# Anion-π Catalysis


**2016/5/7**
**D1 Hiroyuki Mutoh**

# Contents

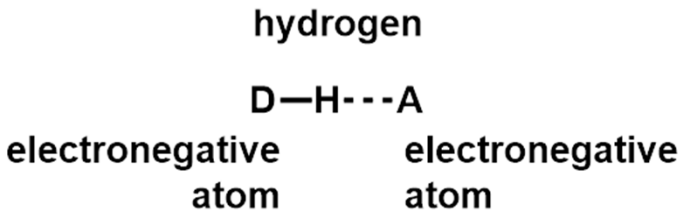
# Non-covalent Interaction

• non-covalent interactions:

supramolecular chemistry, drug-receptor interaction, protein folding, etc.

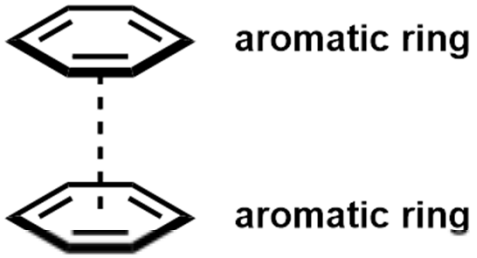
› hydrogen bond

protein secondary structure, water



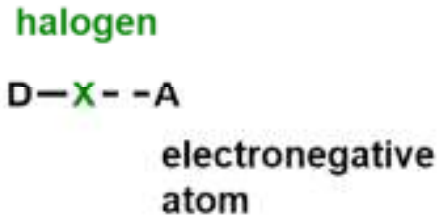

› π-π stacking

side chains of amino acids, DNA and RNA



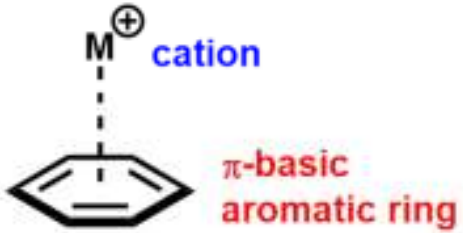

› halogen bond

thyroid hormone recognition

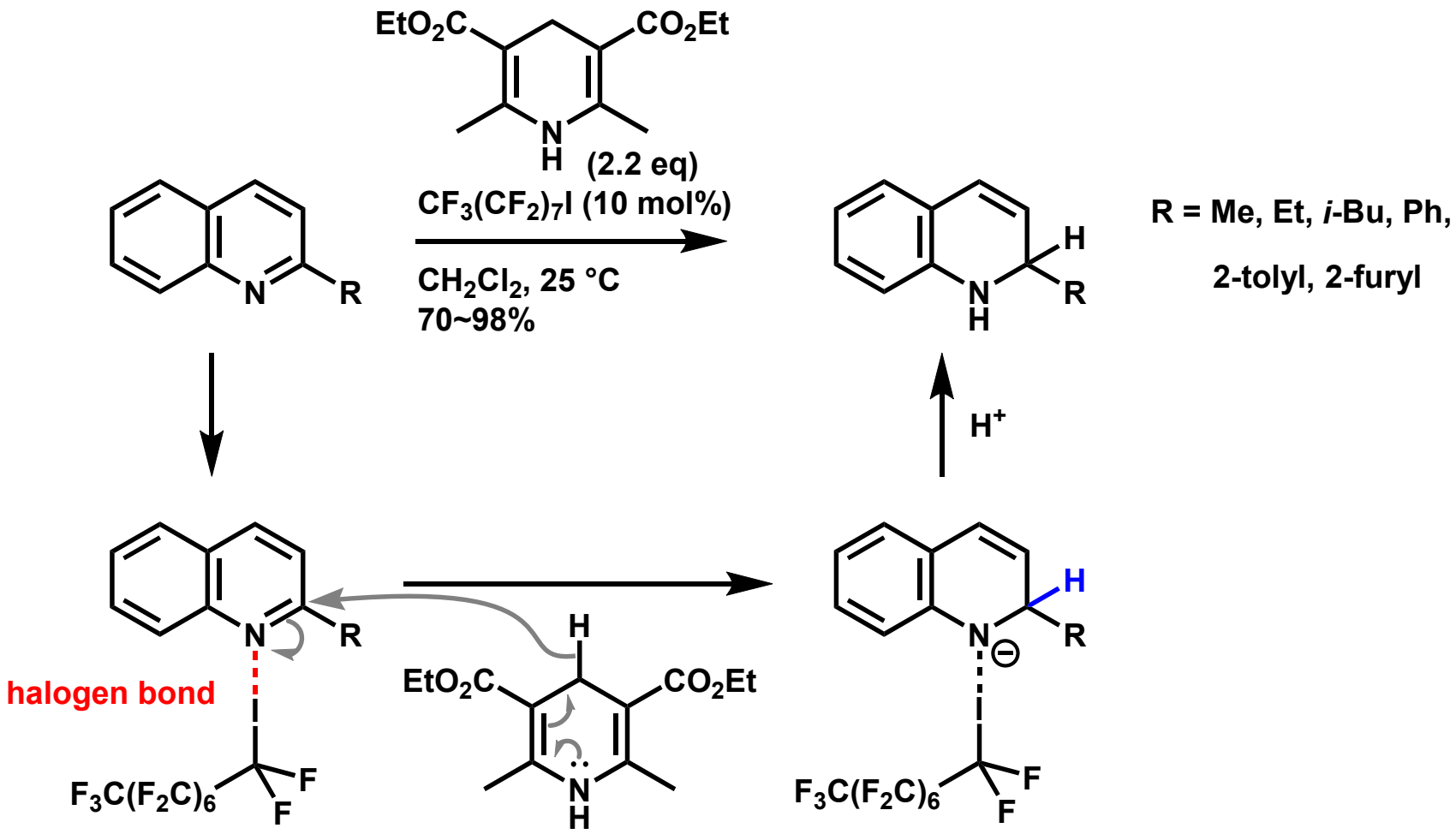



› cation-π interaction

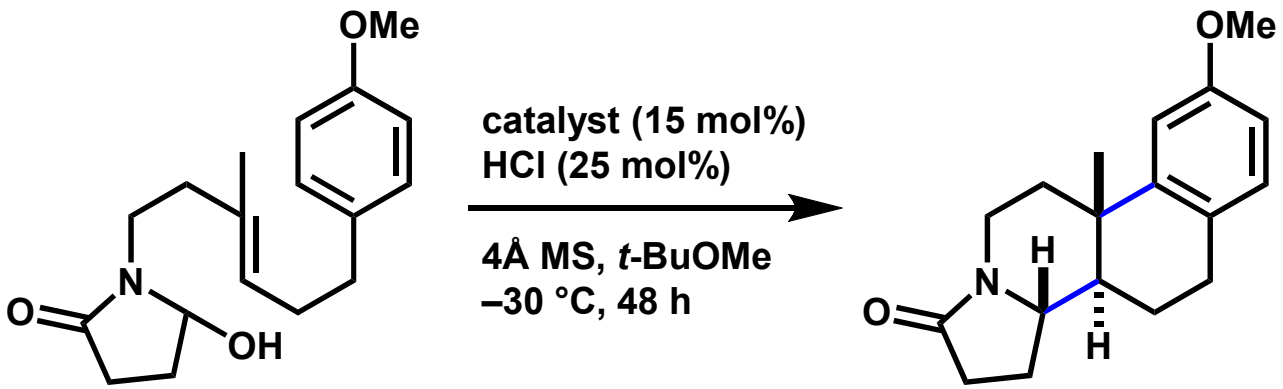
cation cyclization of steroidal compounds

