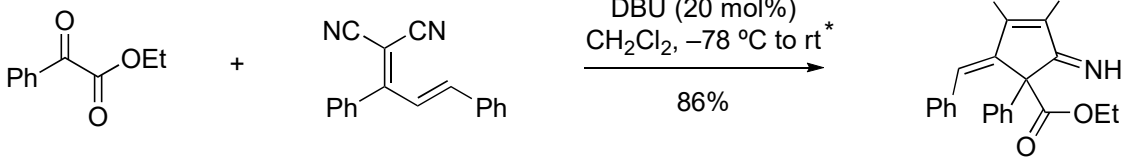
Problem Session (4)

2025.6.14 D1 Shintaro Fukaya

Please provide the reaction mechanisms for the following reactions.

1

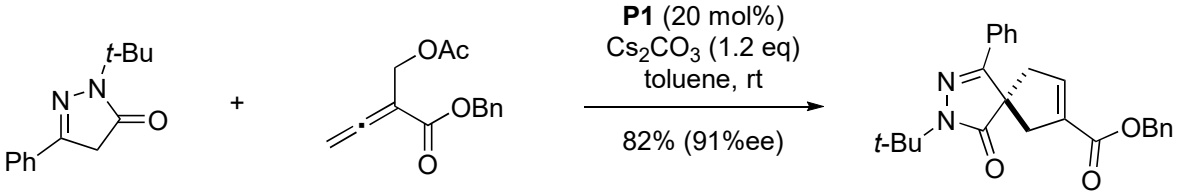


1-1 **1-2** (1.1 eq) **1-3**

*Procedure:
$P(NMe_2)_3$ was added dropwise to a stirred mixture of **1-1**, **1-2**, and DBU in CH_2Cl_2 at –78 ºC. The resulting mixture was then slowly warmed to room temperature and stirred for 4 h.

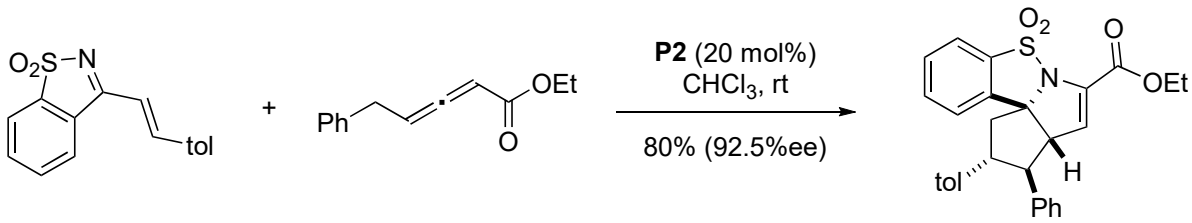
2

[1]

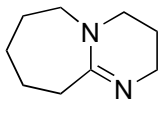


2-1 (1.2 eq) **2-2** **2-3**

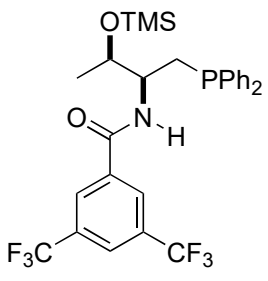
[2]



