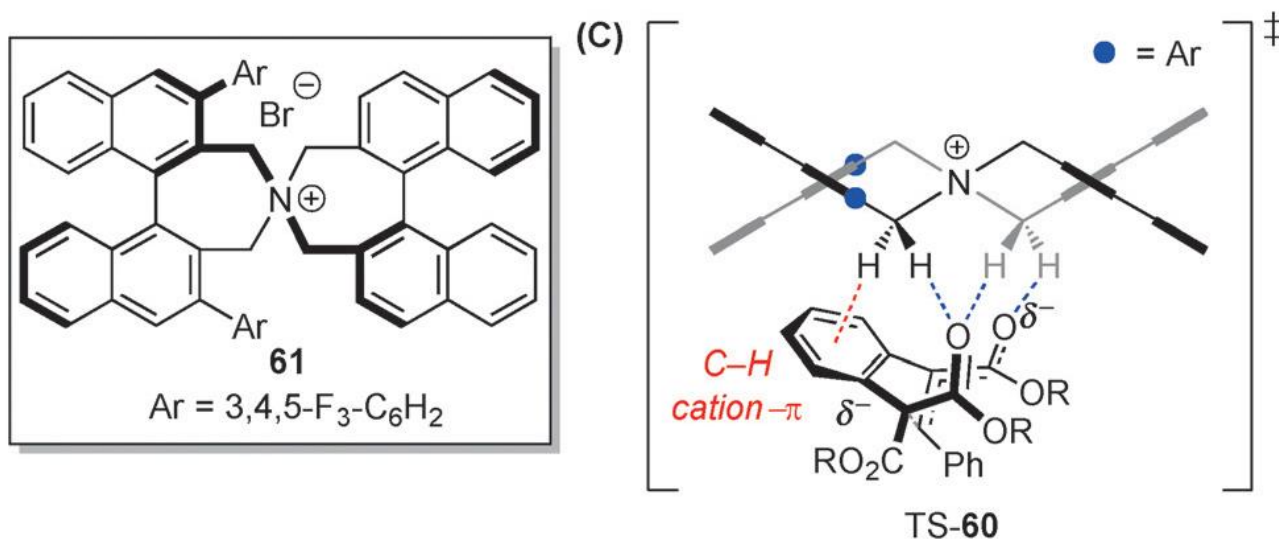
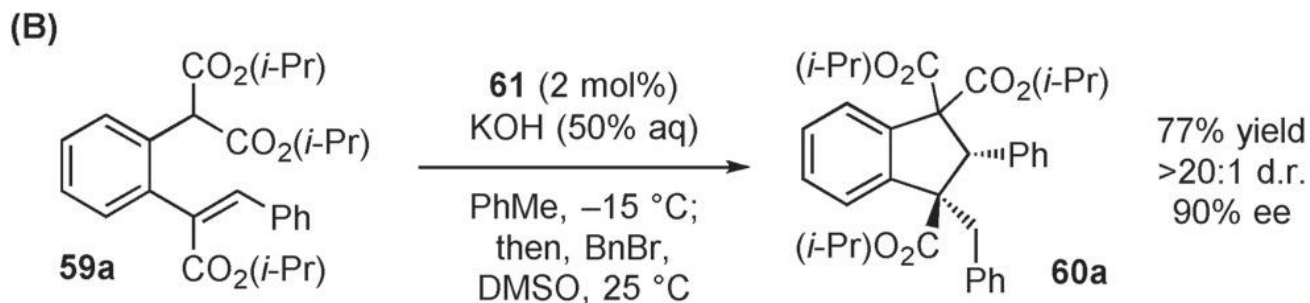
# Catalyst–Substrate Cation– $\pi$ Interactions

## Quinolinium Ion Promoted Macrocyclization Reactions



# Catalyst–Substrate Cation– $\pi$ Interactions

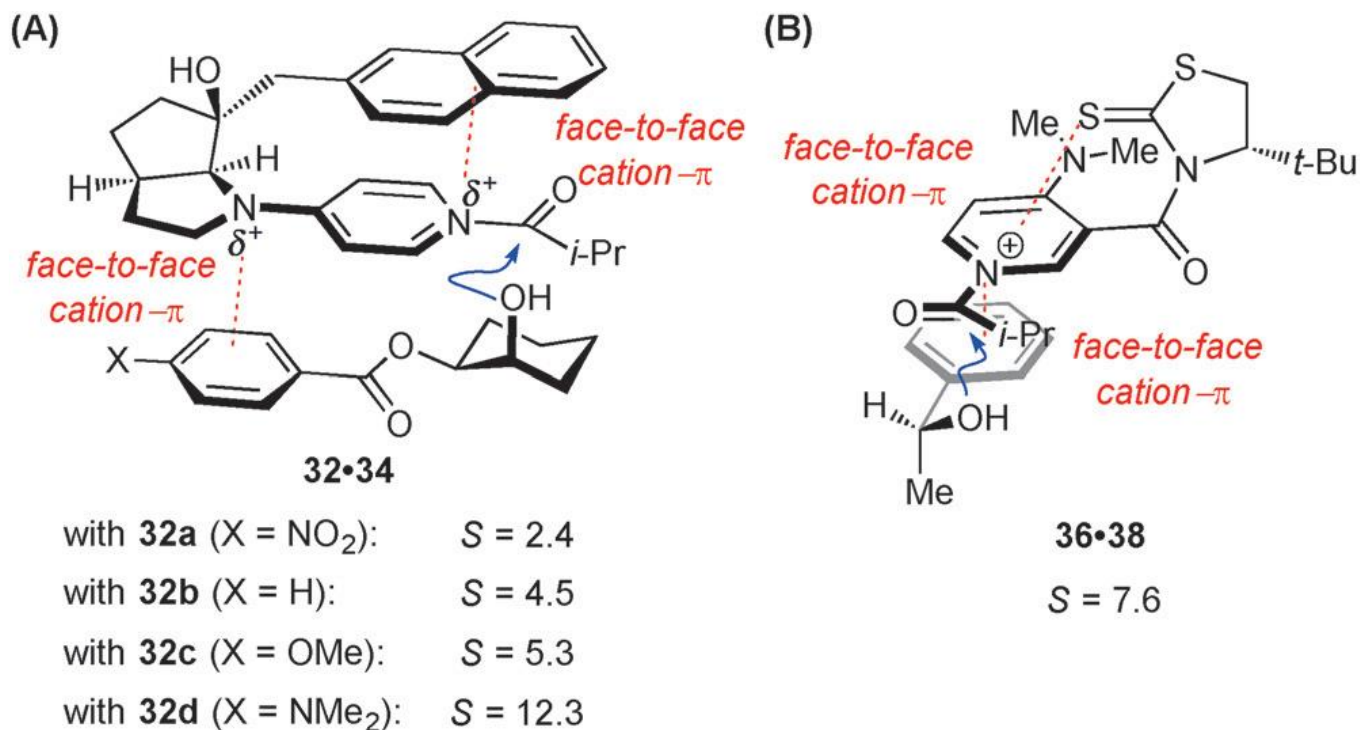
## Chiral Ammonium Ion Catalyzed 5-endo-trig Cyclizations



C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton, M. D. Smith, *Nat. Chem.* **2015**, *7*, 171.