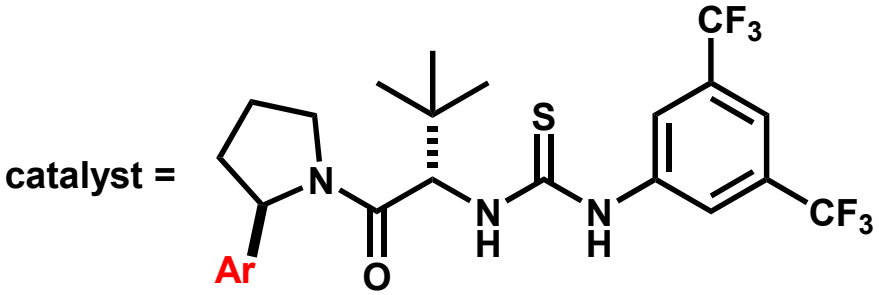


# Catalysis with Halogen Bonds

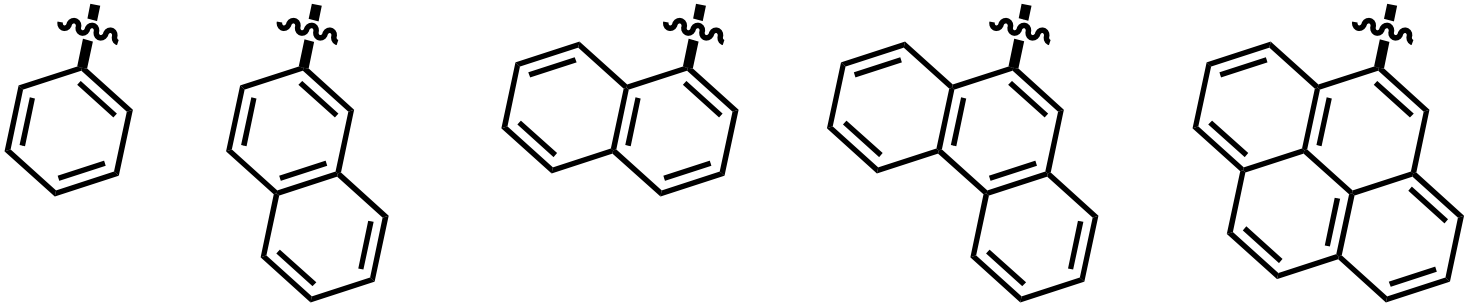


# Cation-π Catalysis




Ar =

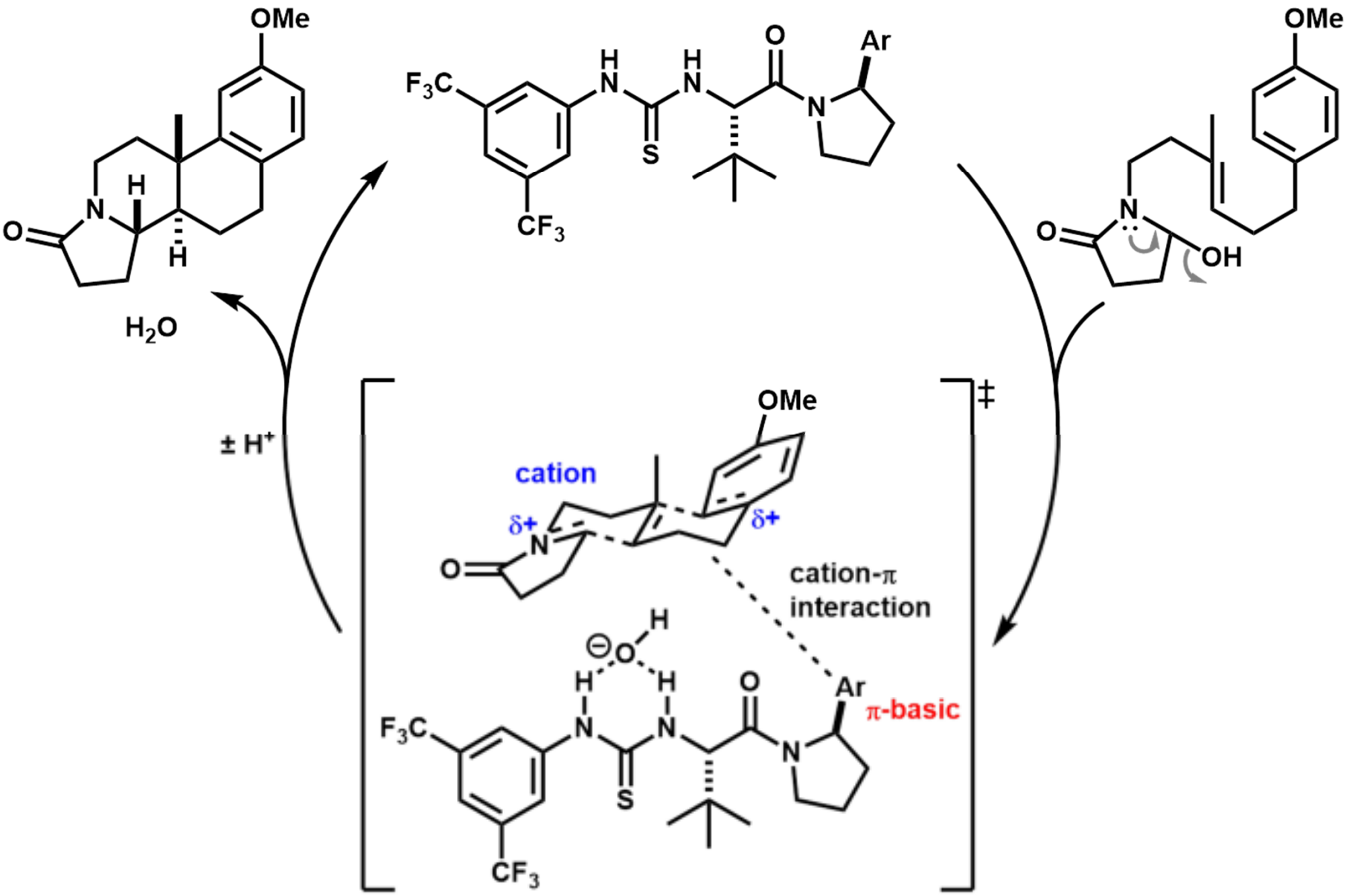


| 12% | 33% | 46% | 52% | 78% |
|---|---|---|---|---|
| 25% ee | 61% ee | 60% ee | 87% ee | 95% ee |



Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

# Proposed Mechanism of Cation-π Catalysis

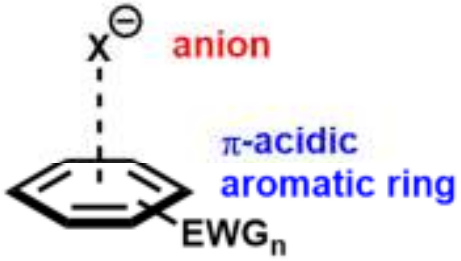



Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

# Contents

# Anion-π Interaction

• **Anion-π interaction:**




**non-covalent interaction between charge neutral π-acidic (electron defficient) aromatic rings and anions (20~70 kJ/mol)**

• **Theoretical studies of anion-π interaction:**

Mascal, M.; Armstrong, A.; Bartberger, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 6274.
Alkorta, I.; Rozas, I.; Elguero, J. *J. Am. Chem. Soc.* **2002**, *124*, 8593.
Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3389.

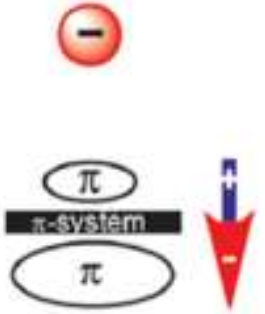
• **Main contributers to the anion-π interaction:**

› **permanent quadpole moment**

| $C_6F_6$ | $C_6H_6$ |
|---|---|
| $Q_{zz}$ = 9.50 B | –8.45 B |
| $\alpha_{\|\|}$ = 37.7 a.u. | 41.5 a.u. |

**Total charge and dipole moment are zero in neutral and symmetric arenes. Electrostatic term is explained by quadpole moment.**

› **anion-induced polarization**



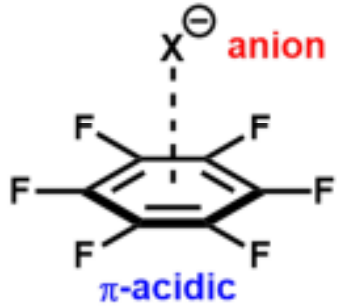



Frontera, A.; Gamez, P.; Mascal, M.; Mooibroek, T. J.; Reedijk, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 9564.

# Experimental Examples of Anion-π Interaction

- **First experimental observation of anion-π interaction:**

Hiraoka, K.; Mizuse, S.; Yamabe, S. *J. Phys. Chem.* **1987**, *91*, 5294.

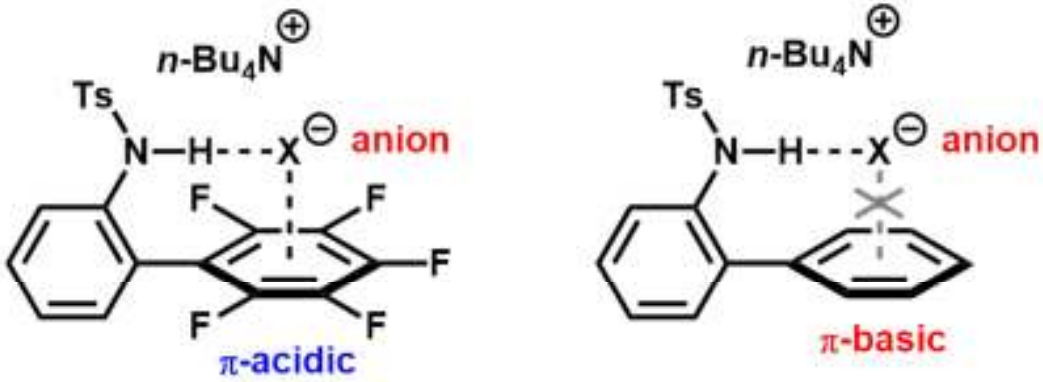



**The gas-phase clustering reactions were studied by the pulsed electron-beam high-pressure mass spectrometer and molecular orbital calculation.**

**$X^-$ = $Cl^-$, $Br^-$, $I^-$**

- **One of the evidence of anion-π interaction in solution:**

Berryman, O. B.; Hof, F.; Hynes, M. J. ; Johnson, D.W. *Chem. Commun.* **2006**, 506.




**$X^-$ = $Cl^-$, $Br^-$, $I^-$**

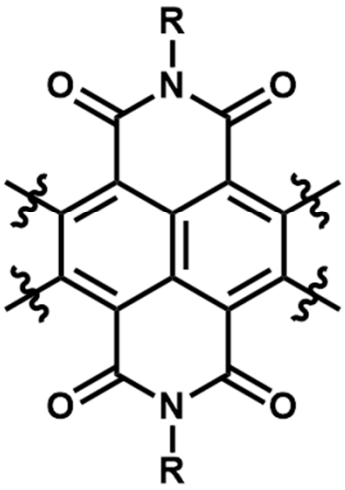
**$pK_a$ = 20 ~ 34 [$M^{-1}$ ]**

**$pK_a$ < 1 [$M^{-1}$ ]**

**$^1$H NMR spectroscopic titration experiments in $CDCl_3$**

# Naphthalene Diimide (1)

- Naphthalene Diimide (NDI)



