Organic reaction “on water”

2016. 10. 1. (sat.)

Takumi Matsueda (M2)

Today's topic

1. Introduction

2. Investigation of "on water"

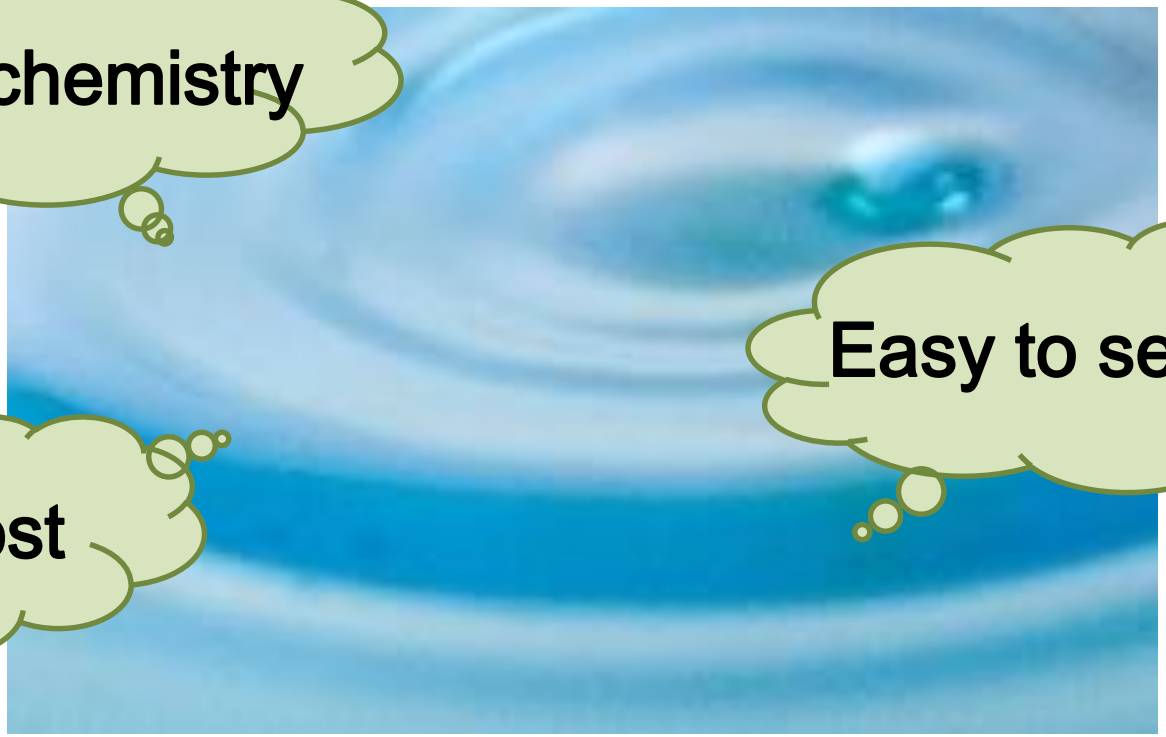
   -Bulk & surface water
   -Theoretical study (Diels-Alder)

3. Application of "on water"

   -Fluorine effect (aldol reaction)
   -*ortho*-Diamination (C-H activation)

4. Summary

The importance of water



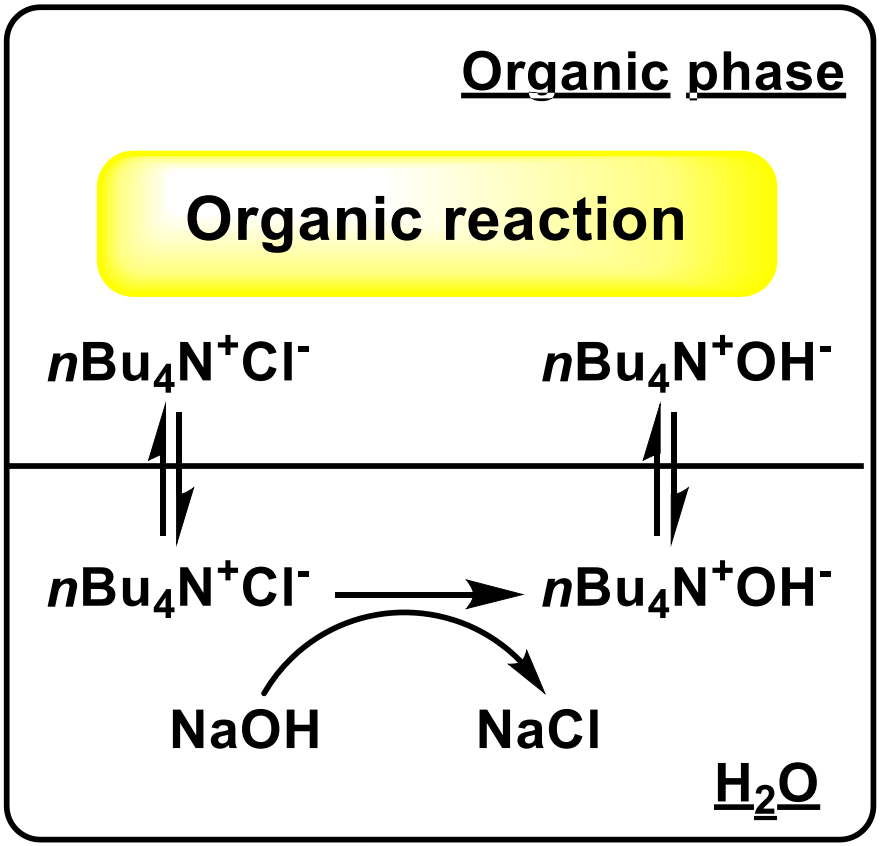
Green chemistry

Easy to separate

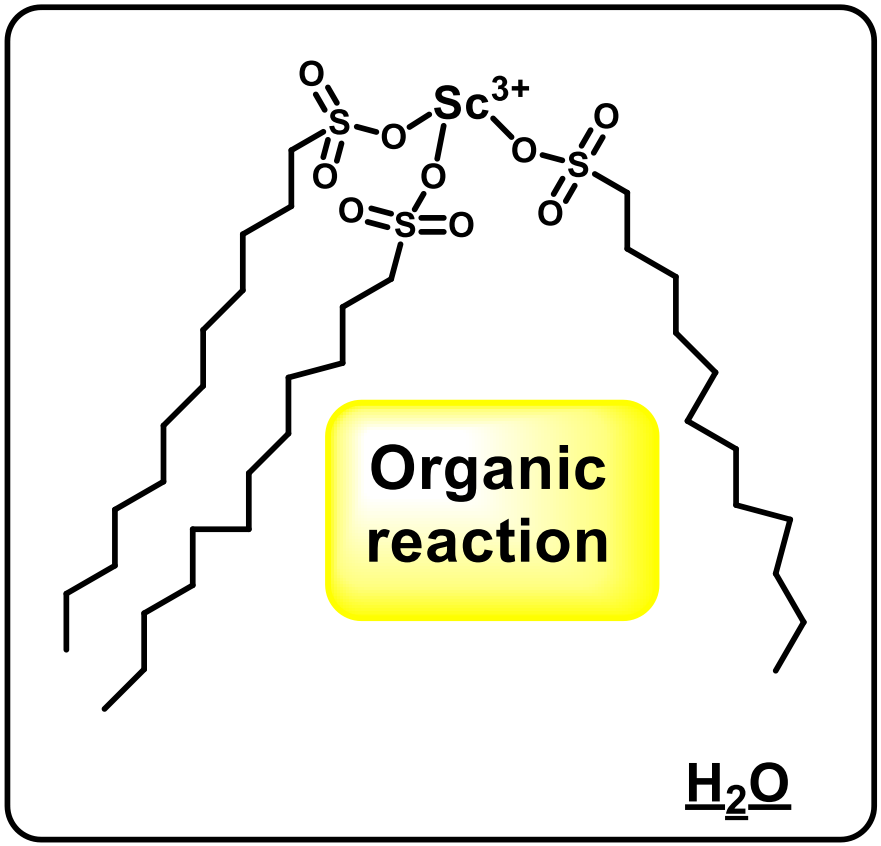
Low cost

☹Low solubility
☹Decomposition of reagent

Use of water in organic synthesis



Use of PTC
(Phase-Transfer Catalyst)



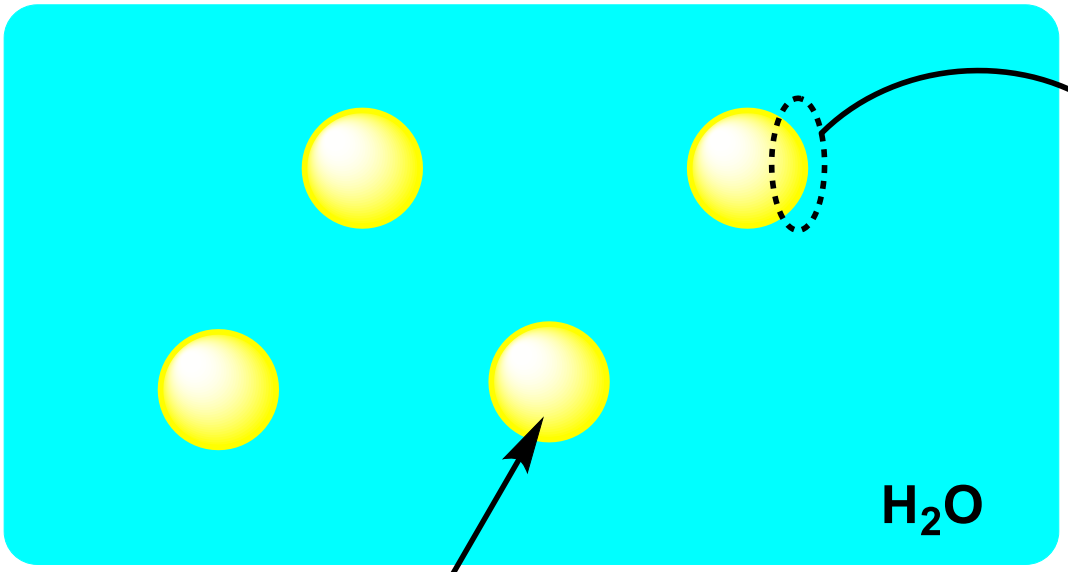
Use of LASC
(Lewis Acid-Surfactant-Combined Catalyst)

Kajino's lit seminar (2015)

Separated reactant + water = “on water”

PTC
LASC ⇨ Organic reaction in hydrophobic phase

Today's topic



Organic reaction on the surface of water

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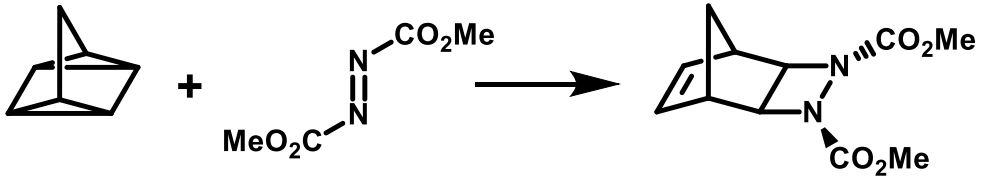
"On water" reaction

Organic reactant (separated from water)

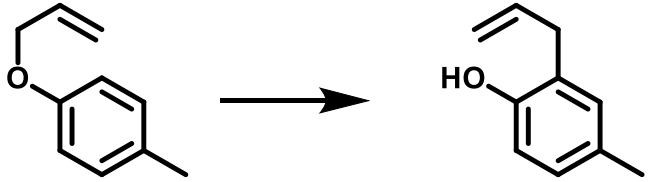
"in water" reaction
= reaction dissolved in water

Organic reaction promoted by “on water”

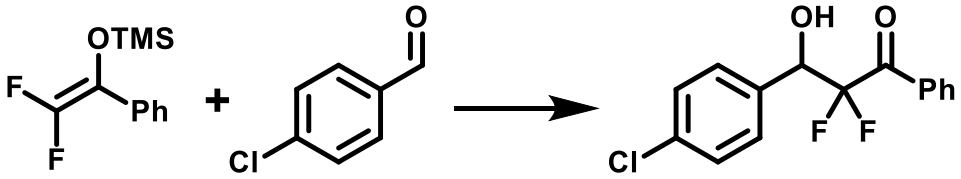
Diels-Alder



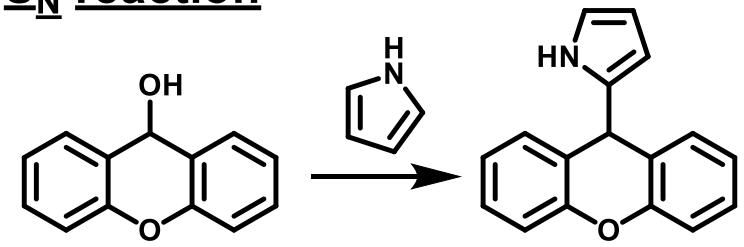
Claisen rearrangement



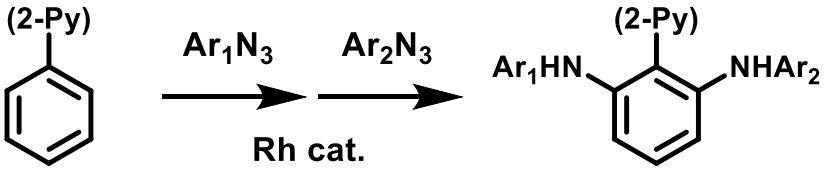
Aldol



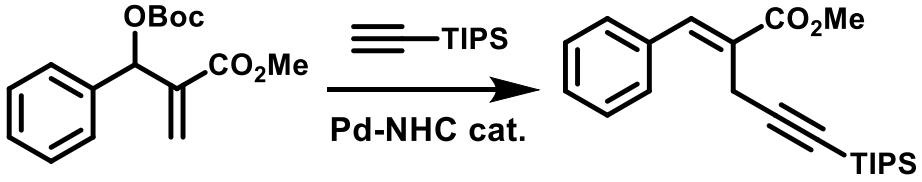
S_N reaction



C-H activation



Tsuji-Trost



Sharpless, K. B. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279

Wolfarth, E. F., White, W. N. *J. Org. Chem.* **1970**, *35*, 3585

Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

Zoli, L. Cozzi, P. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 4162-4166

Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

Chaojun, L. *et al. J. Org. Chem.* **2015**, *80*, 6283-6290

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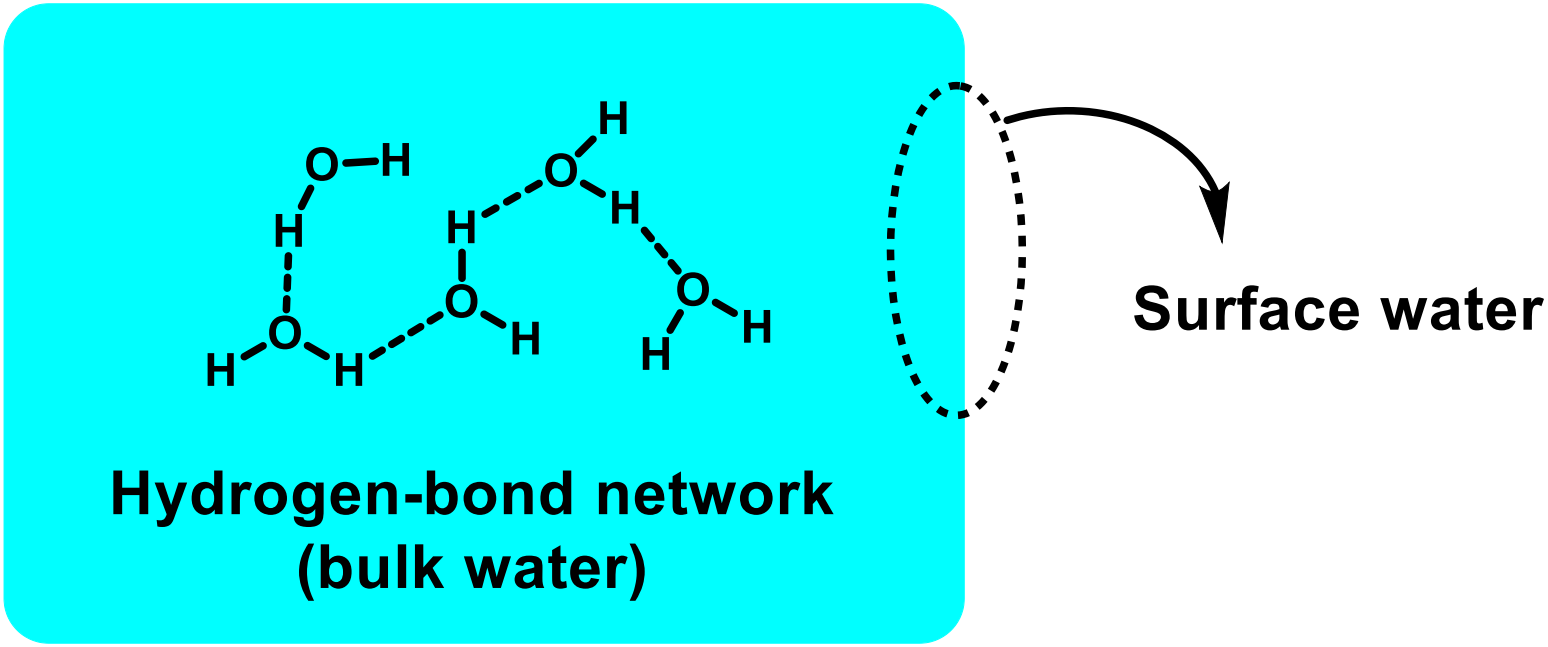
4. Summary

