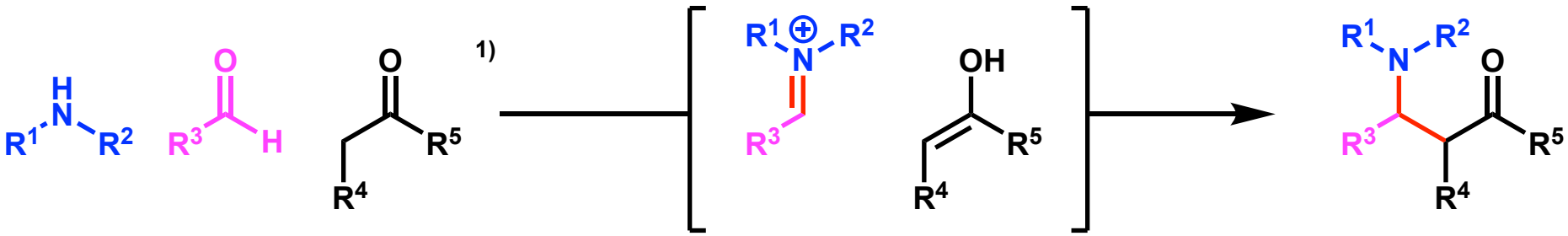
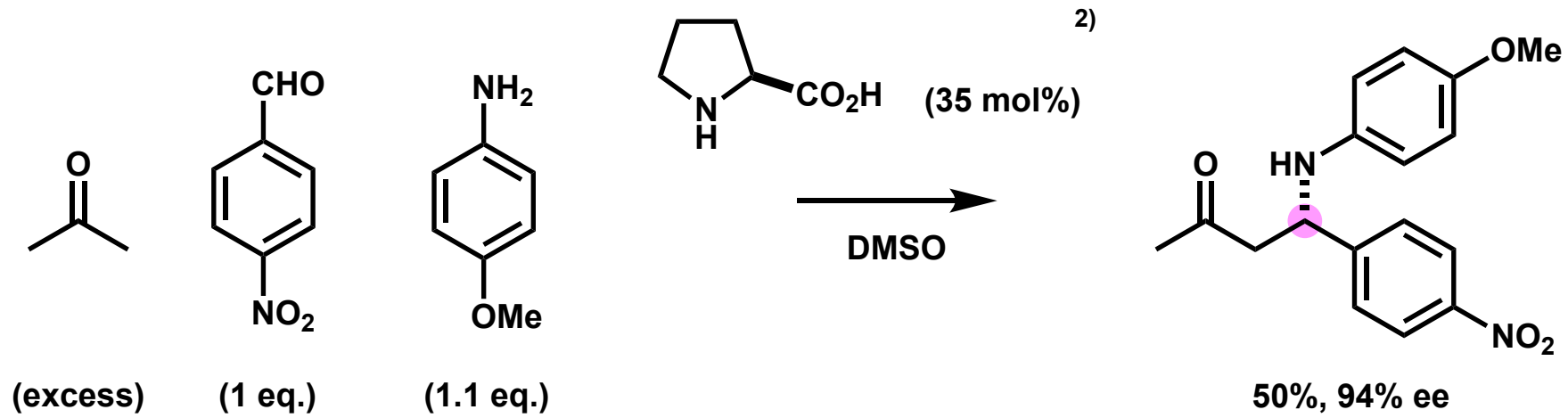
Direct Asymmetric Vinylogous Mannich Reaction