› electron-defficient aromatic scaffold

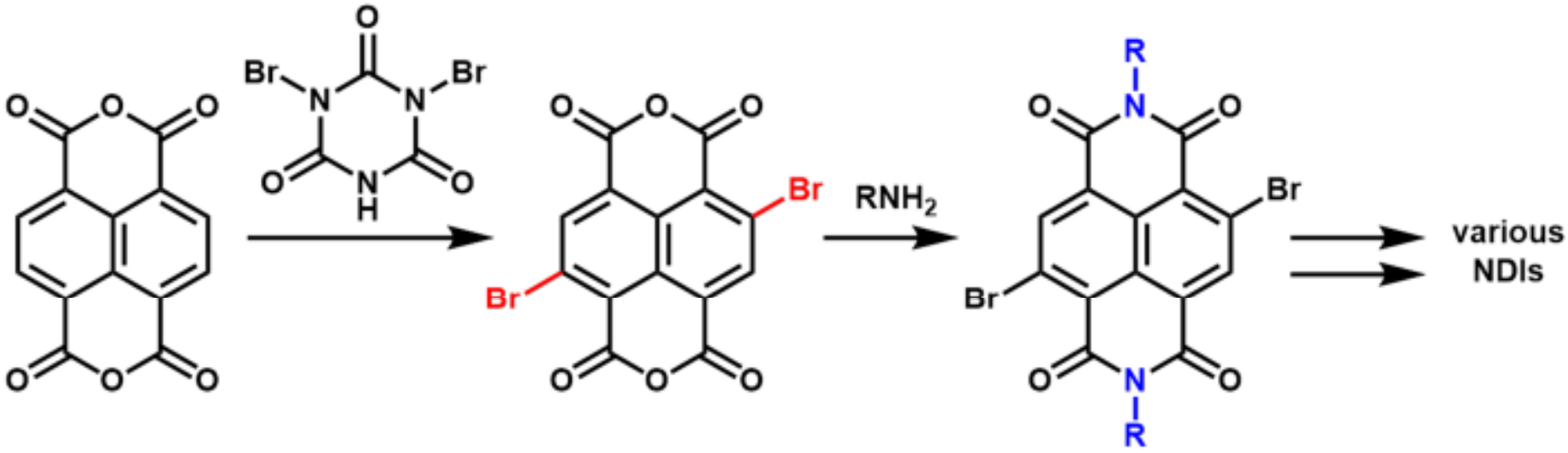
› easy structural modification

» supramolecular, photochemical and electrochemical applications

› large quadrupole moment and high π-acidity

» anion-π interaction

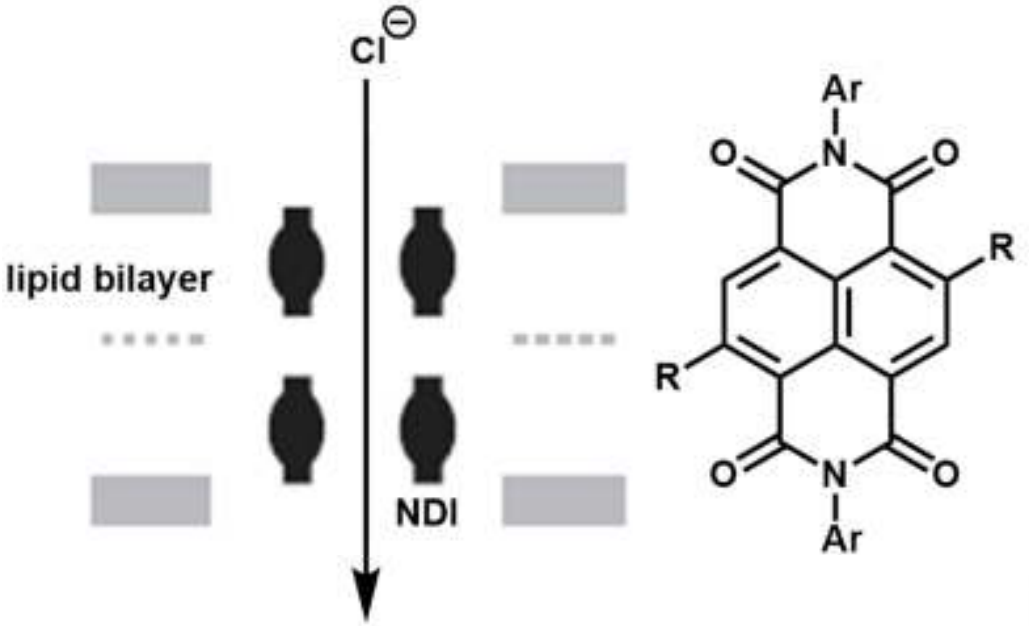
- Synthesis of NDI derivatives




Zhao, Y.; Beuchat, C.; Domoto, Y.; Gajewy, J.; Wilson, A.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2014**, *136*, 2101

120714 LS Hiroaki ITOH

# Naphthalene Diimide (2)



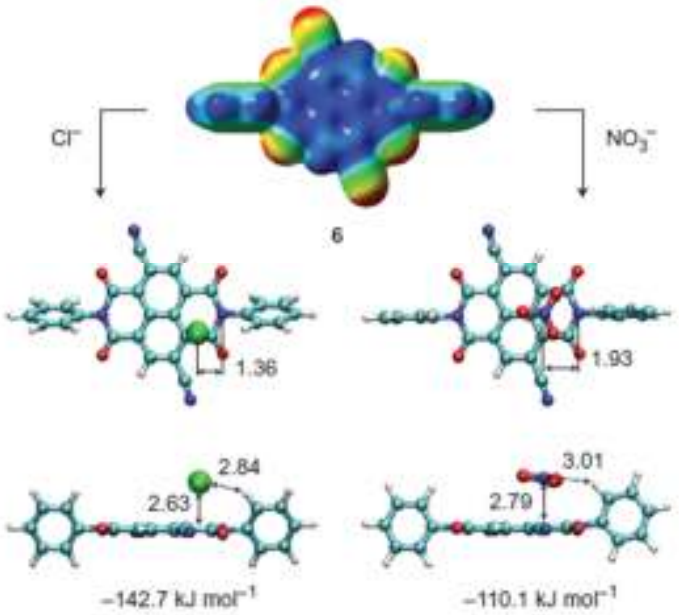




**Figure 4 | Molecular modelling of anion–π interactions.** Electrostatic potential surface (blue positive, red negative; ±150 kJ mol$^{-1}$, MP2/6-311++G**//PBE1PBE/6-311G**) and density functional theory optimized structures of 1:1 chloride and nitrate complexes of NDI **6** (C, cyan; H, white; O, red; N, blue; Cl$^-$, green) with indication of anion location (Å) and interaction energies.

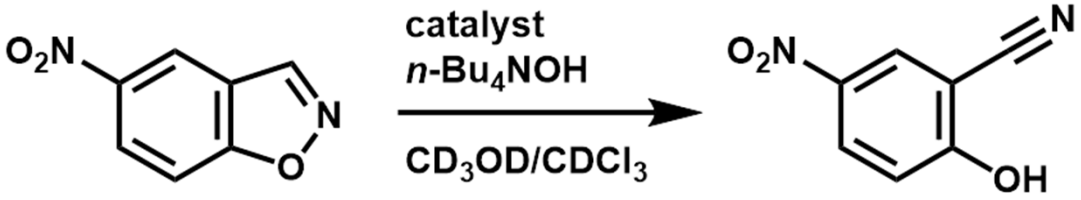
- **NDI derivatives have anion transport activity.**
- **Theoretical calculations, ESI-MS-MS analysis and UV-vis absorption indicate that NDIs stabilize anion in the ground state.**

→ **NDI derivatives would stabilize anionic intermediate and transition state by anion-π interaction.**

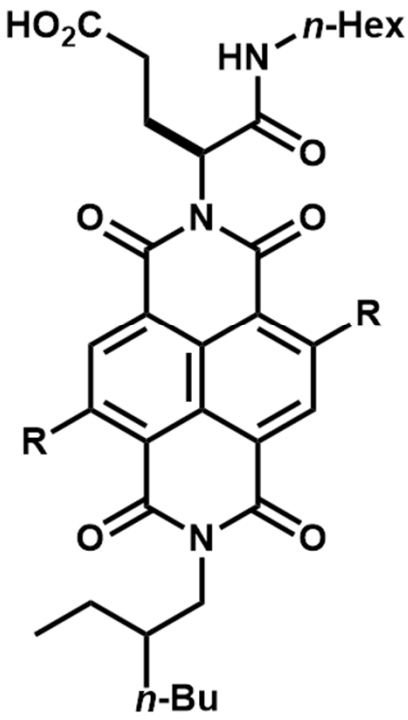
Dawson, R. E.; Hennig, A.; Weimann, D. P.; Emery, D.; Ravikumar, V.; Montenegro, J.; Takeuchi, T.; Gabutti, S.; Mayor, M.; Mareda, J.; Schalley, C. A.; Matile, S. *Nat. Chem.* **2010**, *2*, 533.

# Contents

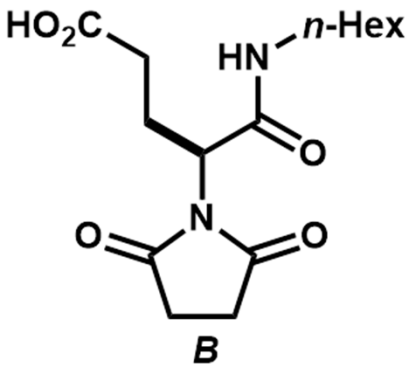
# Anion-π Catalysis of Kemp Elimination (1)



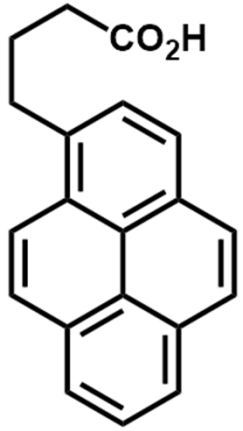

catalyst =



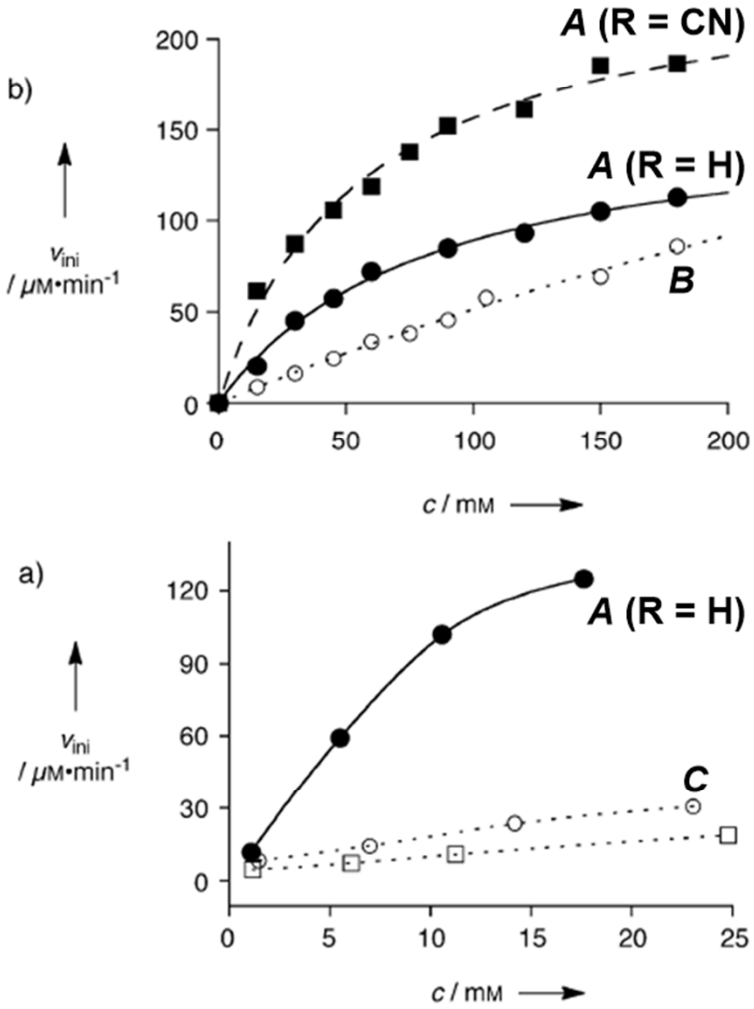

*A* (R = H, CN)




