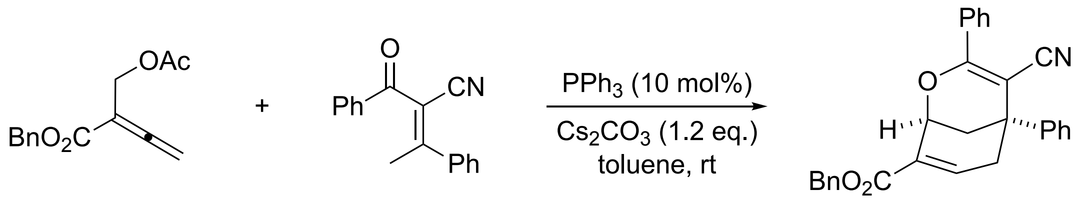
Problem Session (5)

2018. 8. 25. Daiki Kamakura

1) Please provide the reaction mechanisms.
2) Please fill in the blanks **3-4** and **3-5**.

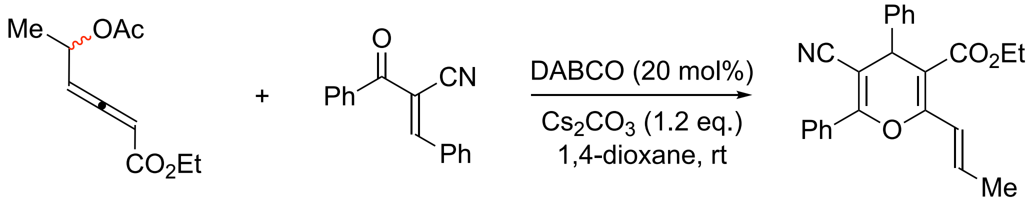
1



1-1 **1-2** 87% **1-3**

2

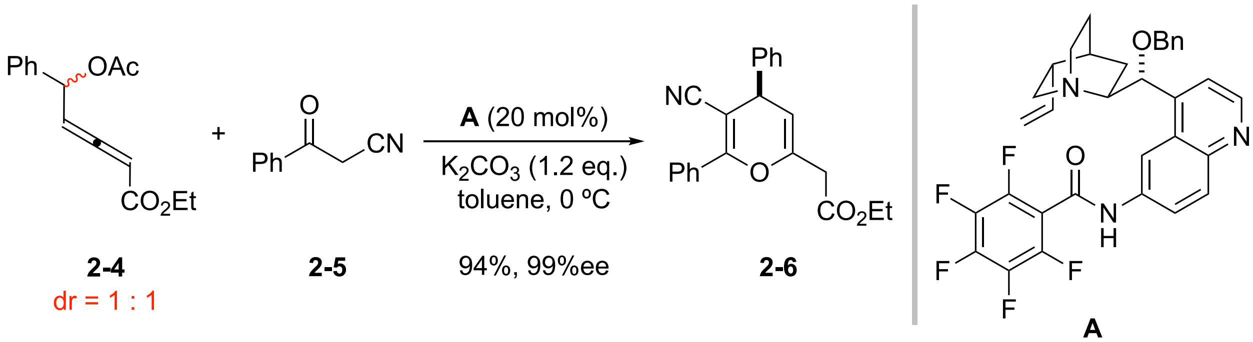
(1)



2-1 **2-2** 80% **2-3**

dr = 1 : 1

(2)

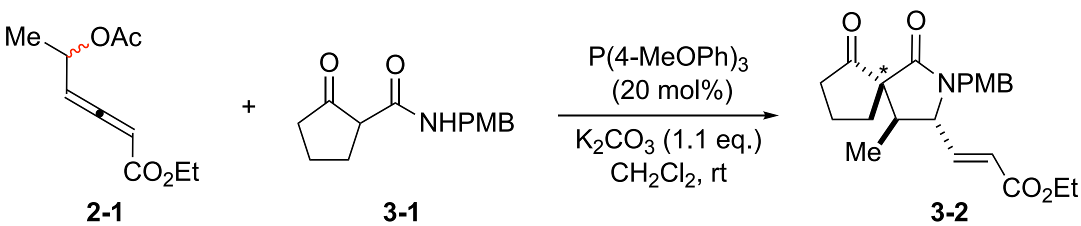


2-4 **2-5** 94%, 99%ee **2-6** **A**

dr = 1 : 1

3

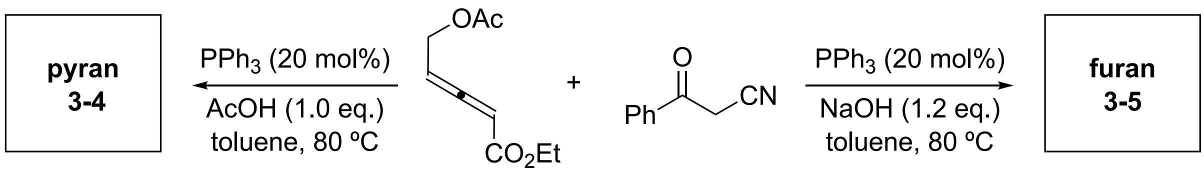
(1)



2-1 **3-1** 76%, dr = 8.3 : 1 **3-2**

dr = 1 : 1

(2)



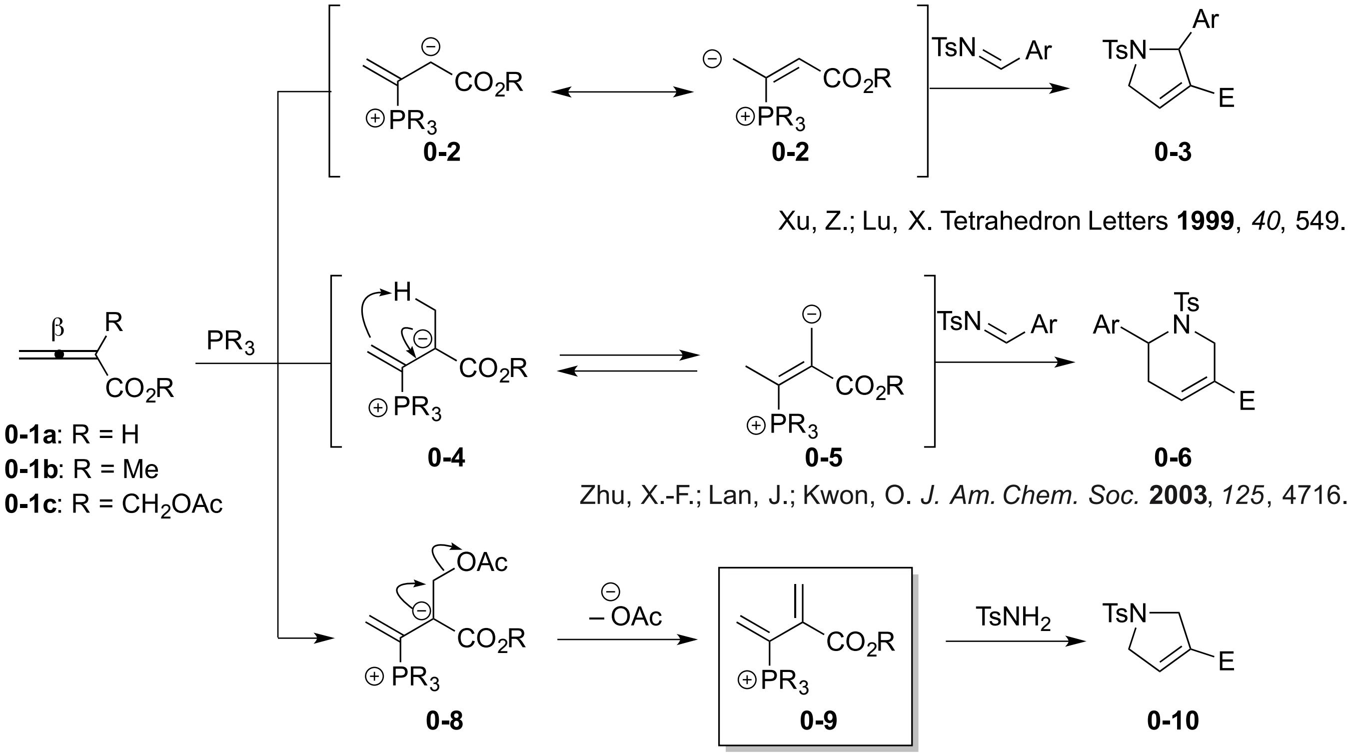
58% **3-3** **2-5** 70%

Problem Session (5)-Answer

2018. 8. 25. Daiki Kamakura

Topic: Reactions of acetoxy allenoate with nucleophilic catalysts

0-1. Introduction

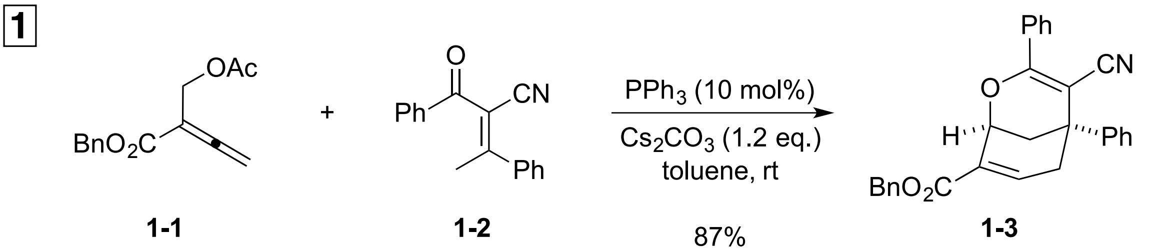


Xu, Z.; Lu, X. Tetrahedron Letters **1999**, *40*, 549.

Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

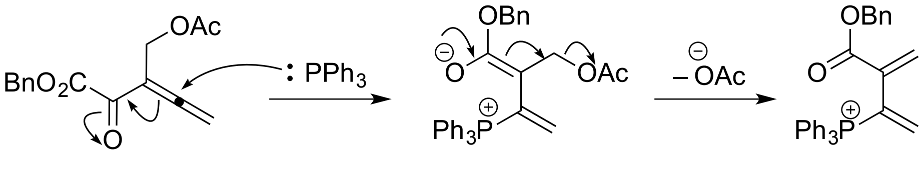
Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Sos.* **2010**, *132*, 2550.

1

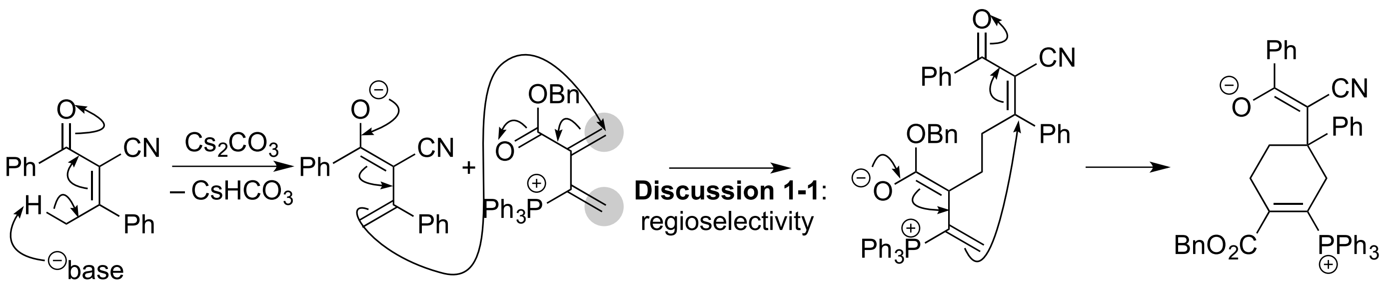


Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400.

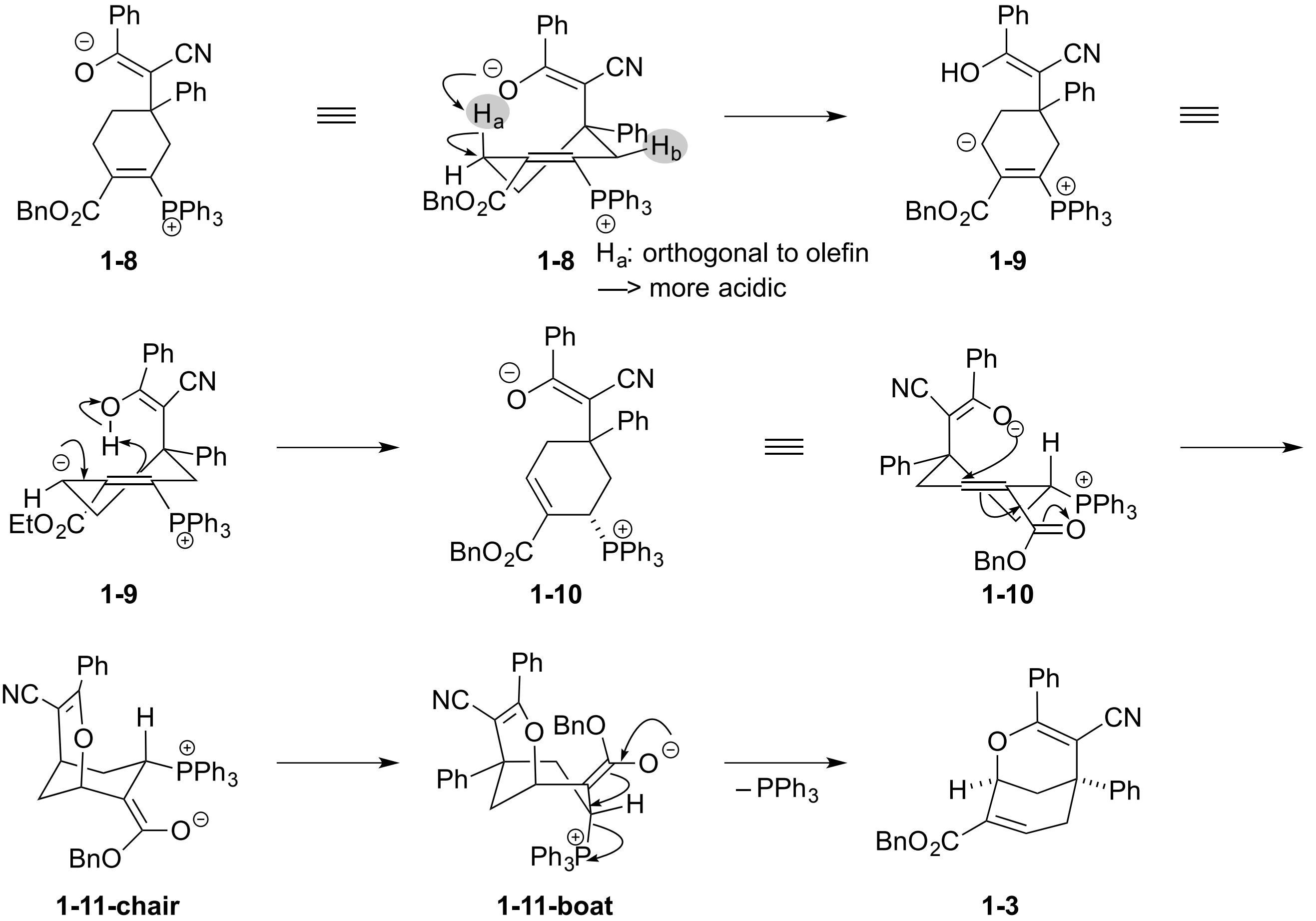
Answer:



1-1 1-4 1-5

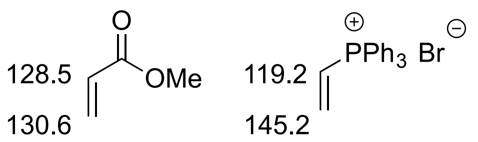


1-2 1-6 1-5 1-7 1-8



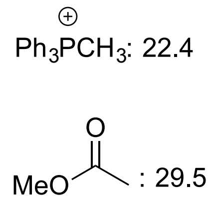
Discussion 1-1. Electrophilicity of vinyl phosphonium

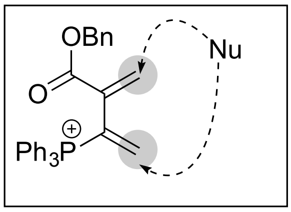
1-1-1. Chemical shifts in $CDCl_3$



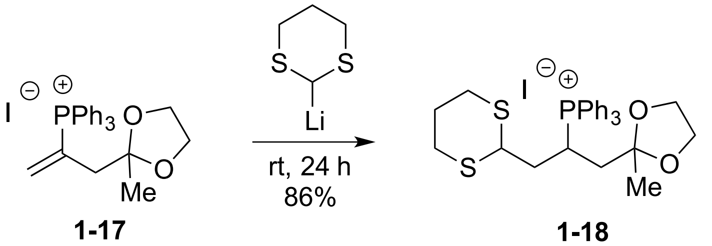
Albright, T. A.; Freeman, W.; Schweizer, E. *J. Am. Chem. Soc.* **1975**, *97*, 2946

1-1-2. pKa value in DMSO



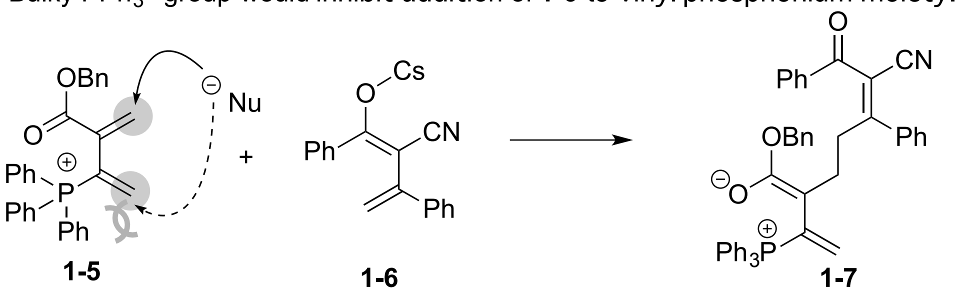


1-1-3. Nucleophilic addition to vinyl phosphonium

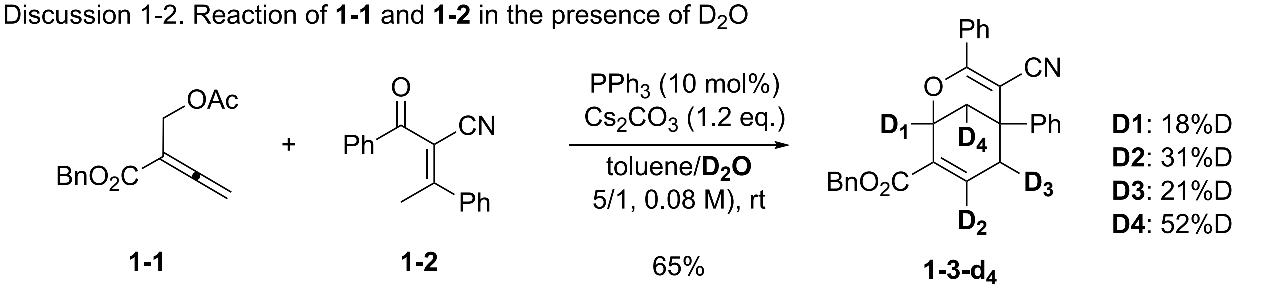


Cristau, H.-J.; Hamad, K. E.; Torreilles, E. *Phosphorus, Sulfur and Silicon* **1992**, *66*, 47.