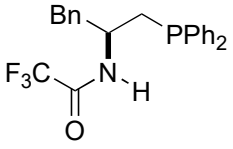
2-4 **2-5** (2.0 eq) **2-6**



DBU



P1



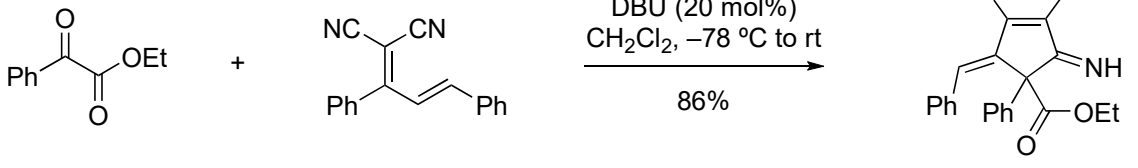
P2

Problem Session (4) -Answer-

2025.6.14 D1 Shintaro Fukaya

topic: Phosphine-promoted annulation reactions

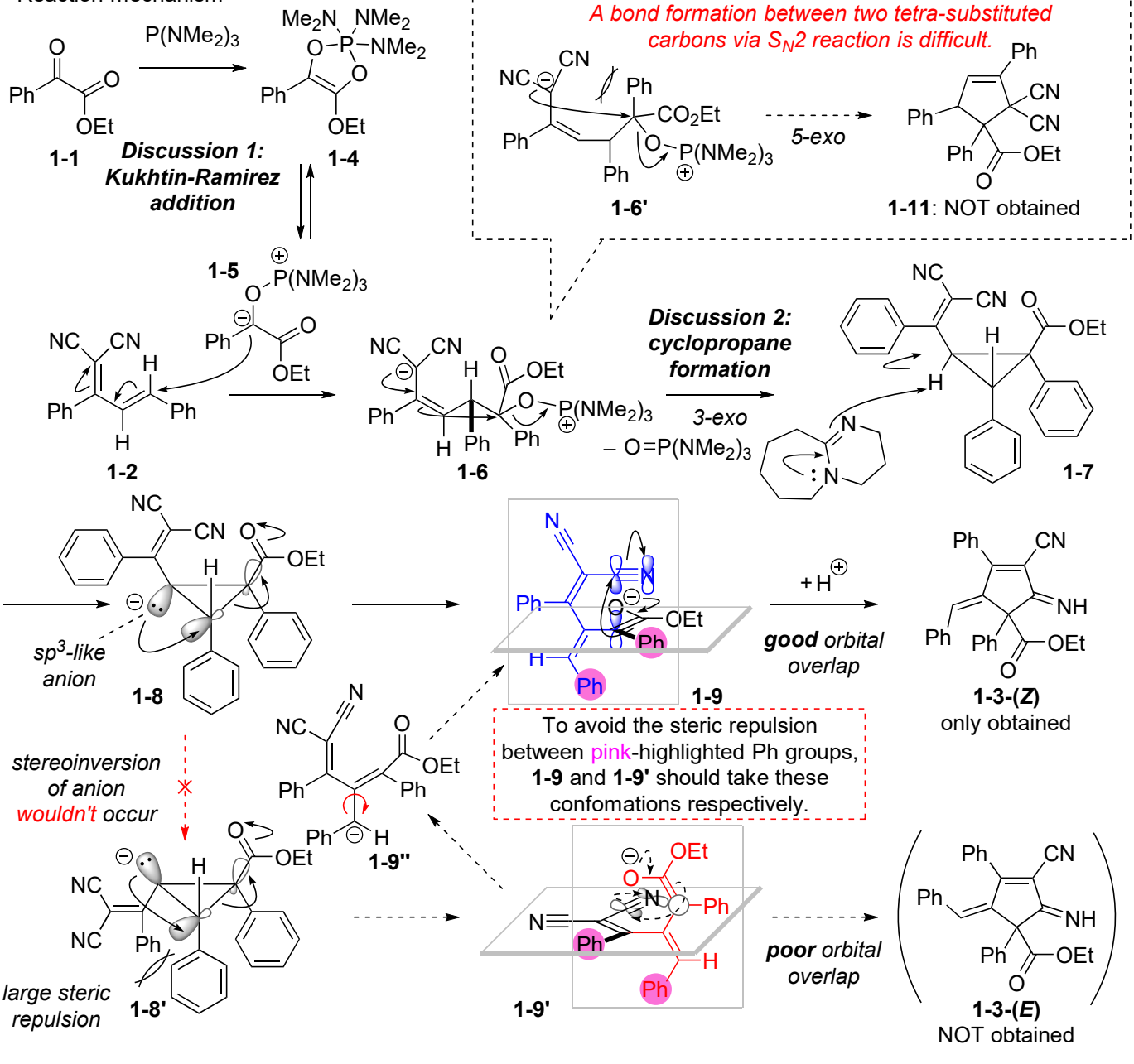
1



1-1 **1-2** (1.1 eq) **1-3**

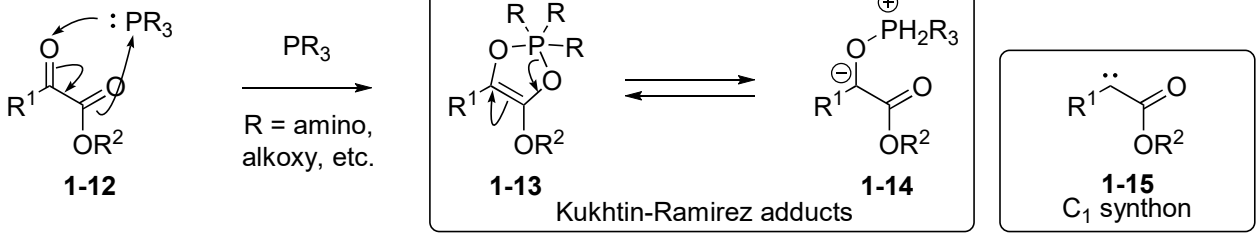
Zhou, R.; Zhang, K.; Han, L.; Chen, Y.; Li, R.; He, Z. *Chem. Eur. J.* **2016**, *22*, 5883.

・Reaction mechanism

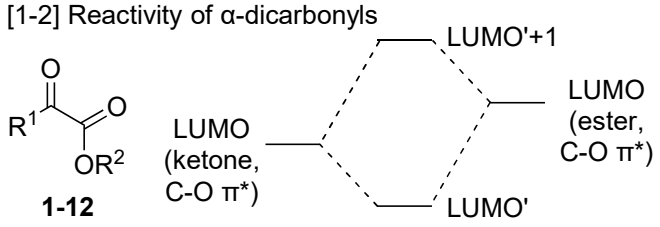


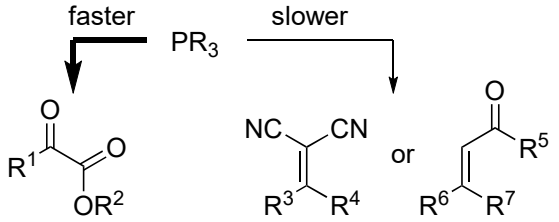
Discussion 1: Kukhtin-Ramirez addition

[1-1] Kukhtin-Ramirez addition



[1-2] Reactivity of α-dicarbonyls





✓: α-Dicarbonyls (**1-12**) exhibit high electrophilicity because of the generation of LUMO'.

✓: high affinity between P and O

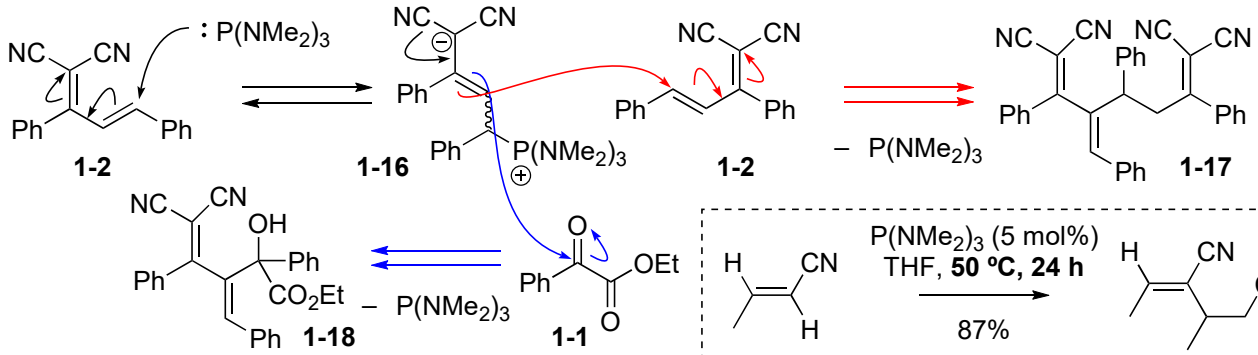
PR_3 reacts with α-dicarbonyls faster than α,β-unsaturated carbonyl compounds. In many cases, PR_3 is added at -78 ºC followed by warming, suggesting that the reaction selectivity can be controlled by initiating from low temperature.

review: Liu, Y.; Sun, F.; He, Z. *Tetrahedron Lett.* **2018**, *59*, 4136.

[1-3] Possible side reactions

[1-3-1] vinylogous Morita-Baylis-Hillman reaction (known as Rauhut-Currier reaction)

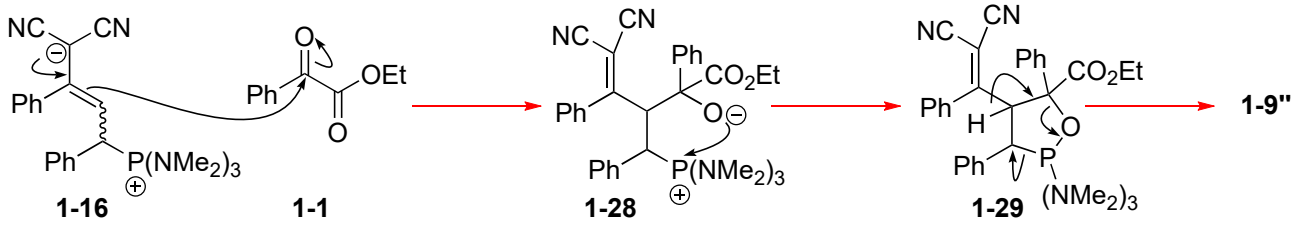
(**review** of this type of reactions: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069.)



This type of reactions require elevated temperatures (e.g., 50 ºC) to proceed even with a simple substrate (**1-19**).

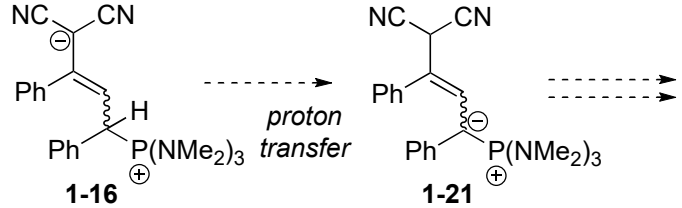
Jenner, G. *Tetrahedron Lett.* **2000**, *41*, 3091.