*B*

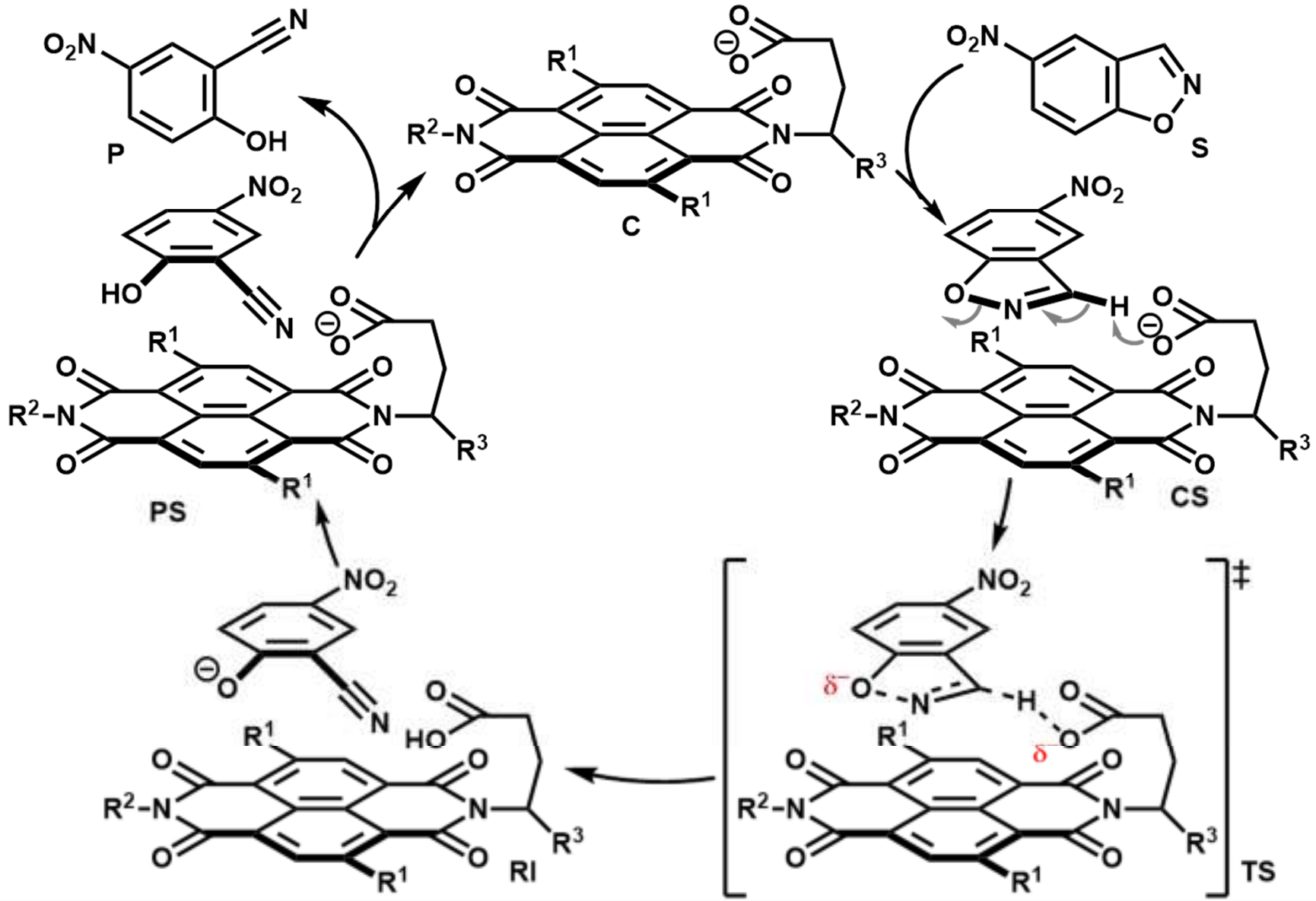



*C*



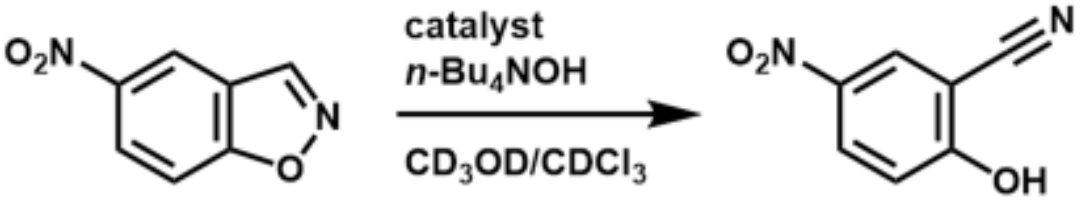

Zhao, Y.; Domoto, Y.; Orentas, E.; Beuchat, C.; Emery, D.; Mareda, J.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 9940.

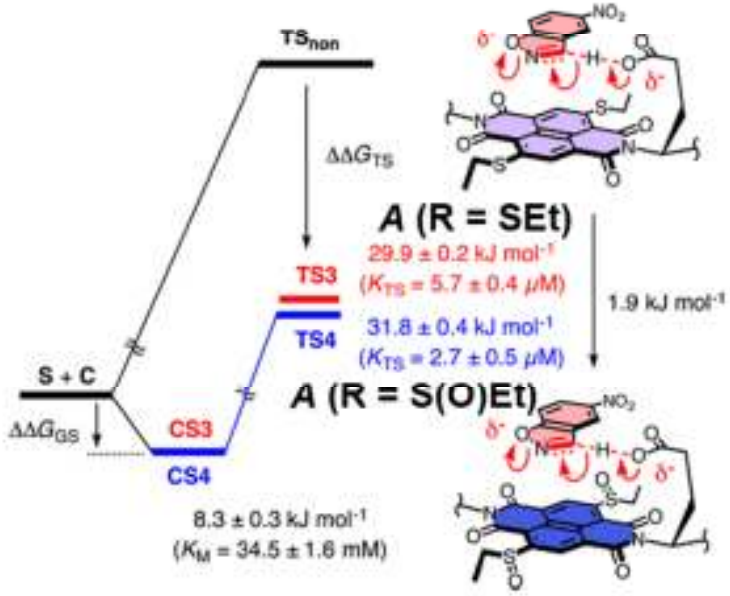
# Proposed Mechanism of Kemp Elimination




1) Zhao, Y.; Domoto, Y.; Orentas, E.; Beuchat, C.; Emery, D.; Mareda, J.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 9940. 2) Zhao, Y.; Beuchat, C.; Domoto, Y.; Gajewy, J.; Wilson, A.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2014**, *136*, 2101.

# Anion-π Catalysis of Kemp Elimination (2)




$v_{int} = k_{cat}$ [C] [S]/($K_M$ + [S])

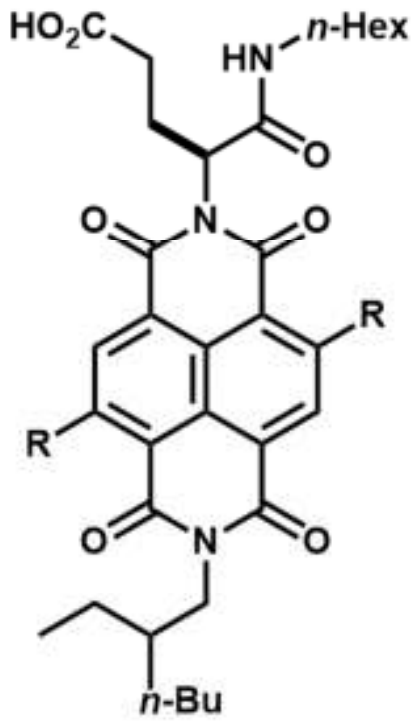
$K_{TS} = k_{non}K_M/k_{cat}$

$\Delta\Delta G_{TS} = -RT \ln K_{TS}$

$\Delta\Delta G_{CS} = -RT \ln K_M$

$k_{non}$: the rate constant of uncatalyzed reaction

catalyst =



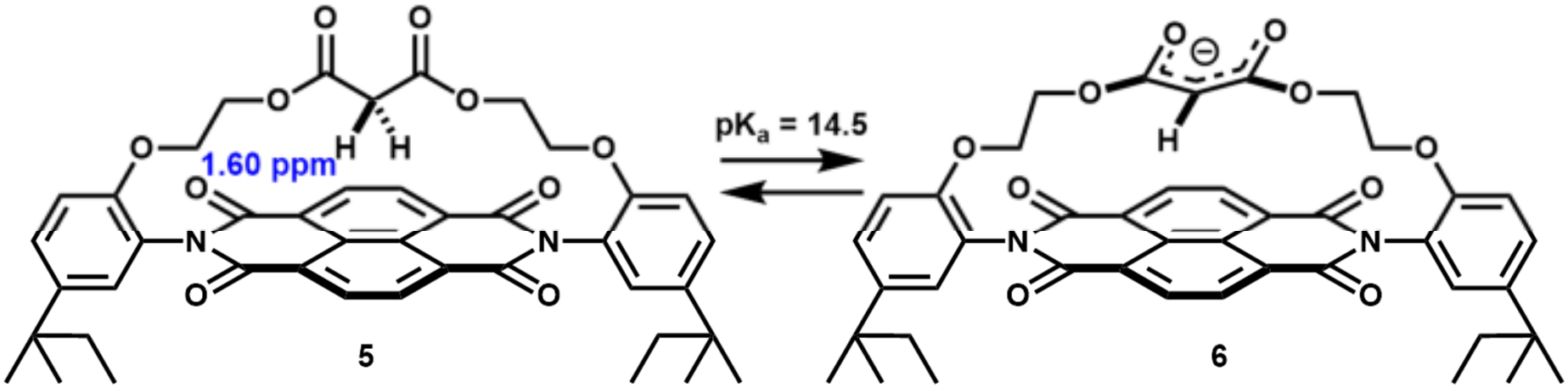

*A* (R = H, SEt, S(O)Et)

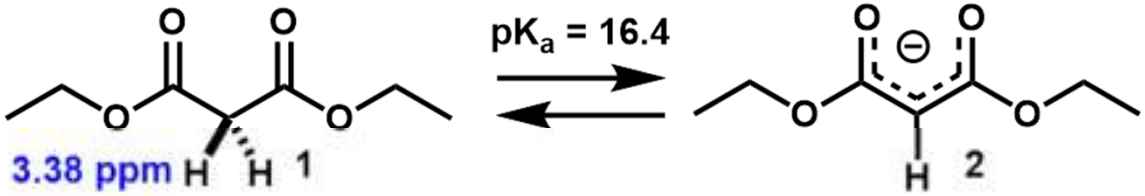
| entry | catalyst | $\Delta\Delta G_{TS}$ [kJ/mol] | $\Delta\Delta G_{CS}$ [kJ/mol] | LUMO energy of NDI [eV] |
|---|---|---|---|---|
| 1 | *A* (R = H) | 28.3 ± 0.4 | 6.2 ± 0.2 | –4.31 |
| 2 | *A* (R = SEt) | 29.9 ± 0.2 | 8.3 ± 0.1 | –3.93 |
| 3 | *A* (R = S(O)Et) | 31.8 ± 0.4 | 8.3 ± 0.3 | –4.46 |

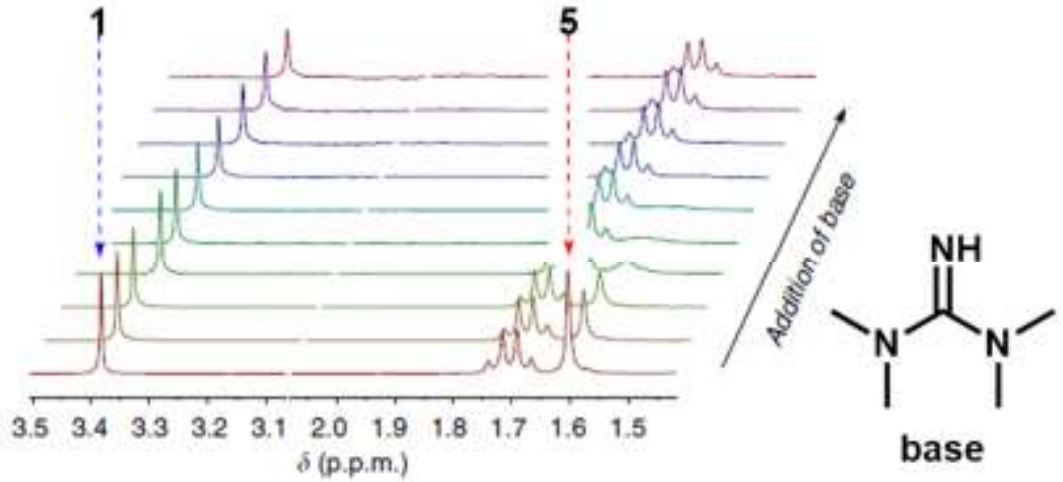
Zhao, Y.; Beuchat, C.; Domoto, Y.; Gajewy, J.; Wilson, A.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2014**, *136*, 2101.