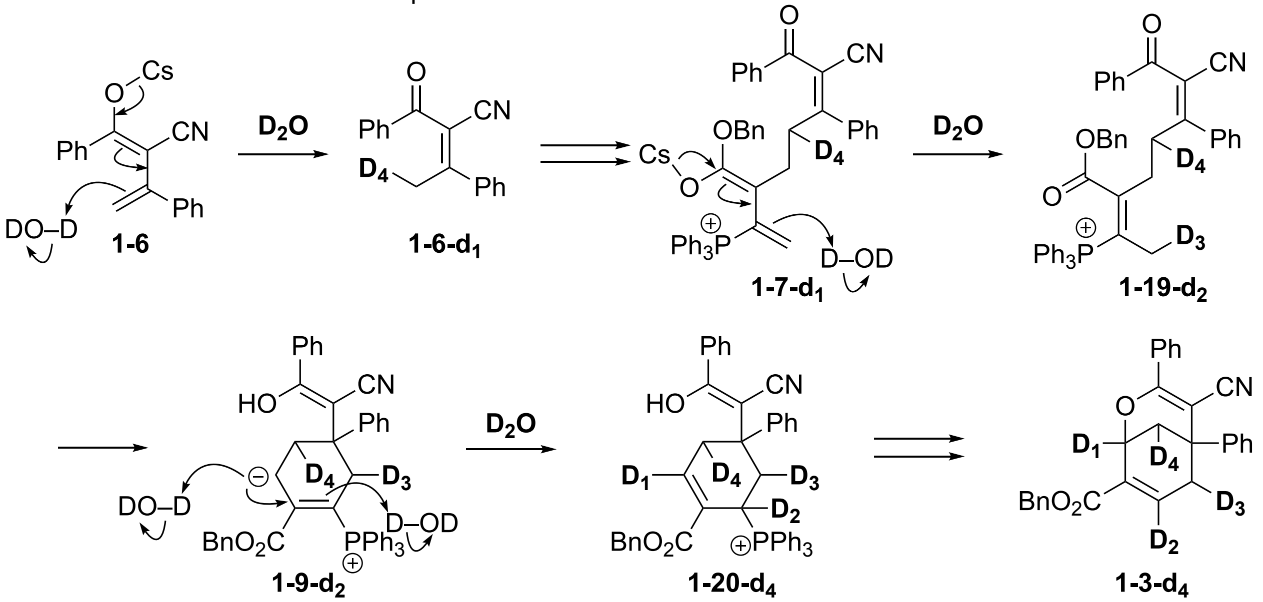
——> Bulky PPh_3^+ group would inhibit addition of **1-6** to vinyl phosphonium moiety.



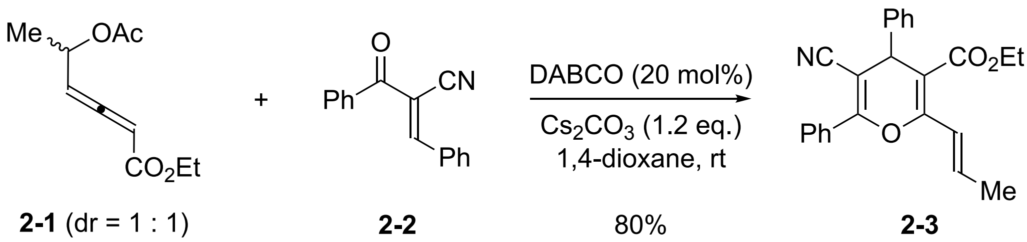
Discussion 1-2. Reaction of **1-1** and **1-2** in the presence of D_2O



<Possible mechanism for the incorporation of D>

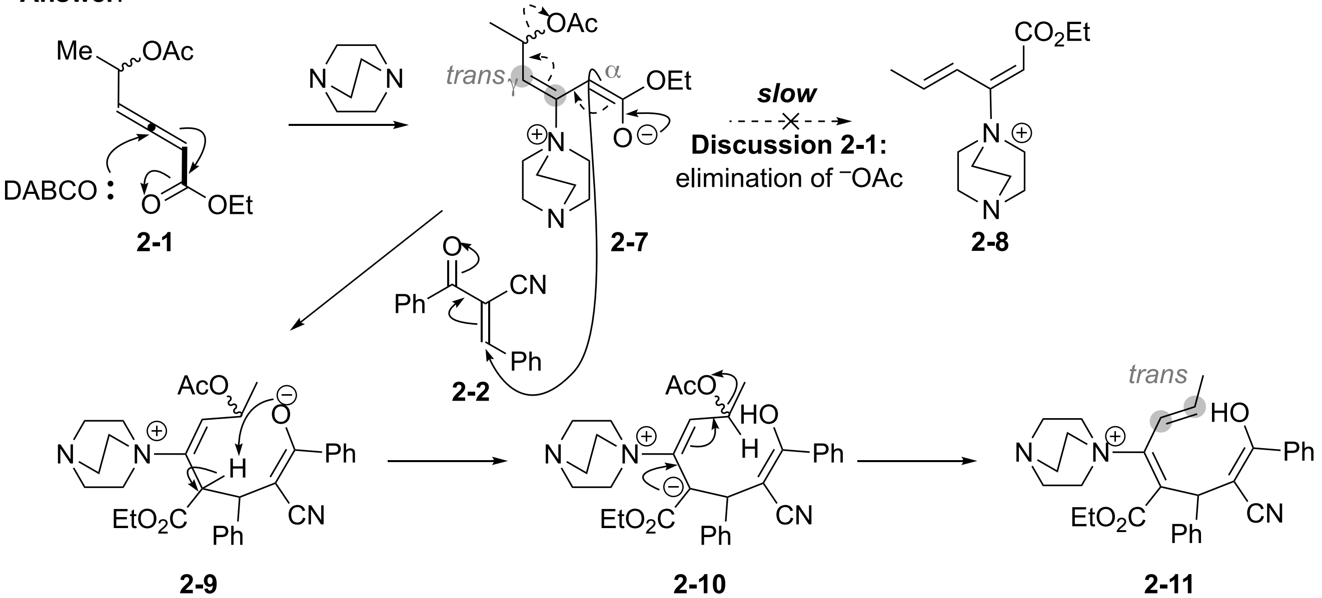


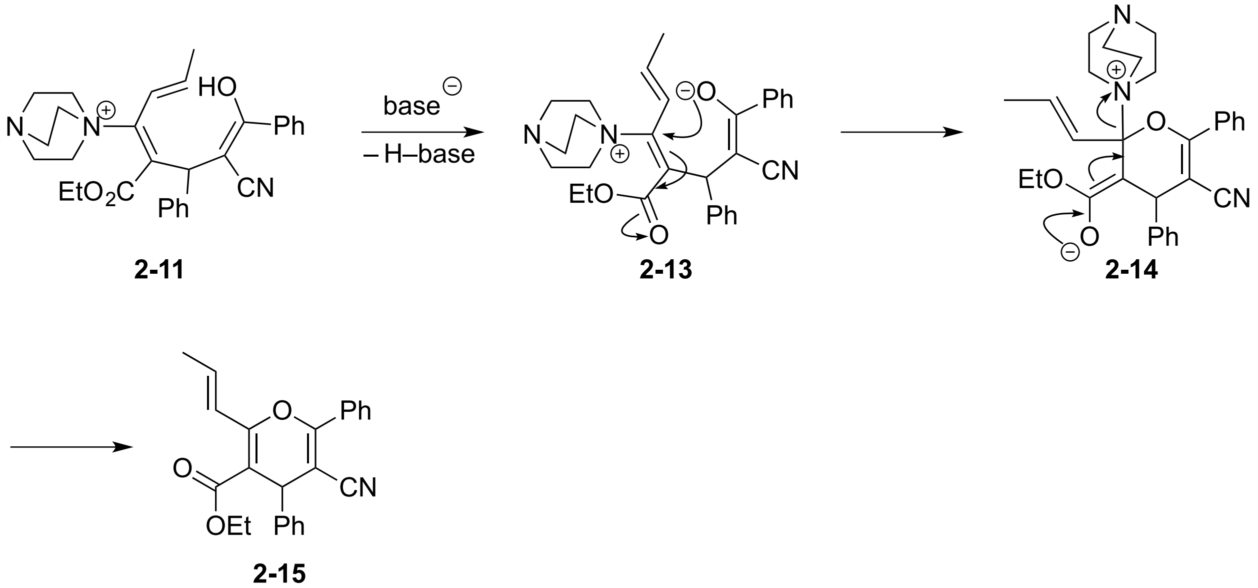
2 (1)



Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. *Org. Lett.* **2015**, *17*, 1106.