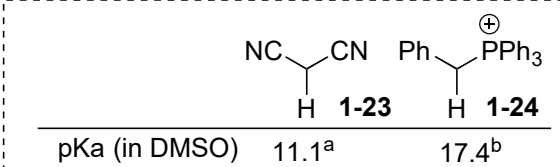
another possible pathway to **1-9"** (and to **1-3**)



The population of **1-16** seems quite low because $P(NMe_2)_3$ should react with **1-1** to form **1-4** preferentially.

[1-3-2] Phosphorus-ylide formation





a) *J. Am. Chem. Soc.* **1975**, *97*, 7006.
b) *J. Am. Chem. Soc.* **1994**, *116*, 968.

Considering the reported pKa values shown in the box, phosphorus-ylide (**1-21**) formation wouldn't occur.

[1-4] Reactivity of $P(NMe_2)_3$

Huang, Y.; Wang, N.; Wu, Z.-G.; Wu, X.; Wang, M.; Huang, W.; Zi, Y. *Org. Lett.* **2023**, *25*, 7595.

As shown in table 1, $P(OMe)_3$ and PPh_3 are not suitable for Kukhtin-Ramirez addition.

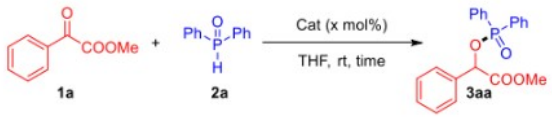
P(V) can be stabilized by electron donation of three NMe_2 group. In the case of OMe or Ph, their electron donating abilities seem to be not enough.

Furthermore, the following P=O bond dissociation enthalpies have been reported:
(Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10605.)

$(Et_2N)_3P{=}O$: 156 kcal/mol
$(EtO)_3P{=}O$: 151 kcal/mol
$Ph_3P{=}O$: 127 kcal/mol

Based on above comparison, it can be said that amine substituents stabilize P(V) effectively.

Table 1. Optimization of the Reaction Conditions[a]

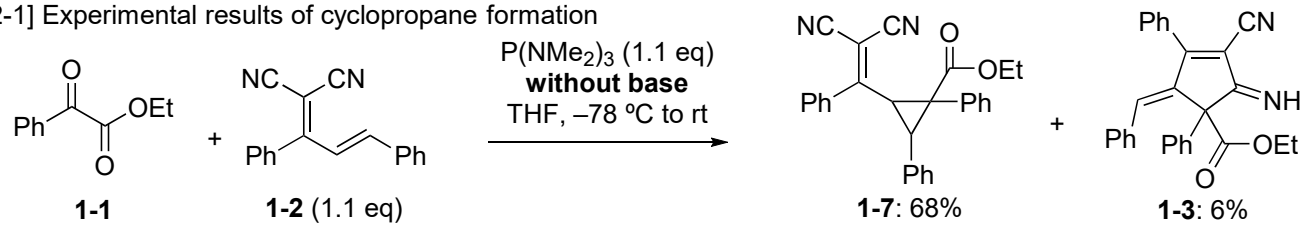


entry	catalyst (*x* mol %)	time (h)	yield (%)[b]
1	$P(NMe_2)_3$ (110)	1	99
2	$P(NMe_2)_3$ (20)	1	99
3	$P(NMe_2)_3$ (10)	1	98
4	$P(NMe_2)_3$ (5)	1	35
5	$P(NMe_2)_3$ (5)	2	61
6	$P(NMe_2)_3$ (10)	0.5	87
7	tris(1-pyrrolidinyl)phosphine (10)	2	68
8	PPh_3 (10)	2	trace
9	P^nBu_3 (10)	2	trace
10	$P(OEt)_3$ (10)	2	trace

[a]Reaction conditions unless otherwise noted: **1a** (0.55 mmol, 1.1 equiv), **2a** (0.50 mmol), THF (2 mL), rt. [b]Isolated yields.

Discussion 2: Cyclopropane formation

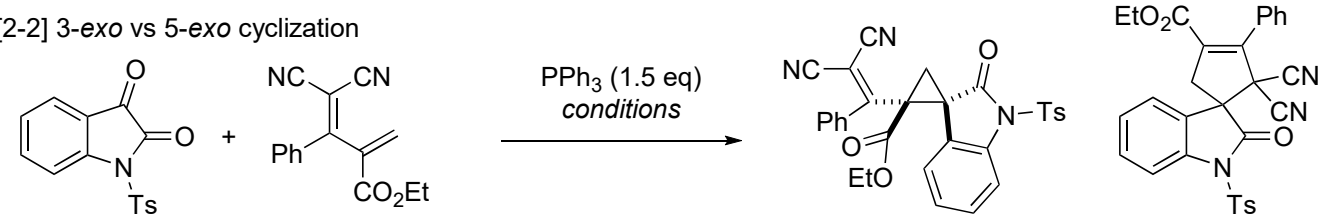
[2-1] Experimental results of cyclopropane formation



1-1 **1-2** (1.1 eq)

When the reaction conducted without base (DBU), cyclopropane **1-7** was mainly isolated.

[2-2] 3-*exo* vs 5-*exo* cyclization



1-24 (1.5 eq) **1-25** **1-26 (3-*exo*)** **1-27 (5-*exo*)**

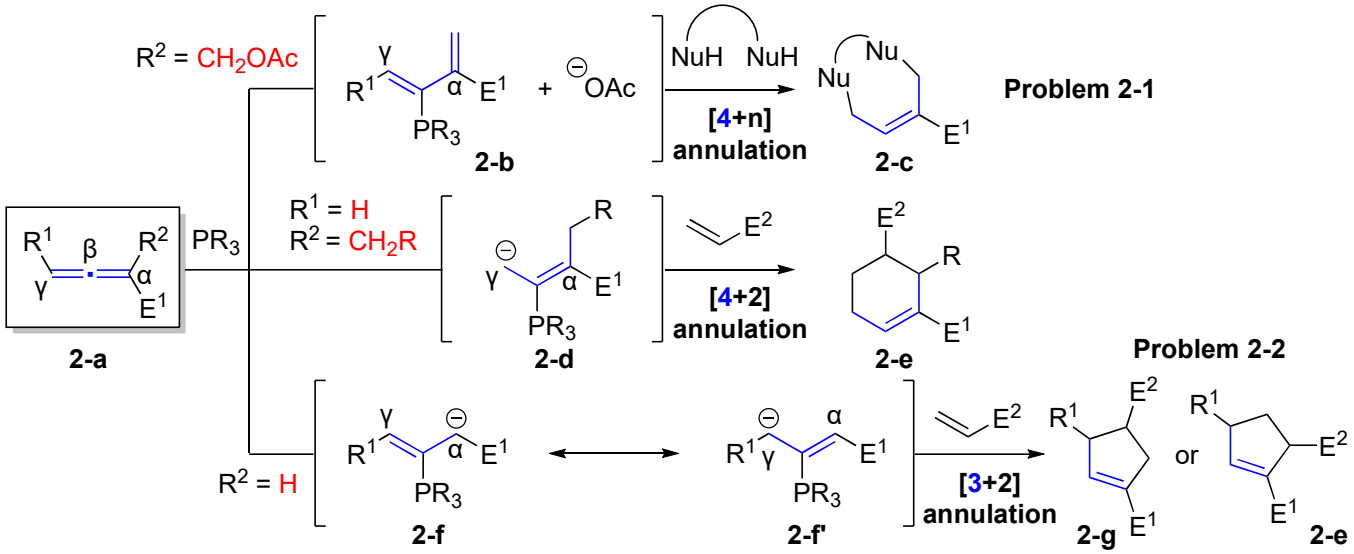
SM	*conditions*	**1-26 (3-*exo*)**	**1-27 (5-*exo*)**
1-24 + 1-25	toluene, 60 ºC	83%	0%
1-24 + 1-25	LiCl (3.0 eq), $(CH_2Cl)_2$, 80 ºC	0%	83%
1-26	LiCl (3.0 eq), $(CH_2Cl)_2$, 80 ºC	0%	28%