The nature of water

Bulk & surface water

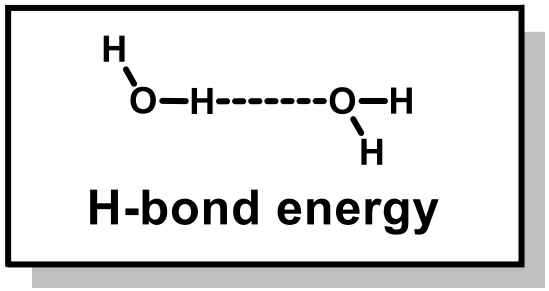


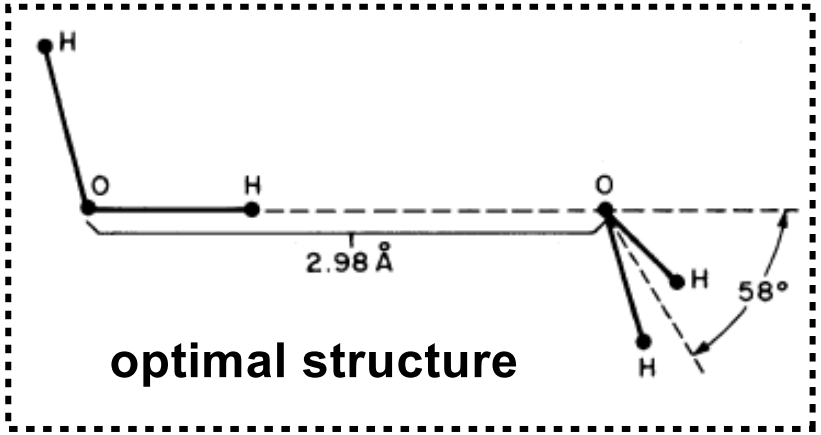
⇨ H-bond energy of bulk water

⇨ The environment of surface water

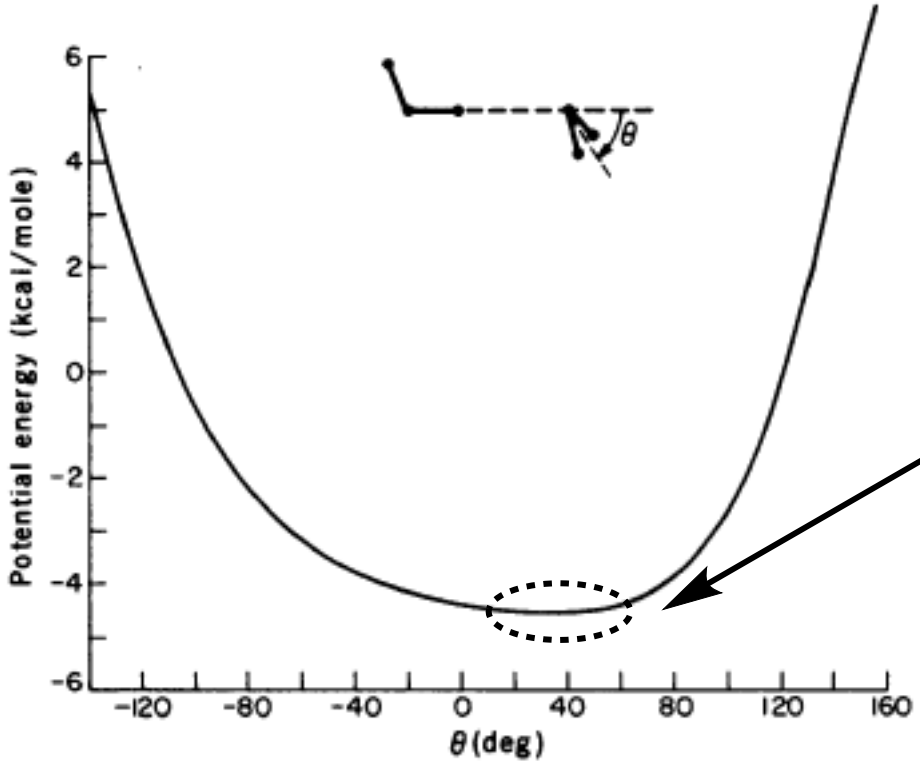
H-bond energy of dimer H_2O

H_2O dimer model (gas phase)





Dyke, T. R. *J. Chem. Phys.* **1977**, *66*, 498



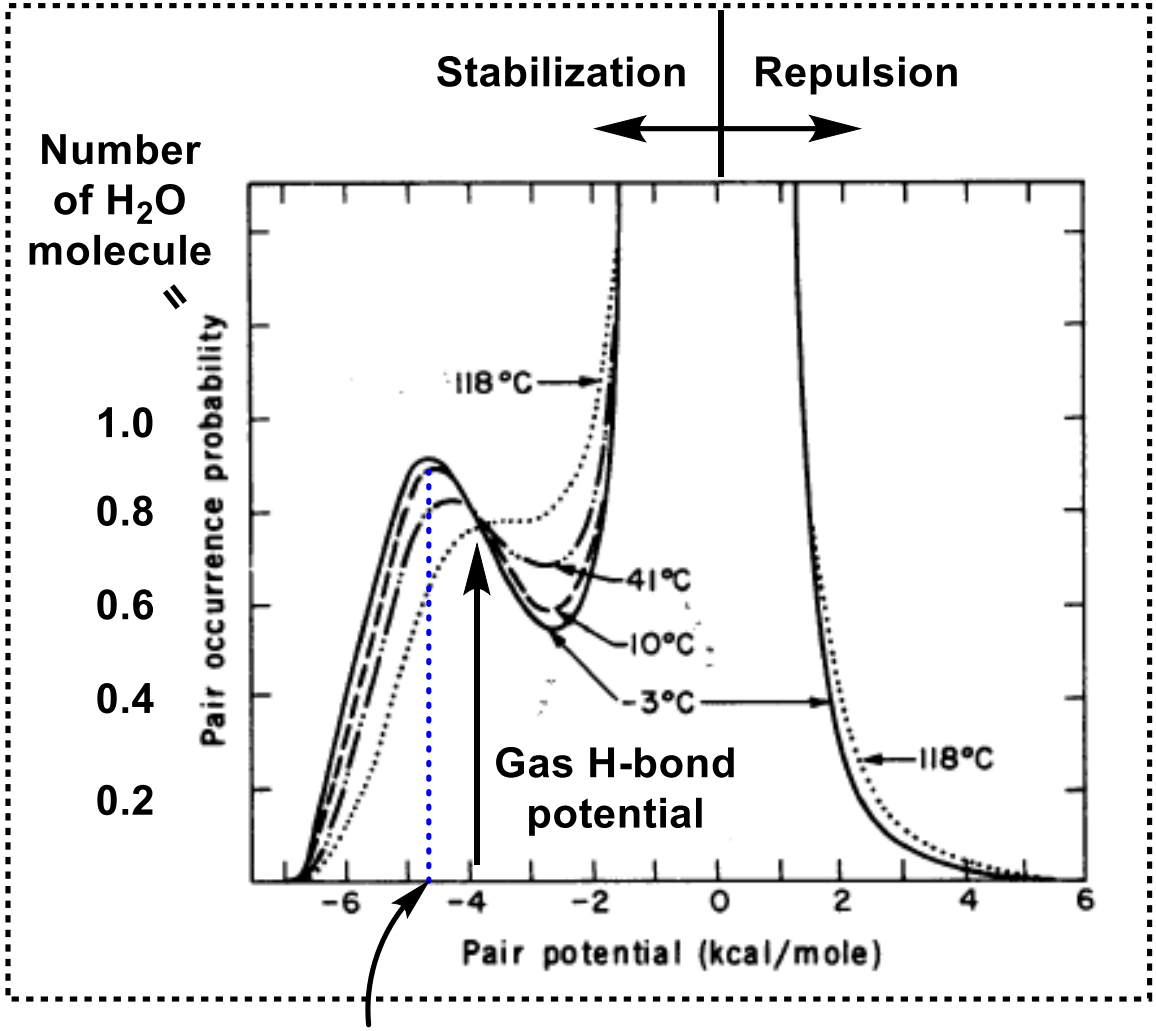
Potential energy = -4 kcal/mol

Clementi, E. *J. Chem. Phys.* **1973**, *59*, 1325

Stillinger, F. H. *Science* **1980**, *209*, 451-457

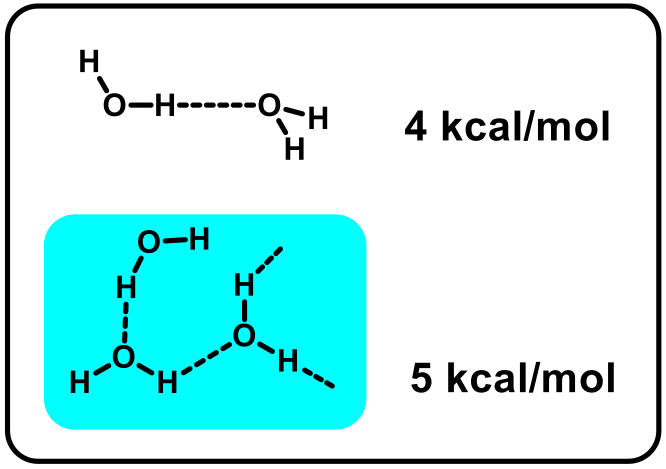
H-bond energy of bulk H_2O

Distribution of effective pair potential



Effective pair potential
= The strength of H-bond

Computer simulation
(216 molecules of H_2O)

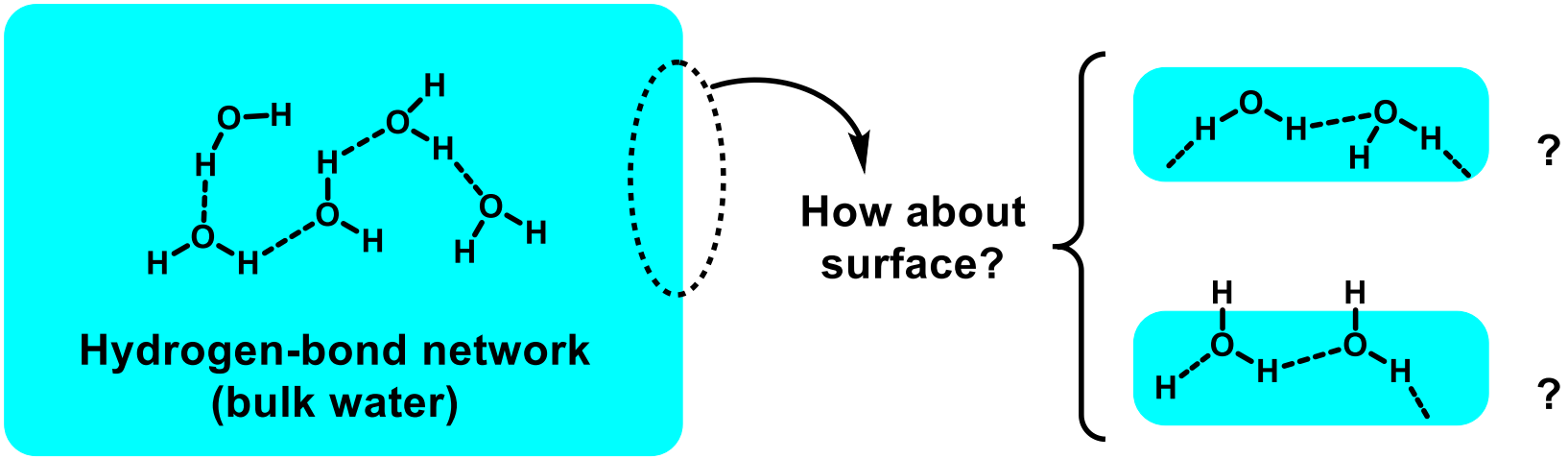


Highest probability of H-bond potential(≈ 5 kcal/mol)

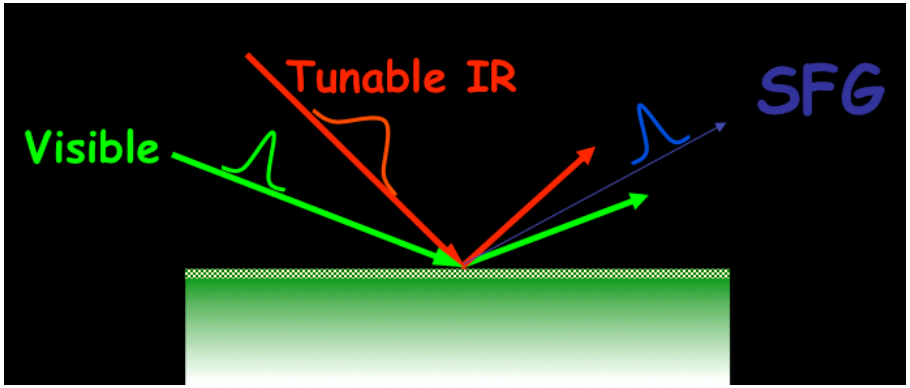
Stillinger, F. H. *Science* **1980**, *209*, 451-457

Water surface

Bulk & surface of water



How to measure the environment of surface



SFG

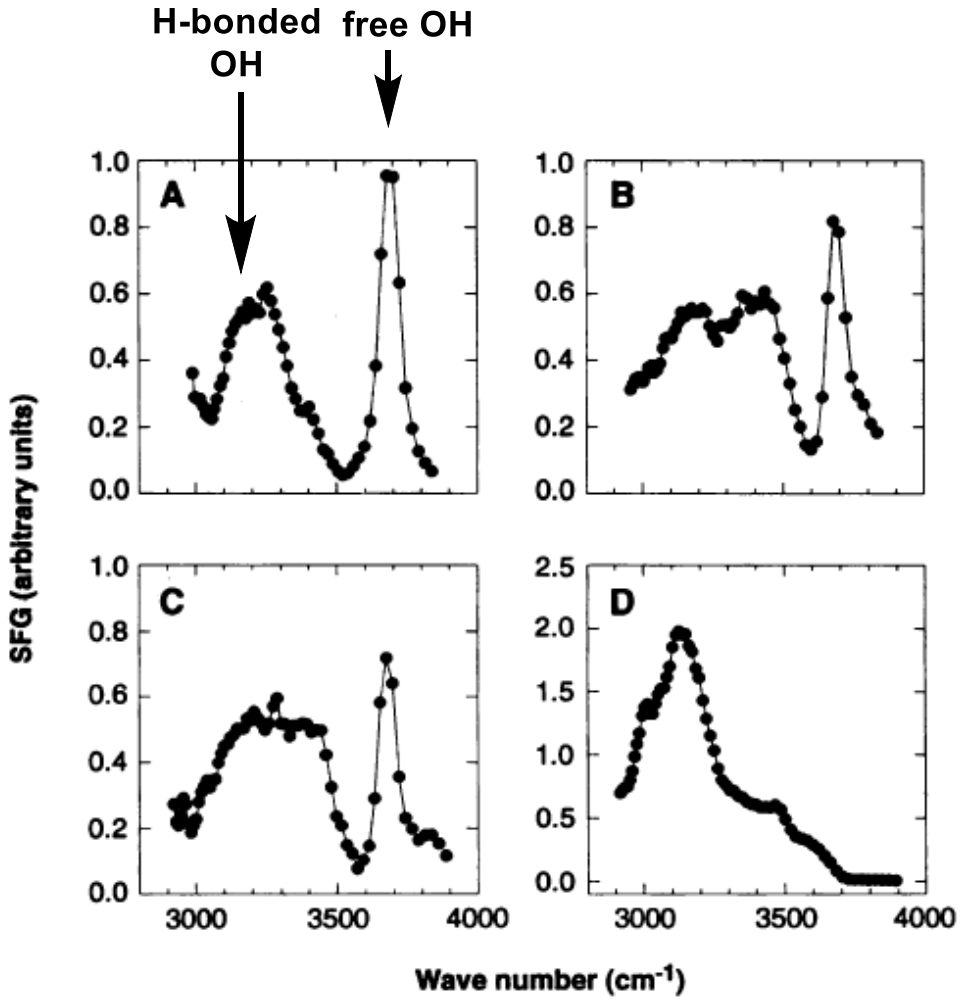
(Sum-Frequency Generation Spectroscopy)