# Catalyst–Substrate Cation– $\pi$ Interactions

## Heterocycle-Catalyzed Acyl Transfer Reactions



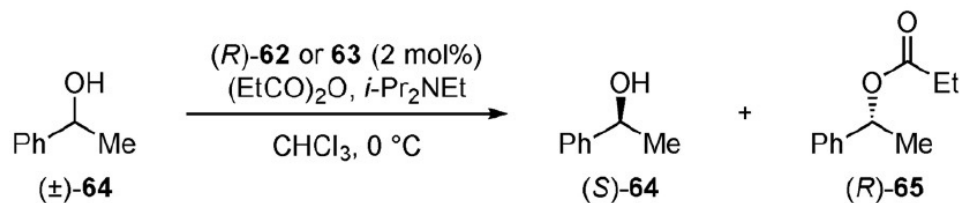
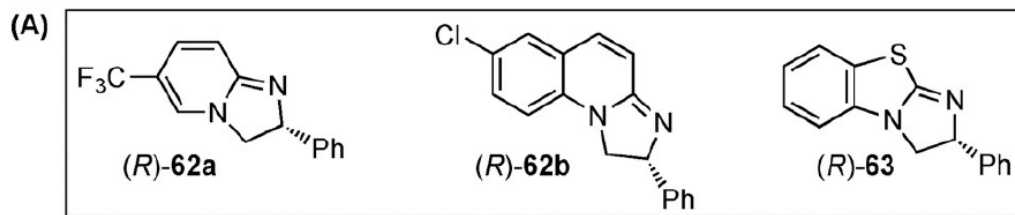
T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169.

S. Yamada, T. Misono, Y. Iwai, *Tetrahedron Lett.* **2005**, *46*, 2239.

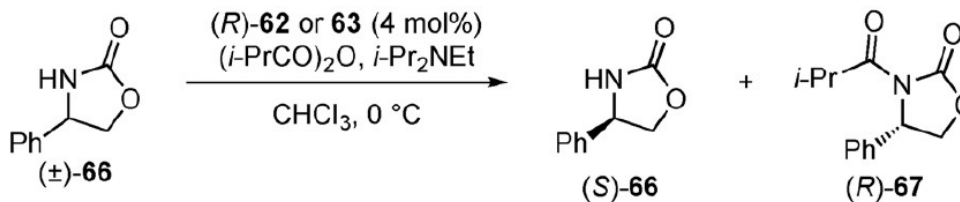
S. Yamada, T. Misono, Y. Iwai, A. Masumizu, Y. Akiyama, *J. Org. Chem.* **2006**, *71*, 6872–6880.

# Catalyst–Substrate Cation– $\pi$ Interactions

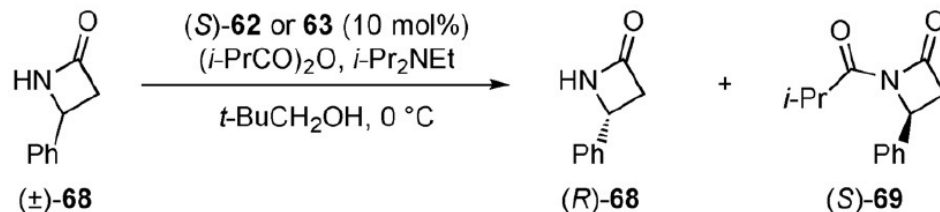
## Heterocycle-Catalyzed Acyl Transfer Reactions



with **62a**:  $S = 26$   
with **62b**:  $S = 33$   
with **63**:  $S = 80$



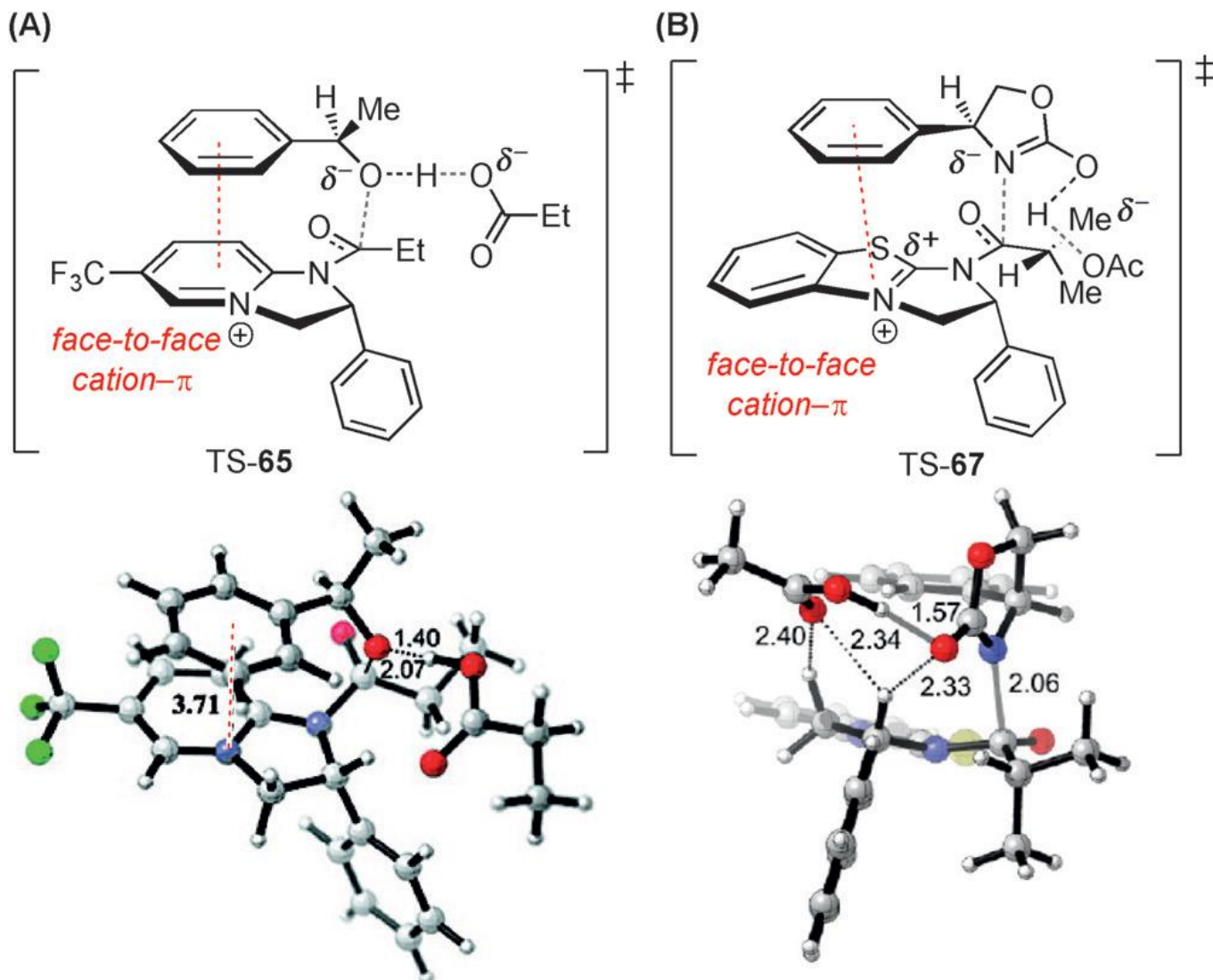
with **62b**:  $S = 17$   
with **63**:  $S = 200$