5-exo cyclization required high temperature and Li^+ activation.

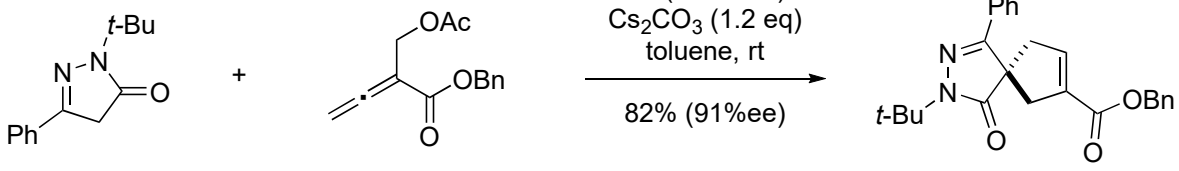
Zhang, L.; Lu, H.; Xu, G.-Q.; Wang, Z.-Y.; Xu, P.-F. *J. Org. Chem.* **2017**, *82*, 5782.

2 ■Overview of the reaction modes of allenoates in Phisphine-catalyzed annulation reactions

review: Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344.
Also refer to 140208_PS_Tomoya_Yamashita



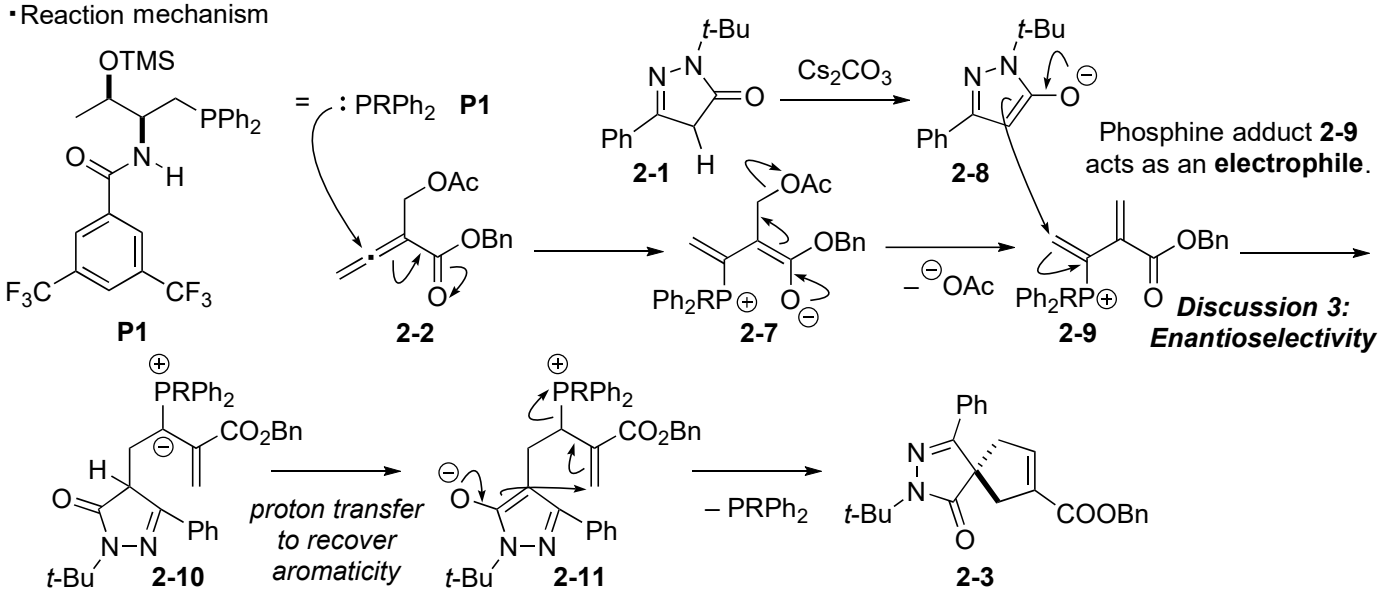
[1]



2-1 (1.2 eq) **2-2** **2-3**

Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 5643.

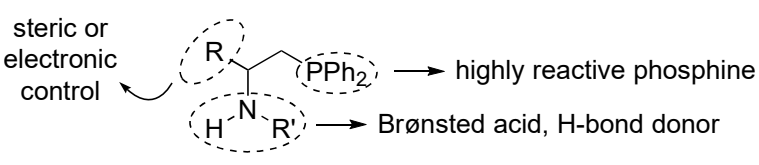
▪Reaction mechanism

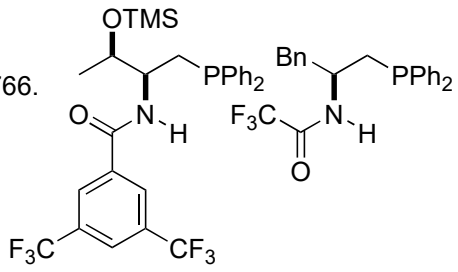


Discussion 3: Enantioselectivity

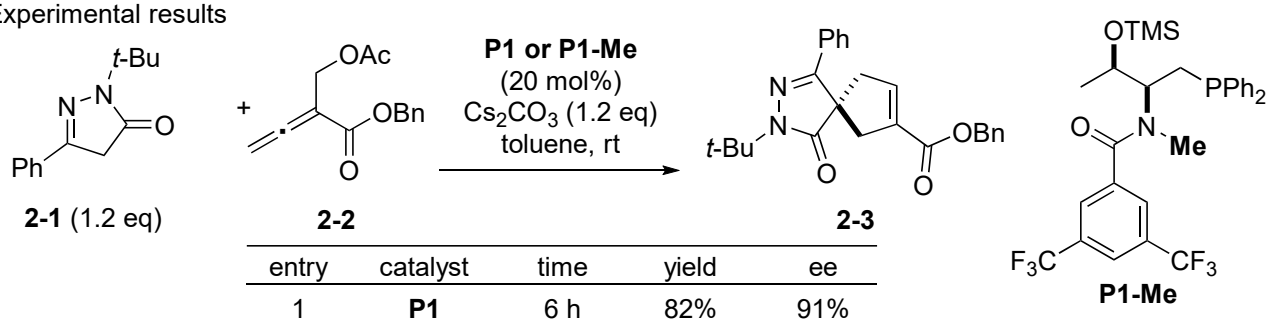
[3-1] Amino acid based multifunctional chiral phosphines

review: Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, 2766.