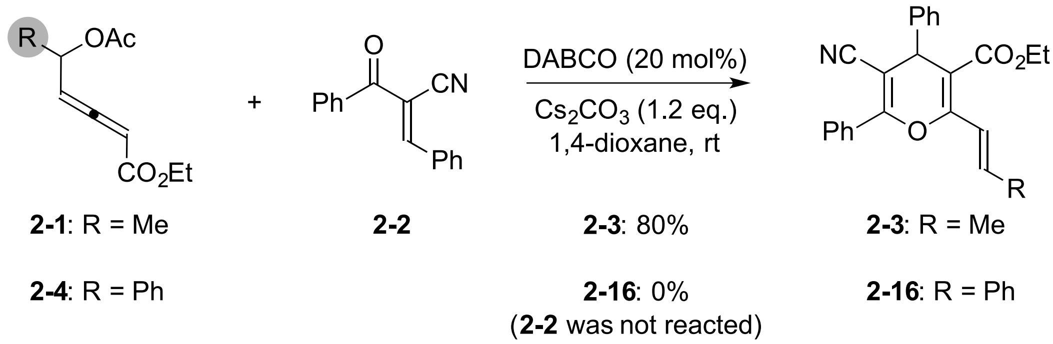
Answer:



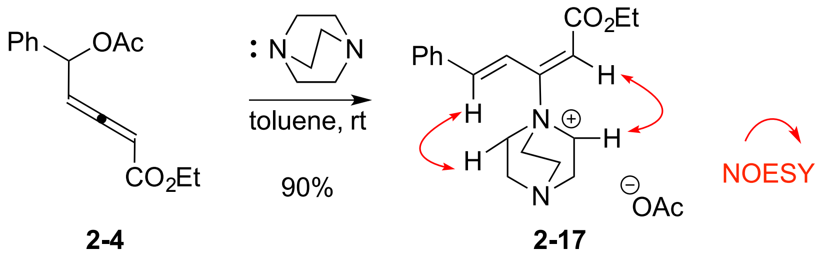


Discission 2-1: Elimination of acetoxy group

2-1-1. Effect of substituents

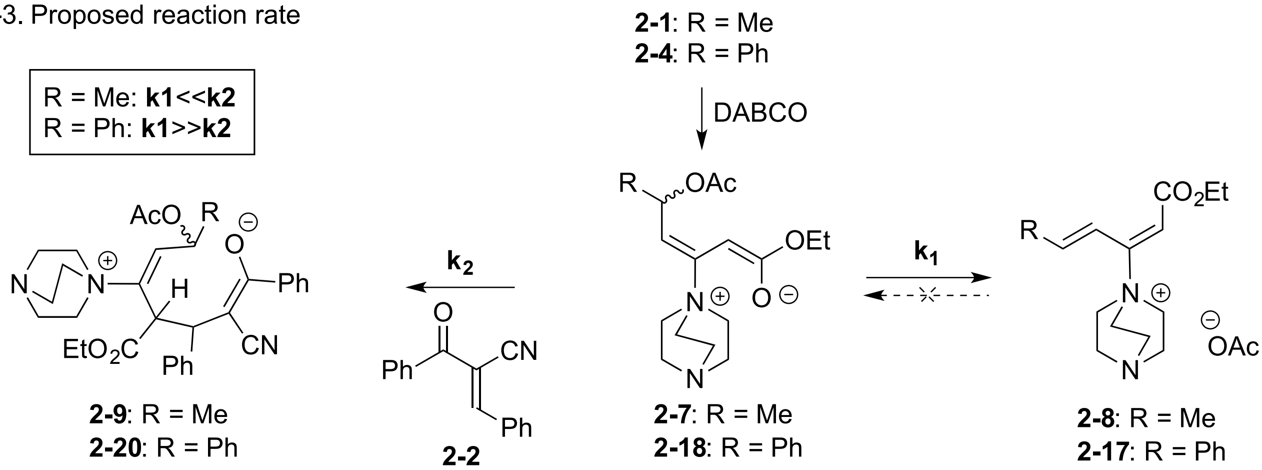


2-1-2. Reaction of **2-** with DABCO

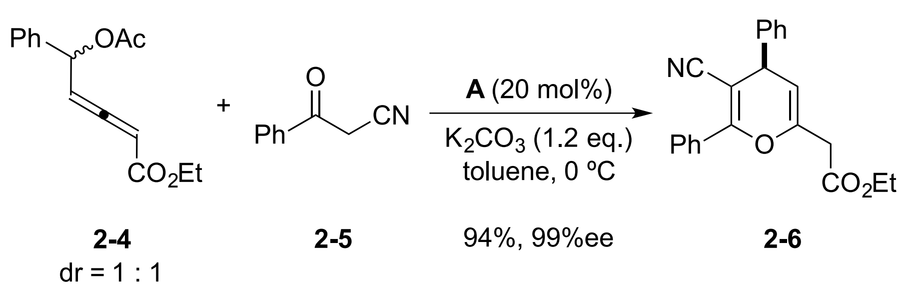


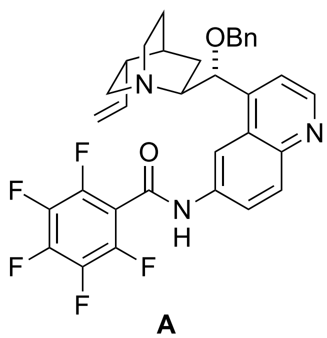
2-1-3. Proposed reaction rate

R = Me: **k1**<<**k2**
R = Ph: **k1**>>**k2**

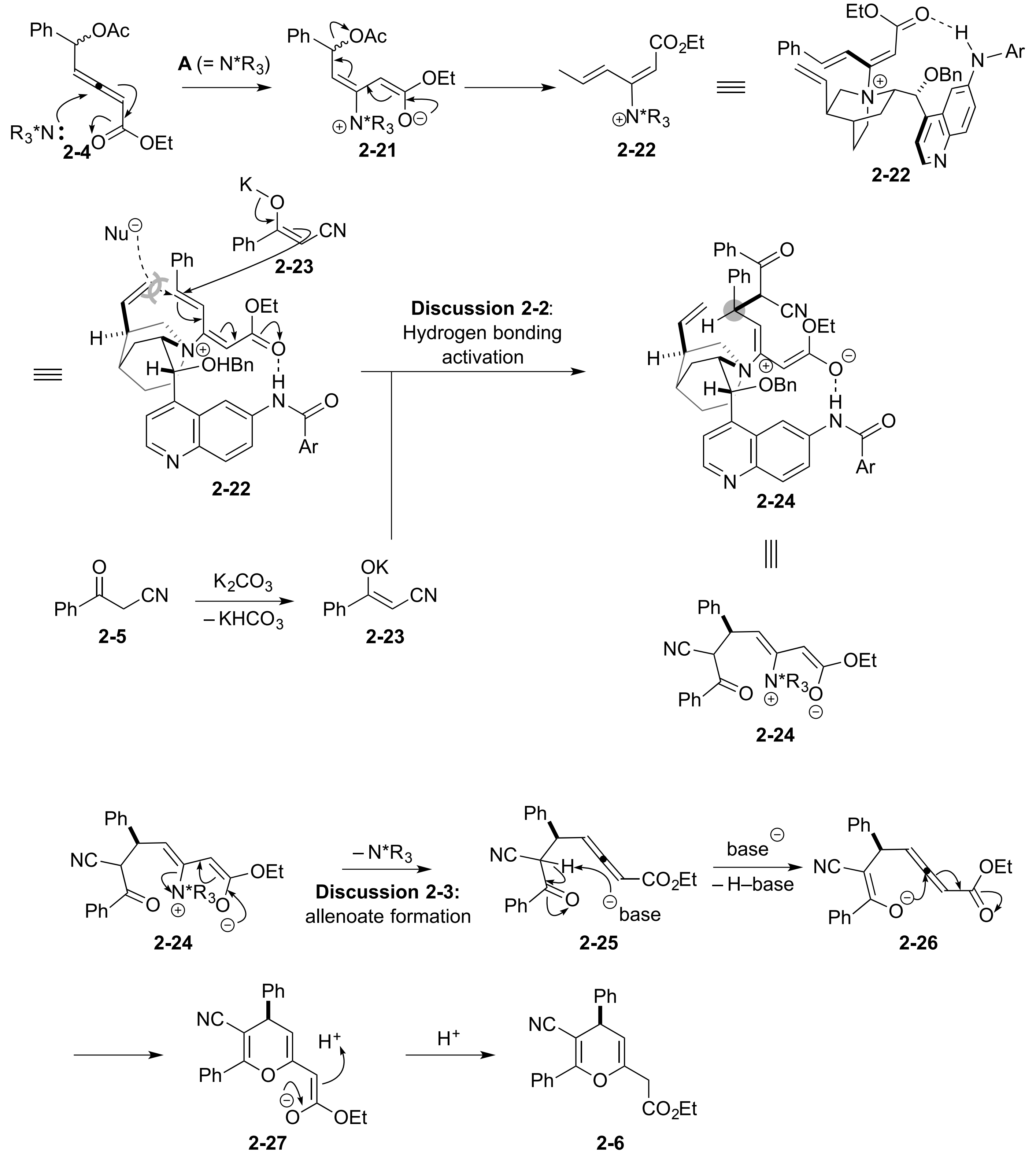


2 (2)