with **62b**:  $S = 17$   
with **63**: no reaction

# Catalyst–Substrate Cation– $\pi$ Interactions

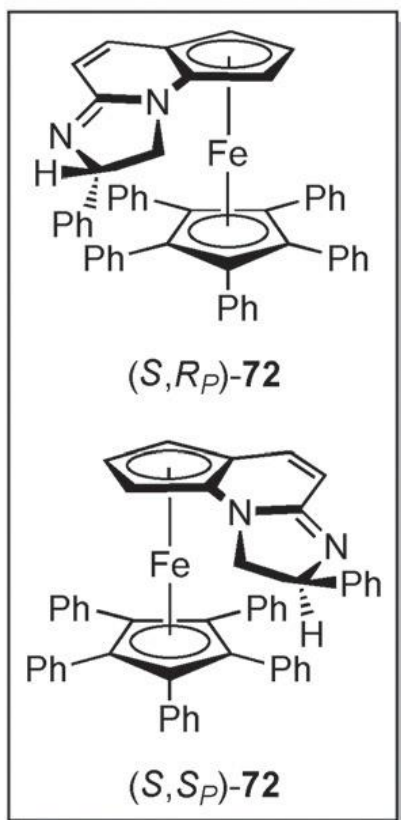
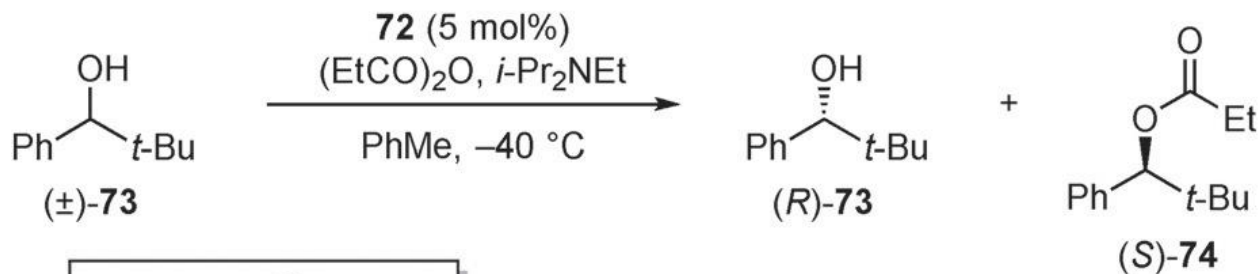
## Heterocycle-Catalyzed Acyl Transfer Reactions



X. Yang, V. D. Bumbu, P. Liu, X. Li, H. Jiang, E. W. Uffman, L. Guo, W. Zhang, X. Jiang, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2012**, *134*, 17605.

# Catalyst–Substrate Cation– $\pi$ Interactions

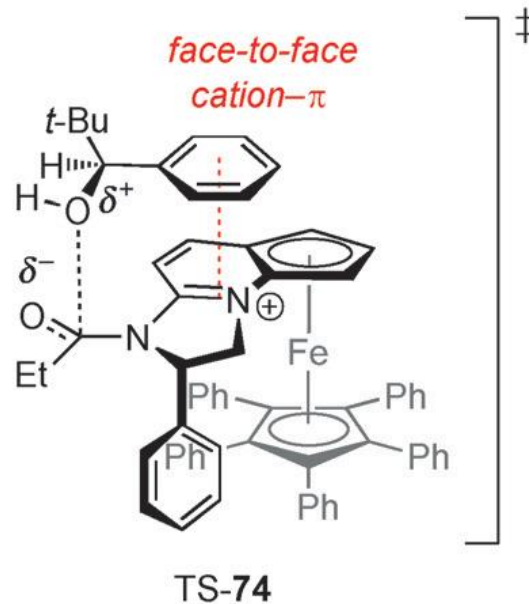
## Heterocycle-Catalyzed Acyl Transfer Reactions



with (S,R<sub>p</sub>)-72: *S* = 1892

with (S,S<sub>p</sub>)-72: no reaction

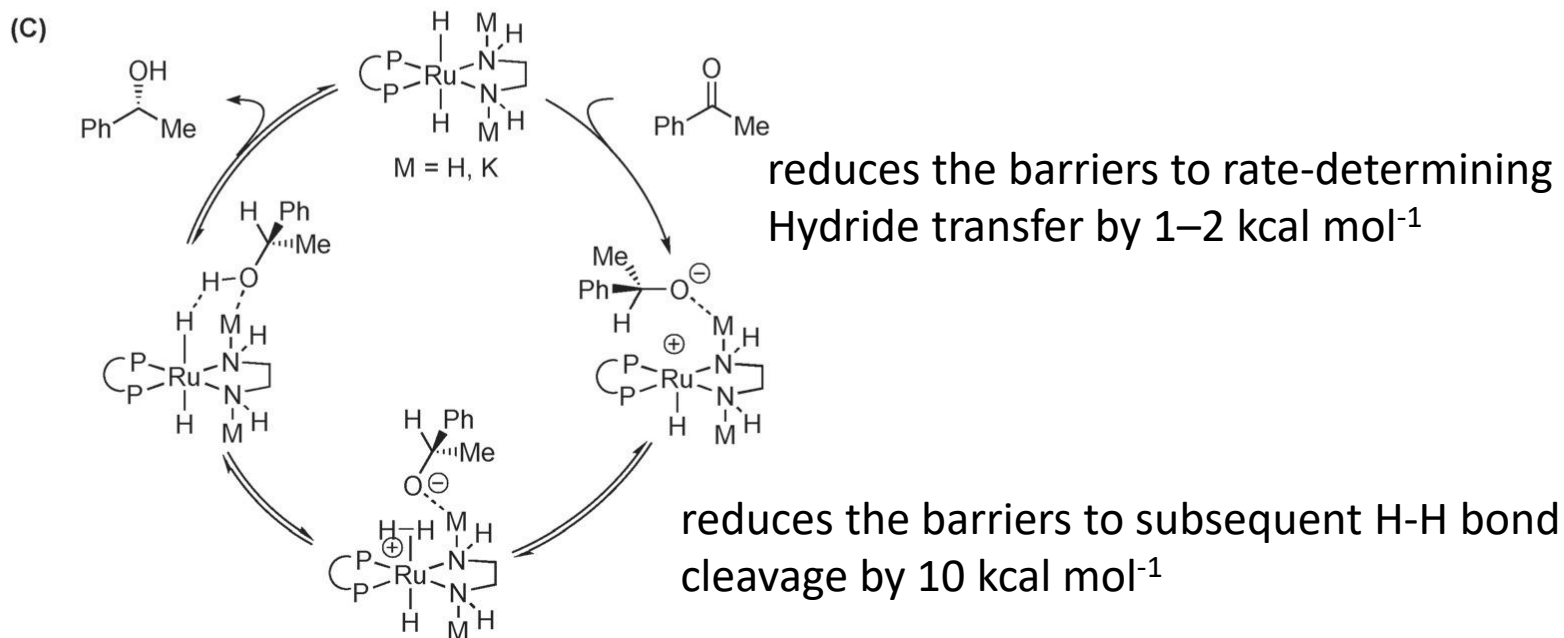
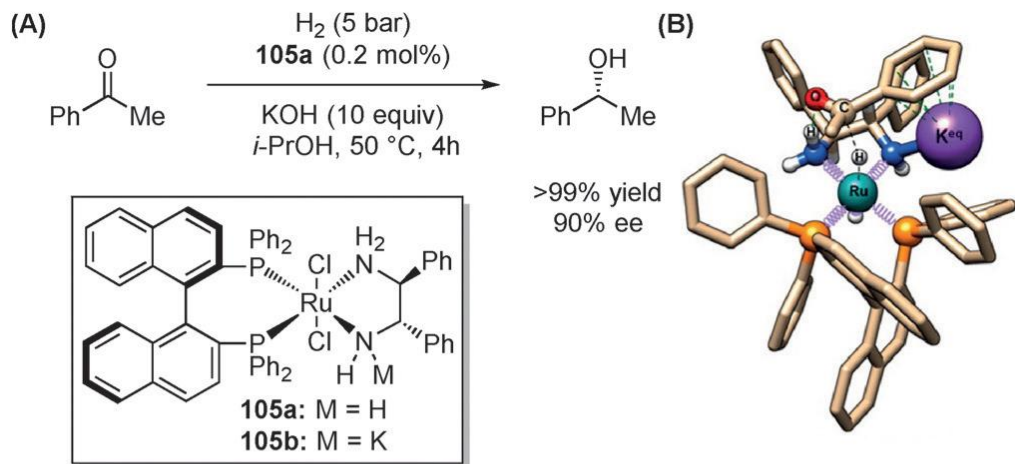
via:





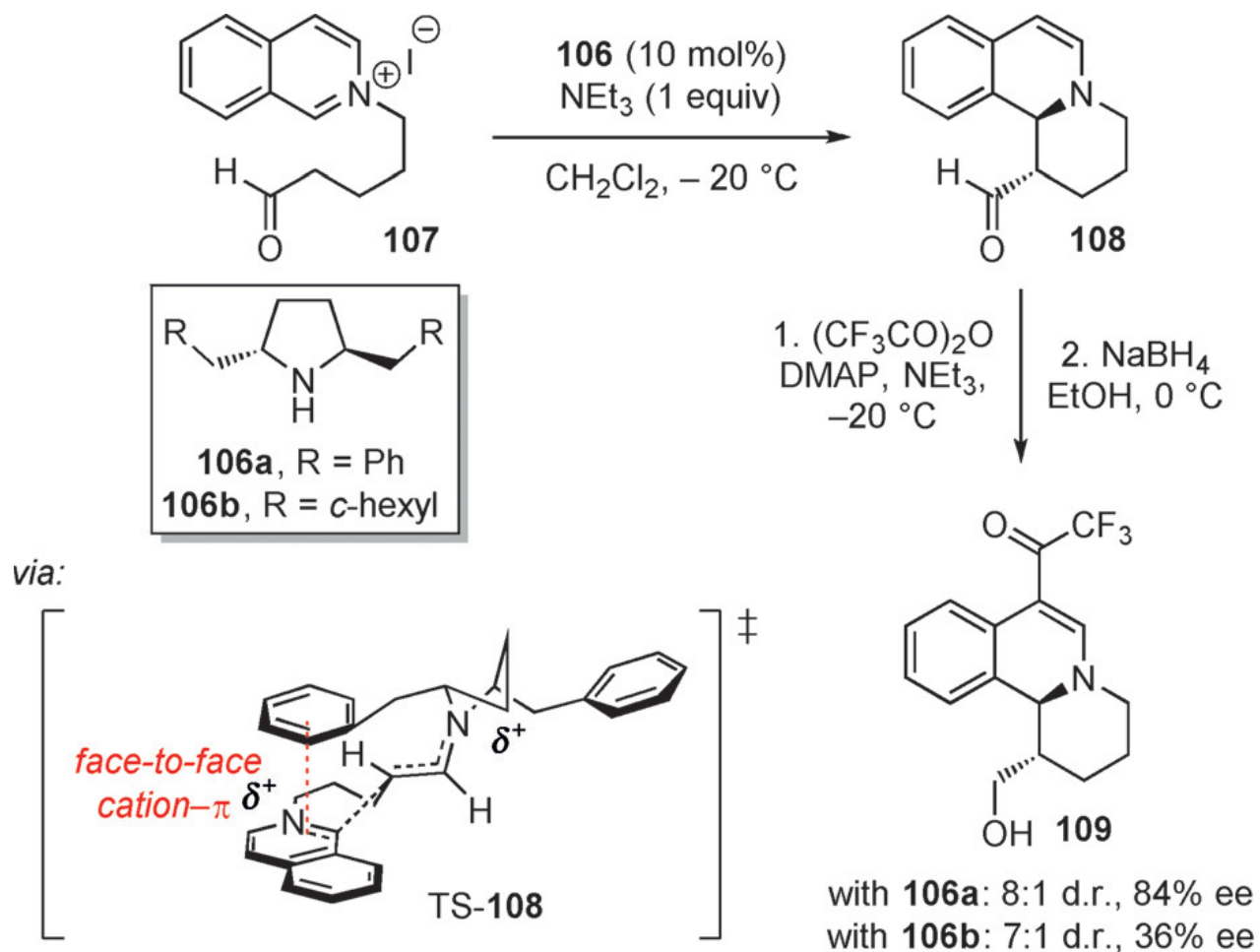
# Catalyst–Substrate Cation– $\pi$ Interactions