2021.5.8. Literature Seminar
M1 Hibiki Asai

Contents

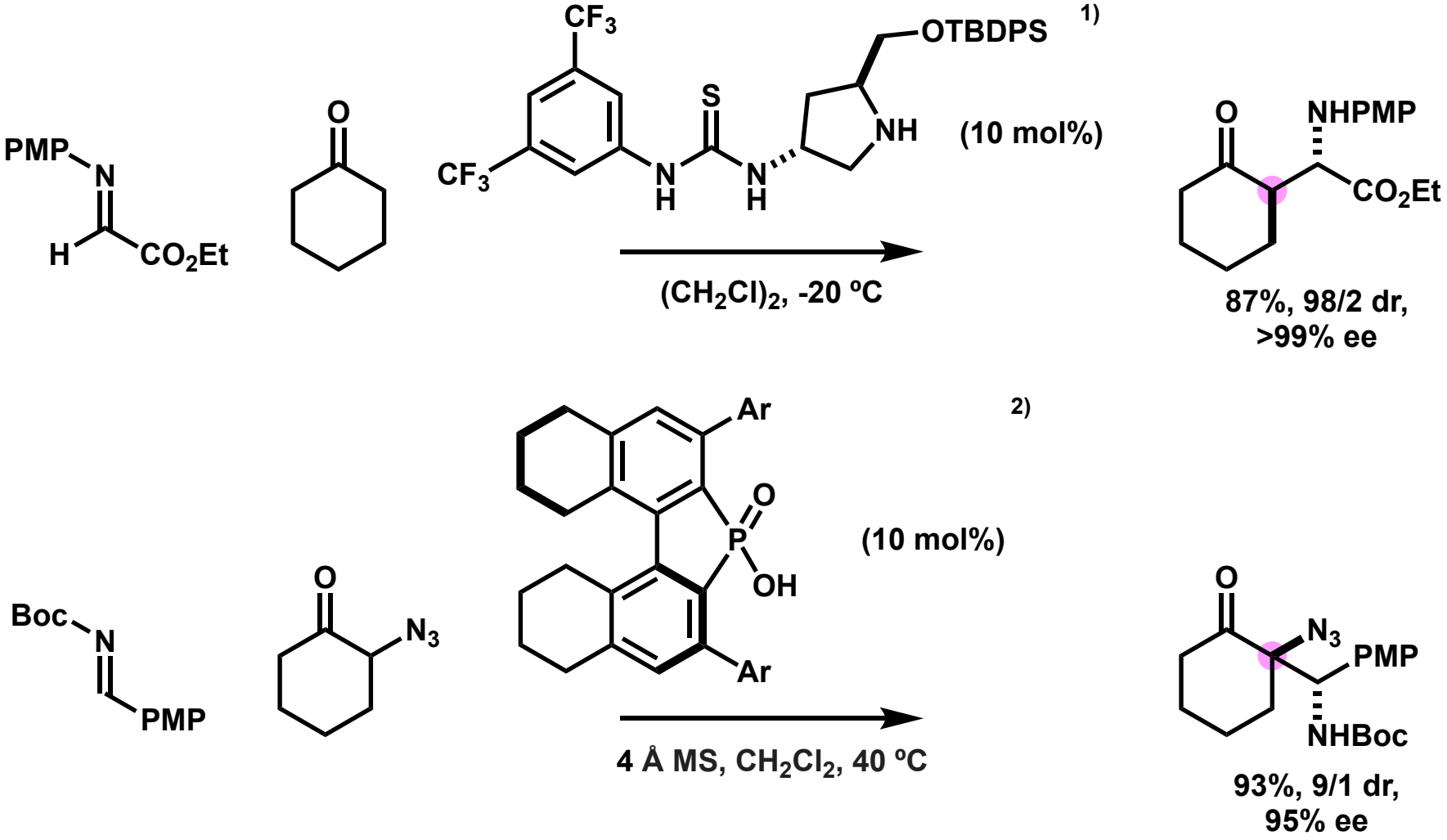
Mannich Reaction

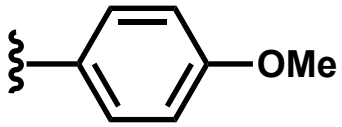




1) Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647. 2) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

Asymmetric Mannich Reaction (1)

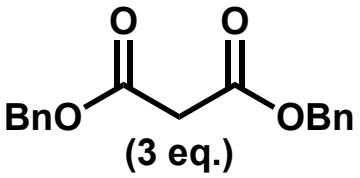


PMP =  OMe

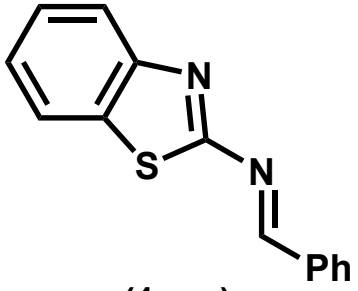
Ar = 9-anthracenyl

1) Zhang, H.; Chuan, Y.; Li, Z.; Peng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2288. 2) Ye, X.; Pan, Y.; Yang, X. *Chem, Commun.*, **2020**, *56*, 98.

Asymmetric Mannich Reaction (2)



(3 eq.)



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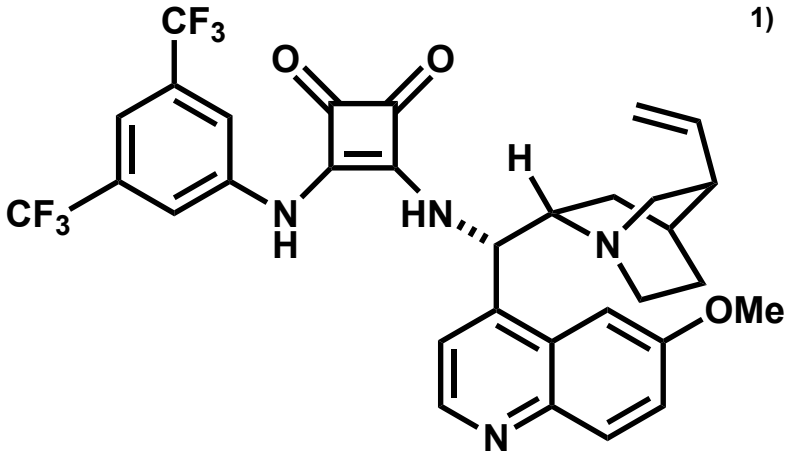
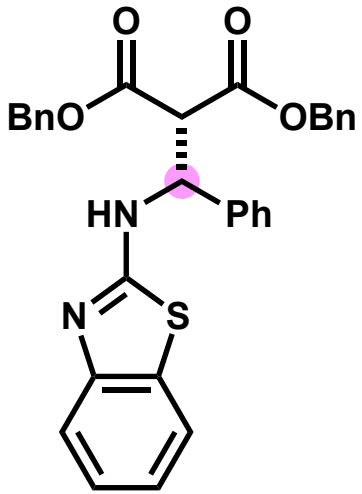