A (20 mol%)
K_2CO_3 (1.2 eq.)
toluene, 0 ºC
94%, 99%ee
2-4
dr = 1 : 1
2-5
2-6

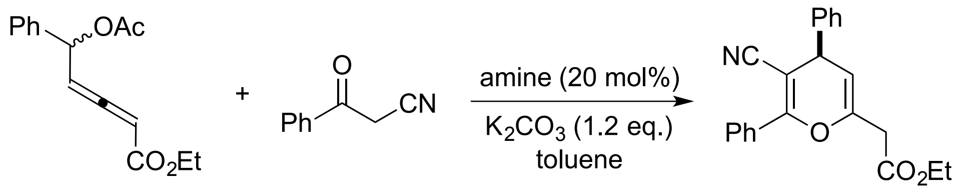

A

Answer:

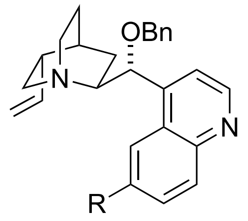

A (= N*R3)
2-4
2-21
2-22
2-23
Discussion 2-2:
Hydrogen bonding
activation
2-24
K_2CO_3
– $KHCO_3$
2-5
– N*R3
Discussion 2-3:
allenoate formation
2-25
base
– H–base
2-26
2-27
H^+
2-6

Discussion 2-2: Hydrogen bonding activation

2-2-1. Effects of the amine catalyst



2-4 (dr = 1 : 1) **2-5** **2-6**

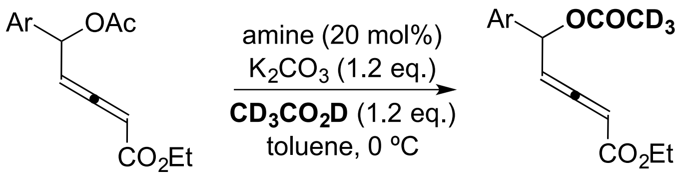


A: R = $NHCOC_6F_5$
B: R = $NHCO(4\text{-}MeO\text{-}C_6H_4)$
C: R = OMe

Table 1

entry	amine	temp. (ºC)	yield (%)	ee (%)
1	**A**	0 ºC	94	99
2	**B**	0 ºC	35	89
3	**C**	rt	<5	—

2-2-2. Reaction of **2-28** with amine catalyst in the presence of CD_3CO_2D

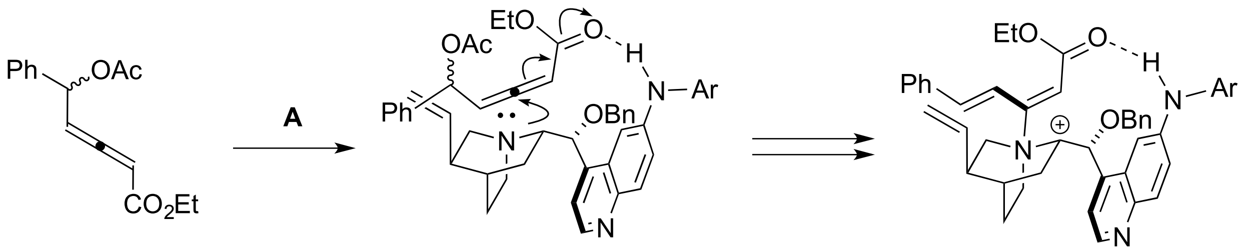


2-28: Ar = 4-Br-C_6H_4 **2-28-d$_3$**

Table 2

entry	amine	results
1	**A**	**2-28**: 53%, **2-28-d$_3$**: 30%
2	**C**	**2-28**: 90%, **2-28-d$_3$**: 0%
3	DABCO	**2-28**: 61%, **2-28-d$_3$**: 0%

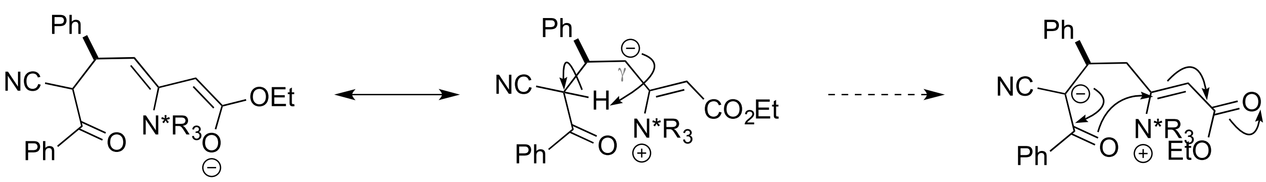
——> These results indicated that allenoate was activated by acidic amide proton



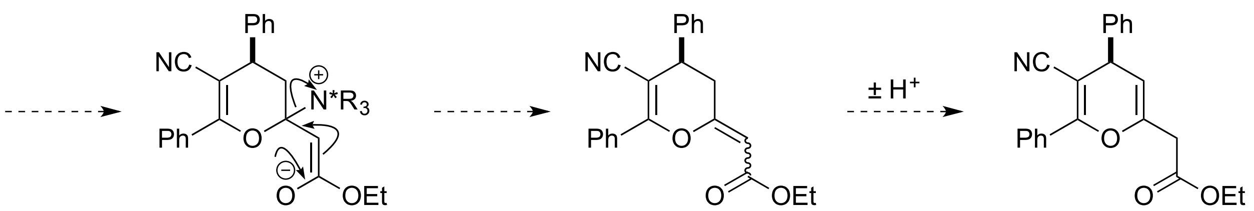
2-4 **2-29** **2-22**

Discussion 2-3: Another possible pathwas toward **2-6**

2-3-1. Possibility of intramolecular deprotonation pathway

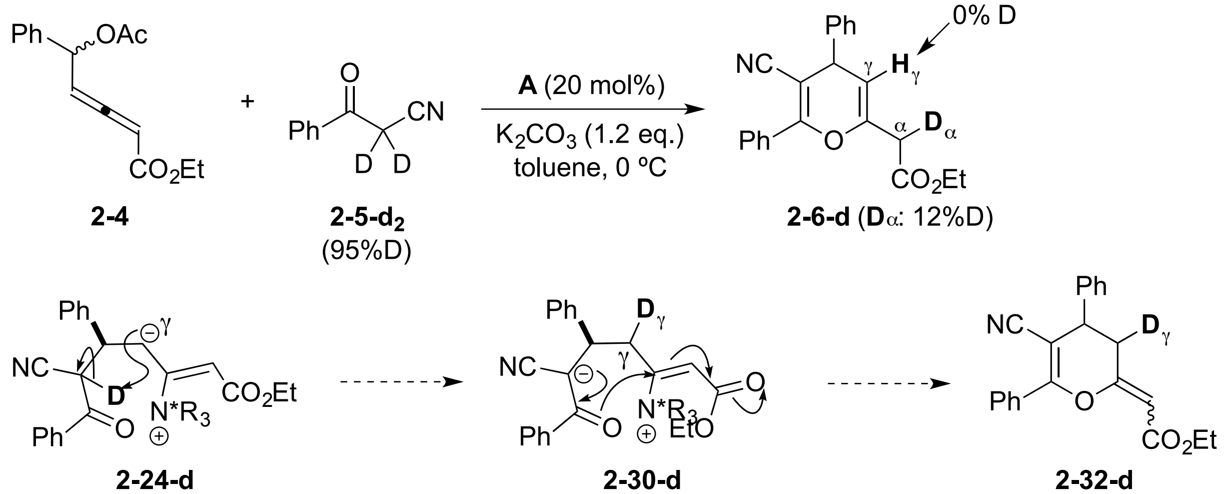


2-24 **2-24** **2-30**



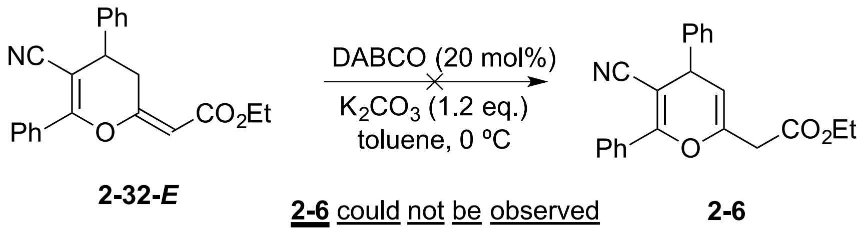
2-31 **2-32** **2-6**

2-3-2. Reaction of **2-4** with **2-5-d₂**

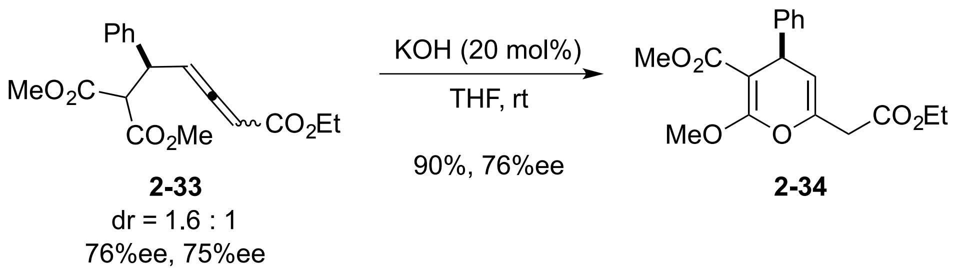


⟶ if intramolecular deprotonation (**2-24** –> **2-30**) proceeded, D was introduced at γ position.