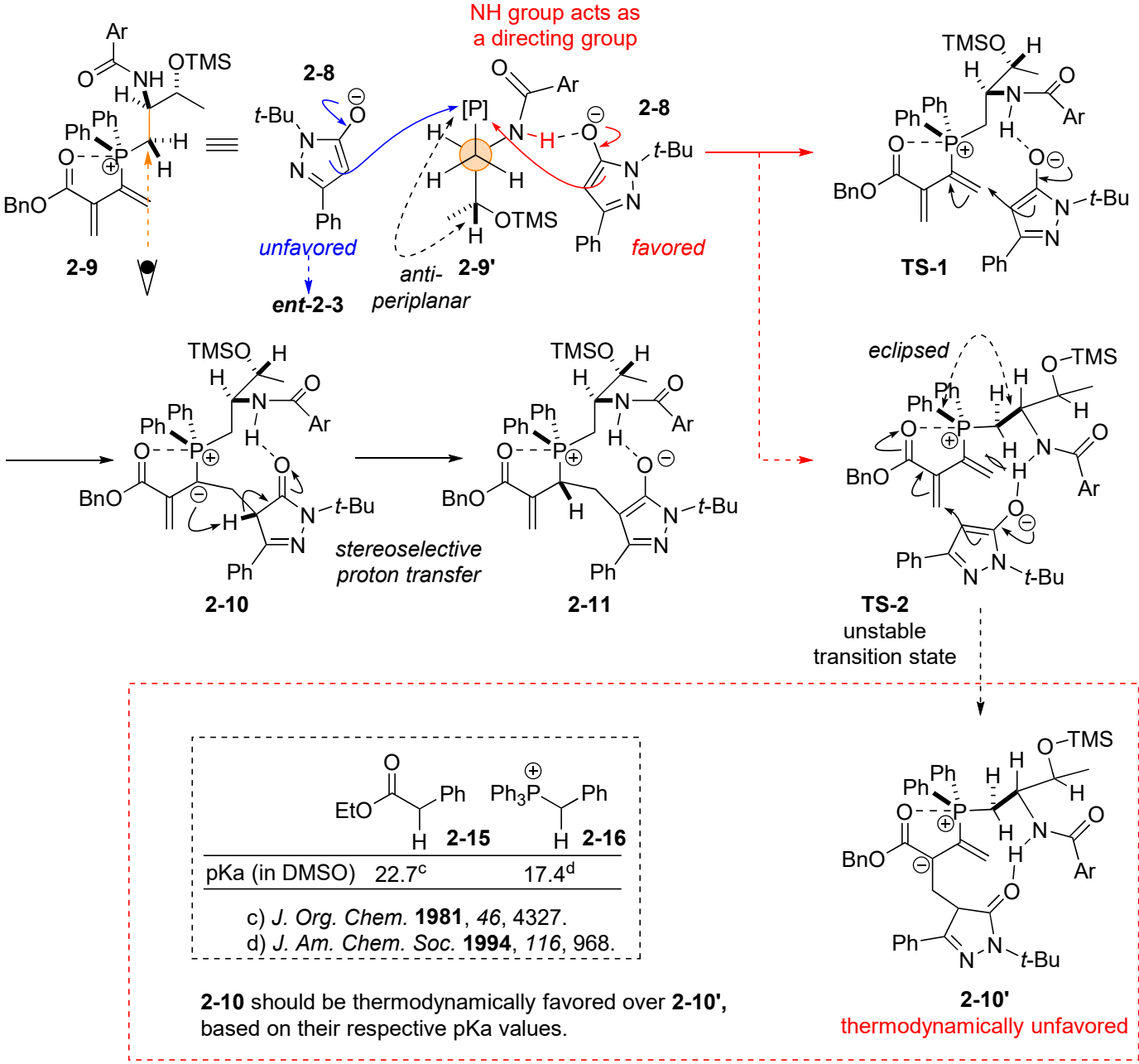
[3-2] Experimental results



entry	catalyst	time	yield	ee
1	**P1**	6 h	82%	91%
2	**P1-Me**	15 h	**36%**	**19%**

The use of N-methylated **P1-Me** resulted in decreased yield and enantiomeric excess (ee), suggesting that **hydrogen bonding between NH and enolate 2-8 is crucial for both the reaction efficiency and the stereochemistries.**

[3-3] Hydrogen bonding directed nucleophilic addition of enolate **2-8**



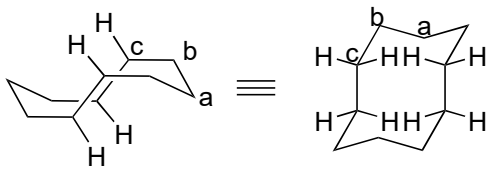
pKa (in DMSO)	22.7[c]	17.4[d]

c) *J. Org. Chem.* **1981**, *46*, 4327.
d) *J. Am. Chem. Soc.* **1994**, *116*, 968.

2-10 should be thermodynamically favored over **2-10'**, based on their respective pKa values.

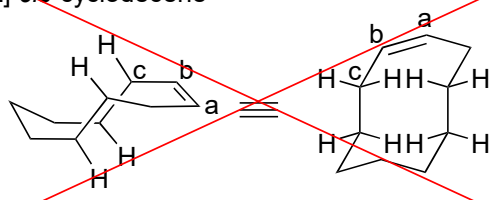
[3-4] Stable conformation of 10-membered ring system

[3-4-1] cyclodecane



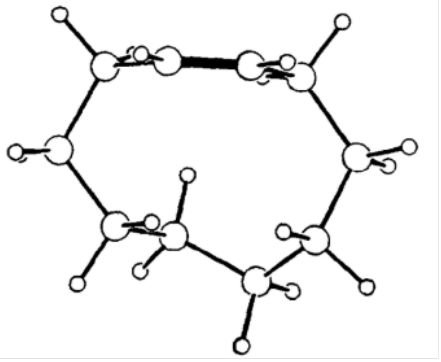
boat-chair-boat[ref.(a)(b)]

[3-4-2] *cis*-cyclodecene



In the case of cis-cyclodecene, cis-olefin should lie in position a-b.