... IR on surface

https://staff.aist.go.jp/t-miyamae/research/research_SFG.html

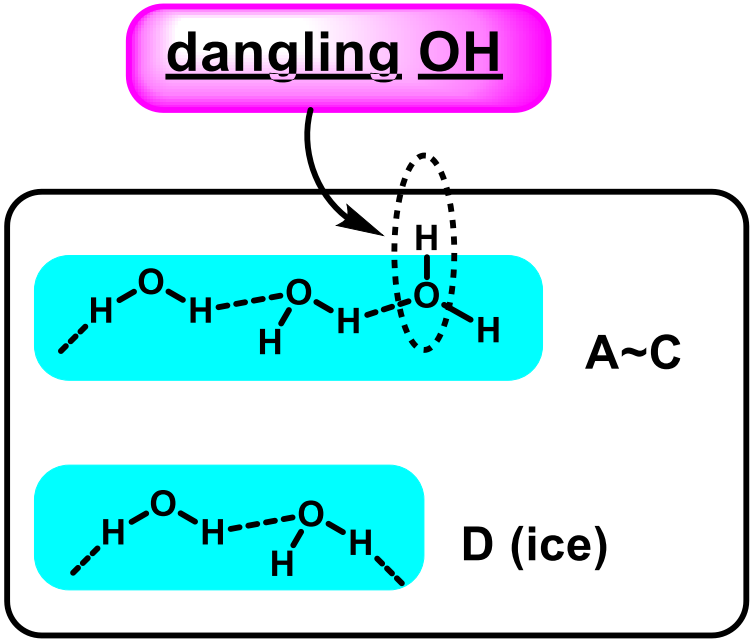
Environment of water surface

SFG spectrum of water-non water surface



OTS = $C_{18}H_{37}SiCl_3$ (coating of quartz)

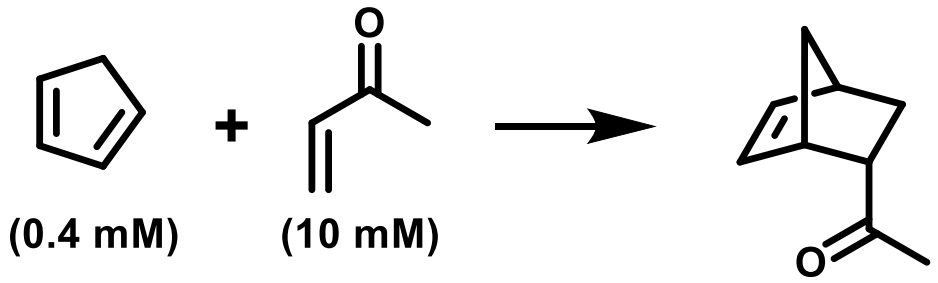
a) quartz-OTS-water interface
b) air-water interface
c) hexane-water interface
d) quartz-ice interface



Hickerson, W., Hammer, W. *Science* **1994**, *264*, 826-828

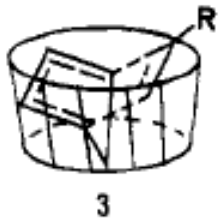
Diels-Alder on water

First report of DA reaction on water



(0.4 mM) (10 mM)

solvent	additive	k ($\times 10^5$ $M^{-1}s^{-1}$)
isooctane[b]		5.94 ± 0.3
MeOH		75.5
H_2O		4400 ± 70
H_2O	LiCl (4.86 M)	10800
H_2O	$C(NH_2)_3{}^+Cl^-$ (4.86 M)	4300
H_2O	β-cyclodextrin (10 mM)[c,f]	10900
H_2O	α-cyclodextrin (10 mM)[c,f]	2610



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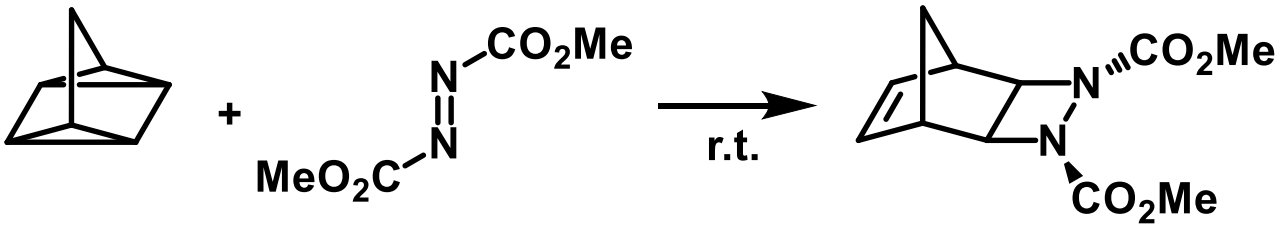
DA in β-cyclodextrin

Acceleration of Diels-Alder reaction
... Hydrophobic effect?

Breslow, R., Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817

Faster than neat condition

[2σ+2σ+2π] cycloaddition on water



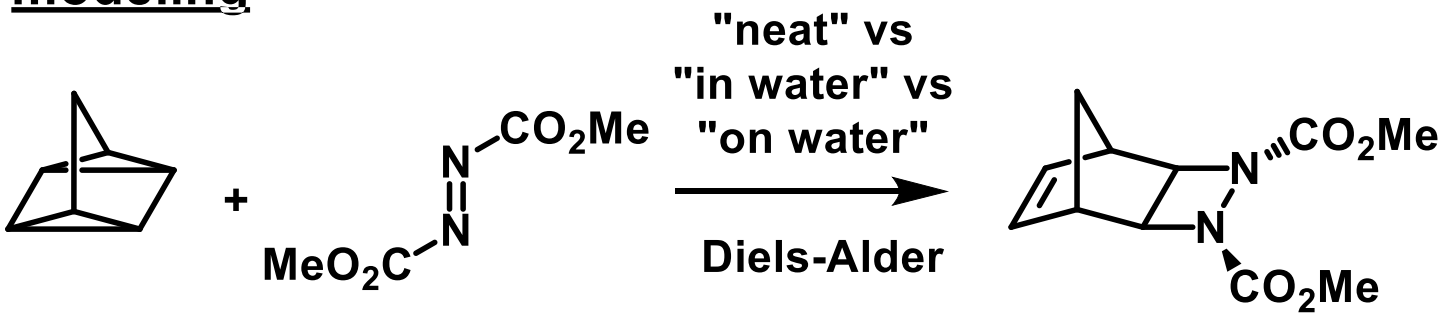
Solvent	Conc. [M][b]	Time to completion
toluene	2	> 120 h
EtOAc	2	> 120 h
CH_3CN	2	84 h
CH_2Cl_2	2	72 h
DMSO	2	36 h
MeOH	2	18 h
neat	4.53	48 h
on D_2O	4.53	45 min
on C_6F_{14}	4.53	36 h
on H_2O	**4.53**	**10 min**
$MeOH/H_2O$ (3:1, homogeneous)	2	4 h
$MeOH/H_2O$ (1:1, heterogeneous)	4.53	10 min
$MeOH/H_2O$ (1:3, heterogeneous)	4.53	10 min

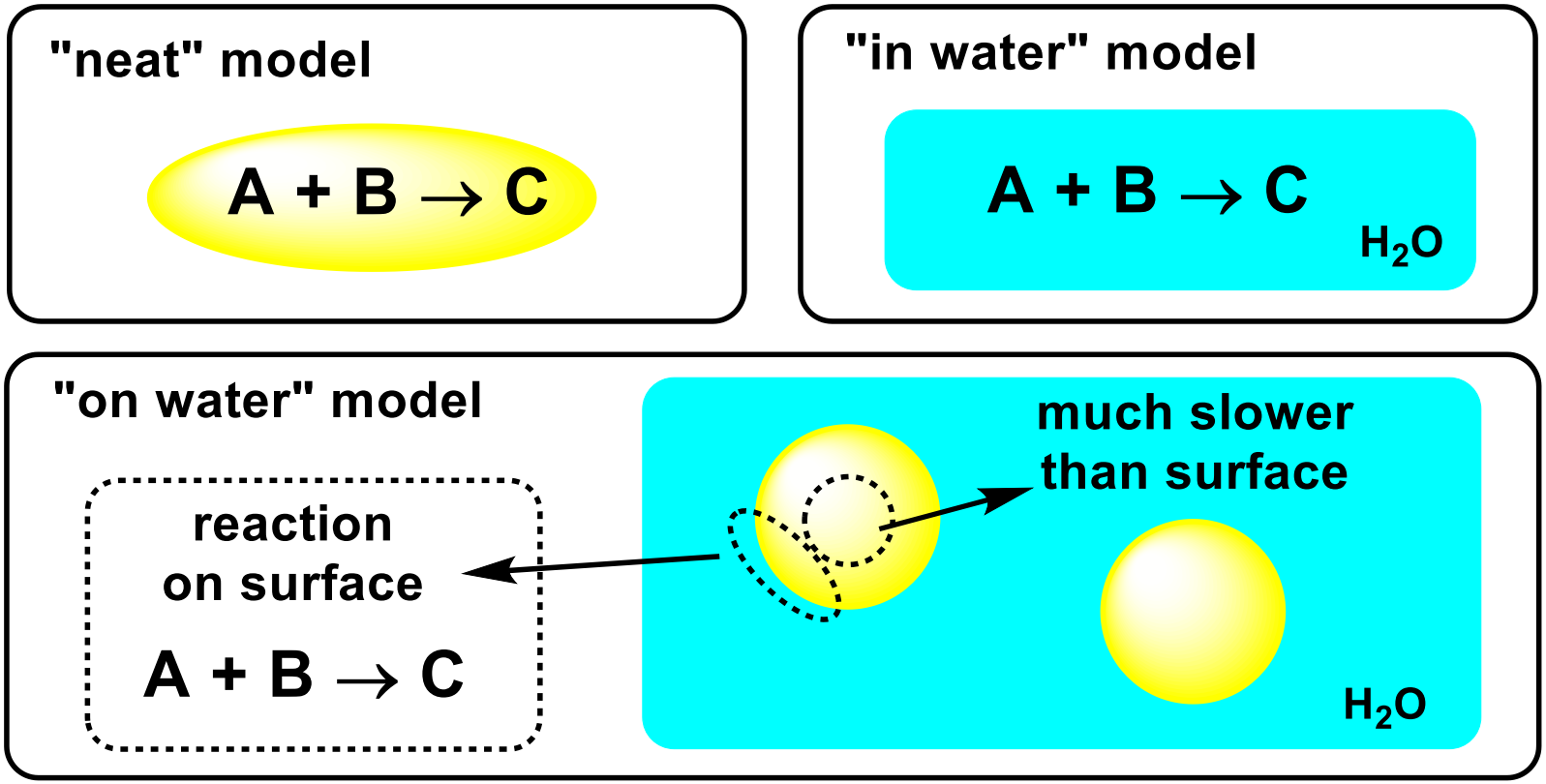
Heterogeneous (= on water)

Sharpless, K. B. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279

Theoretical study

Condition modeling





Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

"Neat" & "in water"

$A + B \rightarrow C$

neat

$$-\frac{d[A]}{dt} = k_N[A]Z_N n_B(t) = 0.5\, k_N Z_N [A] \Rightarrow k_N = -\frac{2}{Z_N t}\ln\frac{[A]}{a}$$

- [A] = conc. of A @ t
- Z_N = bulk coordination number (= 6)
- $n_B(t)$ = "mole fraction" of B @ t (= 0.5)

($a = [A]_0$)

in water

$A + B \rightarrow C$ in H_2O

$$-\frac{d[A]}{dt} = k_H[A]Z_H n_B(t) \quad (Z_H = 6)$$

$$n_B(t) = \frac{[B]}{[A]+[B]+M_0^*} \approx \frac{[B]}{M_0}$$

$$-\frac{d[A]}{dt} = \frac{k_H Z_H}{M_0}[A][B] \approx \frac{k_H Z_H}{M_0}[A]^2$$

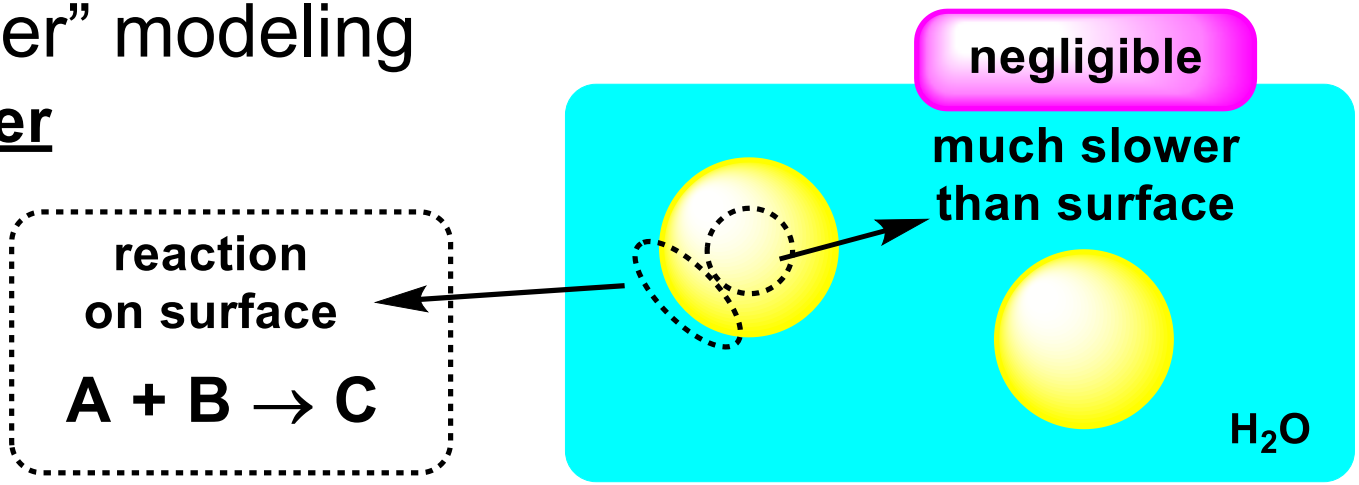
$$\Rightarrow k_H = \frac{M_0}{Z_H}\frac{1}{t}\left(\frac{1}{[A]} - \frac{1}{a}\right)$$

(* $M_0 = [H_2O]$ (= 32 M))

Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

"On water" modeling

on water



$$-\frac{d[A]}{dt} = k[A]Z_S n_B(t)$$

Surface reaction ... Count only A on surface

$$[A] \rightarrow \frac{A_S(t)}{\text{droplet vol.}} \quad \text{(per droplet)}$$

$$d[A] \rightarrow \frac{dA(t)}{\text{total vol.}} = \frac{dA(t)}{\text{droplet vol.} \times Nd}$$

$$-\frac{dA(t)}{dt} = k_S N_d \bar{A}_S(t) Z_S n_B(t)$$

- A(t) = total molecules of A
- $A_s(t)$ = average number of A on surface
- N_d = total droplets
- $Z_s = 4$

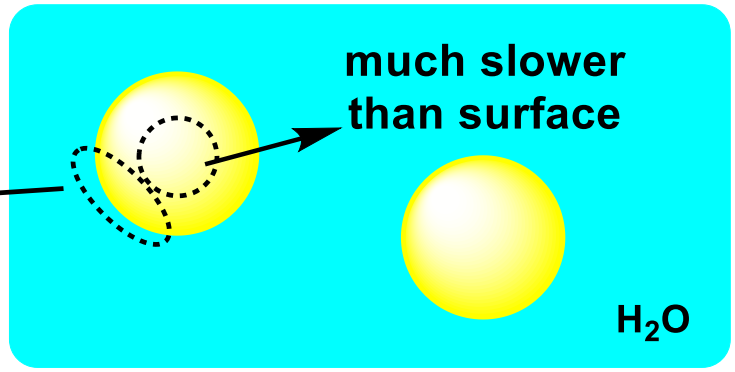
Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