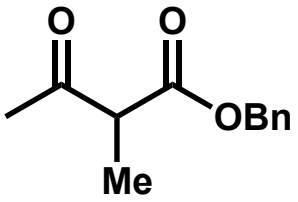
1)

(10 mol%)

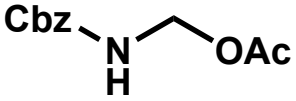
$CHCl_3$, -15 °C



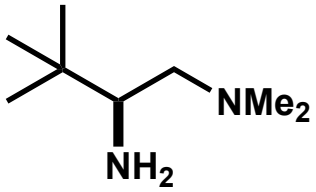
99%, 98% ee



(1 eq.)



(1.5 eq.)

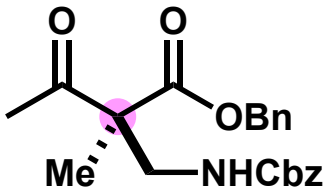


2)

(20 mol%)

m-$NO_2C_6H_4CO_2H$ (50 mol%)

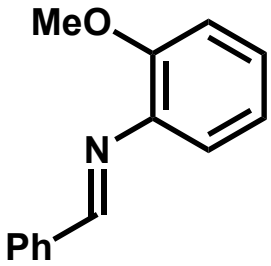
$CHCl_3$, 60 °C

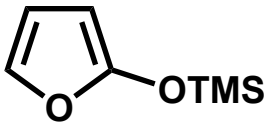


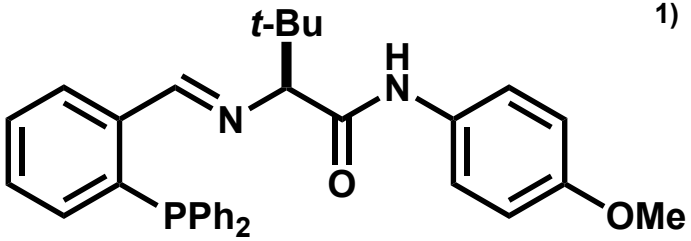
92%, >99% ee

1) He, H.-X.; Du, D.-M. *RSC Adv.*, **2013**, *3*, 16349. 2) You, Y.; Zhang, L.; Cui, L.; Mi, X.; Luo, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13814.

Vinylogous Asymmetric Mannich Reaction (1)



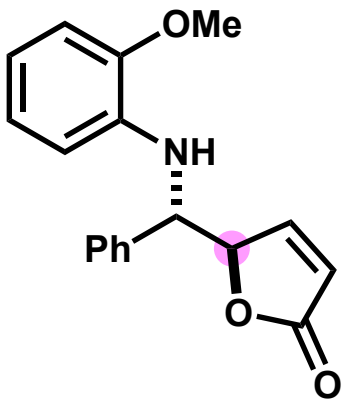




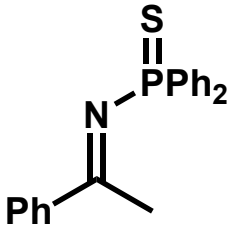
1)

(1 mol%)

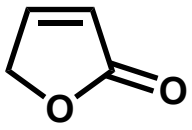
AgOAc (1 mol%)
i-PrOH (1.1 eq.)
THF, -78 ºC



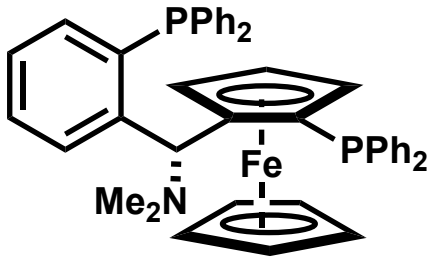
82%, >99/1 dr, 96% ee



(1 eq.)



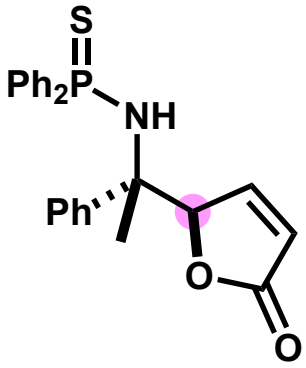
(3 eq.)