# Contents

# Stabilization of Enolate Anion on π-acidic Surfaces



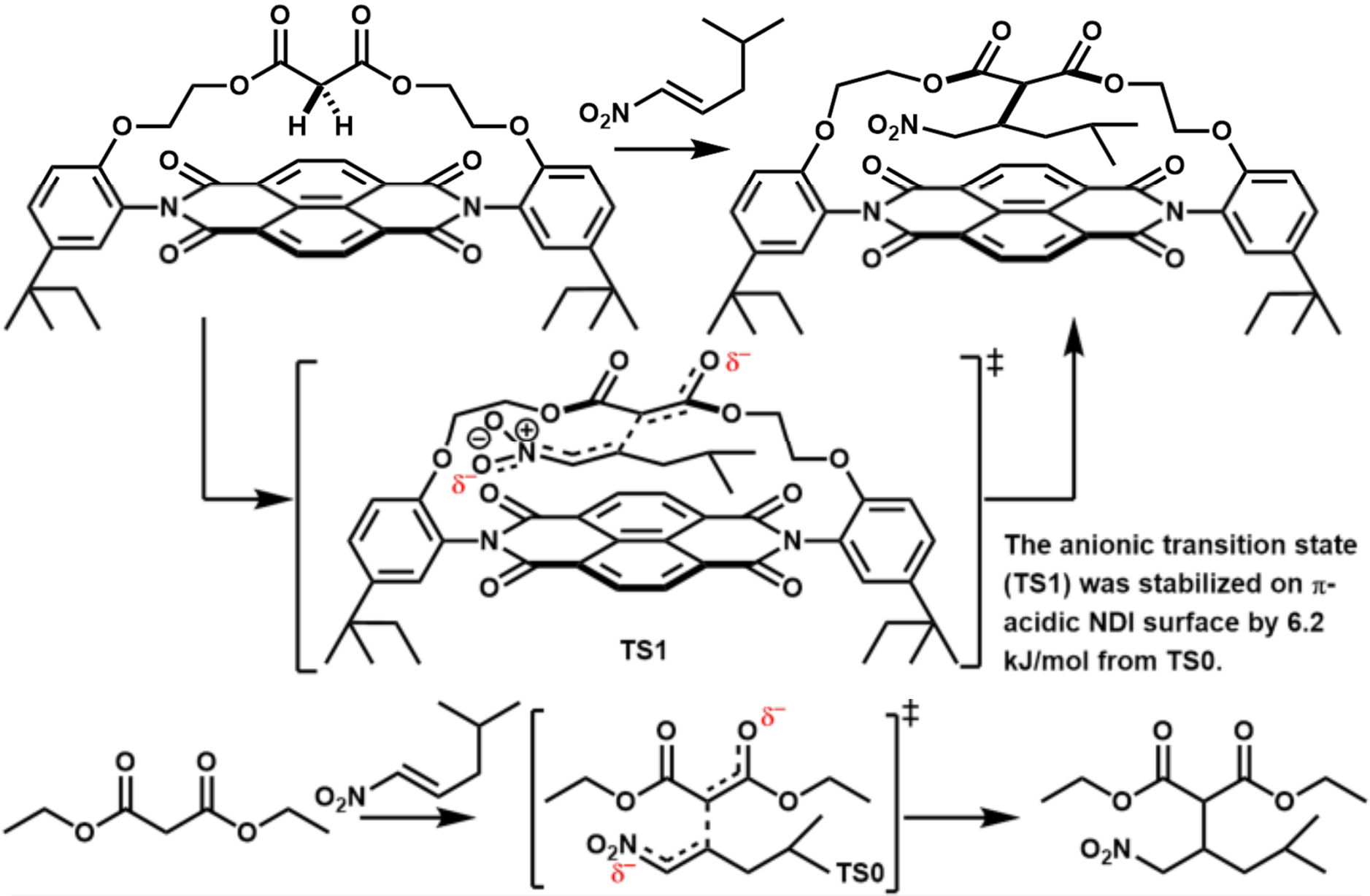




The enolate anion was stabilized on π-acidic NDI surface by 4.7 kJ/mol.

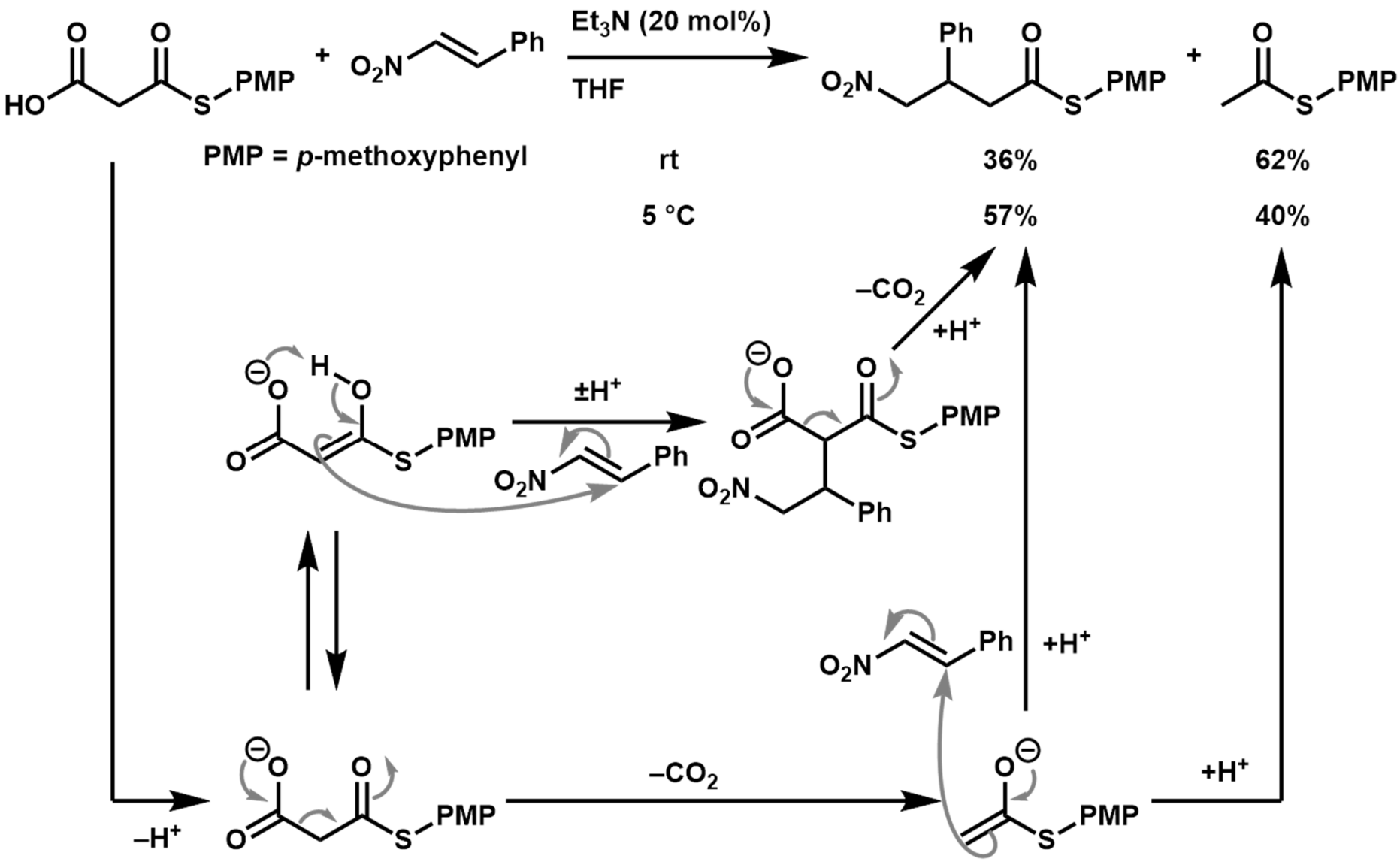
Zhao, Y.; Sakai, N.; Matile, S. *Nat. Commun.* **2014**, *5*, 3911.