"On water"

on water

reaction on surface

$A + B \rightarrow C$



$$-\frac{dA(t)}{dt} = k_S N_d \bar{A}_S(t) Z_S n_B(t) = \frac{3A(t)}{0.8 r_0 \rho_a^{1/3}} k_s Z_s n_B(t) \left(= \frac{3A(t)}{0.8 r_0 \rho_a^{1/3}} 0.5 k_s Z_s \right)$$

$$k_S = -\frac{1}{Z_S t} \frac{1}{n_B(0)} \frac{0.8 r_0 \rho_A^{1/3}}{3} \ln \frac{A(t)}{A_0}$$

mole of A @ t = 0

$$A(t) \approx N_d \frac{4\pi}{3} r(t)^3 \rho_a$$

$$A_s(t) \approx 4\pi r(t)^2 \rho_a^{2/3}$$

$$\frac{N_d A_s(t)}{A(t)} \approx \frac{3}{r(t)\rho_a^{1/3}} \approx \frac{3}{0.8 r_0 \rho_a^{1/3}}$$

the size of droplet when the reaction proceeds 50%

Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

Experimental (model) & theoretical (DFT)

	neat reaction	homogeneous reaction	surface reaction
reaction time (= t(s))	48 h	4 h	10 min
yield (%) (= 1-[A]/a)	85	82[a]	82
concentration (M) (= a)	4.5	2	4.5
k (experiments)	$4 \times 10^{-6}\ s^{-1}$	$2 \times 10^{-4}\ M^{-1}\ s^{-1}$ (or $9 \times 10^{-4}\ s^{-1}$)[b]	$0.5\ s^{-1}$[c]
k (theory) *	$5 \times 10^{-7}\ s^{-1}$	$2 \times 10^{-4}\ s^{-1}$	$0.2\ s^{-1}$

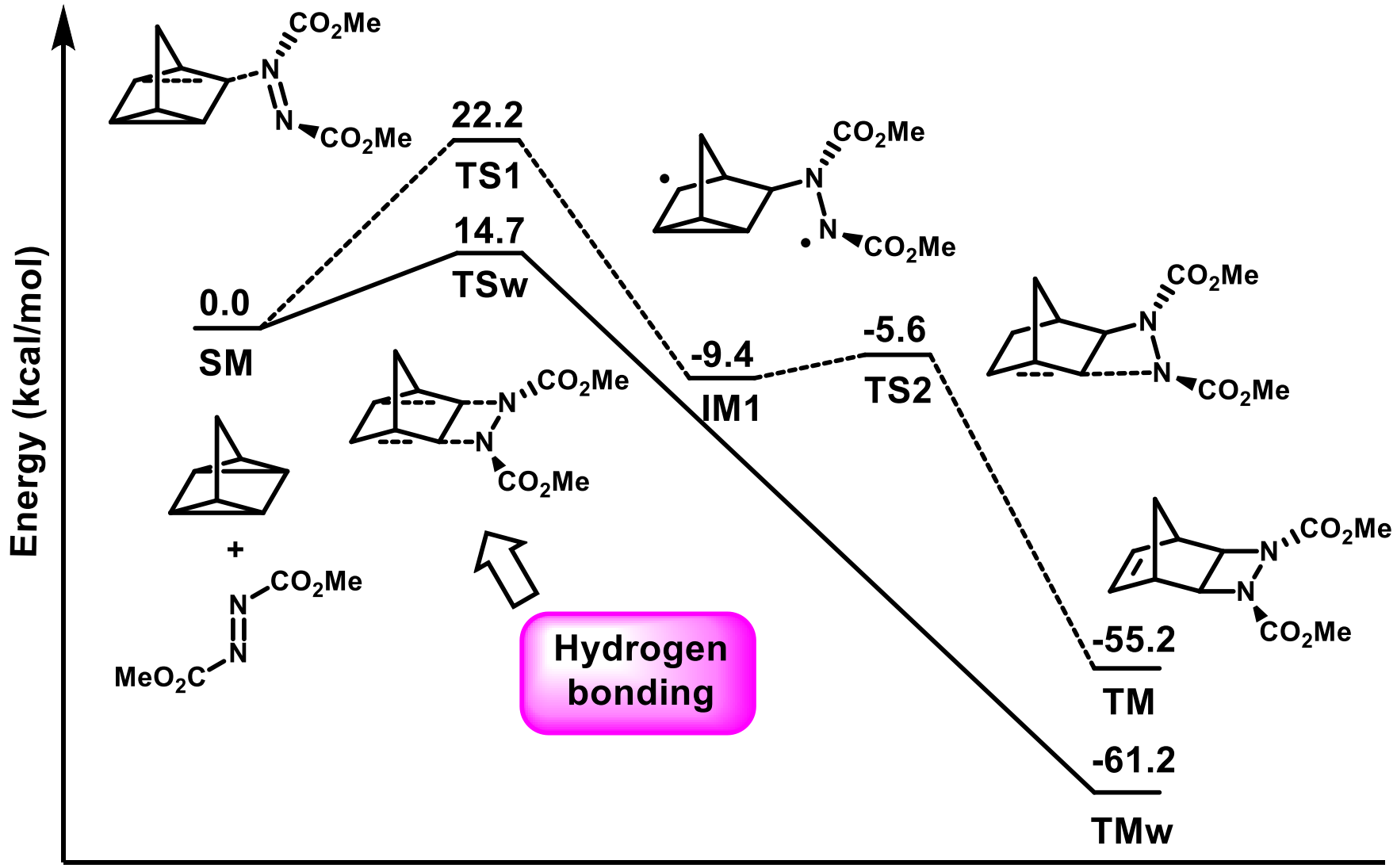
***k (theory) was caluculated from DFT calculation data**

- **Assign the surface condition for k_N ... $k_N = 9.5 \times 10^{-4}\ (s^{-1})$**

⇒ **The modeling of surface reaction is appropriate**

Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

TS study (without vs with water)

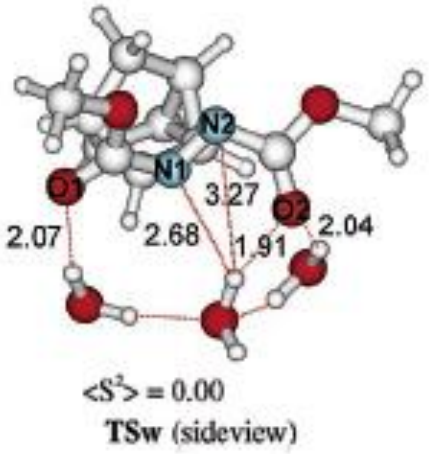


Energy diagram calculated by DFT (UB3LYP/6-31+G(d))

Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

H-bond availability (in vs on water)

TSw



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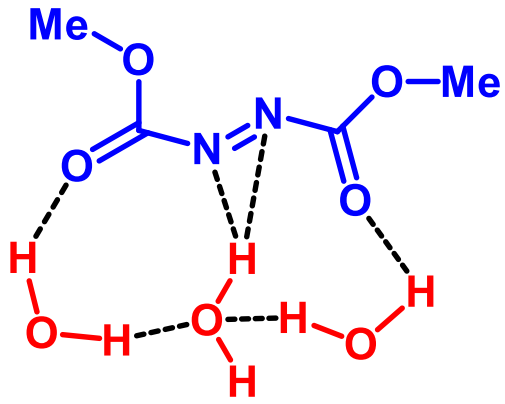
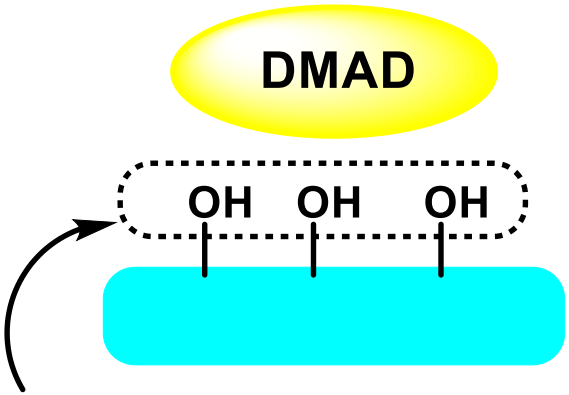


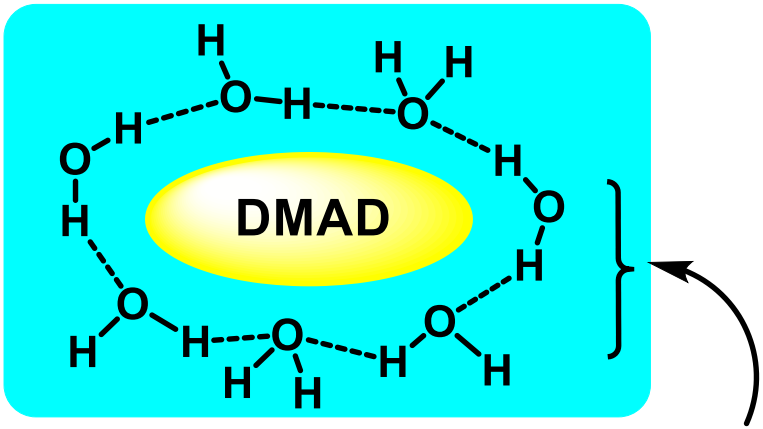
TSw (DMAD + hydrogen bond)

"on water"



Free "dangling OH" (DMAD-H-bond: 2-4 kcal/mol)

"In water"

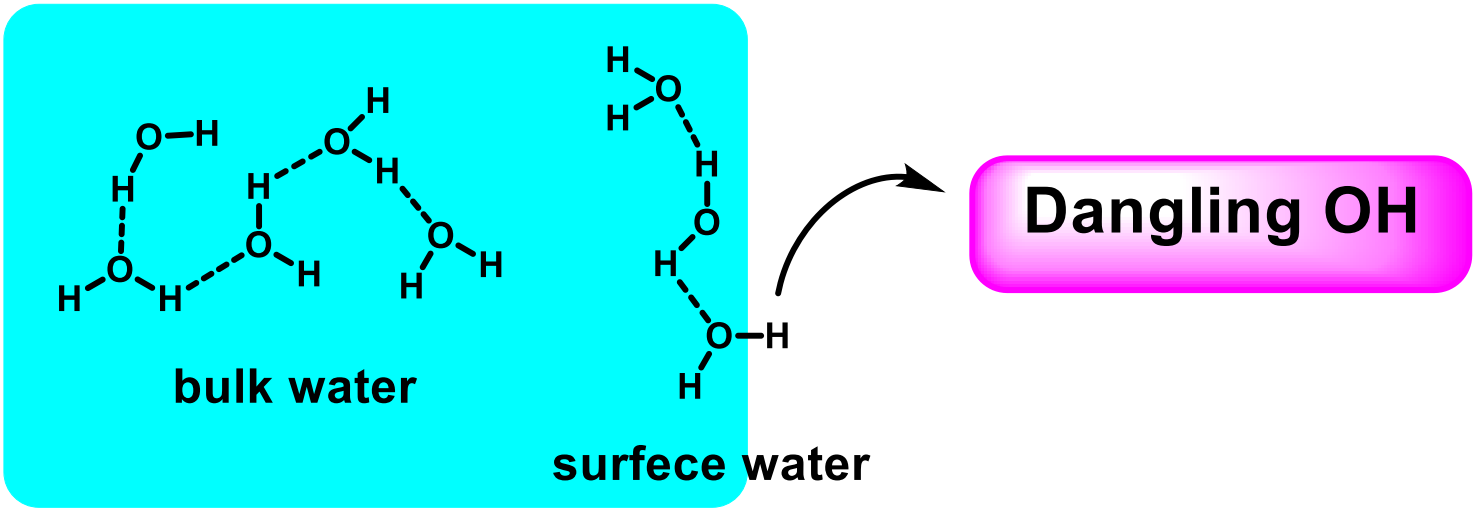


Required to break H-bond network (5 kcal/mol)

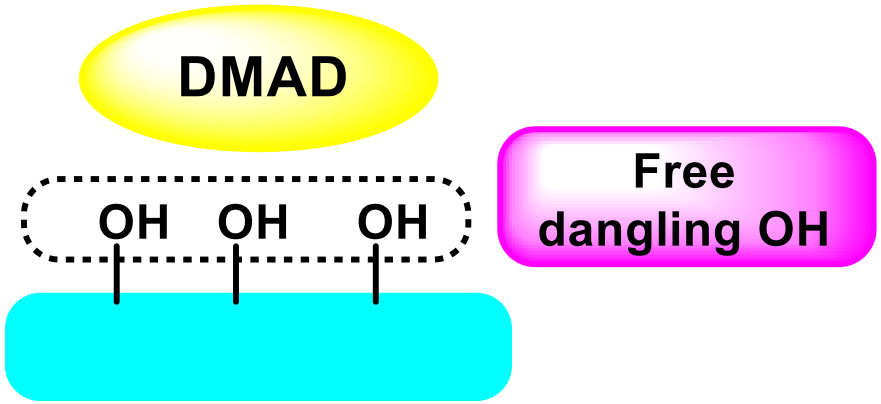
Marcus, R. A., Yousung, J. *J. Am. Chem. Soc.* **2007**, *129*, 5492-5502

Short summary

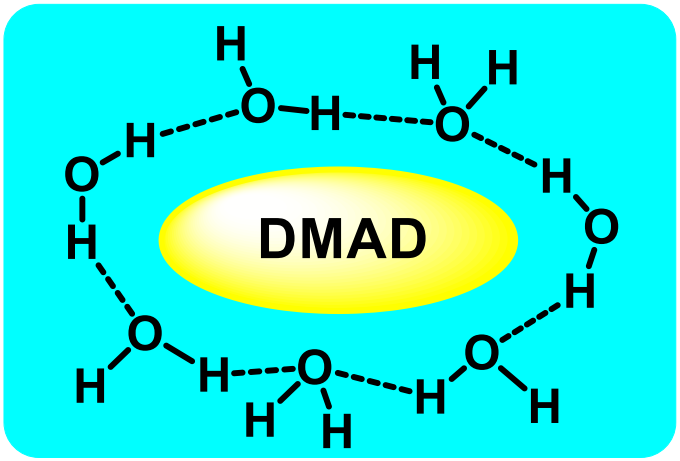
The difference between on & in water



"on water"



"In water"



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3. Application of "on water"

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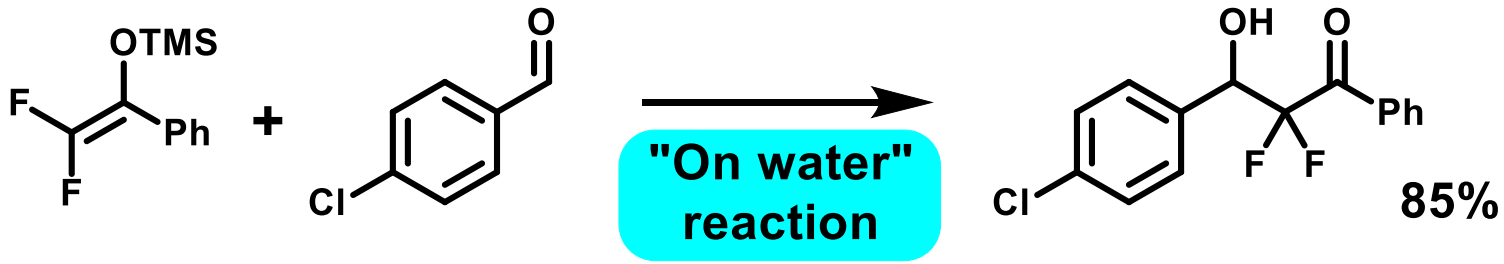
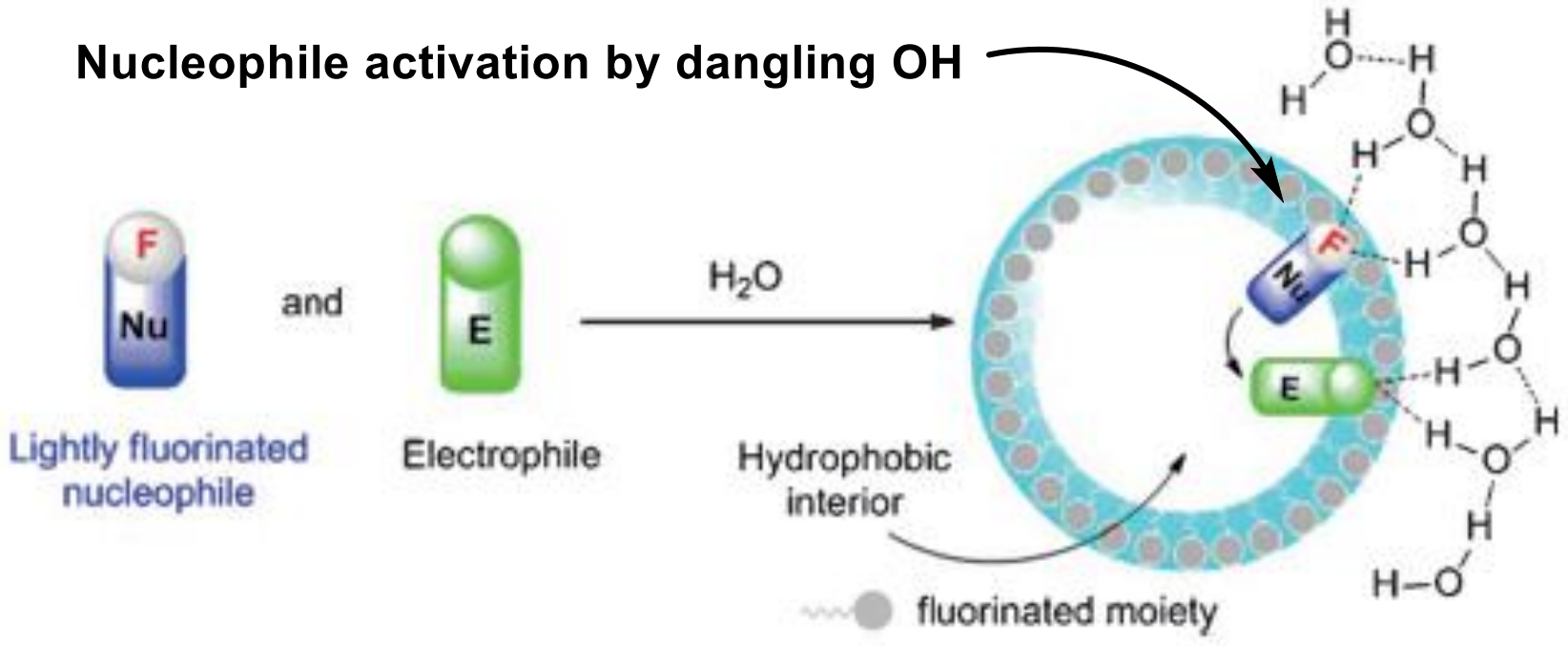
4. Summary