(a) Pawar, D. M.; Smith, S. V.; Mark, H. L.; Odom, M. R.; Noe, E. A. *J. Am. Chem. Soc.* **1998**, *120*, 10715.
(b) 240921_PS_Yuto_Hikone

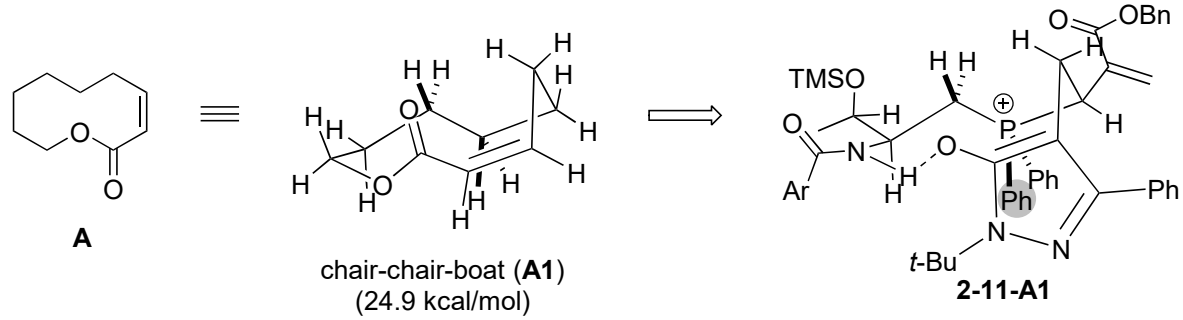


Cyclodecene would take this conformation.

[3-4-3] 10-membered α,β-unsaturated lactone (**A**)

Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

2-11 has hydrogen bonding between enolate O and NH.
Therefore, it would be more feasible to consider **10-membered α,β-unsaturated lactone-type transition state** rather than simple *cis*-cyclodecene-type transition state.

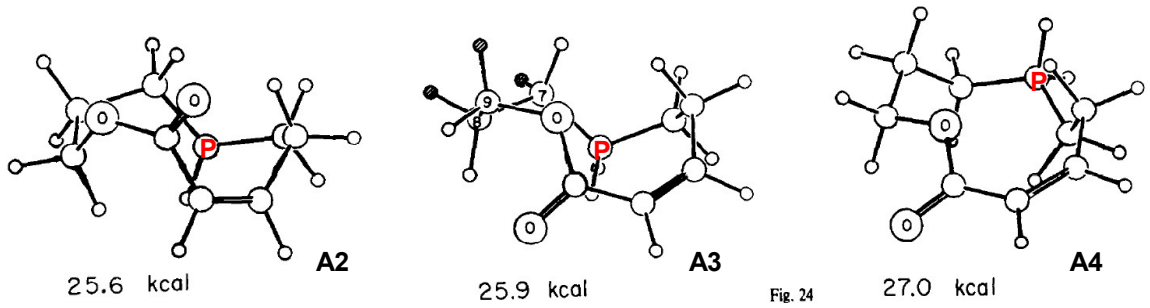


A

chair-chair-boat (**A1**)
(24.9 kcal/mol)

2-11-A1

chair-chair-boat confomer **A1** was mentioned as the most stable one, but in the case of **2-11**, there seems to be large steric repulsion derived from highlighted Ph group.



A2 25.6 kcal

A3 25.9 kcal

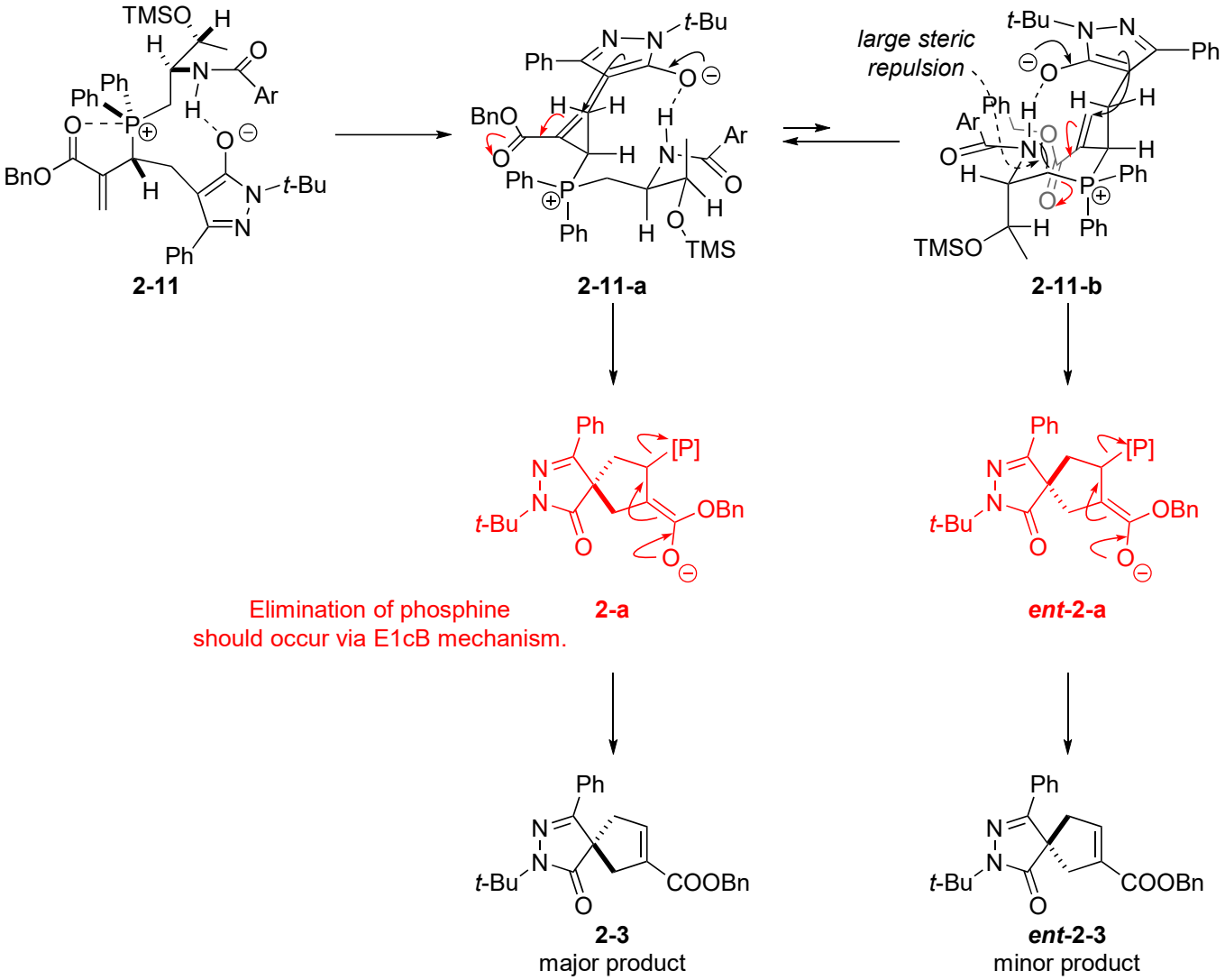
A4 27.0 kcal

Fig. 24

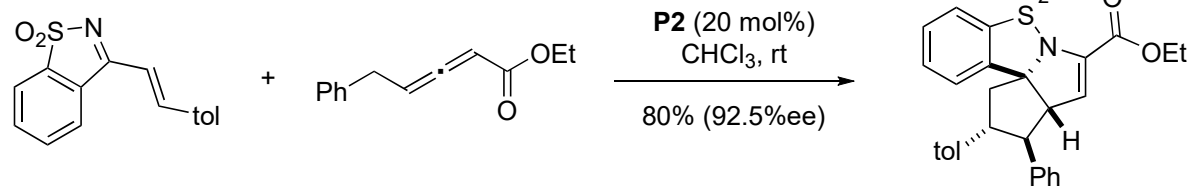
Three other conformers **A2, A3,** and **A4** were also mentioned in the paper, and to avoid the steric repulsion derived from P-Ph, **A4** is the best one.
(In the conformer **A4**, two Ph group of P both directed to outside of the 10-membered ring system.)