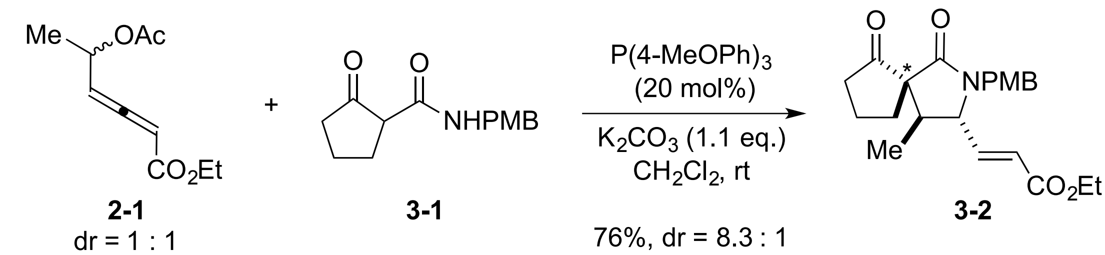
2-3-3. Attempted isomerization of **2-32**



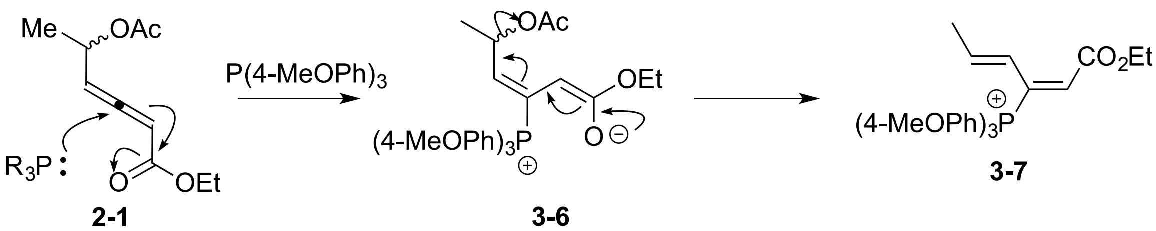
2-3-4. Attempted cyclization of allenoate **2-33**

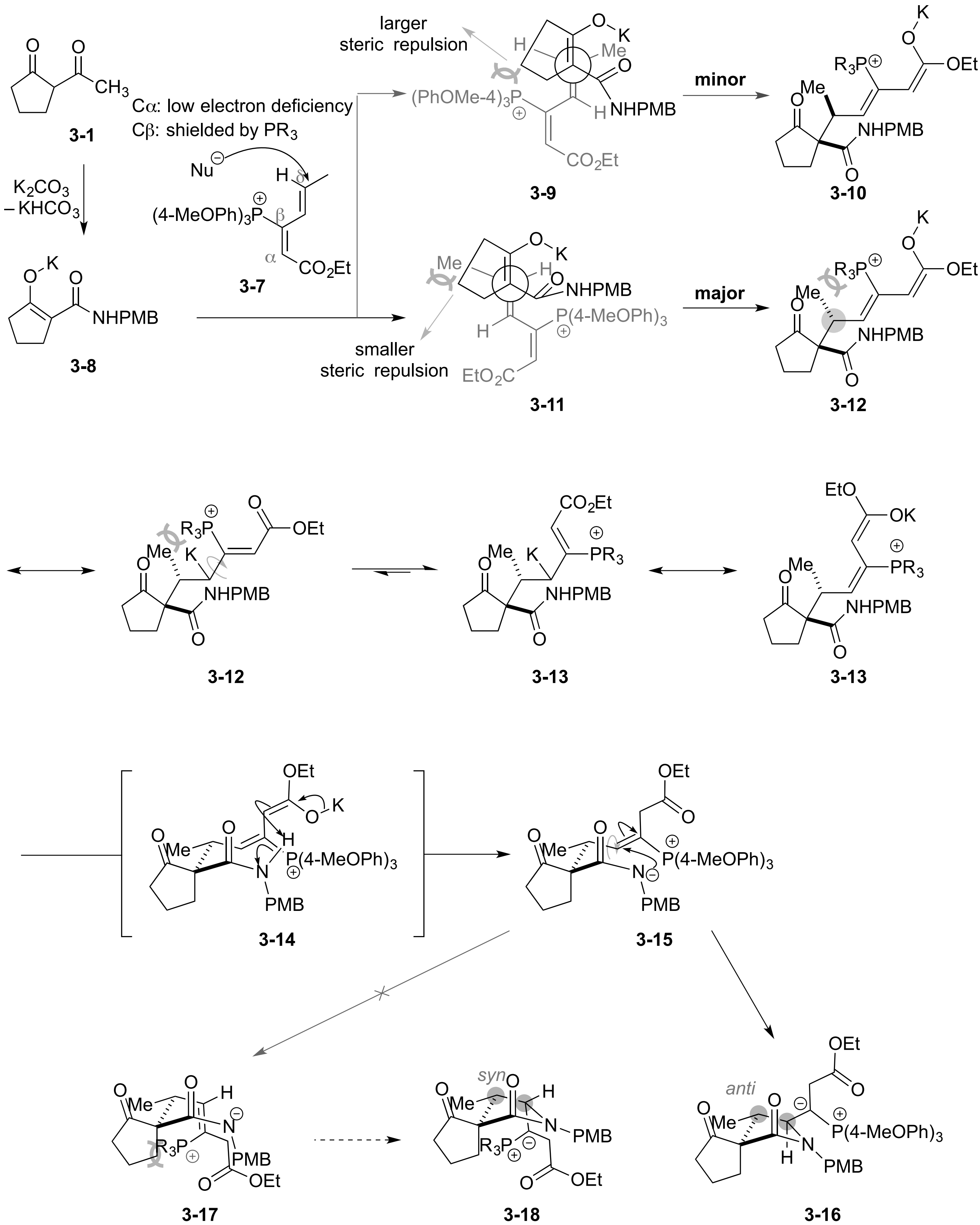


3 (1)

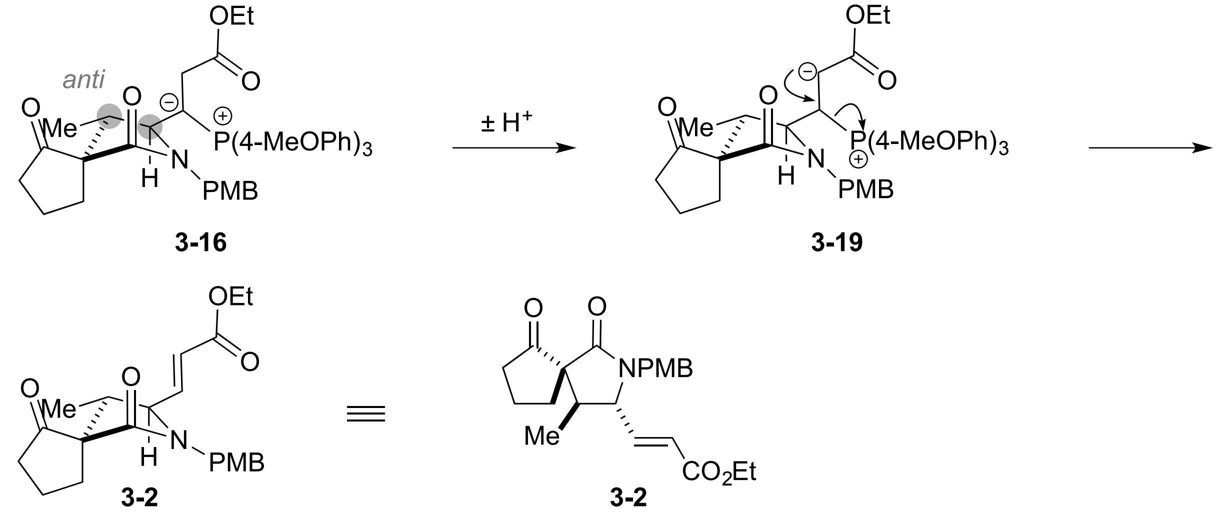


Answer:

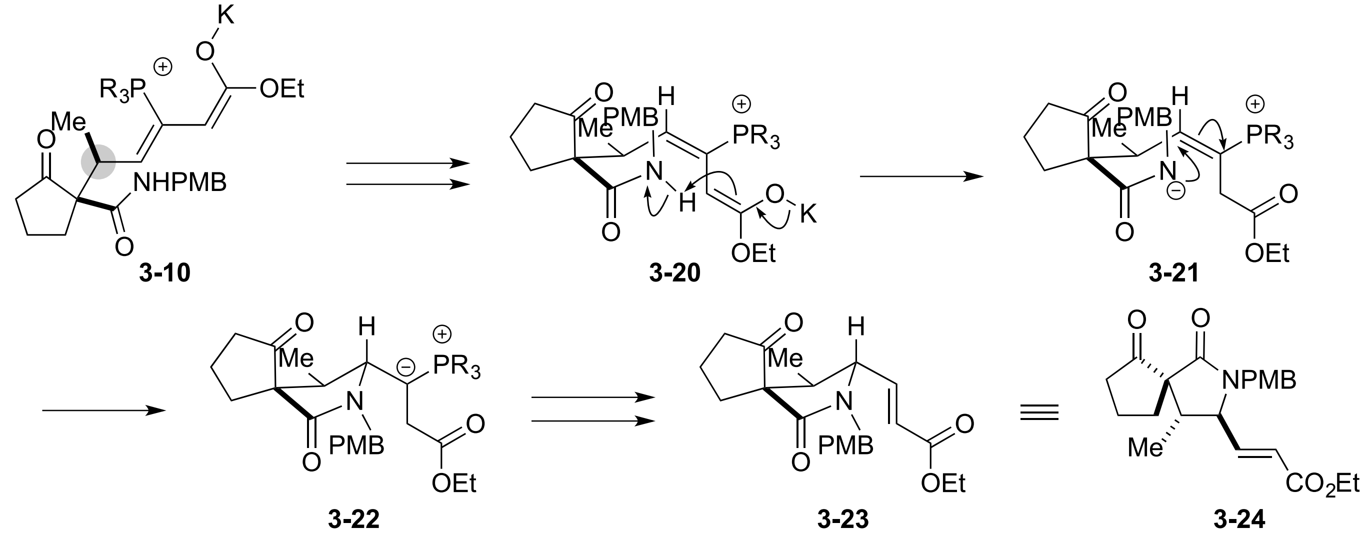




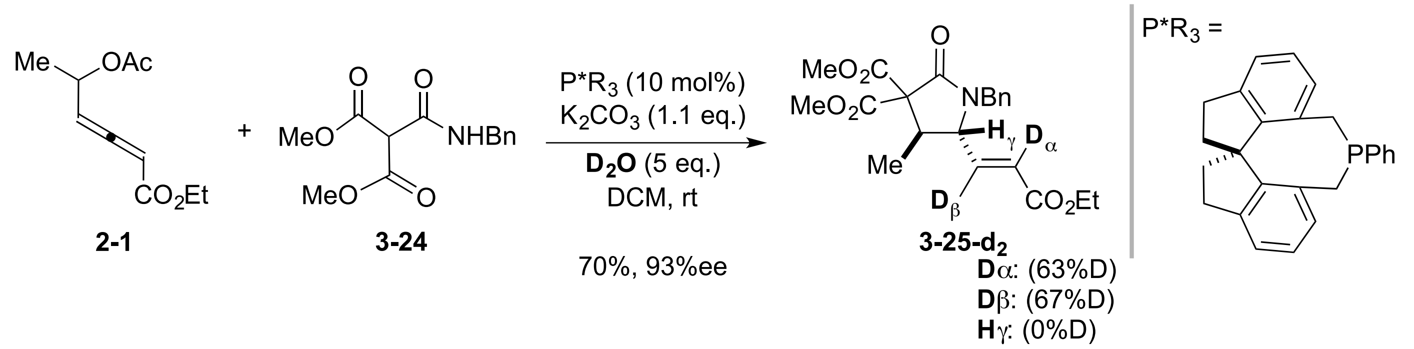
Cα: low electron deficiency
Cβ: shielded by PR3
larger steric repulsion
smaller steric repulsion
minor
major
K2CO3 – KHCO3
(4-MeOPh)3P
(PhOMe-4)3P
P(4-MeOPh)3
NHPMB
CO2Et
OEt
PMB
syn
anti
3-1
3-7
3-8
3-9
3-10
3-11
3-12
3-13
3-14
3-15
3-16
3-17
3-18



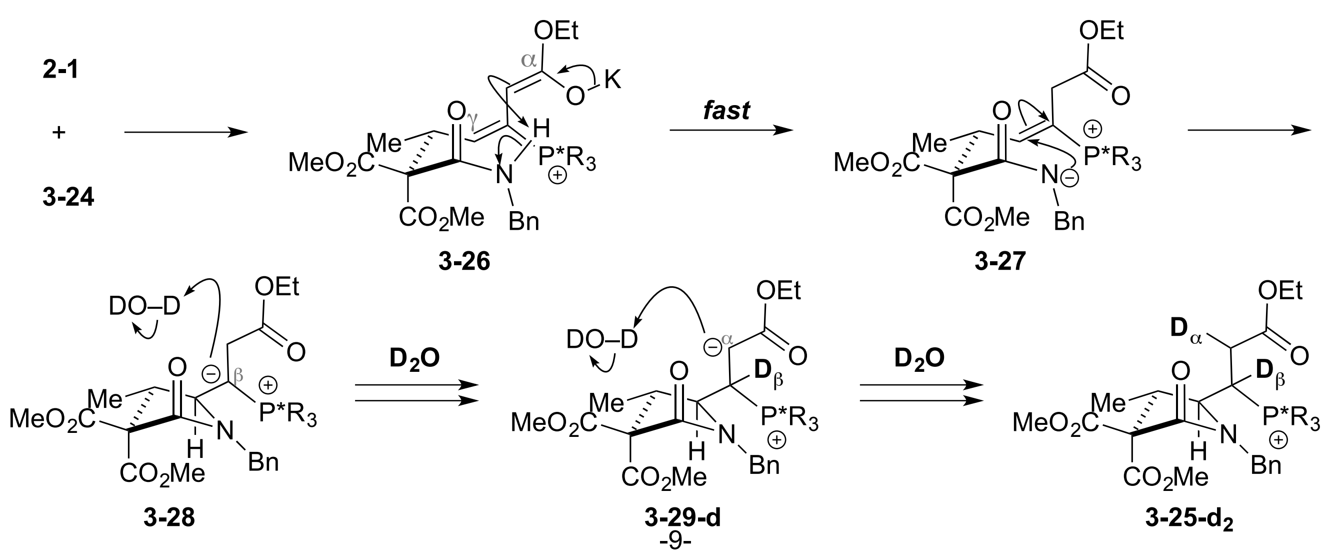
<Reactions from minor isomer **3-7**>



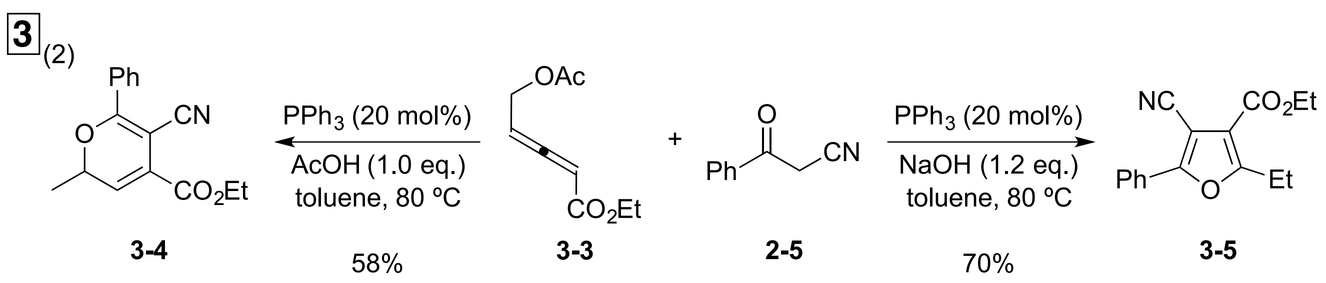
Discussion 3-1: Reaction of **2-1** and **3-1** in the presence of $\mathbf{D_2O}$



<Possible mechanism for the incorporation of D>



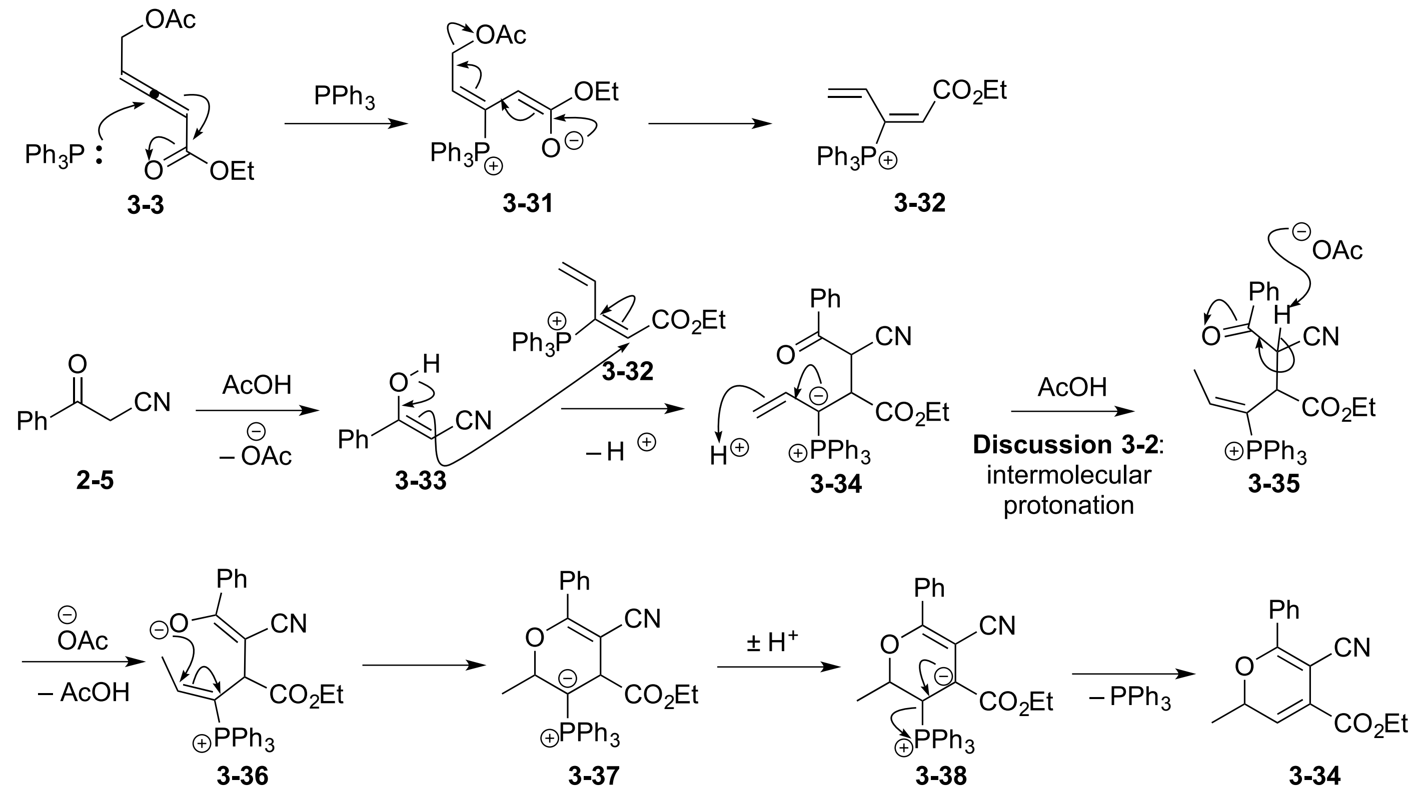
3 (2)