Fluorine effect : Aldol reaction on water

Aldol reaction using di-F-enoxysilane



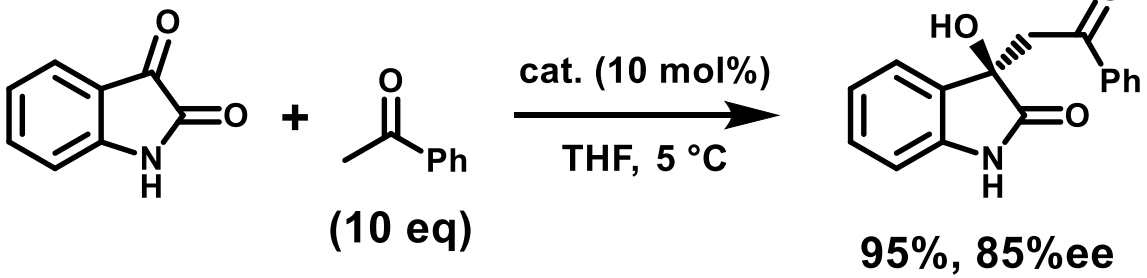
Nucleophile activation by dangling OH

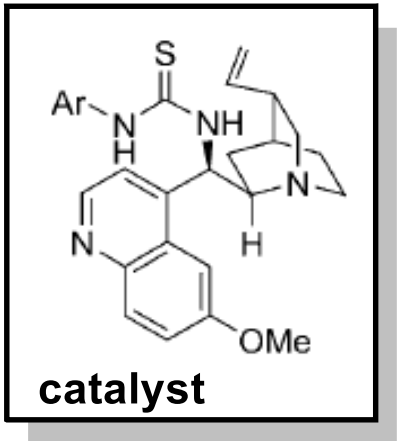


Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

Previous research background

Aldol reaction of unactivated ketone

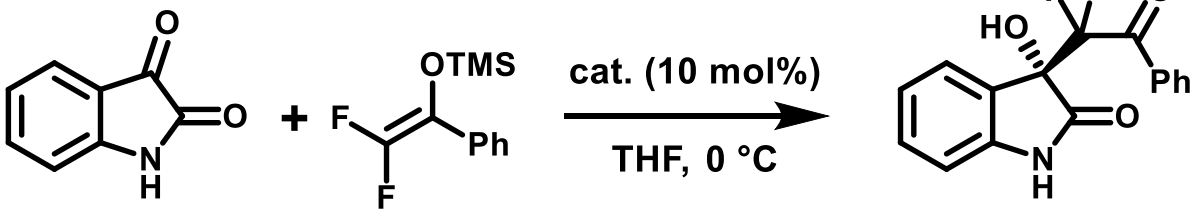


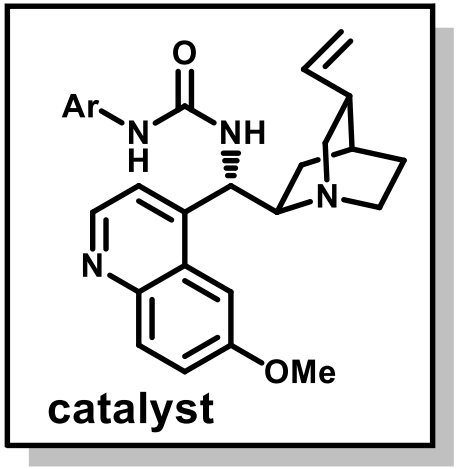


(Ar = 3,5-$(CF_3)_2$-C_6H_3)

Zhou, J. *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 9460-9464

Aldol reaction of difluorinated enoxysilane

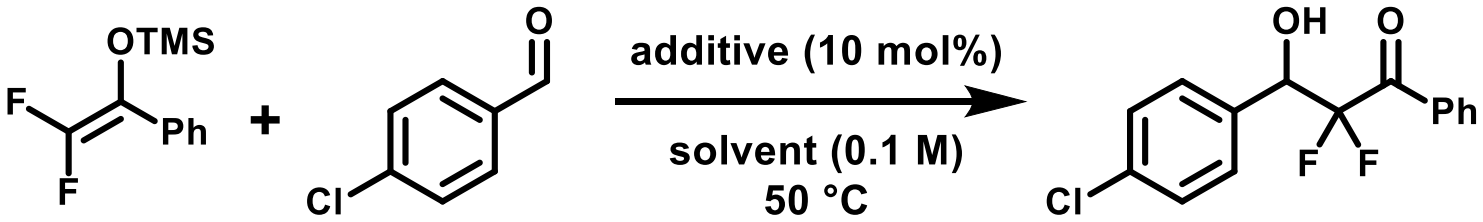




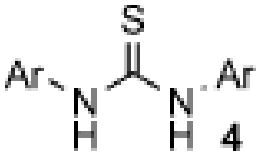
(Ar = 3,5-$(CF_3)_2$-C_6H_3)

Zhou, J. *et al. Chem. Commun.* **2012**, *48*, 1919-1921

Solvent effect



(2 eq) (1 eq)

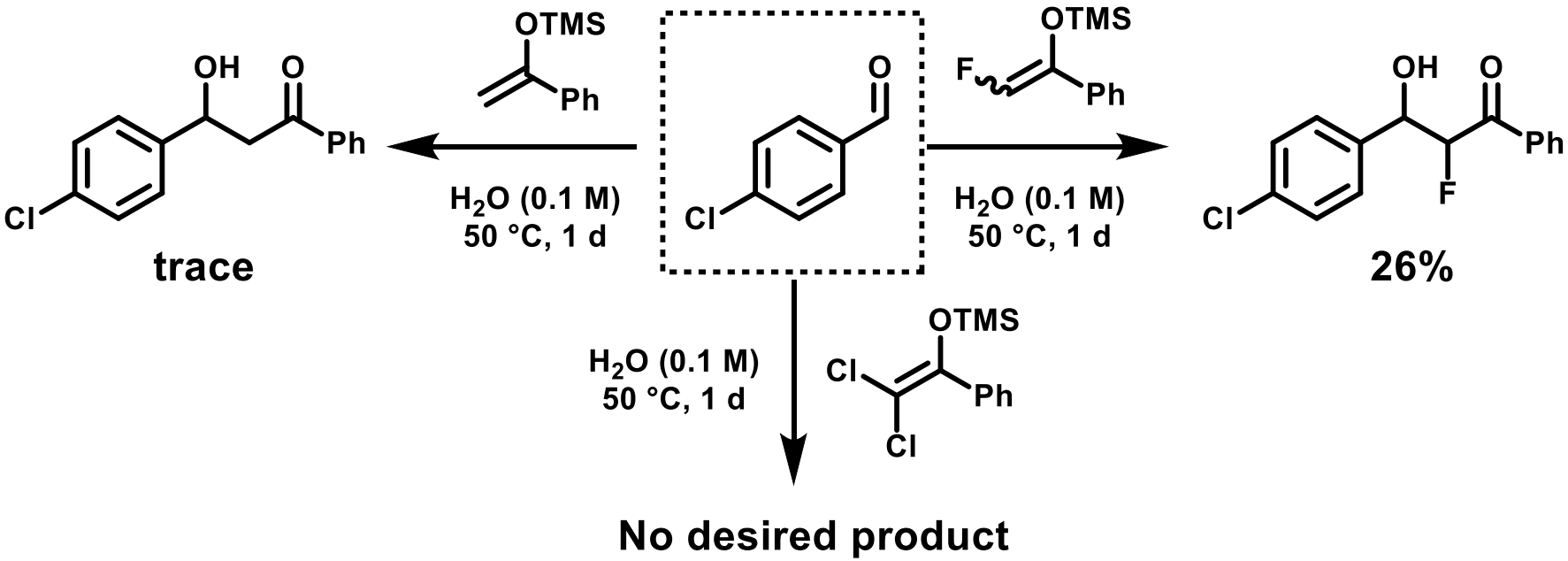
Solvent	Additive	*t* [h]	Yield [%][b]
H_2O	–	10	85
THF	DMAP	72	10
THF	 4	144	43
THF/H_2O[c] (=7/1, Homogeneous)		24	21
H_2O	$PhSO_3H$	10	70
H_2O	4-$C_{12}H_{25}C_6H_4SO_3H$	10	77
H_2O	$C_{12}H_{25}SO_3Na$	10	79
neat	–	10	–

(Ar = 3,5-CF_3-C_6H_3)

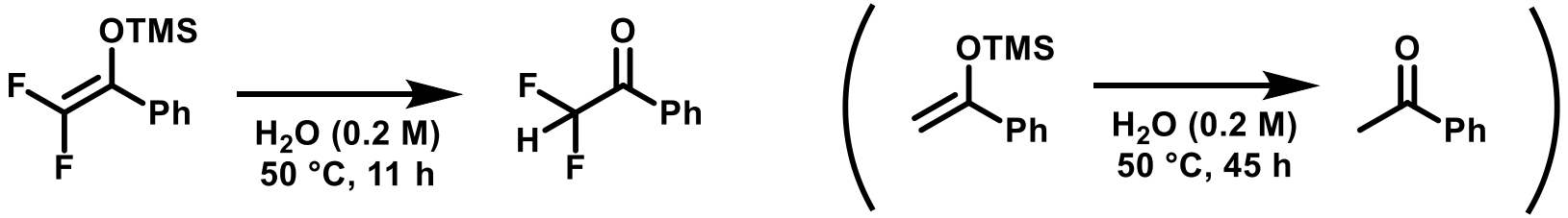
Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

Difluorine effect on water

Importance of di-F-enoxysilane



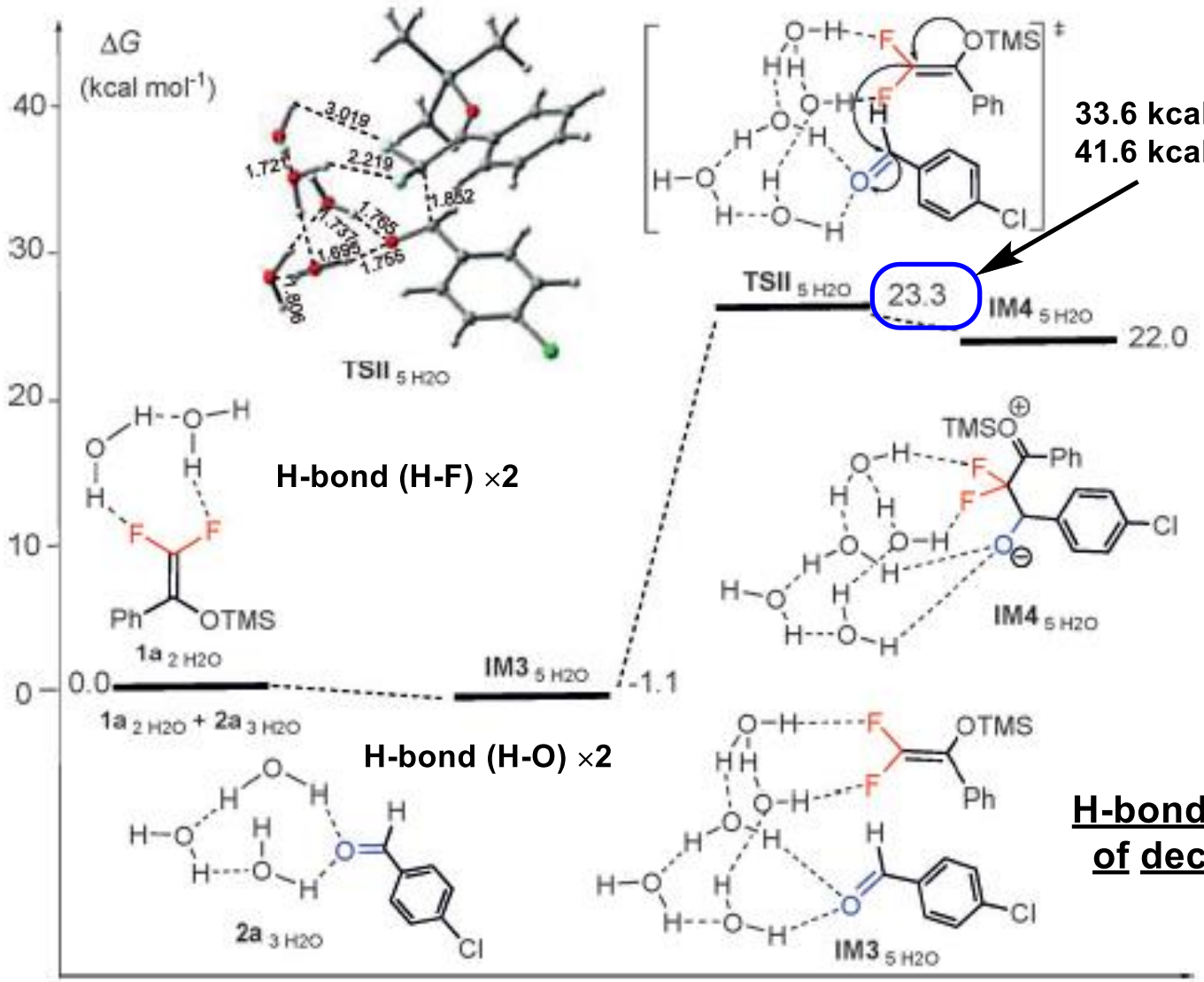
Hydrolysis of di-F-enoxysilane



Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

DFT calculation

Five-water model

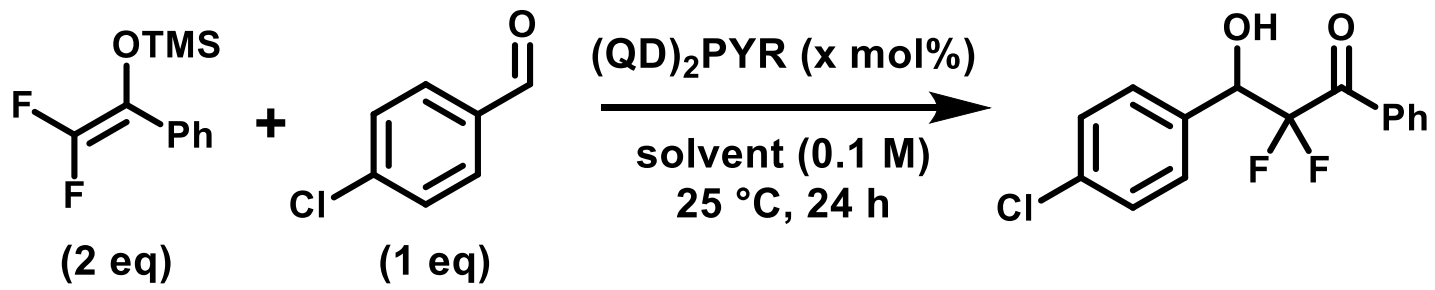


H-bond of H-F is important of decreasing TS energy

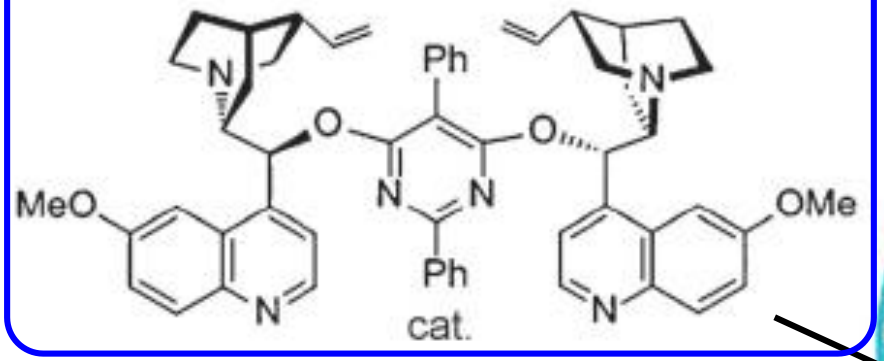
Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