2)

(10 mol%)

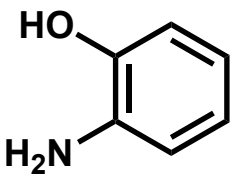
$[Cu(MeCN)_4]PF_6$ (10 mol%)
Et_3N (50 mol%)
THF, 0 ºC



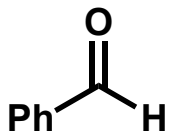
87%, >20:1 dr, 99% ee

1) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7230. 2) Yin, L.; Tanaka, H.; Kumagai, N.; Shibasaki, M. *Angew, Chem, Int, Ed.* **2013**, *52*, 7310.

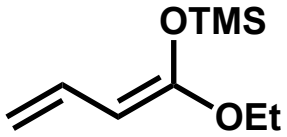
Vinylogous Asymmetric Mannich Reaction (2)



(1 eq.)

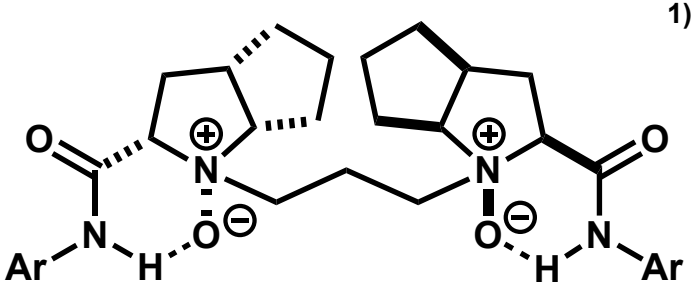


(1 eq.)



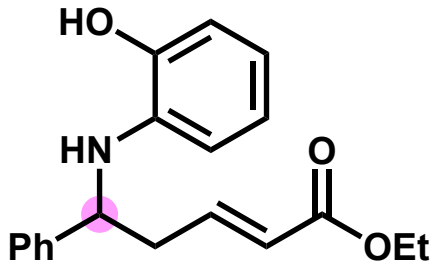
(3 eq.)

1)



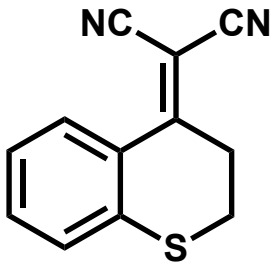
(10 mol%)

$Sc(OTf)_3$ (5 mol%)
t-BuOMe, 0 °C
Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$

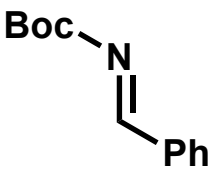


99%, 82% ee

*Absolute configuration was not mentioned.

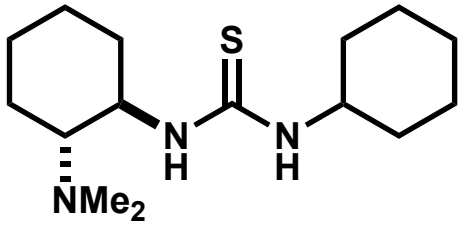


(1 eq.)



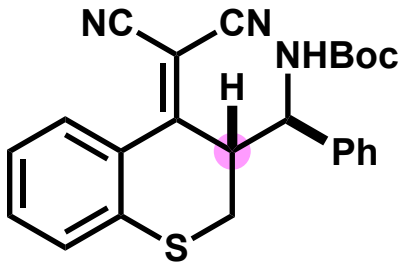
(1.2 eq.)

2)



(0.1 mol%)

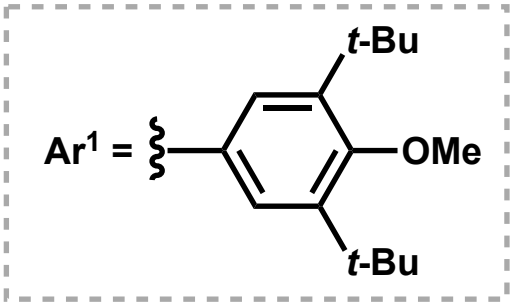
toluene

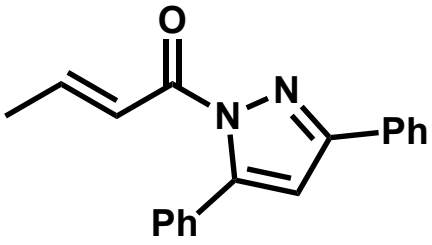


98%, 98% ee

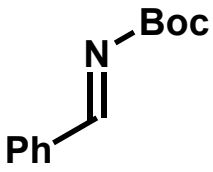
1) Zhan, Q.; Hui, Y.; Zhou, X.; Lin, L.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2010**, *352*, 976. 2) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc*. **2007**, *129*, 1878.