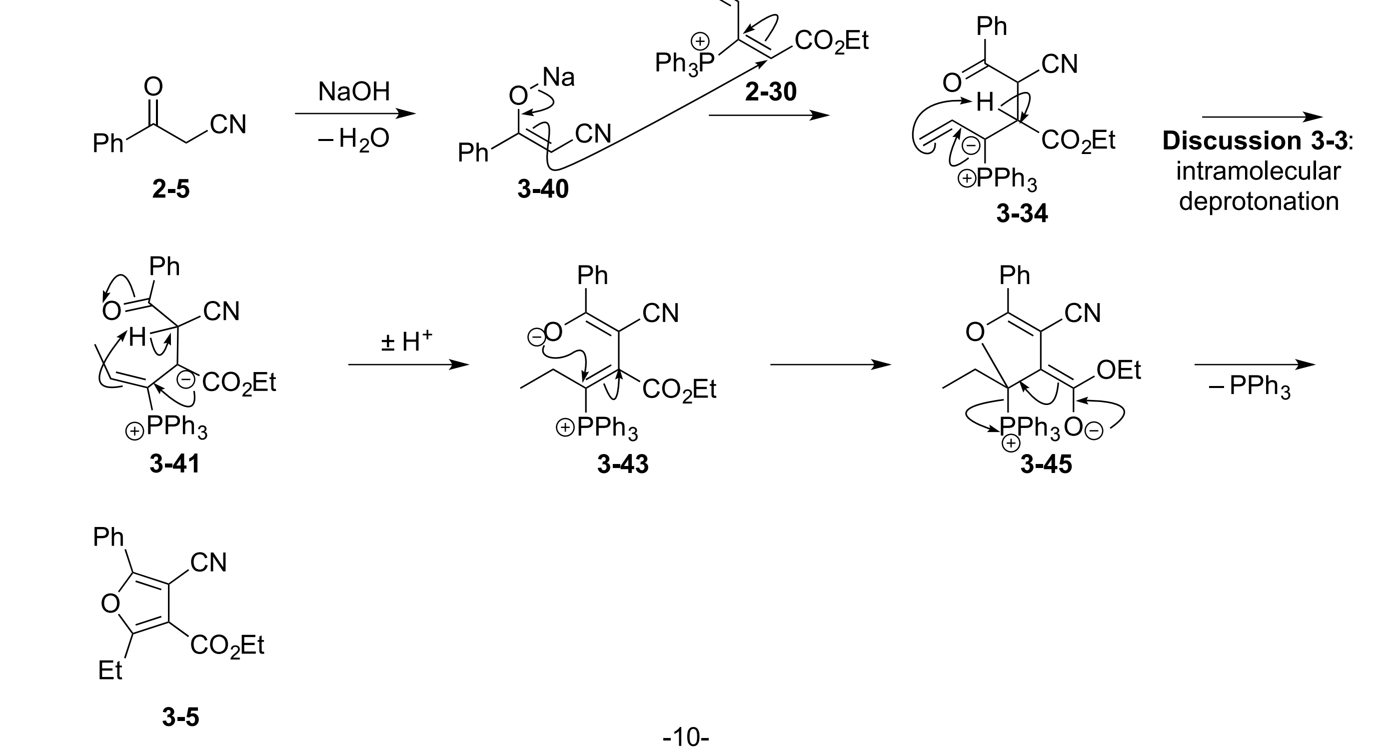
Hu, J.; Dong, W.; Wu, X.-Y.; Tong. X. *Org. Lett.* **2012**, *14*, 5530.

Answer:

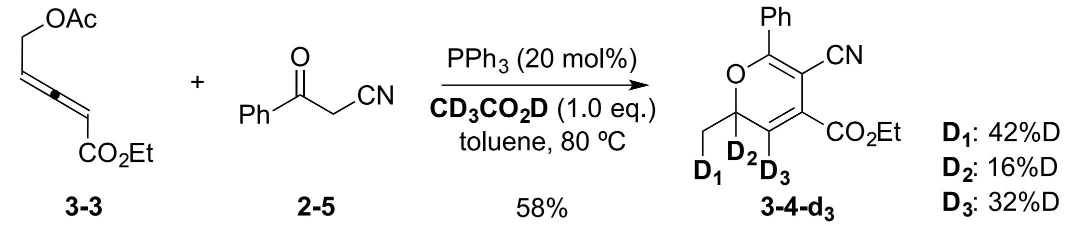
<acidic condition>



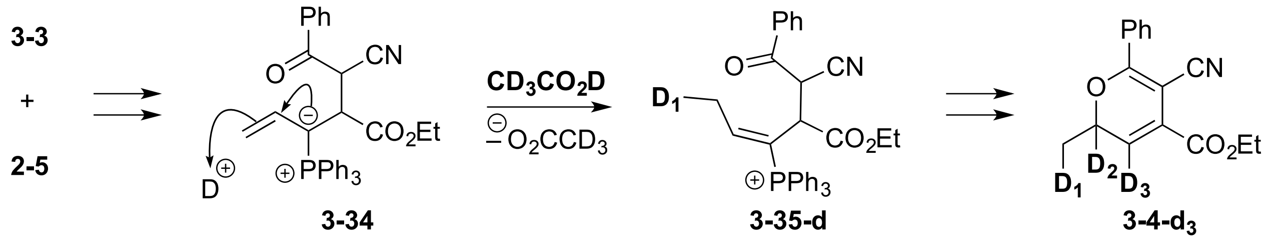
<bacic condition>



Discussion 3-2: Evidence of intermolecular protonation pathway

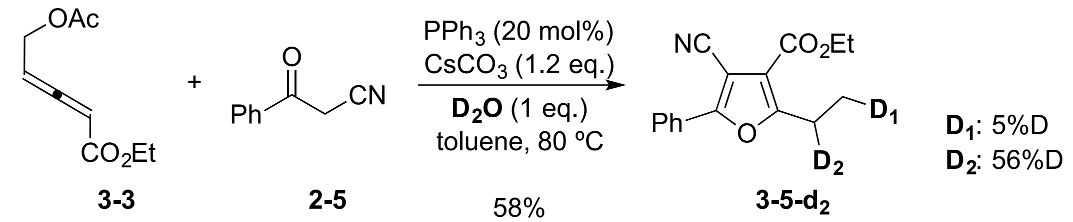


<Possible mechanism for the incorporation of D_1>

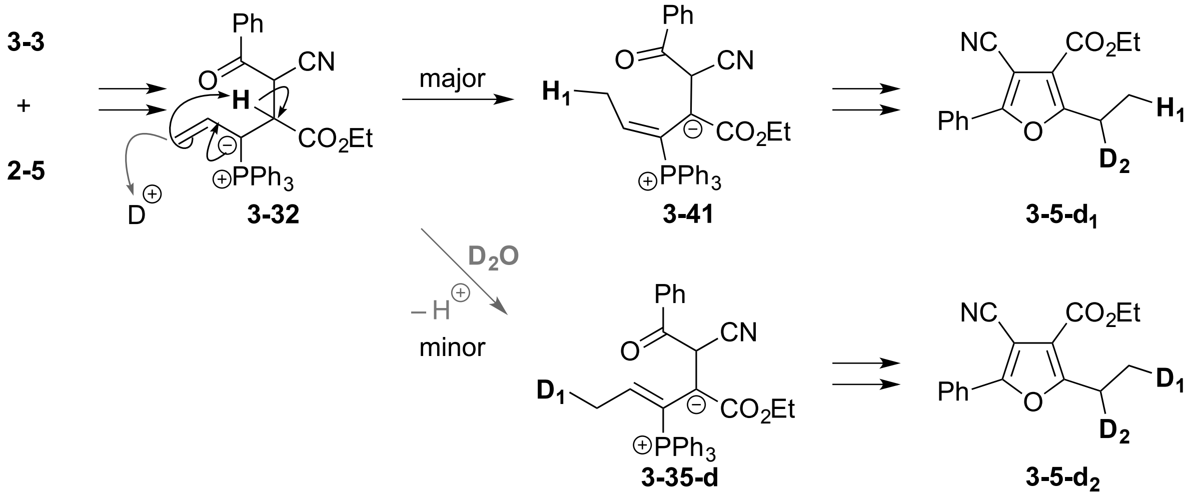


——> Introduction of D_1 supports intermolecular protonation pathway.

Discussion 3-3: Evidence of intrarmolecular deprotonation pathway



<Possible mechanism for the low incorporation of D_1>



——> Low deuteration ratio of D_1 supports intramolecular deprotonation pathway.