In section 3-4-4, **2-11-a** and **2-11-b** were considered as the similar conformers to **A4**.

[3-4-4] Enantioselective annulation



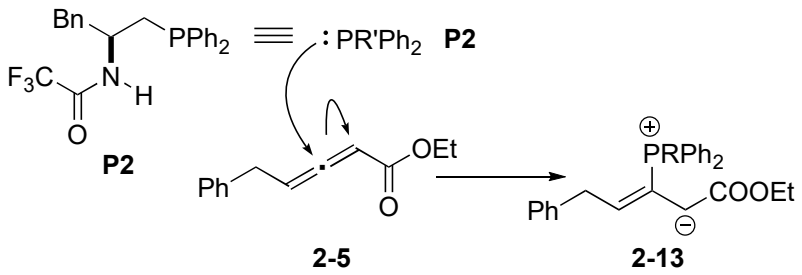
[2]



2-4 **2-5** (2.0 eq) **2-6**

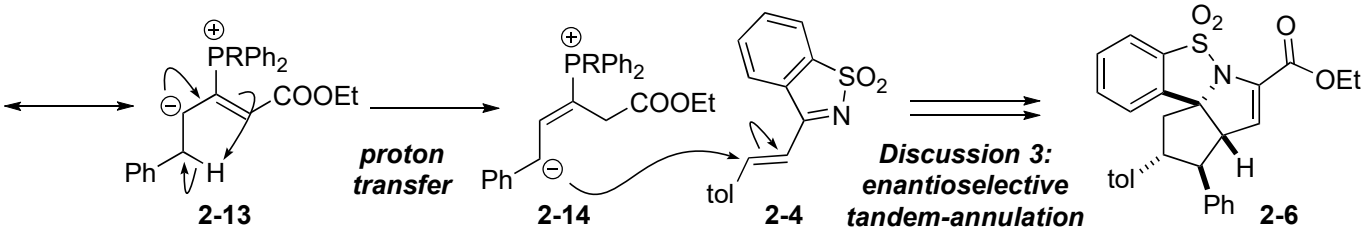
Li, E.; Jin, H.; Jia, P.; Dong, X.; Huang, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 11591.

▪Reaction mechanism



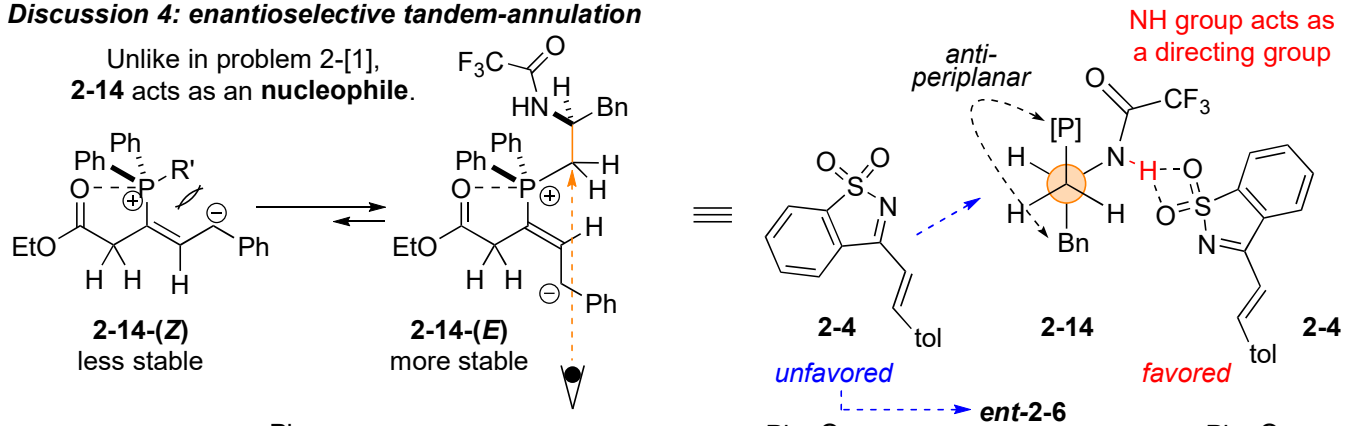
	2-15	**2-16**
pKa (in DMSO)	22.7[c]	17.4[d]

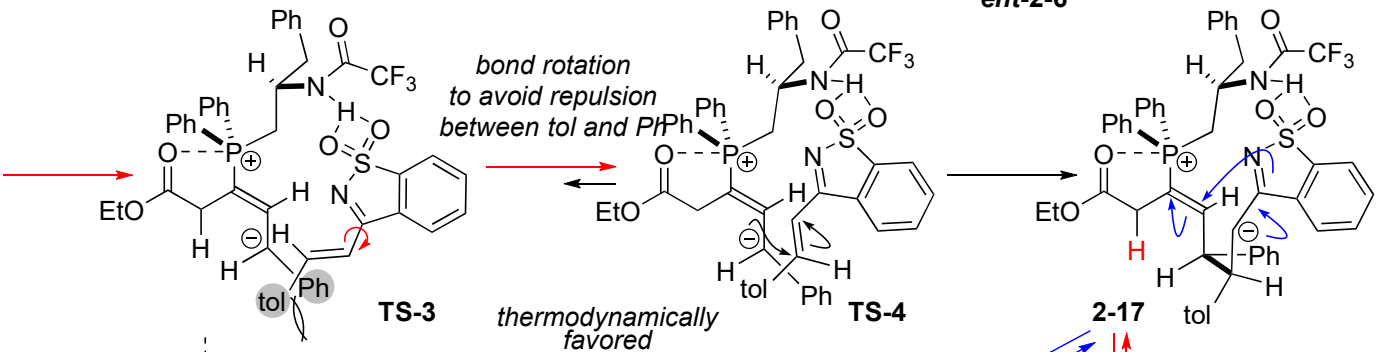
c) *J. Org. Chem.* **1981**, *46*, 4327.
d) *J. Am. Chem. Soc.* **1994**, *116*, 968.