Asymmetric aldol reaction on water

Chiral Lewis base catalyst



$(QD)_2PYR$

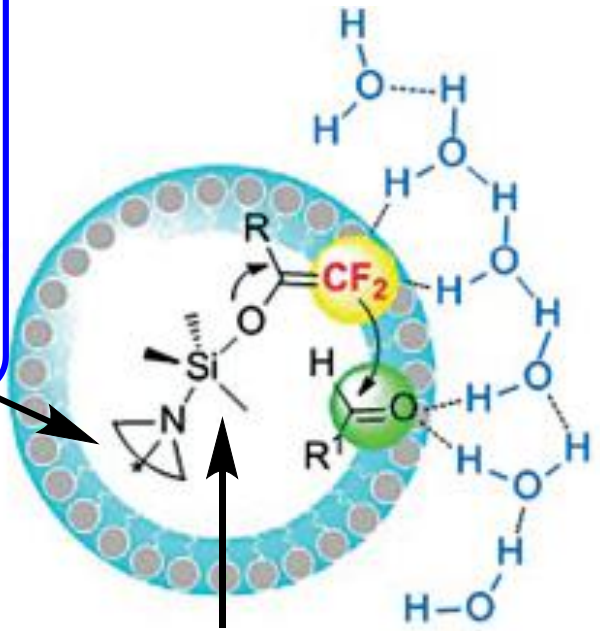


In H_2O, x = 10 mol%, 73%, 39% *ee*

In H_2O, x = 20 mol%, 74%, 48% *ee*

In H_2O, x = 30 mol%, 81%, 53% *ee*

In THF, x = 10 mol%, 15%, 67% *ee*

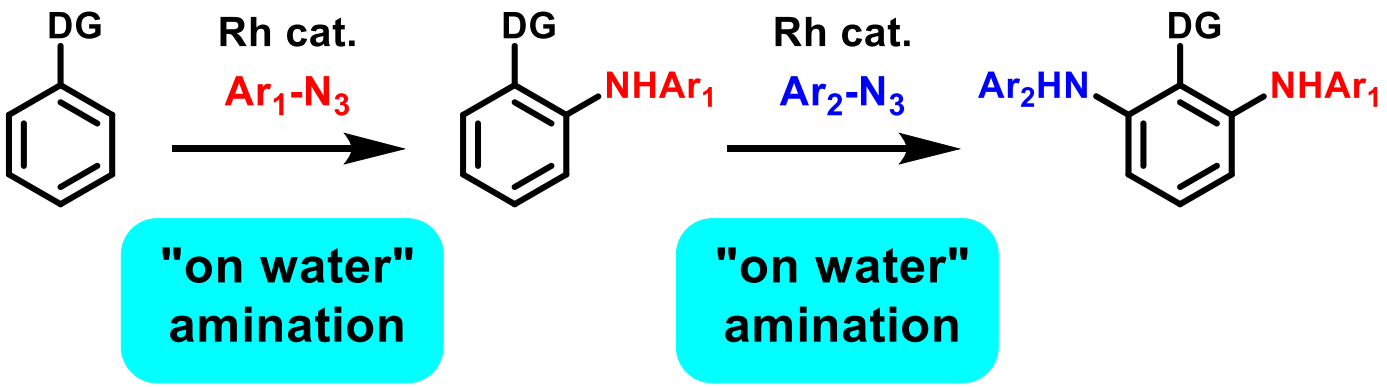


hydrophobic Si moiety

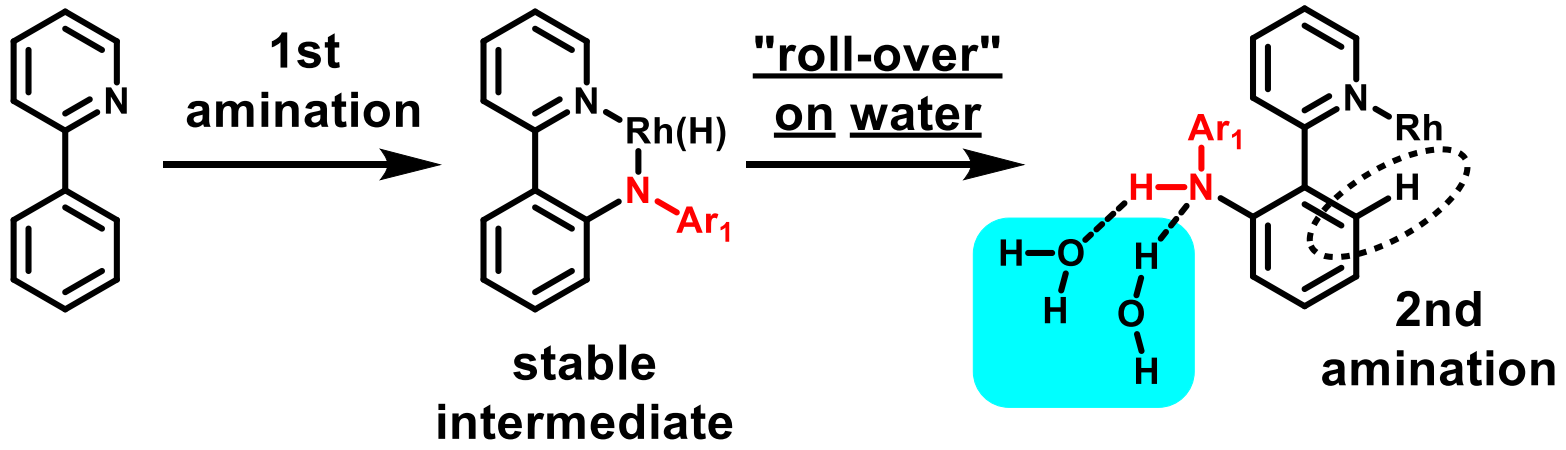
Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

C-H activation : *ortho*-Diamination on water

C-H activation "on water"



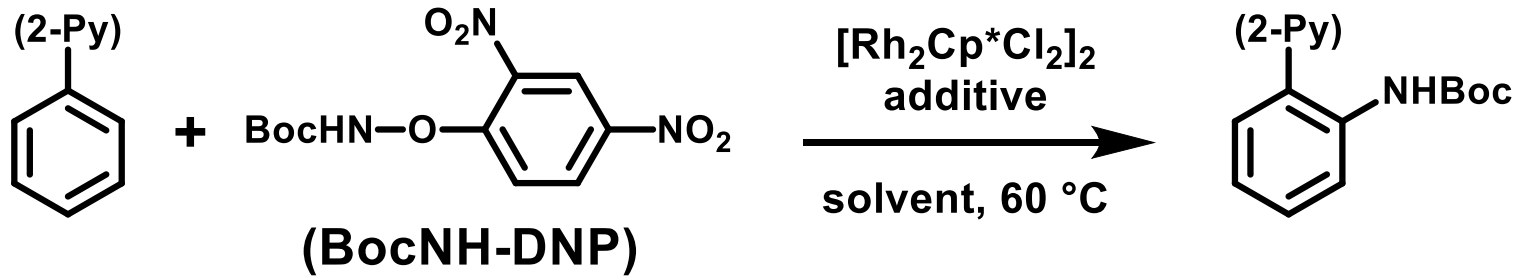
"Roll-over" promoted by H_2O



Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

C-H amination “on water”

Boc amintaion

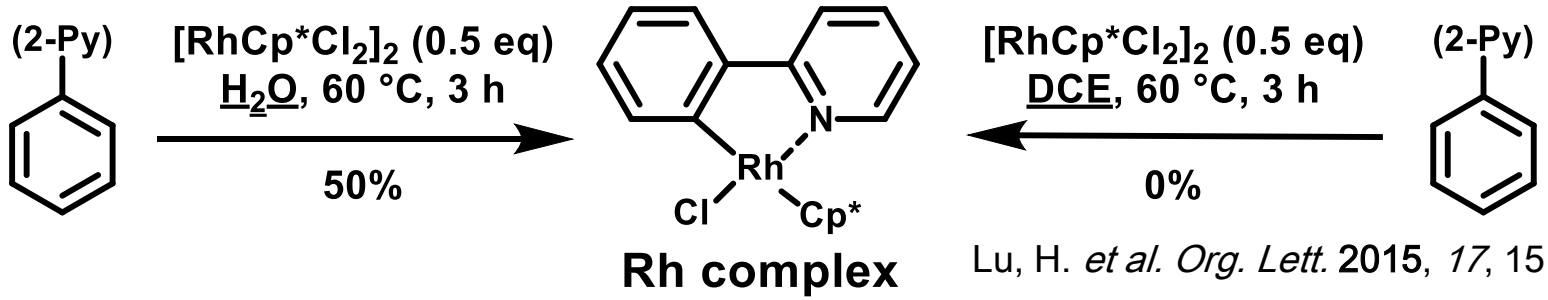


cat. load (mol%)	additive	solvent	time	TM yield (%)
4		H_2O	3 h	88 (i.y. 82)
4		H_2O	10 min	70
2		H_2O	16 h	83
1		H_2O	16 h	65
4	$AgSbF_6$ (8 mol%)	H_2O	3 h	85
4	$NaHCO_3$ (1 eq)	H_2O	3 h	90
4		organic solv.	3 h	<5
4		hexane	3 h	8
4		DMF	3 h	11
4	H_2O (0.2, 1, 10 eq)	DCE	3 h	<5
4	H_2O (10 eq)	IPA	3 h	8
4		- (neat)	16 h	25

Lu, H. *et al. Org. Lett.* **2015**, *17*, 1513-1516

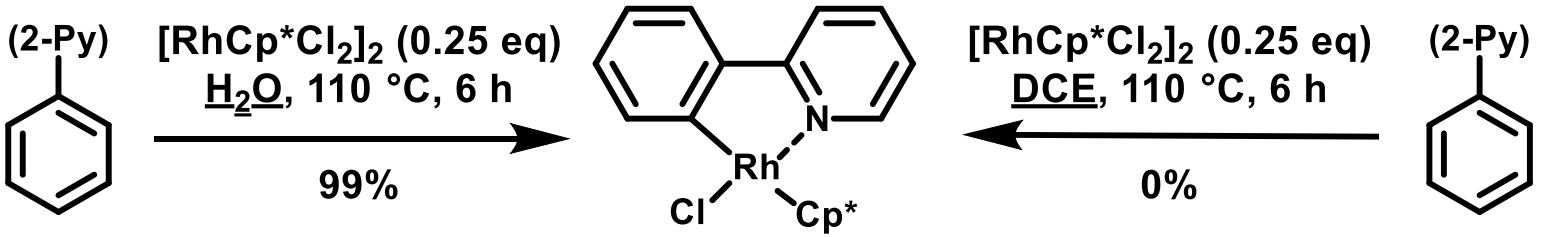
Necessity of “on water” condition

Formation of Rh complex



Rh complex

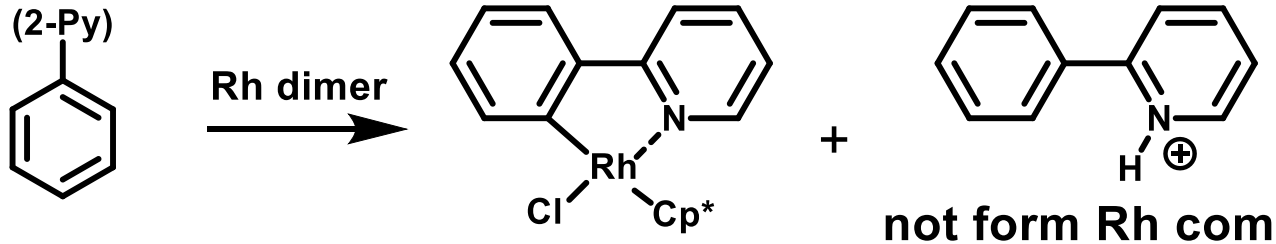
Lu, H. *et al. Org. Lett.* **2015**, *17*, 1513-1516



Rh complex

Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

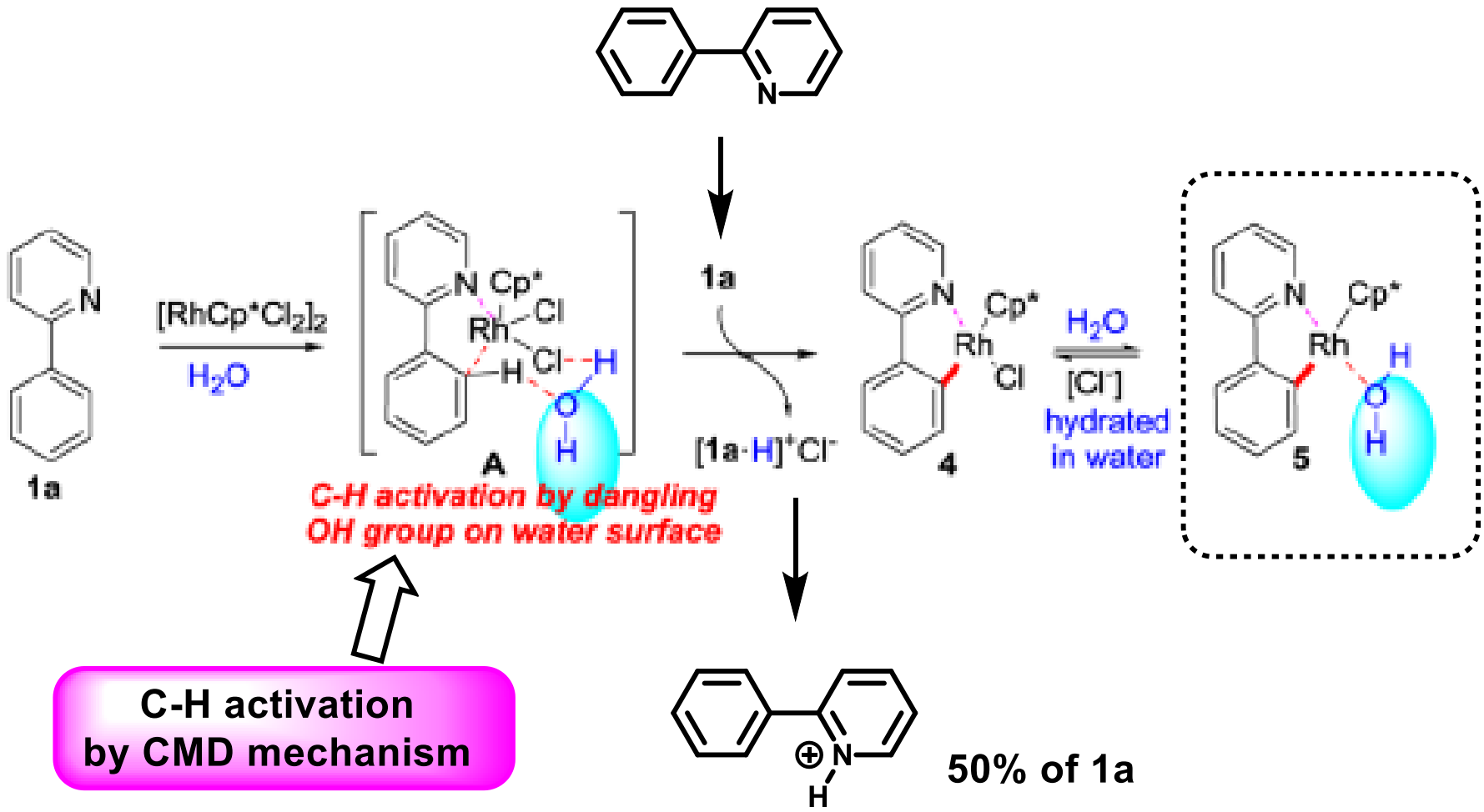
H_2O is important for C-H activation



not form Rh complex

Proposed mechanism

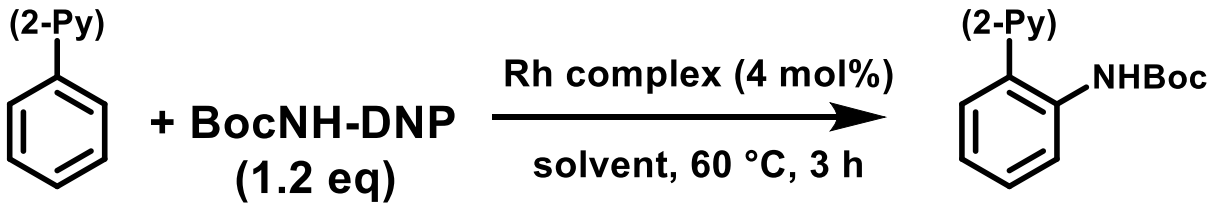
H_2O promoted Rh complex formation



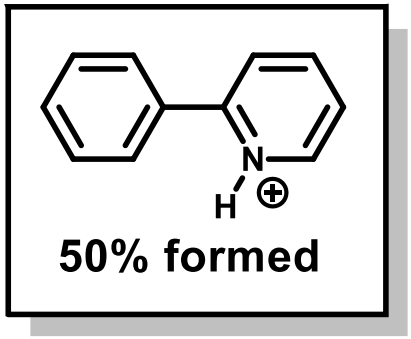
Lu, H. *et al. Org. Lett.* **2015**, *17*, 1513-1516