# Stabilization of Transition State on π-acidic Surfaces



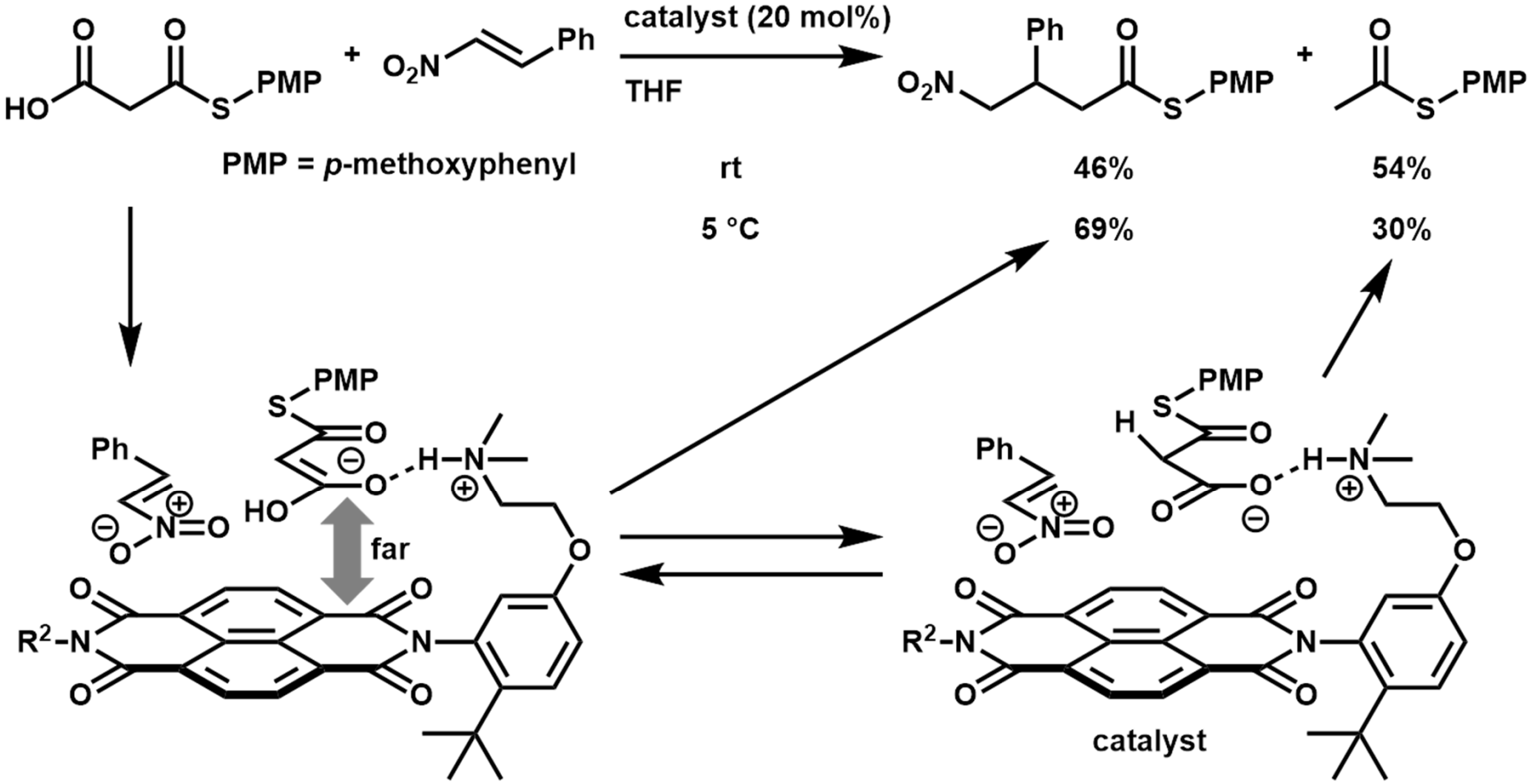

Zhao, Y.; Sakai, N.; Matile, S. *Nat. Commun.* **2014**, *5*, 3911.

# Enolate Addition vs Decarboxylation



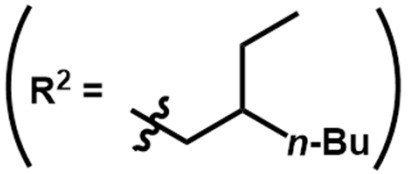

Zhao, Y.; Benz, S.; Sakai, N.; Matile, S. *Chem. Sci.* **2015**, *6*, 6219.

# Anion-π catalysis of Enolate Addition



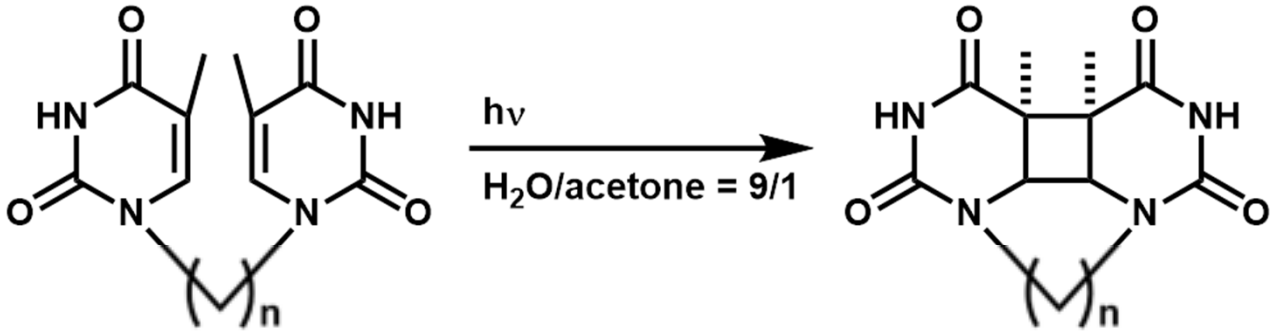

**The enolate anion is far from NDI surface.**

**Stabilization of enolate anion was not enough to react selectively.**

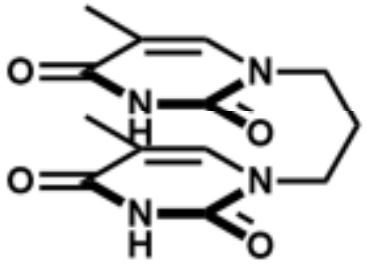



Zhao, Y.; Benz, S.; Sakai, N.; Matile, S. *Chem. Sci.* **2015**, *6*, 6219.

# Leonard Turns




| entry | n | time [a] |
|---|---|---|
| 1 | 2 | 5 |
| 2 | 3 | 1 |
| 3 | 4 | 2.5 |
| 4 | 6 | 20 |
| 5 | - [b] | 40 |



[a] the relative times required for complete reaction

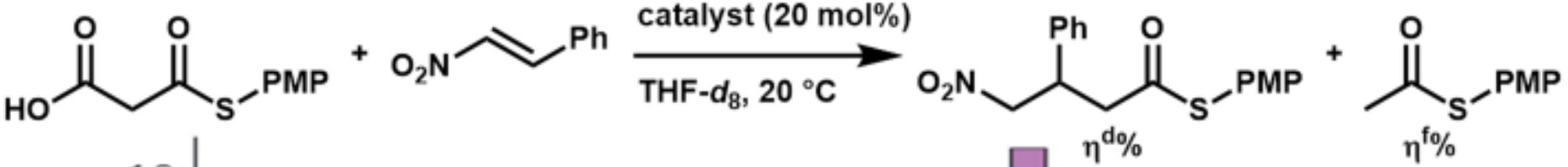
[b] 1-propylthymine was used as a substrate

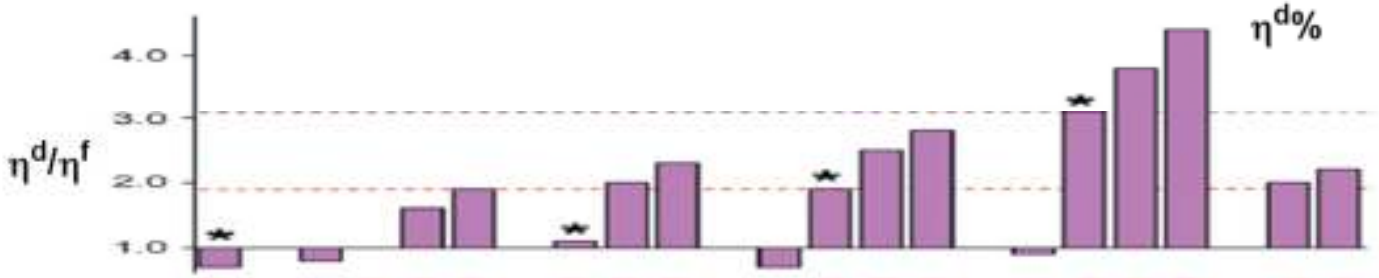
**Trimethylene chain was most efficient for intramolecular dimerization.**


Leonard, N. J.; McCredie, R. S.; Logue, M. W.; Cundall, R. L. *J. Am. Chem. Soc.* **1973**, *95*, 2320.

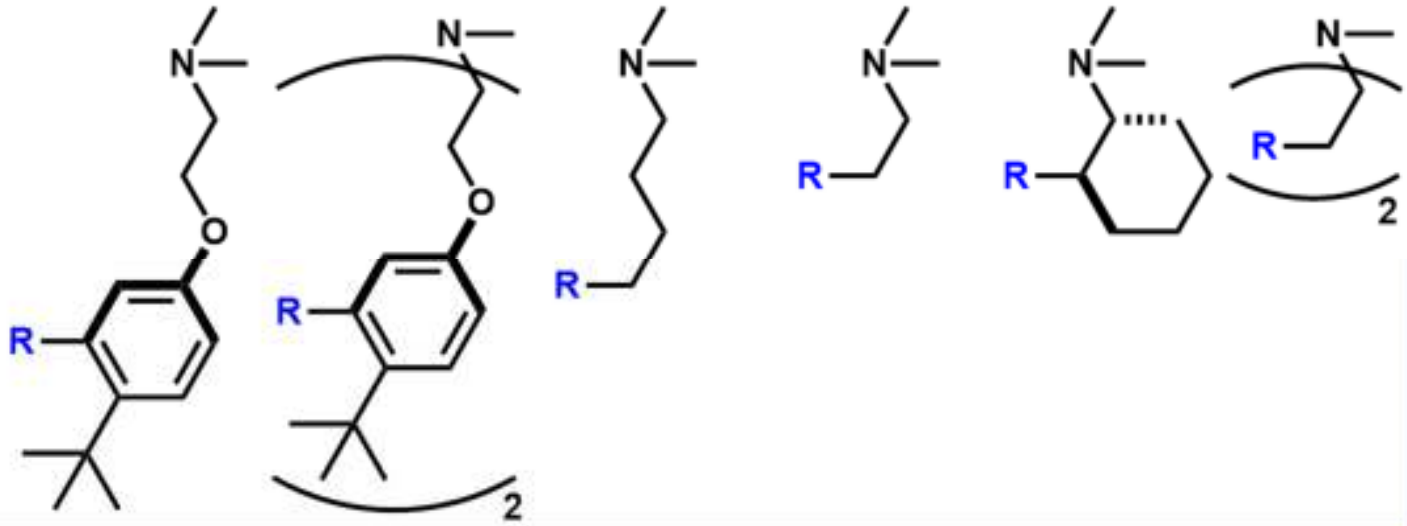
Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423.