Vinylogous Asymmetric Mannich Reaction (3)

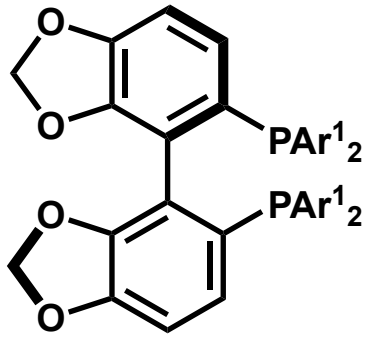




(1 eq.)



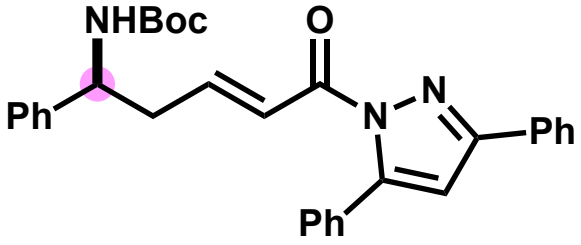
(2 eq.)



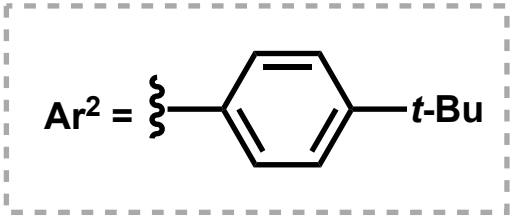
1)

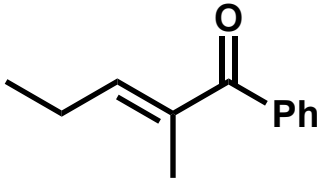
(2 mol%)

$[Cu(MeCN)_4]PF_6$ (2 mol%)
Et_3N (50 mol%)
THF, -20 °C



96%, 97% ee





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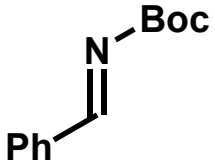
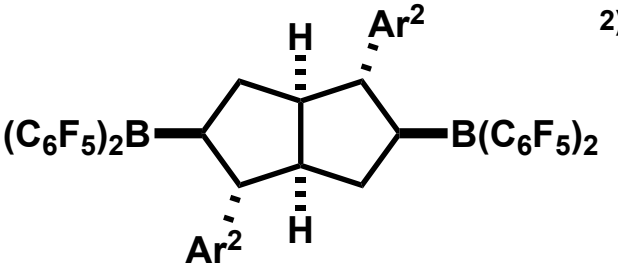


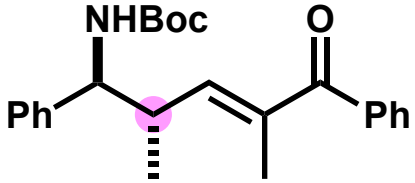
(1.5 eq.)



2)

(5 mol%)

N-methylpiperidine (20 mol%)
$PhCF_3$, 10 °C

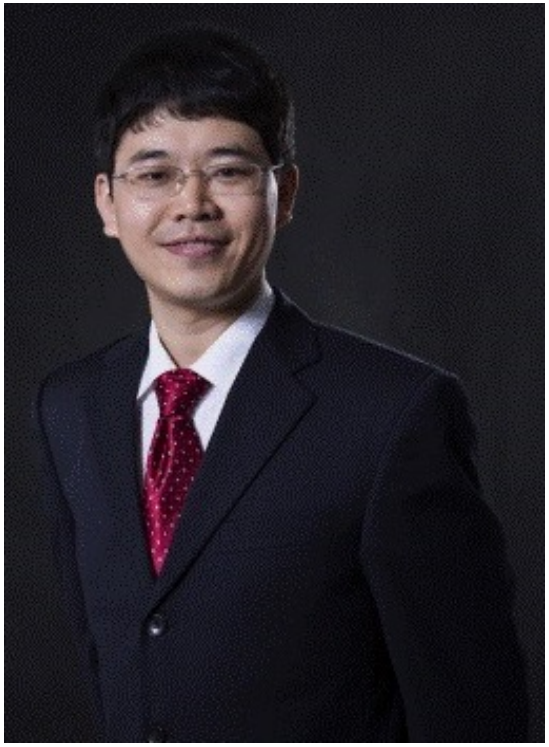


94%, 11/1 dr, 92% ee

1) Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55. 2) Tian, J.-J.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Contents