Mechanical study

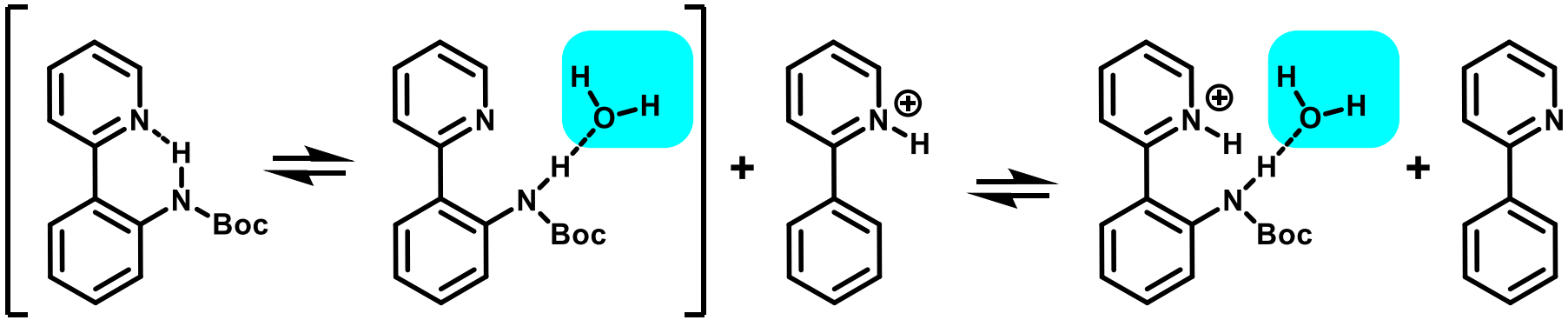
Amination with Rh complex



solvent	condition	yield (%)
H_2O		83
DCE		46
DCE	time : 12 h	48
DCE	additive : $NaHCO_3$ (1 eq)	83



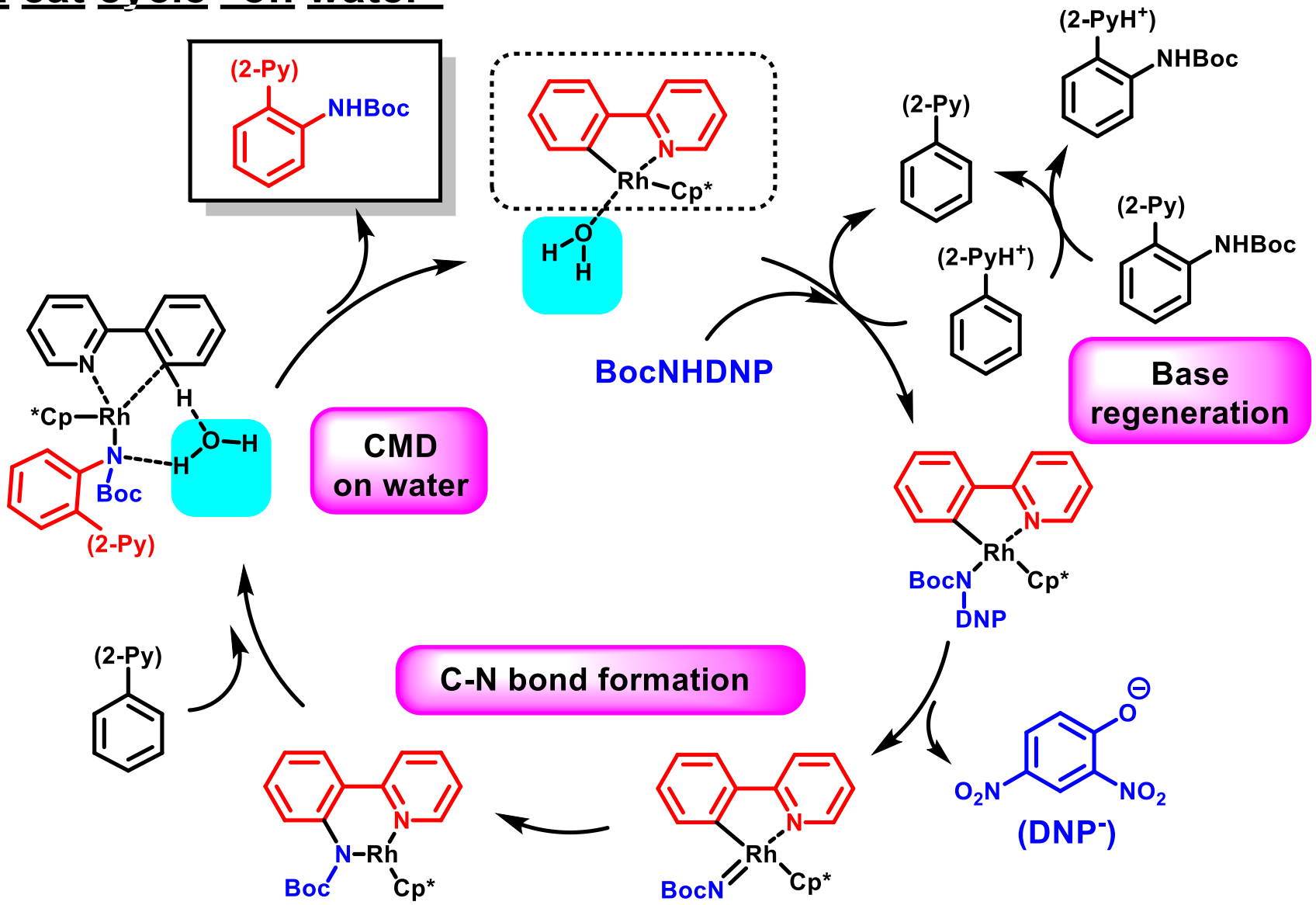
Regeneration of ppy "on water"



Lu, H. *et al. Org. Lett.* **2015**, *17*, 1513-1516

Proposed mechanism

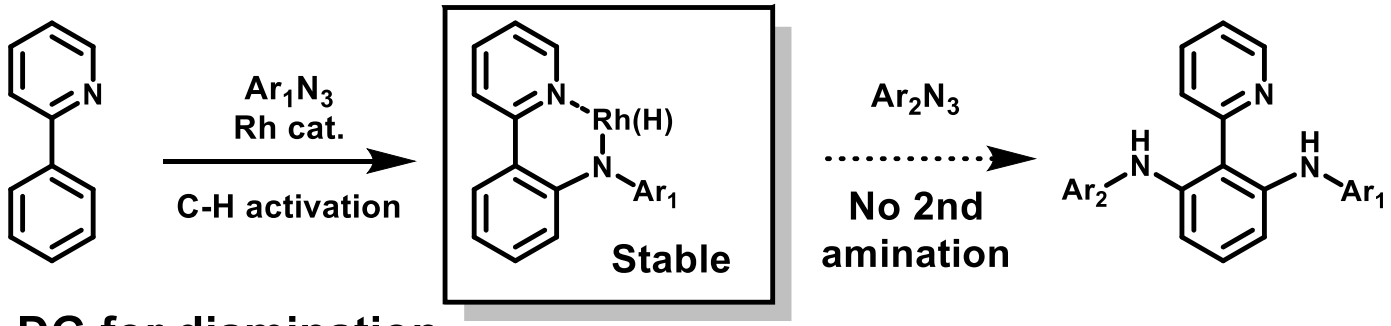
Rh cat cycle "on water"



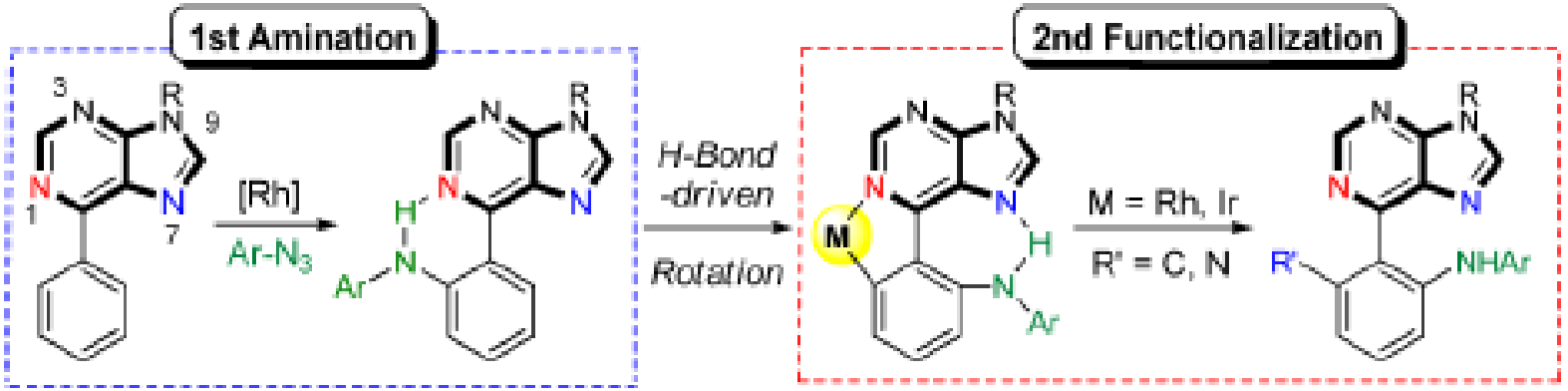
Lu, H. *et al. Org. Lett.* **2015**, *17*, 1513-1516

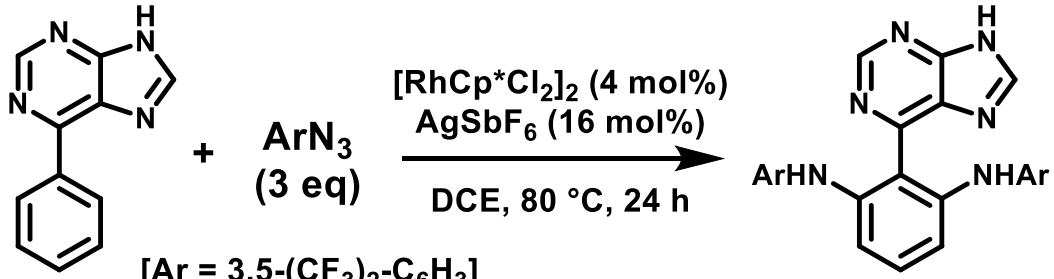
Research background of *ortho*-diamination

Problem of difunctionalization



Purine as DG for diamination





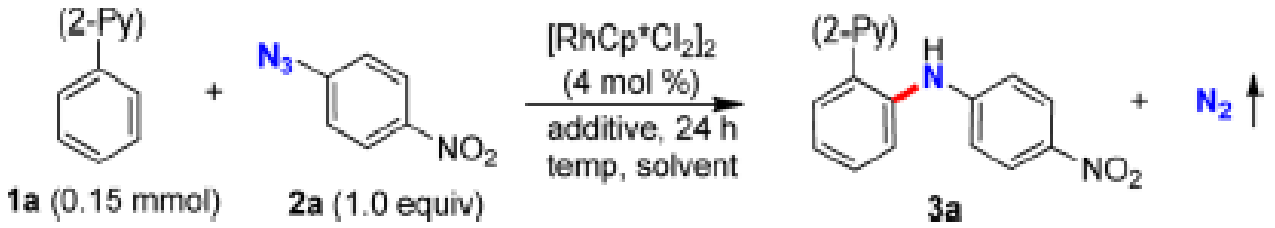
Excess eq of ArN_3
Induce the same NHAr group (one-pot)
Asymmetric amination (two-pot)

95% (< 1% monoNHAr)

Chang, S. *et al. J. Am. Chem. Soc.* **2014**, *136*, 1132-1140

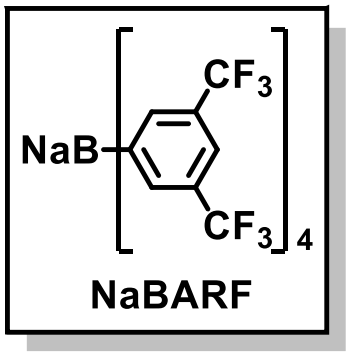
Monoamination “on water”

Solvent & additive effect



1a (0.15 mmol) **2a** (1.0 equiv) **3a**

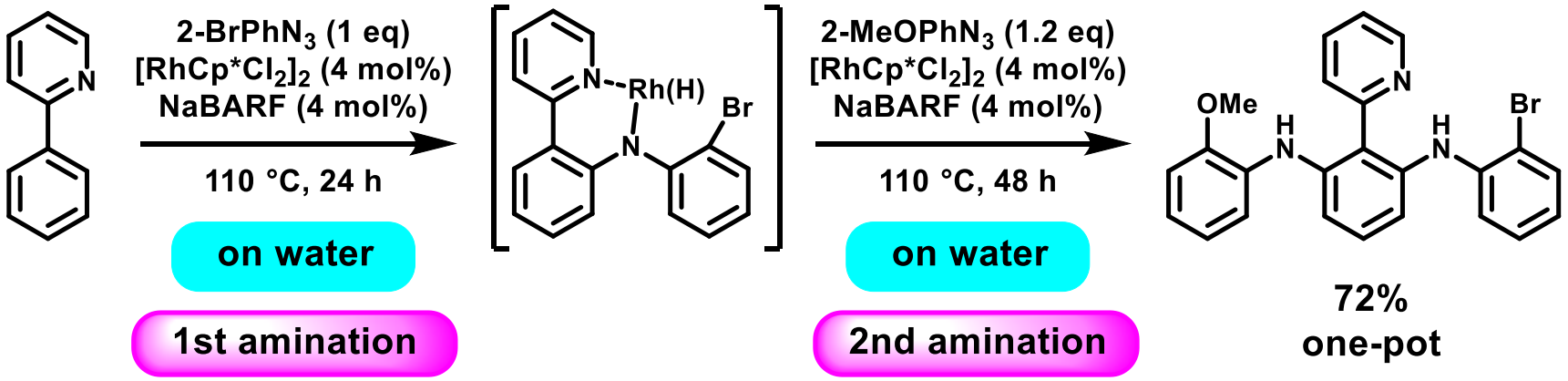
entry	additive (mol %)	solvent	temp (°C)	yield[a] (%)
1	$AgSbF_6$ (16)	H_2O	80	50
2	none	H_2O	80	2
3	$AgCO_3$ (16)	H_2O	80	11
4	$AgBF_4$ (16)	H_2O	80	88
5	NaBARF (16)	H_2O	80	95
6	NaBARF (4)	H_2O	80	90
7	NaBARF (16)	H_2O	110	99
8	NaBARF (4)	H_2O (24 h)	110	99
9[b]	NaBARF (2)	H_2O (Rh cat. 2 mol%)	110	74
10[c]	NaBARF (4)	H_2O (12 h)	110	80
11[d]	NaBARF (4)	organic solvents	110	<10
12	NaBARF (4)	neat	110	<5



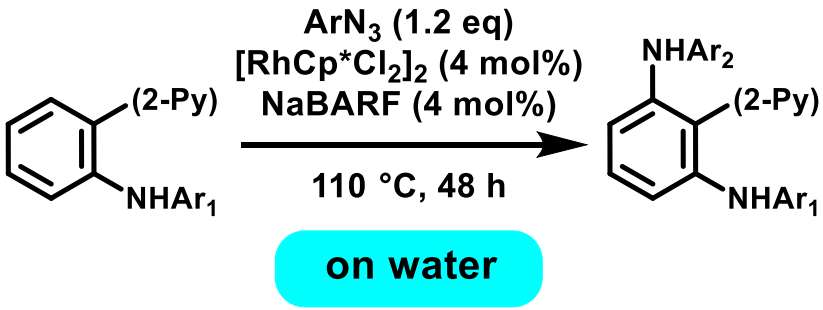
Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