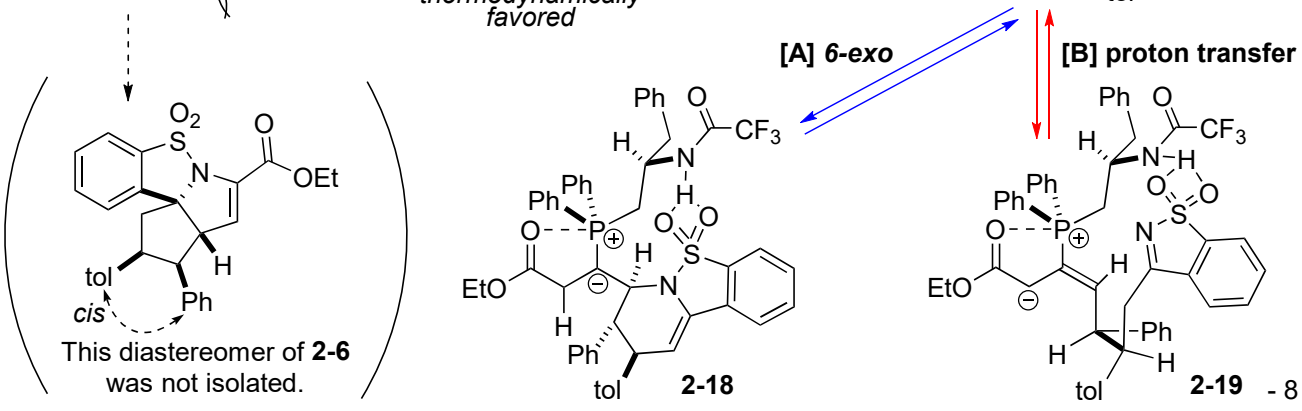


Discussion 4: enantioselective tandem-annulation

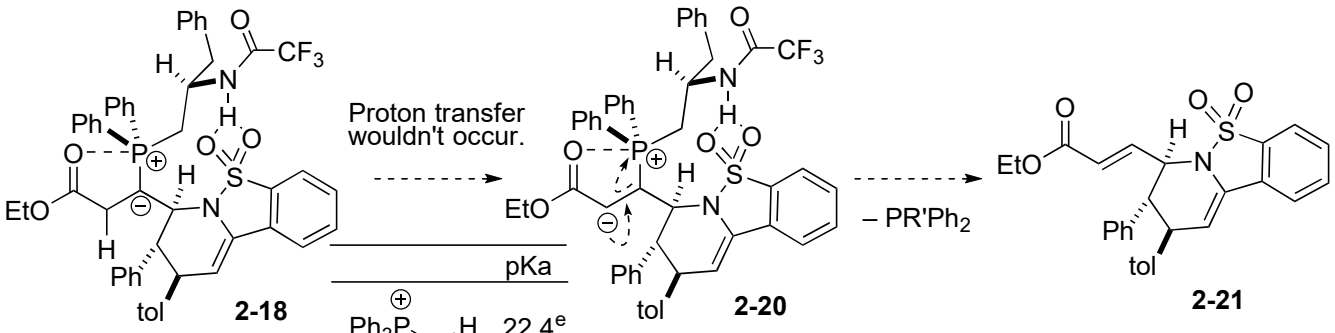
Unlike in problem 2-[1], **2-14** acts as an **nucleophile**.







[A] ***6-exo cyclization***



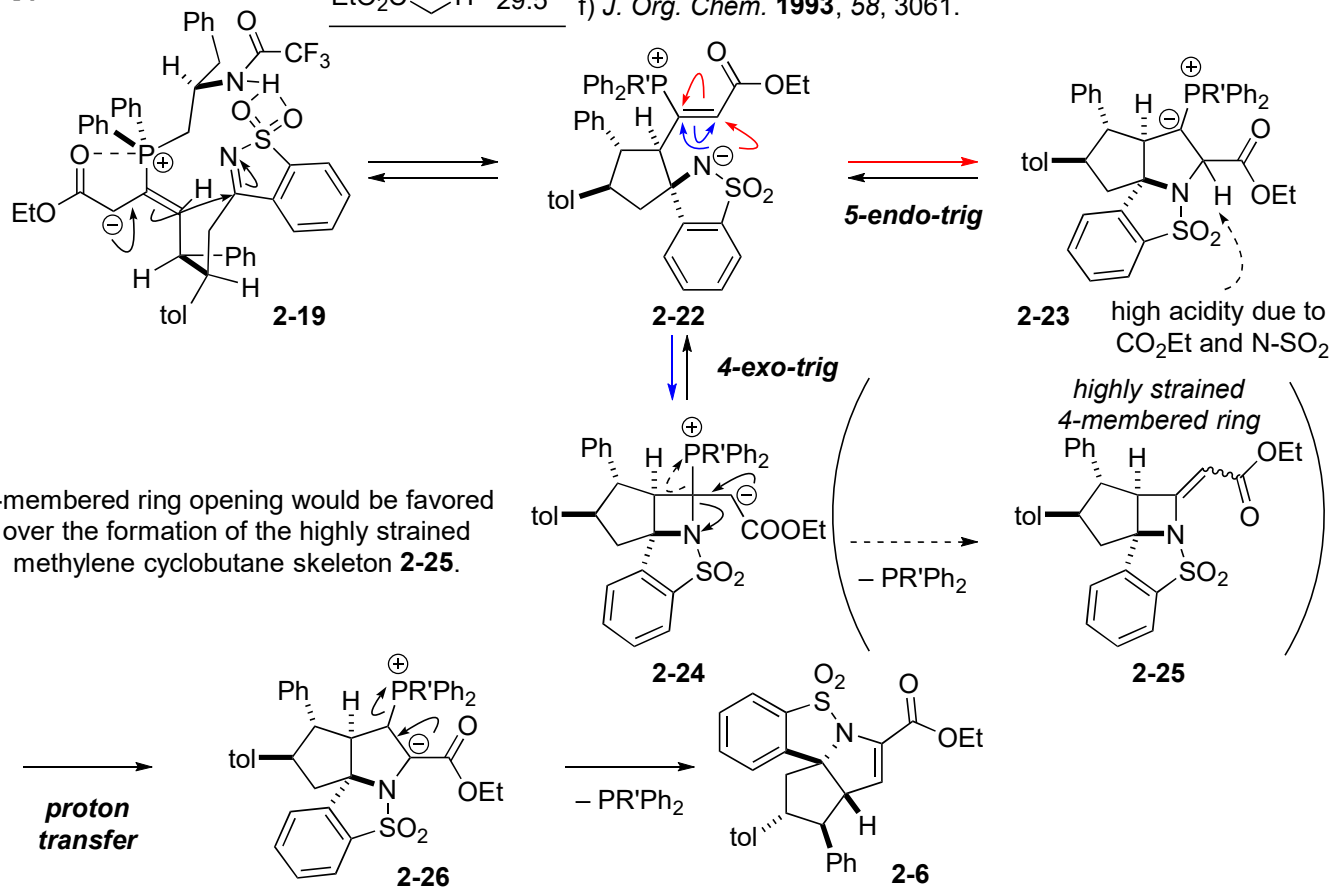
pKa

Ph_3P–H 22.4[e]

EtO_2C–H 29.5[f]

e) *J. Am. Chem. Soc.* **1994**, *116*, 968.
f) *J. Org. Chem.* **1993**, *58*, 3061.

[B] proton transfer



4-membered ring opening would be favored over the formation of the highly strained methylene cyclobutane skeleton **2-25**.