Introduction of Prof. Yin

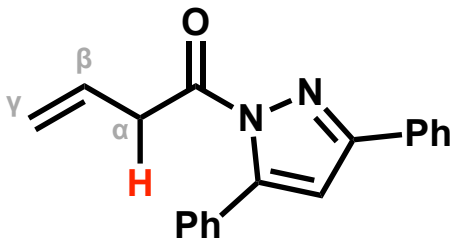


Prof. Liang Yin
2004 B.S. @ Nankai University
2007 M.S. @ Nankai University
2010 Ph.D @ The University of Tokyo (Prof. Masakatsu Shibasaki and Prof. Motomu Kanai)
2010- Postdoctral fellow
@ The University of Tokyo (Prof. Motomu Kanai)
2011- @ Harvard University (Prof. E. J. Corey)
2012- @ Institute of Microbial Chemistry (Prof. Masakatsu Shibasaki)
2014- Professor @ Shanghai Institute of Organic Chemistry

Research topic: organocatalyst, organometallic catalyst, synthsis of natural product

http://people.ucas.ac.cn/~liangyin?language=en

Previous Studies



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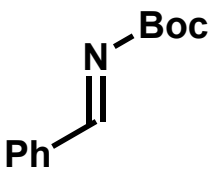
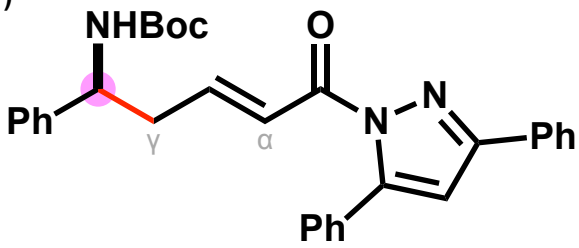


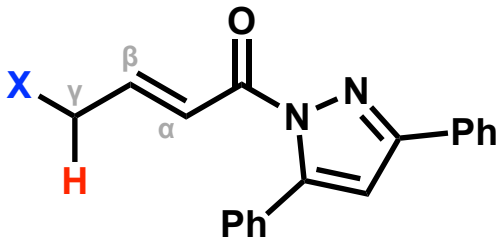
(2 eq.)

(*R*)-DTBM-SEGPHOS (1 mol%) [1)]
$[Cu(MeCN)_4]PF_6$ (1 mol%)
Et_3N (1 mol%)

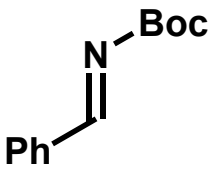
THF, -40 ºC, 8h



93%, γ/α >20/1, 98% ee



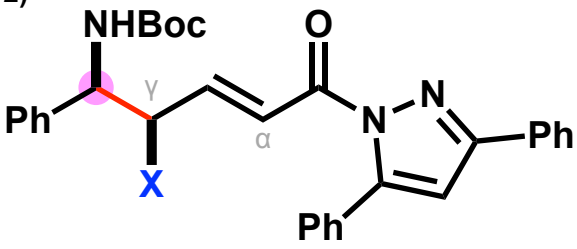
(1 eq.)



(2 eq.)

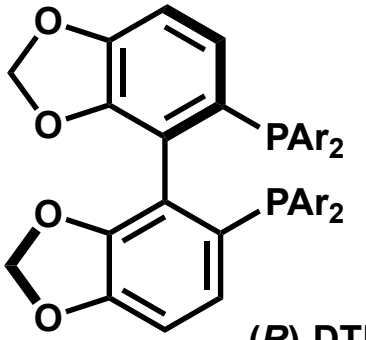
(*R*)-DTBM-SEGPHOS (3-5 mol%) [2)]
$[Cu(MeCN)_4]PF_6$ (3-5 mol%)
Et_3N (3-5 mol%)

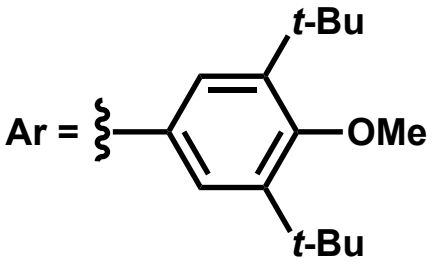
THF, -40 ºC, 12-48h



γ/α >20/1

X = F, 81%, >20/1 dr, >99% ee
X = Cl, 93%, 13/1 dr, >99% ee
X = Br, 89%, 13/1 dr, >99% ee