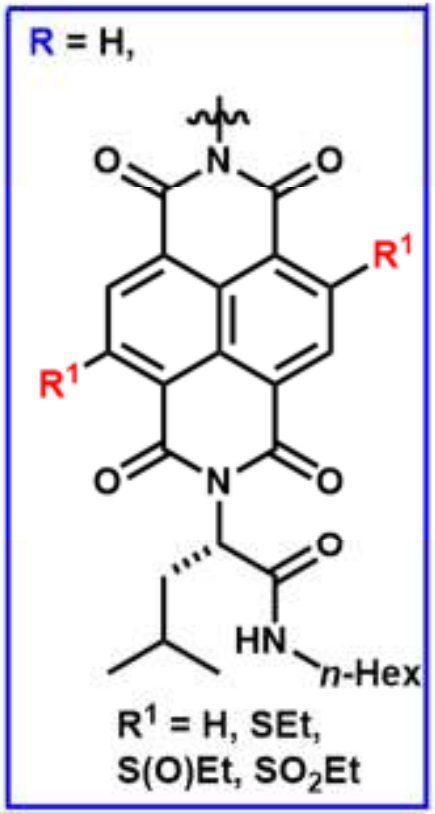
# Anion-π catalysis of Enolate Addition (20 °C)



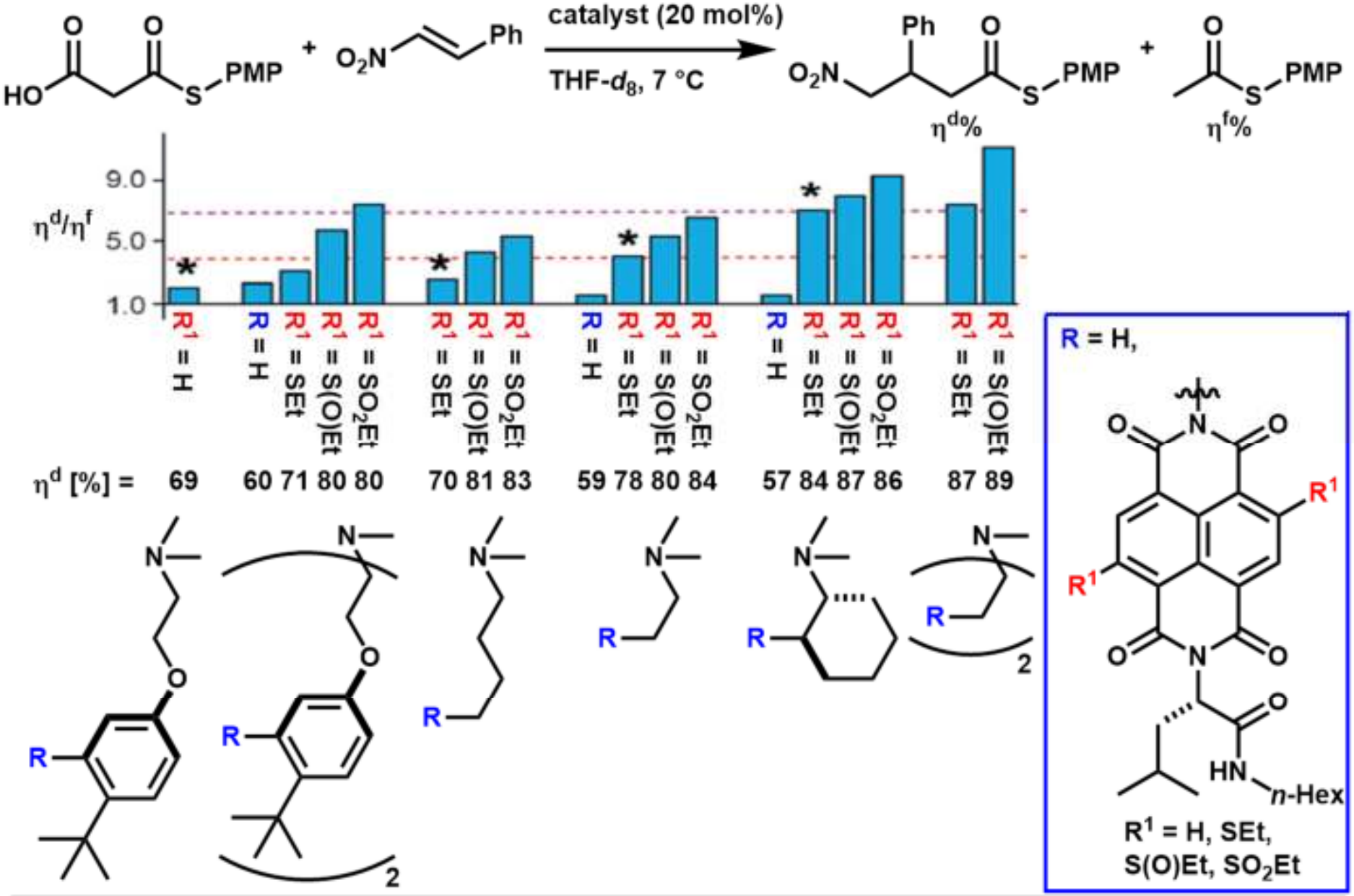

| | $R^1$ = H | R = H | $R^1$ = SEt | $R^1$ = S(O)Et | $R^1$ = $SO_2$Et | $R^1$ = SEt | $R^1$ = S(O)Et | $R^1$ = $SO_2$Et | R = H | $R^1$ = SEt | $R^1$ = S(O)Et | $R^1$ = $SO_2$Et | R = H | $R^1$ = SEt | $R^1$ = S(O)Et | $R^1$ = $SO_2$Et | $R^1$ = SEt | $R^1$ = S(O)Et |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\eta^d$ [%] = | 46 | 37 | 50 | 59 | 59 | 50 | 64 | 68 | 43 | 65 | 68 | 74 | 47 | 74 | 77 | 80 | 51 | 54 |



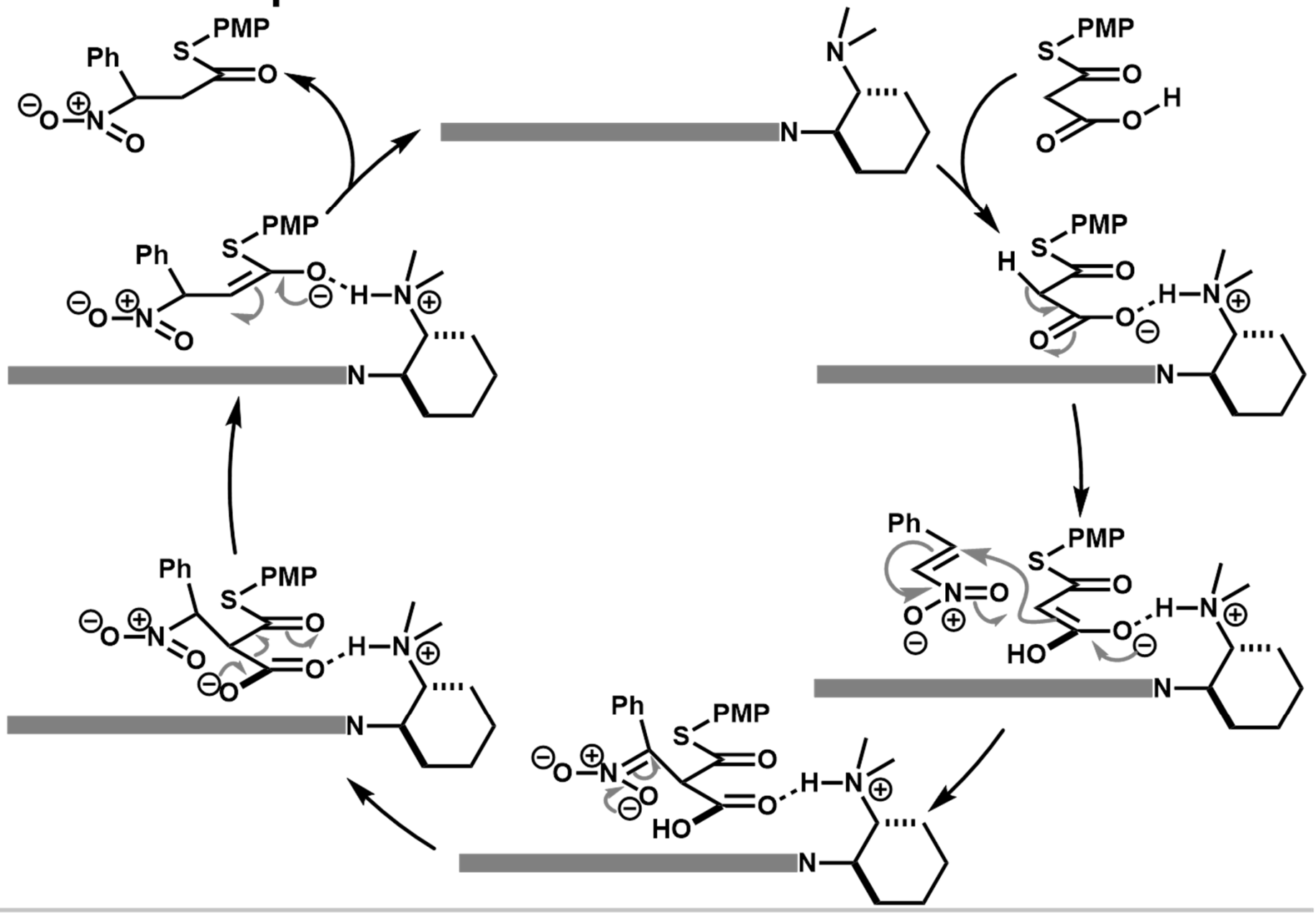

Cotelle, Y.; Benz, S.; Avestro, A.-J.; Ward, T. R.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 4275.

# Anion-π catalysis of Enolate Addition (7 °C)




Cotelle, Y.; Benz, S.; Avestro, A.-J.; Ward, T. R.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 4275.