## Alkali Metal Cation Assisted Ruthenium-Catalyzed Asymmetric Hydrogenation Reactions



# Catalyst–Substrate Cation– $\pi$ Interactions

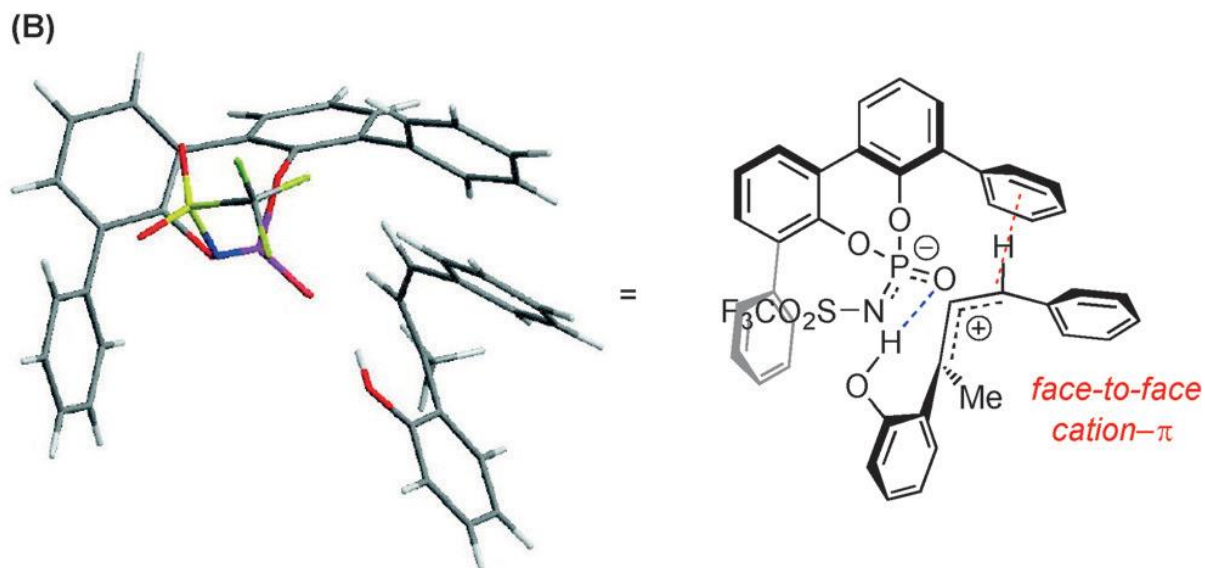
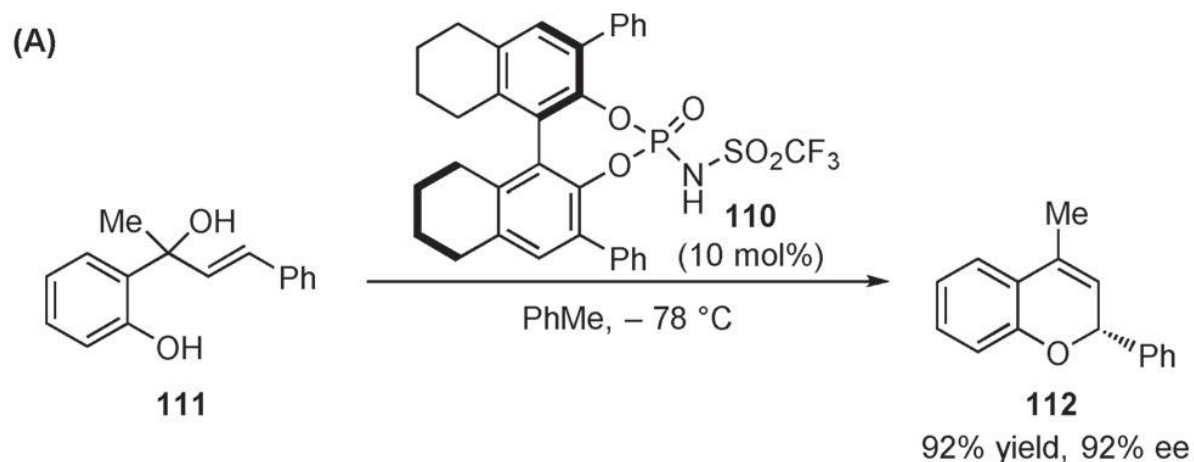
## Pyrrolidine-Catalyzed Mannich Annulation Reactions



K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6058.

# Catalyst–Substrate Cation– $\pi$ Interactions

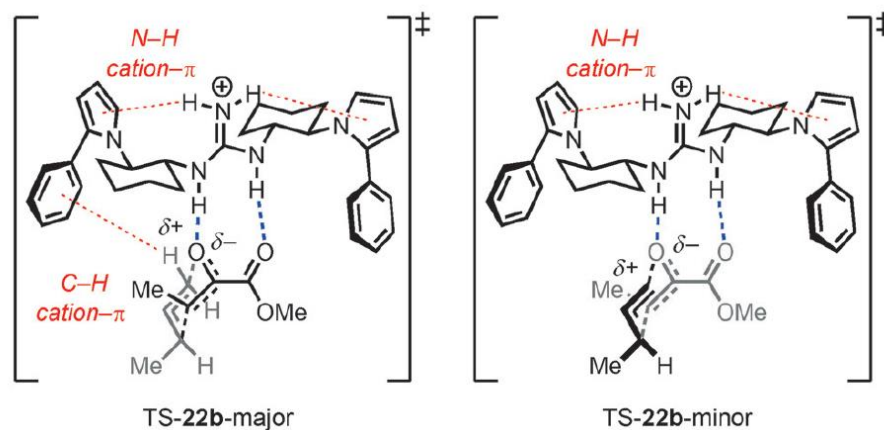
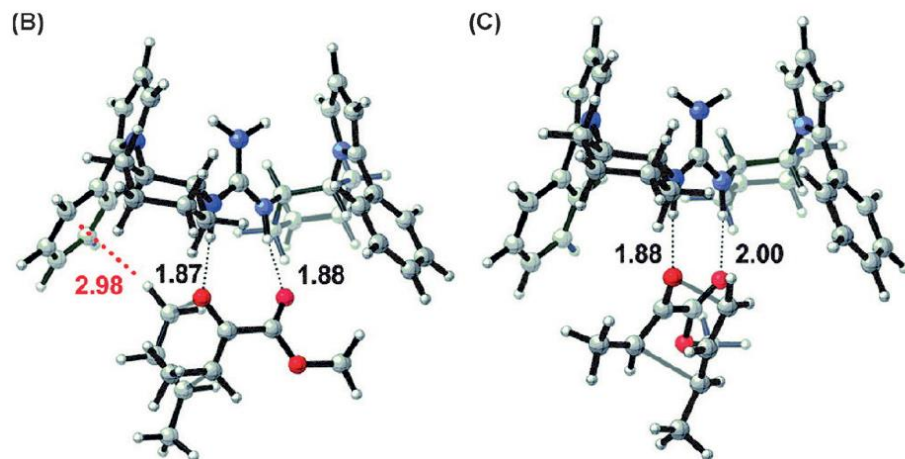
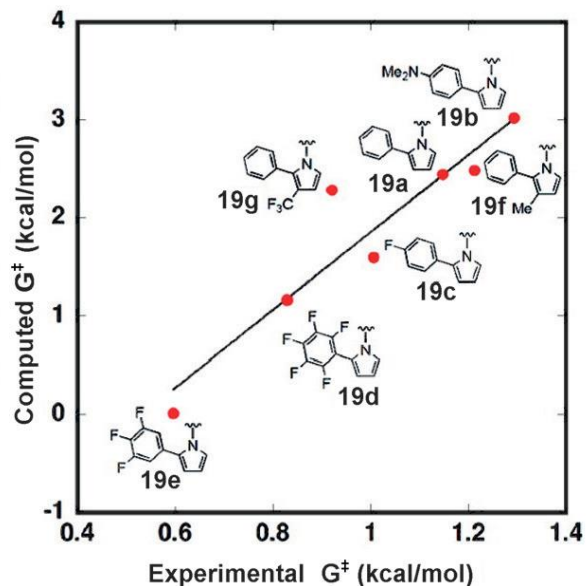
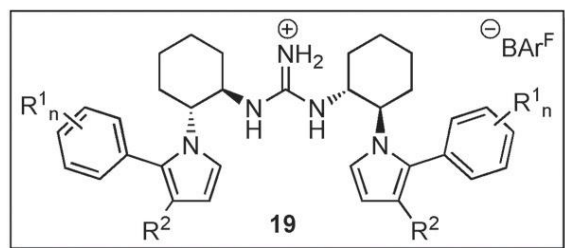
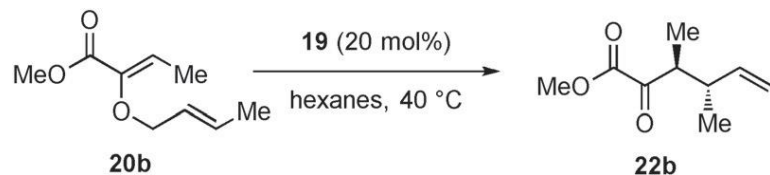
## Phosphoramidate-Catalyzed Allylic Etherifications



M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732.