Diamination “on water”

Asymmetric diamination in one-pot



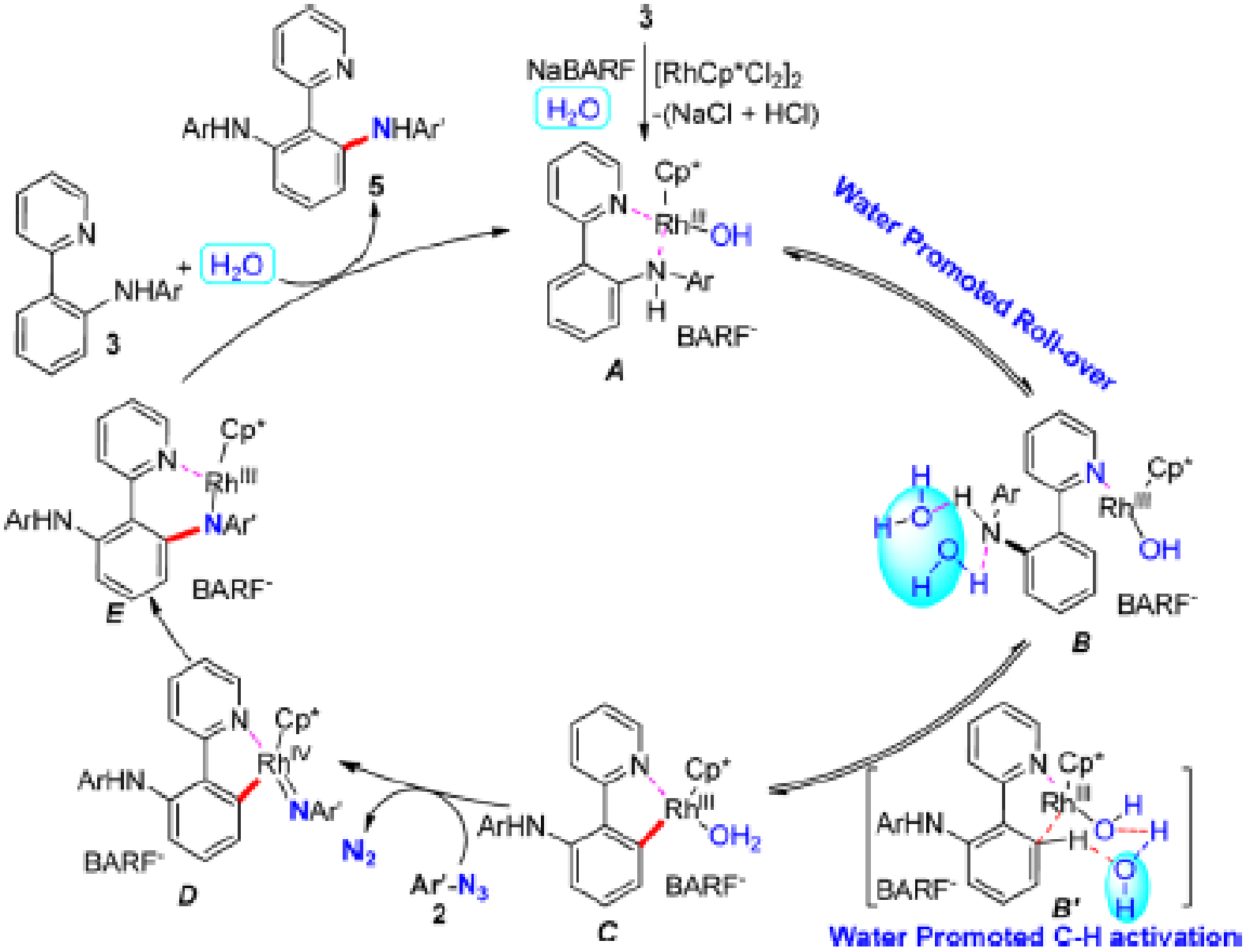
Substituent effect of 2nd amination



1st ortho	1st para	2nd ortho	2nd para	yield (%)
Br	H	Br	H	90
Br	H	MeO	H	96
H	CO_2Et	Br	H	83
H	NO_2	Br	H	72
Br	CO_2Et	Br	H	92
I	Cl	Br	H	90
MeO	H	Br	H	29
Br	H	H	CO_2Et	10
Br	H	H	NO_2	28

Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

Proposed mechanism of diamination



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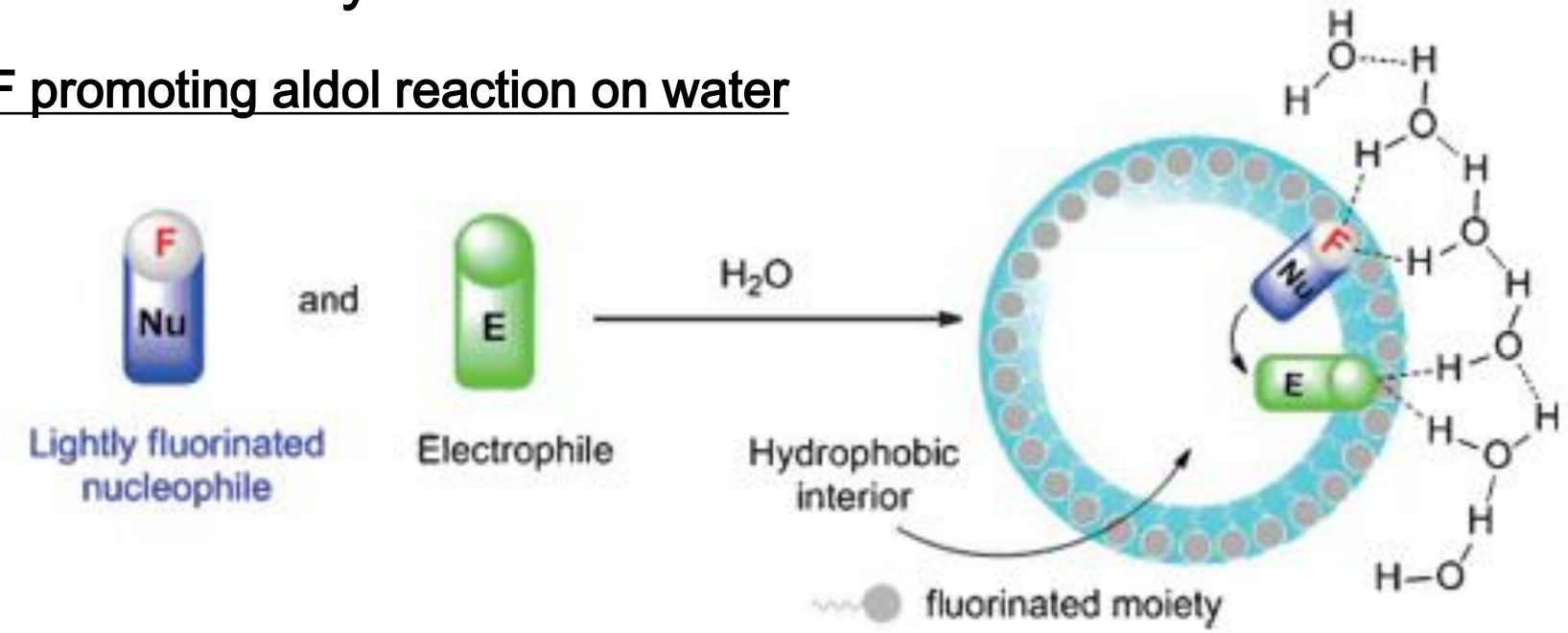
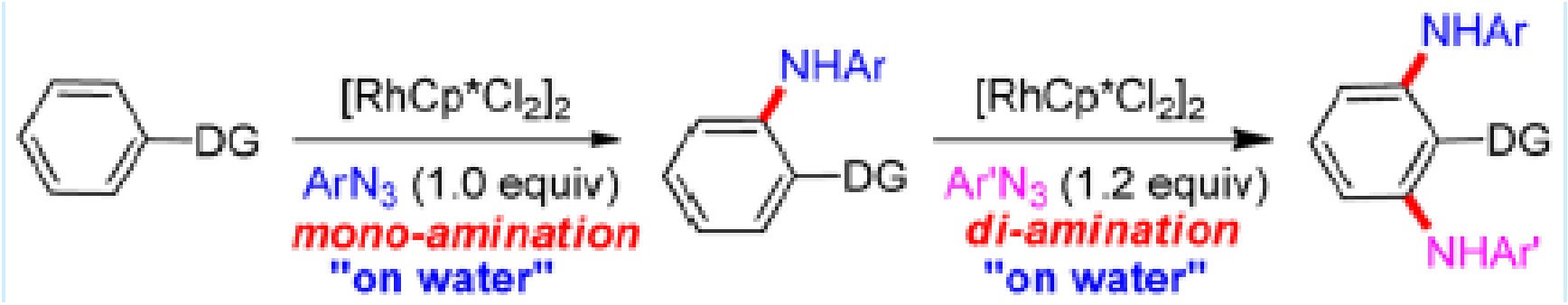
Short summary

Di-F promoting aldol reaction on water



Zhou, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9512-9516

Difunctionalization by "roll-over" on water



Lu, H. *et al. Org. Lett.* **2016**, *18*, 1386-1389

Today's topic

1. Introduction

2. Investigation of "on water"

   -Bulk & surface water
   -Theoretical study of DA

3. Application of "on water"

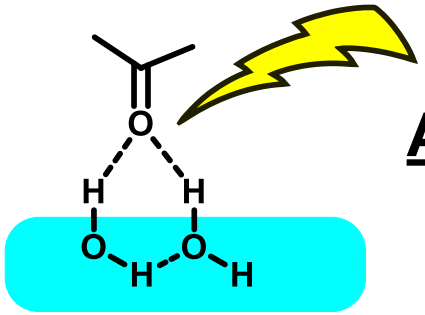
   -Fluorine effect (aldol reaction)
   -*ortho*-Diamination (C-H activation)

4. Summary

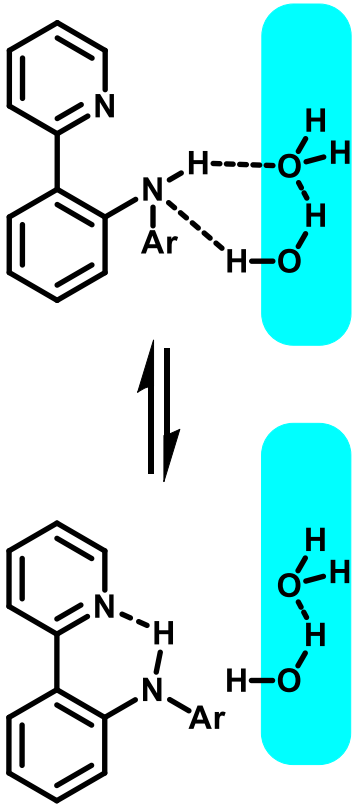
Summary

Characters of on water reaction

- Catalysed by “dangling OH”
- H-bond activation of O, F... atoms
- Break intramolecular H-bond



Activation



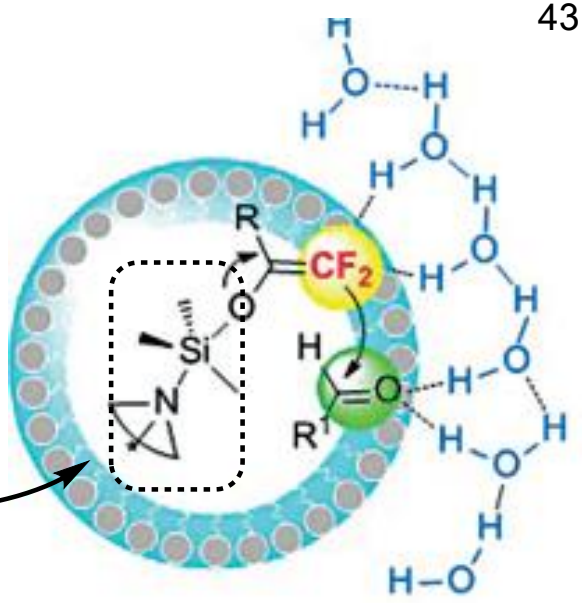
Problematic points of on water reaction

- ☹Low generality ... substrate, metal etc
- ☹Few reports of asymmetric reaction

Future : Organocatalyst on water?

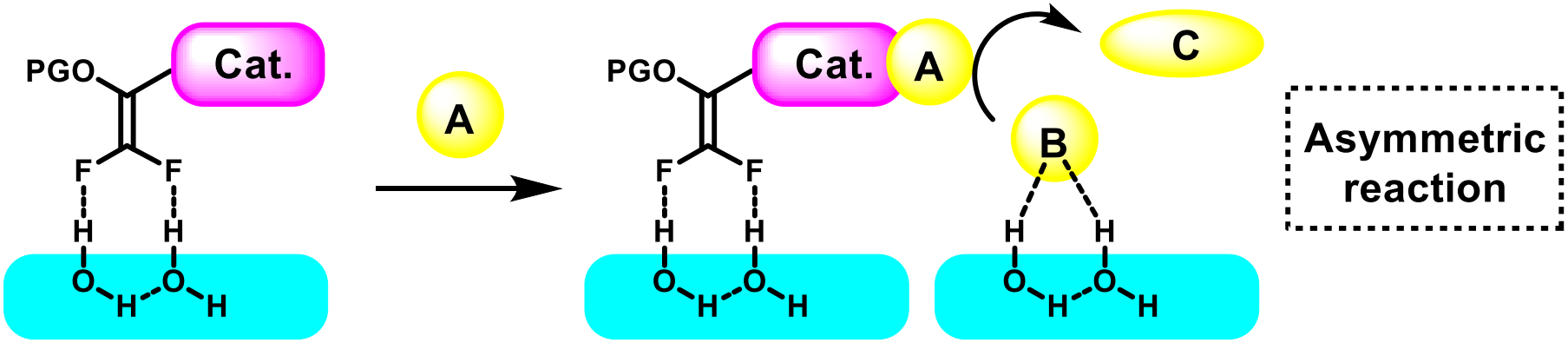
Reaction promoted “on water”

- Activation from hydrophobic site



Reaction not promoted “on water”

- Organocatalyst containig surface recognition moiety
  → Site-selectivity?



Q & A

Q.
On waterって結局は特殊な水素結合を使うという感じだが、
ウレア触媒に比べたメリットがあるのだろうか？（コスト面以外で）

A.
現状存在する有機溶媒中のウレア触媒を活かした不斉反応などと比較するとon waterの不斉反応は例が少なく現段階ではまだメリットが少ないように感じました。On waterは反応剤同士が近傍にある二ート＋水素結合という環境なので、（例えばfutureのような）触媒デザインが確立できれば高濃度条件で早く反応が進行できるというメリットが出てくるのではないかと思います。

Q.
スライド１４、on H_2Oとon D_2Oの違い

A.
これは水と重水の粘度の差による撹拌効率が影響しているといわれています。重水の方が水より粘度が高く撹拌時に生じる油滴半径が大きくなるため反応の完結が遅くなります。（水素結合の強さによる差が原因ならKIEが5~7となるそうですが、今回の反応ではKIE=1.2と影響が小さく水素結合による差ではない要因であると推測できます。）←Marcusらの論文よりJACS 2007,5492

Q.
スライド３８、電子豊富なアリールアミンを先に入れるとダメで後に入れると上手くいく理由はなぜ

A.
このアミノ化における律速段階はアジドがRh錯体に配位する所で、前段階のroll-overやC-H活性化は可逆であることが分かっています。となると反応性は一つ目のアミノ化が終わった基質(分子内安定化あり)と二つ目のアジドの配位能との比較で収率への影響が決まります。一つ目が電子豊富だと分子内安定化が大きいためroll overが遅くなり、かつ二つ目の電子不足なアジドが配位しにくくなるため反応性が低下します。
逆にいえば二つ目のアジドを電子豊富にすることでアジドの配位を有利にし反応の進行につながります。

Q.
海水や水道水みたいな不純物の含まれた水でも使えるのか

A.
実際に使用した例は分かりませが、LiCl塩をいれると疎水分子がより分離しやすくなるなど何かしらの塩を添加することで反応性に影響を与えることはありうると思います。
ちなみに、アンモニアの添加はdangling OHの水素を非共有電子対がトラップしてしまい水素結合による加速を奪ってしまうという負の効果をもたらす添加物の存在なども報告されるため、何でも加えればいいという訳ではなさそうです。（参考：J. Phys. Chem. A 2013, 2446-2454）