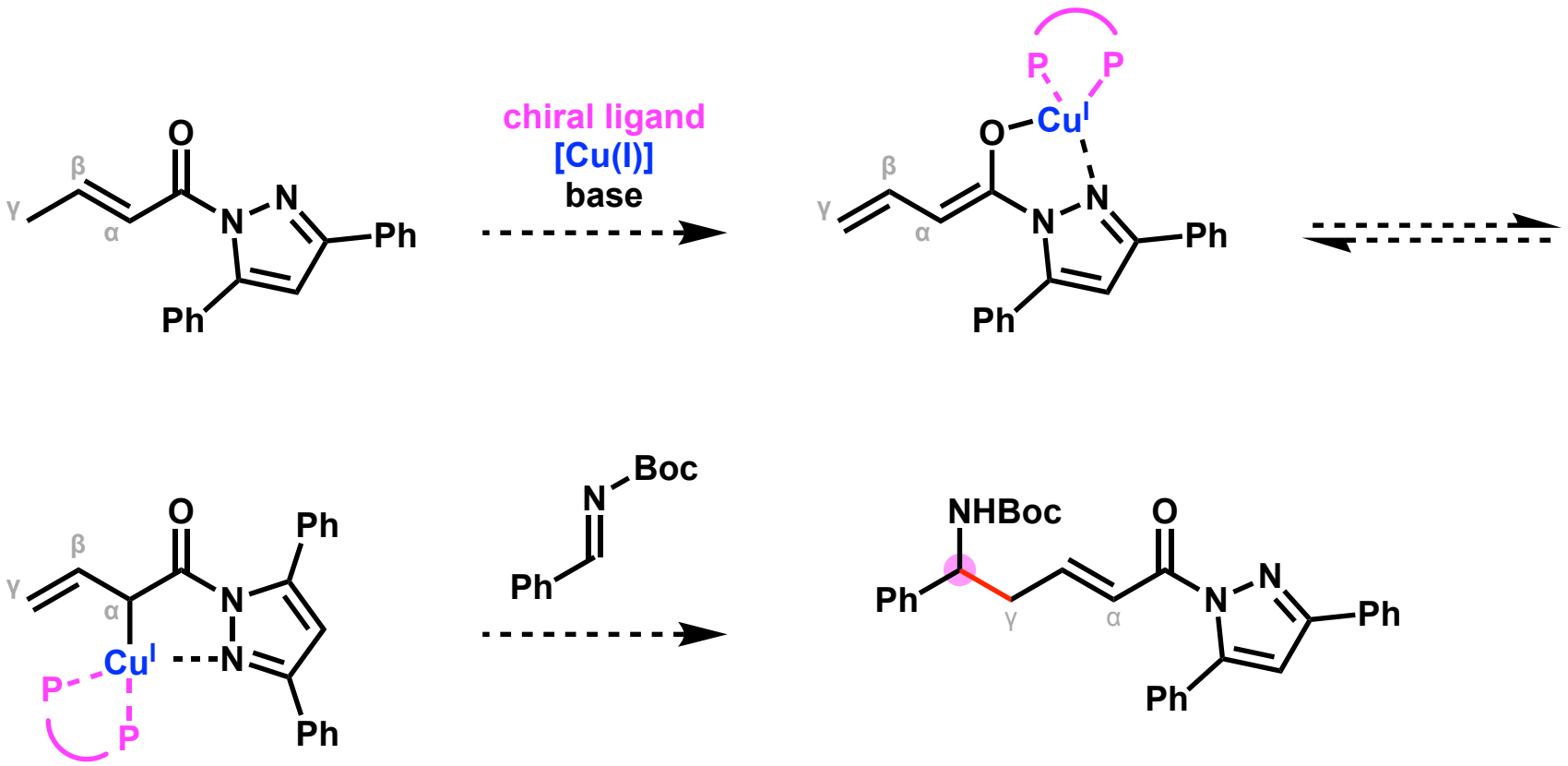




(*R*)-DTBM-SEGPHOS

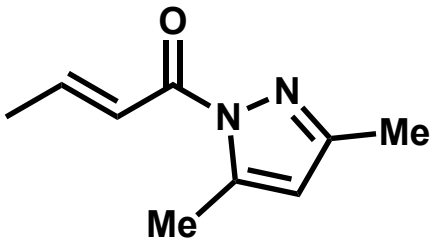
1) Zhan, H.-J.; Shi, C.-Y.; Zhong, F.; Yin, L. *J. Am. Chem. Soc.* **2017**, *139*, 2196. 2) Zhang, F.; Yue, W.-J.; Zhan, H.-J.; Zhang, C.-Y.; Yin, L. *J. Am. Chem. Soc.* **2018**, *140*, 15170.

Extension to α,β-Unsaturated Pyrazoleamides

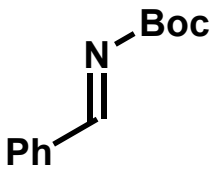


Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55.

Screening of Base



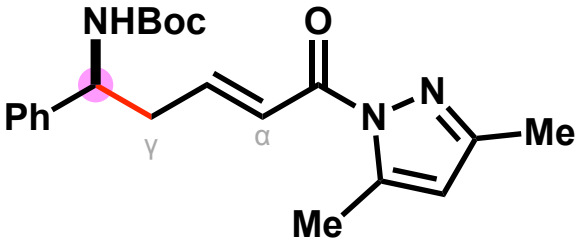
(1 eq.)



(2 eq.)