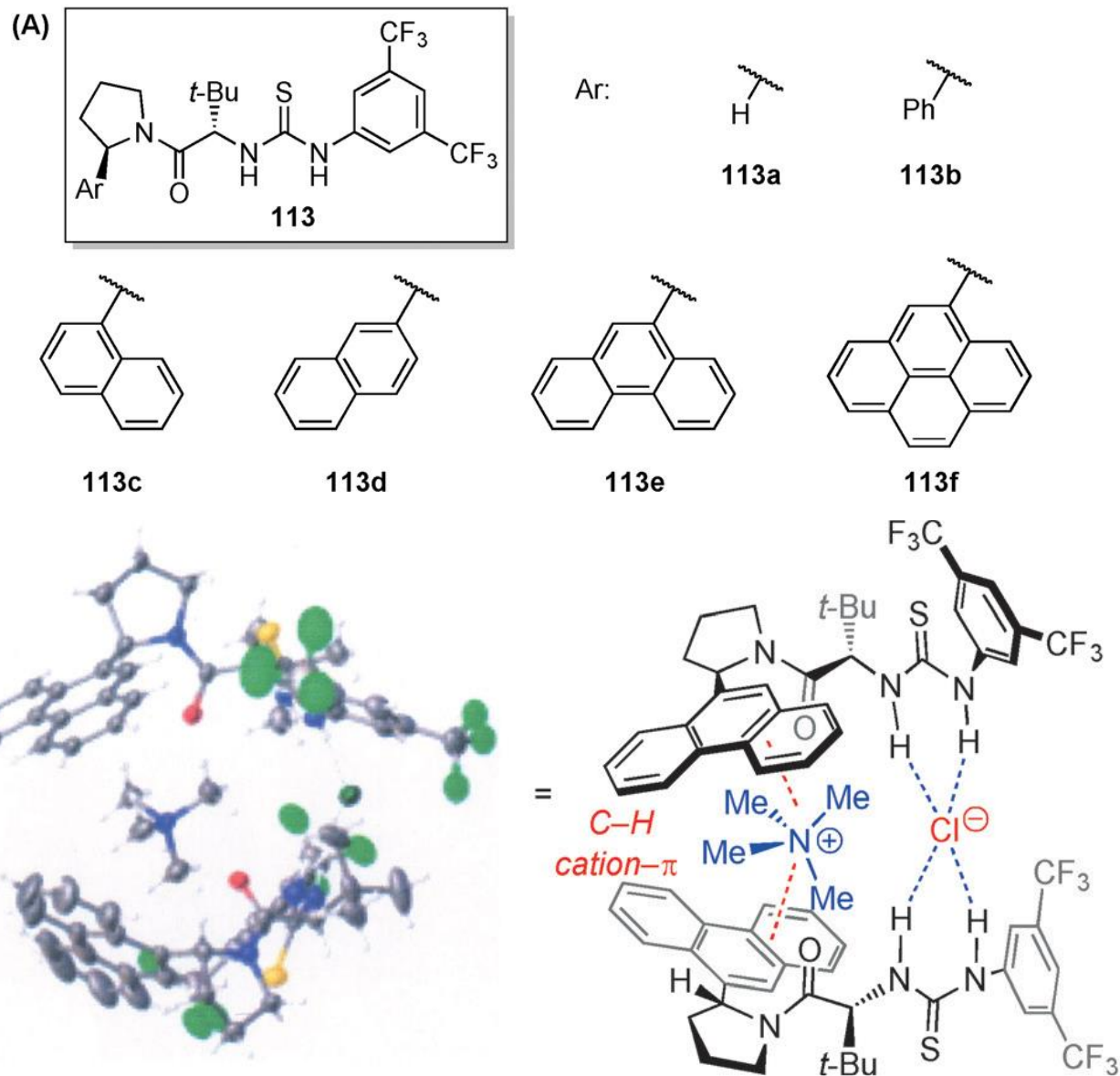
# Catalyst–Substrate Cation– $\pi$ Interactions

## Guanidinium Ion Catalyzed Claisen Rearrangements



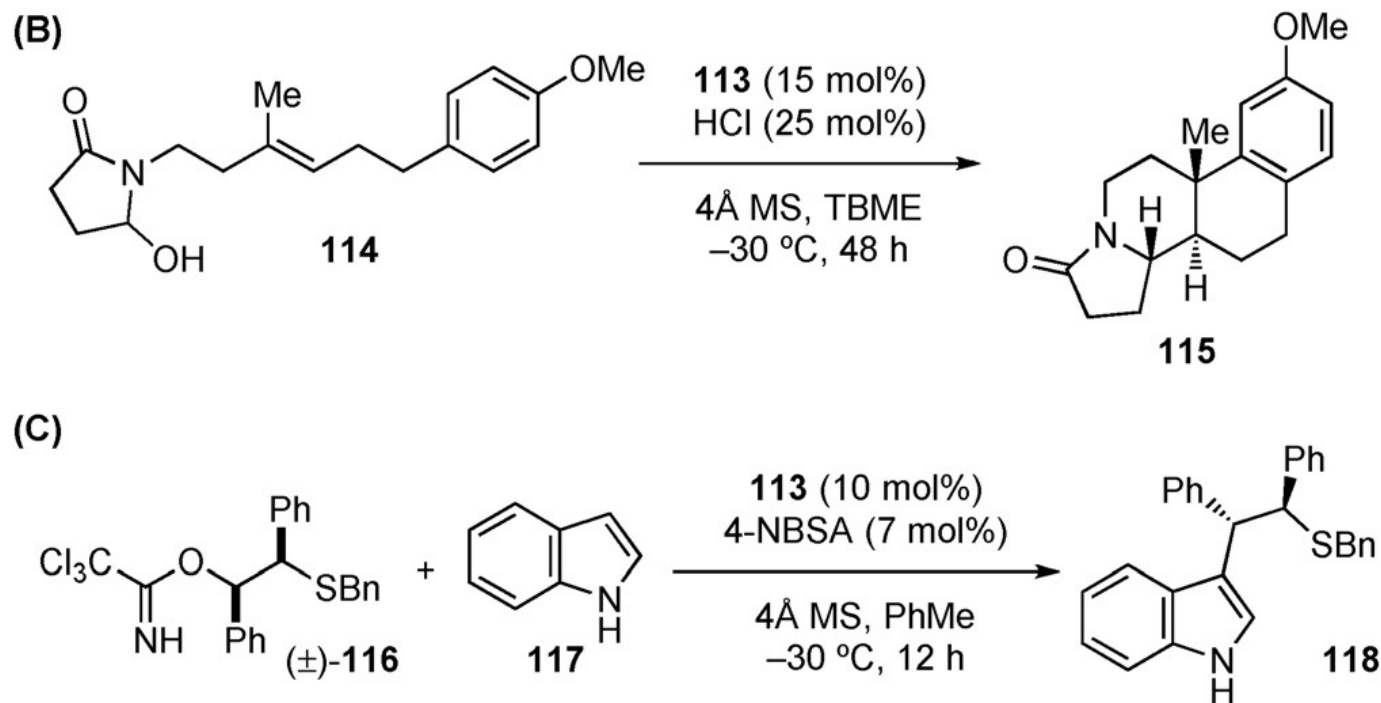
# Catalyst–Substrate Cation– $\pi$ Interactions