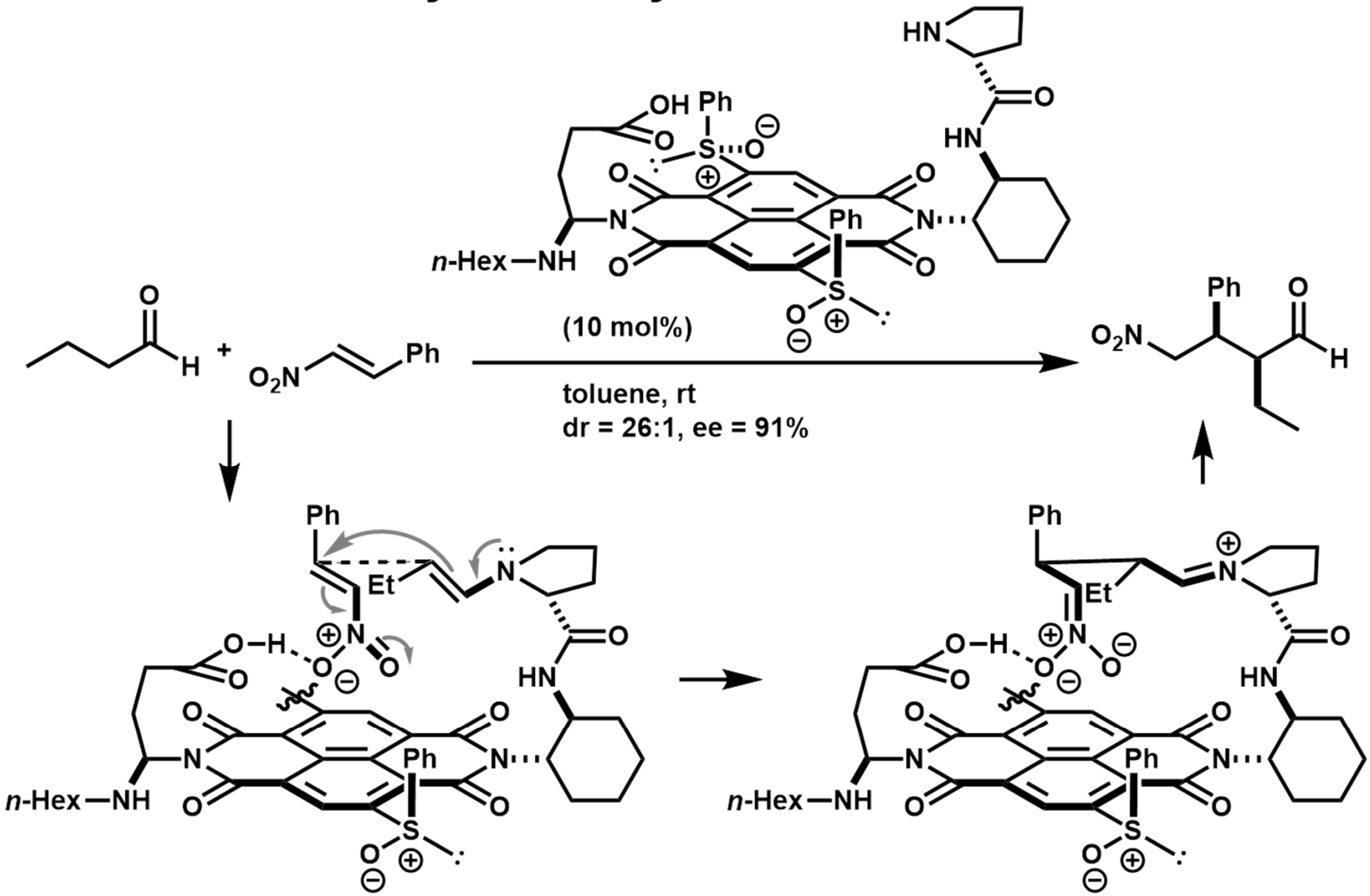
# Proposed Mechanism of Enolate Addition




Cotelle, Y.; Benz, S.; Avestro, A.-J.; Ward, T. R.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 4275.

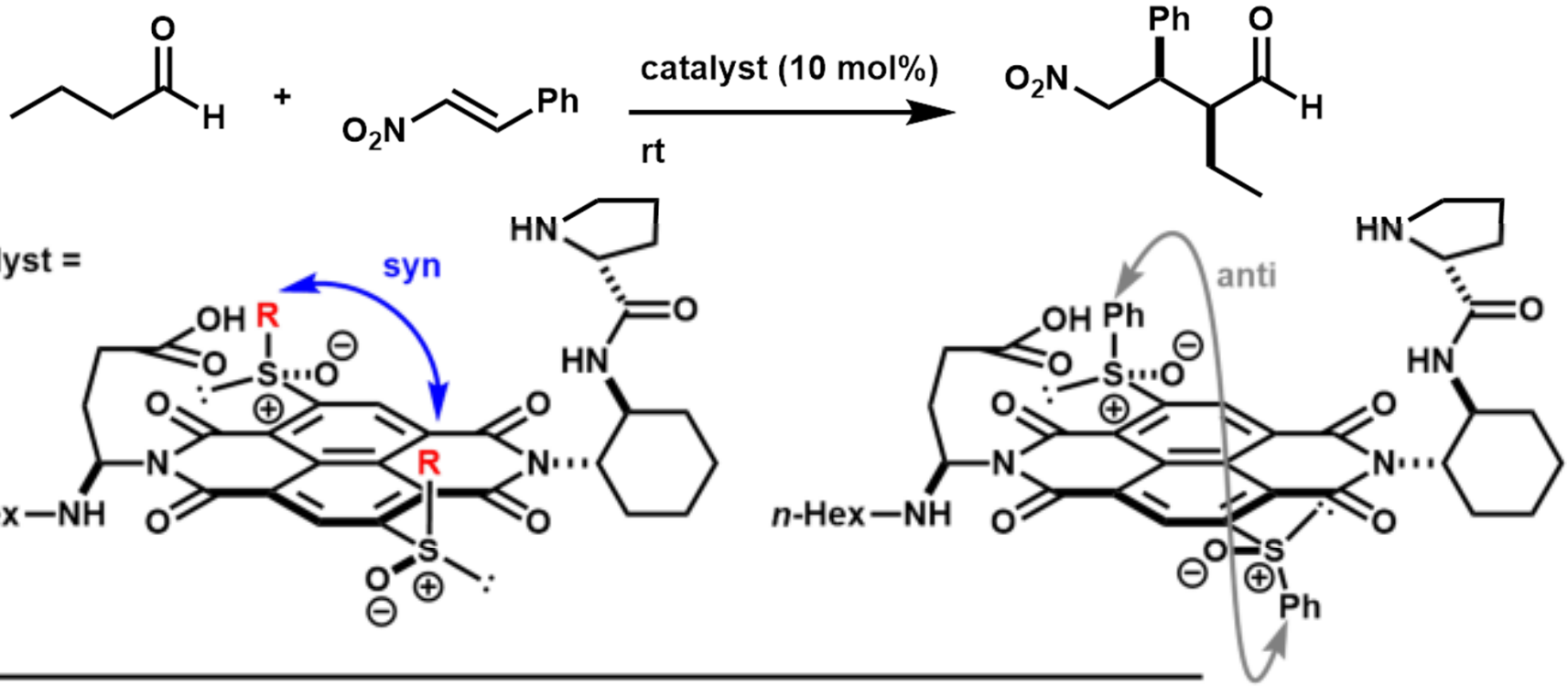
# Contents

# Anion-π Catalysis of Asymmetric Enamin Addition




Akamatsu, M.; Matile, S. *Synlett*, **2016**, *27*, 1041.

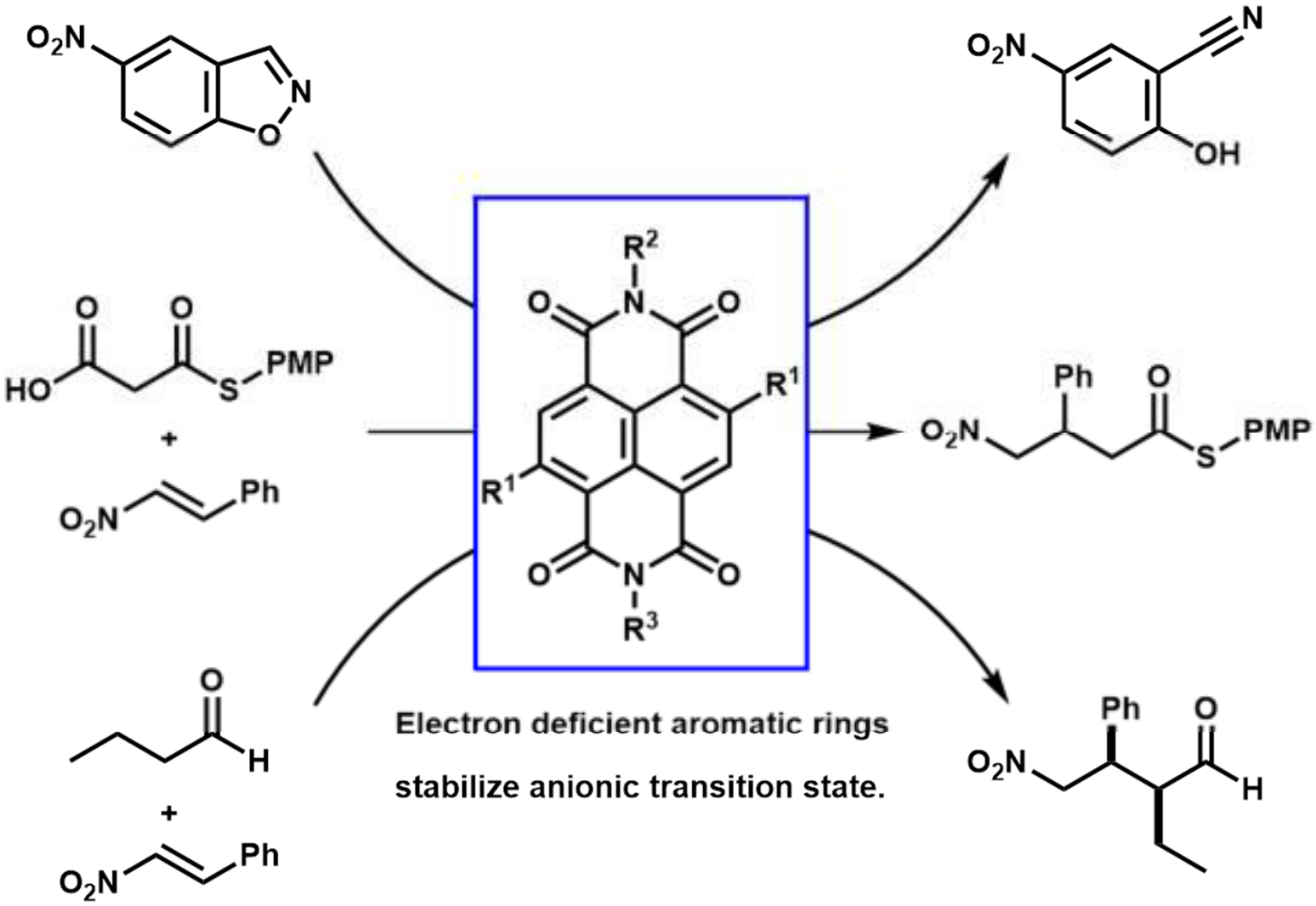
# Anion-π Catalysis of Asymmetric Enamin Addition




| entry | catalysis | solvent | dr | ee [%] |
|---|---|---|---|---|
| 1 | syn, R = Ph | toluene | 26:1 | 91 |
| 2 | anti, R = Ph | toluene | 17:1 | 85 |
| 3 | syn, R = Et | toluene | 23:1 | 64 |
| 4 | syn, R = Ph | nitrobenzene | 3.1:1 | 81 |
| 5 | syn, R = Ph | 1,3-dimethoxybenzene | 9.0:1 | 91 |

Akamatsu, M.; Matile, S. *Synlett*, **2016**, *27*, 1041.

# Summary


Electron deficient aromatic rings
stabilize anionic transition state.