Reactions Catalyzed by Chiral Arylpyrrolidino Thioureas



# Catalyst–Substrate Cation– $\pi$ Interactions

Reactions Catalyzed by Chiral Arylpyrrolidino Thioureas

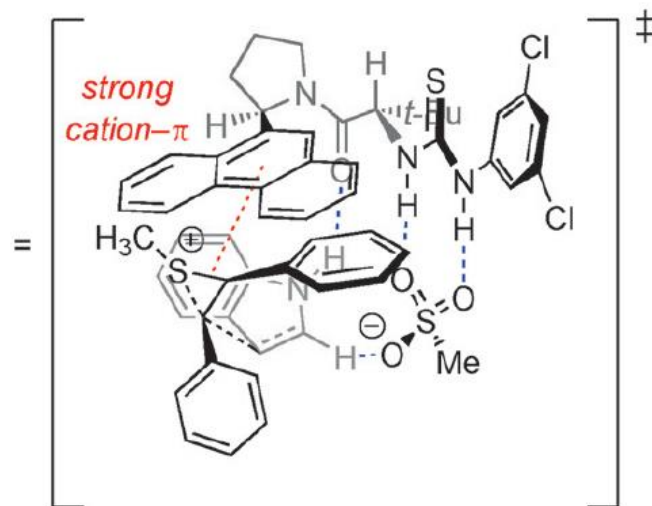
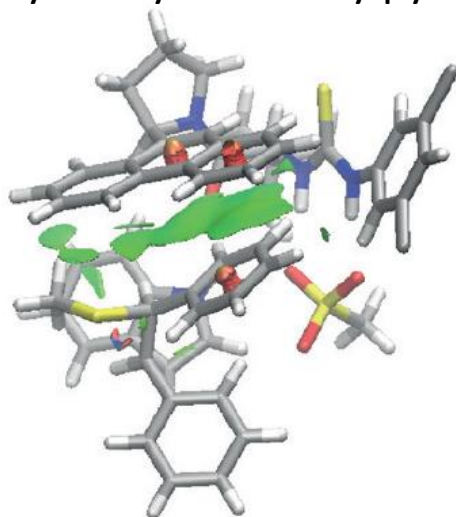


Entry	Product	Yield [%] ( <i>ee</i> [%]) with					
		<b>113 a</b>	<b>113 b</b>	<b>113 c</b>	<b>113 d</b>	<b>113 e</b>	<b>113 f</b>
1	<b>115</b>	n.d.	12 (25)	46 (60)	33 (61)	52 (87)	78 (95)
2	<b>118</b>	15 (12)	72 (73)	84 (84)	80 (85)	93 (93)	91 (91)

# Catalyst–Substrate Cation– $\pi$ Interactions

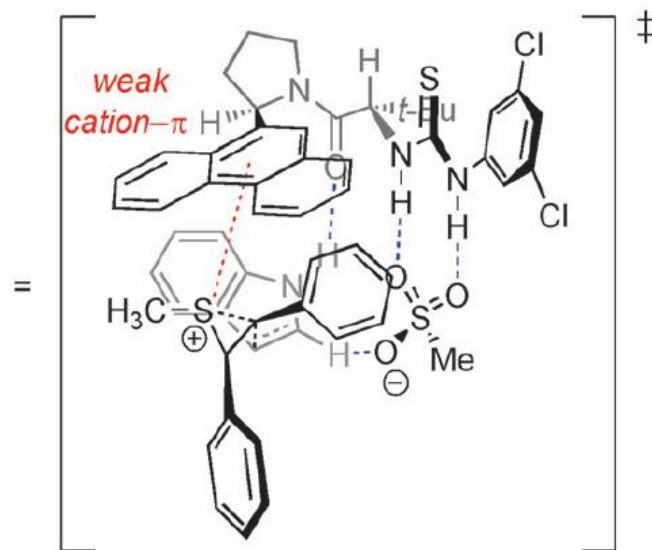
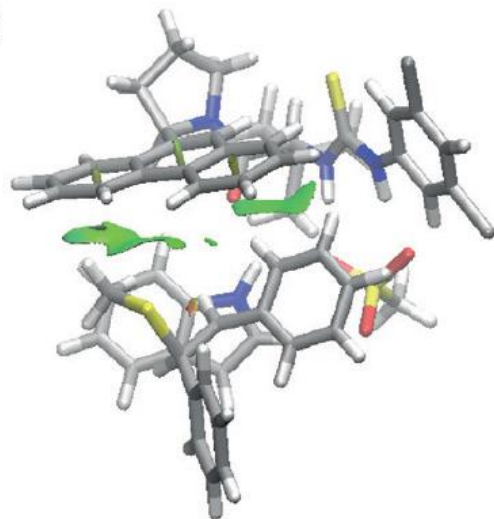
Reactions Catalyzed by Chiral Arylpyrrolidino Thioureas

(C)



TS-118-major

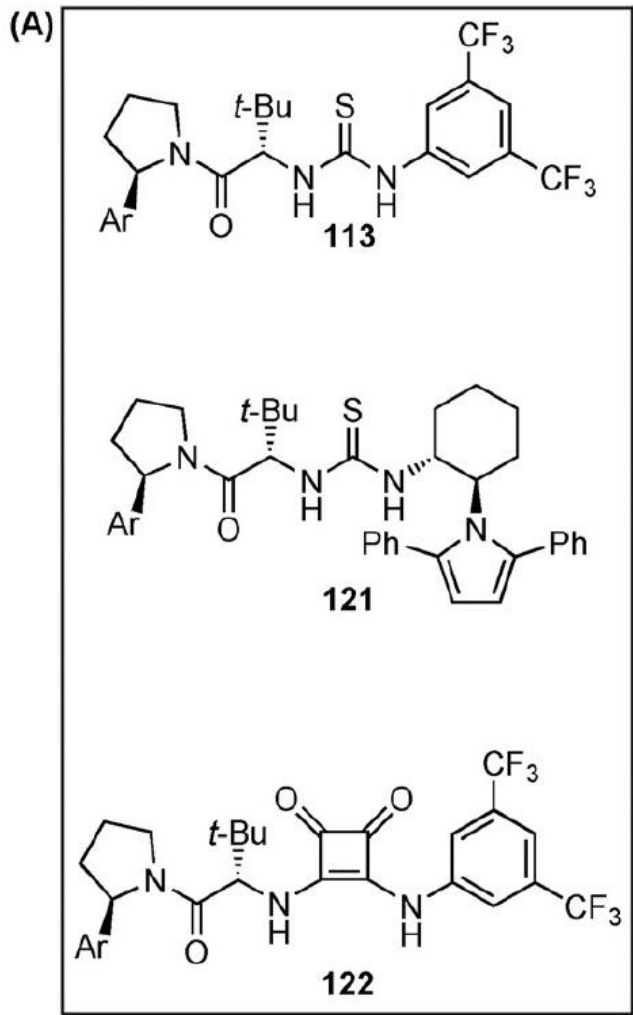
(D)



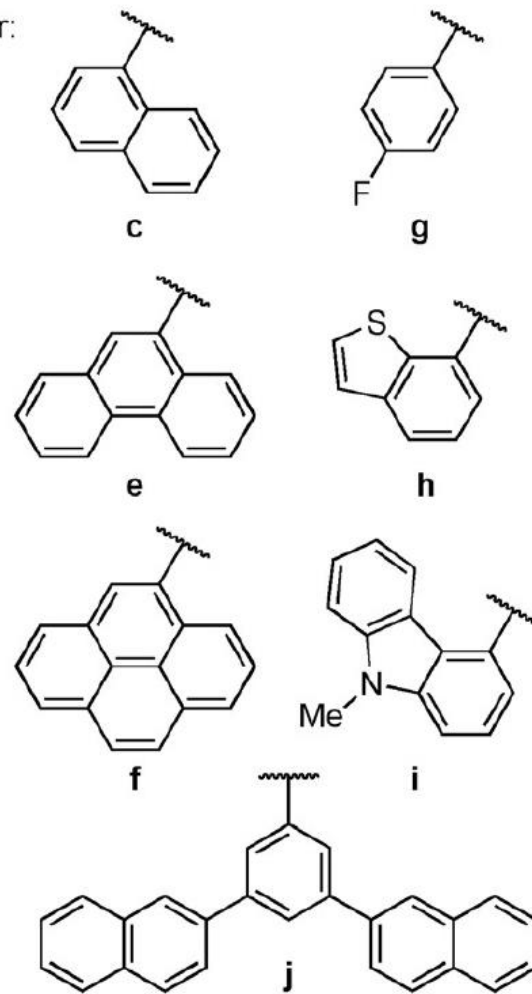
TS-118-minor

# Catalyst–Substrate Cation– $\pi$ Interactions

Reactions Catalyzed by Chiral Arylpyrrolidino Thioureas



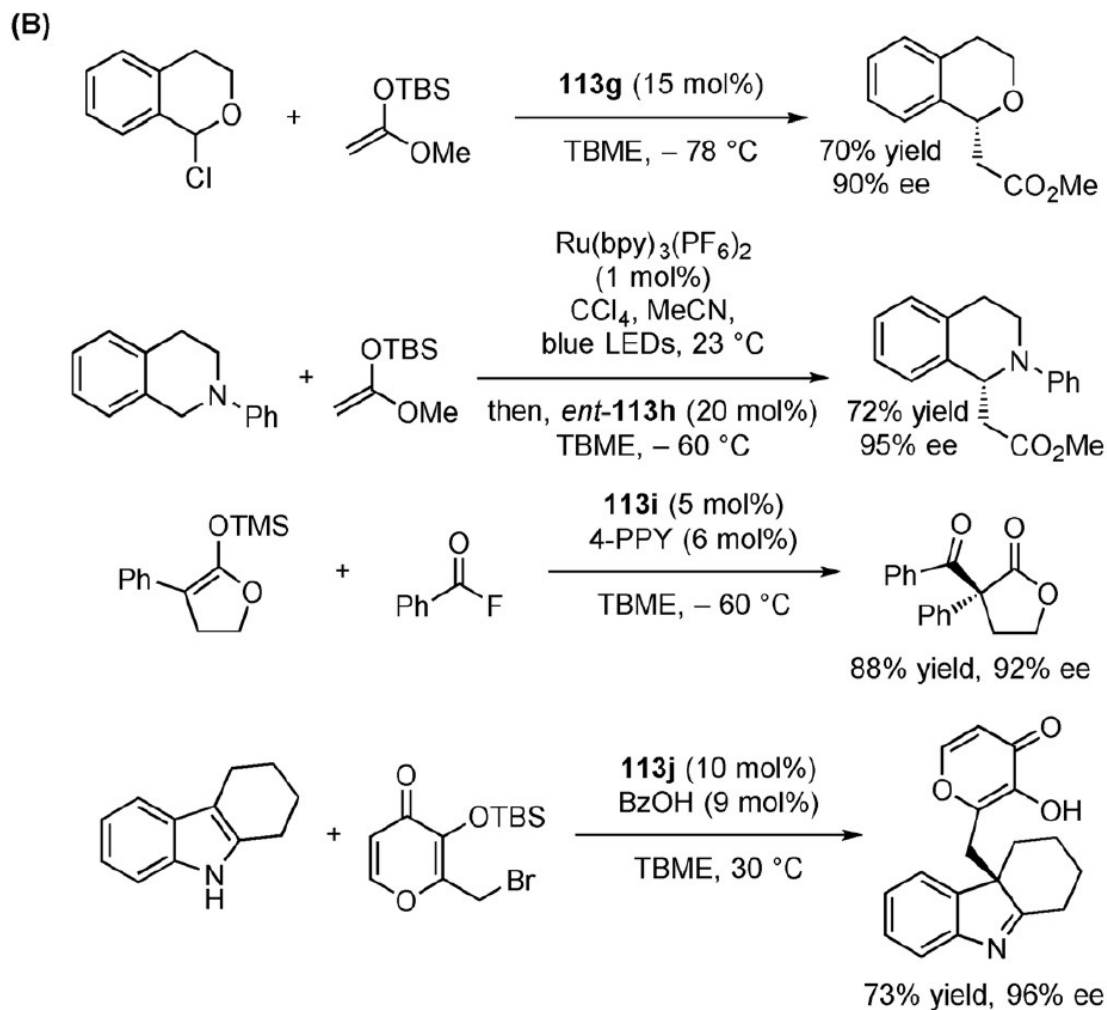
Ar:





# Catalyst–Substrate Cation– $\pi$ Interactions

## Reactions Catalyzed by Chiral Arylpyrrolidino Thioureas



G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson, *Chem. Sci.* **2014**, *5*, 112.

J. A. Birrell, J.-N. Desrosiers, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 13872.

C. S. Yeung, R. E. Ziegler, J. A. Porco, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, *136*, 13614.

A. R. Brown, C. Uyeda, C. A. Brotherton, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 6747.

## Summary and Outlook

Recent efforts have sought to incorporate these attractive cation– $\pi$  interactions into functional catalyst systems in order to influence the rate and selectivity of chemical reactions through the binding of reaction intermediates and the differential stabilization of transition structures.

Research in this field is just beginning to flourish, and its scope will undoubtedly continue to expand with the identification of new modes of reactivity, the design of novel catalyst structures, and the refinement of our current understanding of these noncovalent interactions.