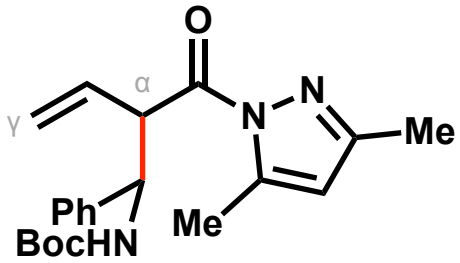
(*R*)-BINAP (5 mol%)
$[Cu(MeCN)_4]PF_6$ (5 mol%)
base (5 mol%)

THF, rt, 12 h

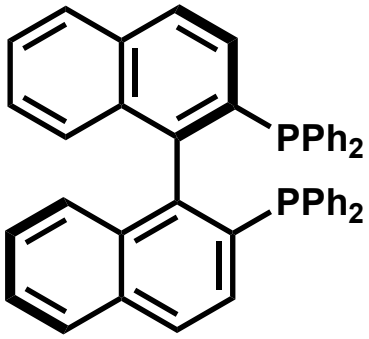


γ-adduct (desired)

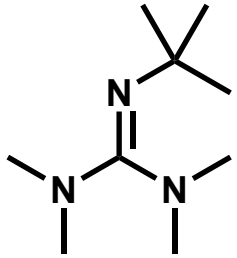
entry	*base*	total yield [%]	γ/α	ee [%]
1	Barton's base	trace	-	-
2	DBU	trace	-	-
3	$(i\text{-Pr})_2NEt$	35	1.3/1	-11
4	Et_3N	44	1/1.3	-7



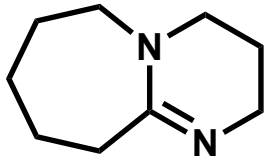
α-adduct (undesired)



(*R*)-BINAP



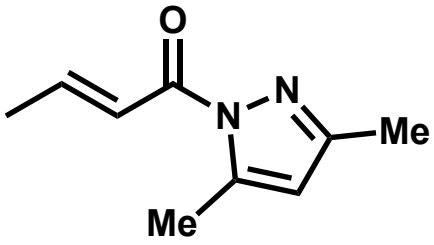
Barton's base



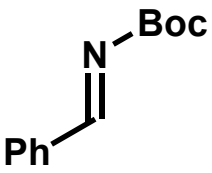
DBU

Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55.

Screening of Ligand



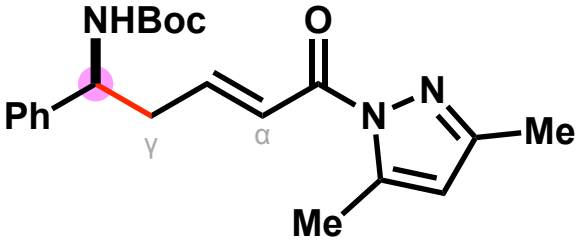
(1 eq.)



(2 eq.)

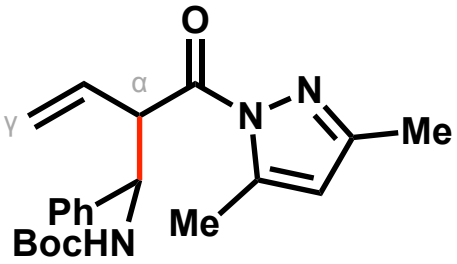
ligand (5 mol%)
$[Cu(MeCN)_4]PF_6$ (5 mol%)
Et_3N (5 mol%)

THF, rt, 12 h



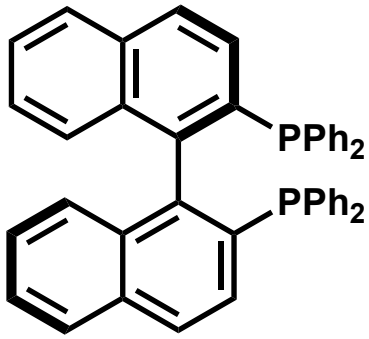
γ-adduct (desired)

entry	*ligand*	total yield [%]	γ/α	ee [%]
1	(*R*)-BINAP	44	1/1.3	-7
2	(*R*)-SEGPHOS	84	1.5/1	17
3	(*R*)-DTBM-SEGPHOS	77	>20/1	94
4 [a)]	(*R*)-DTBM-SEGPHOS	96	>20/1	97

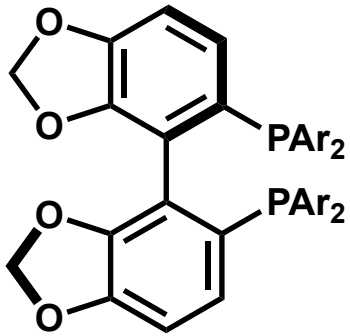


α-adduct (undesired)

a) 2 mol% $[Cu(MeCN)_4]PF_6$, 2 mol% (*R*)-DTBM-SEGPHOS, 50 mol% Et_3N, -20 ºC, 24 h

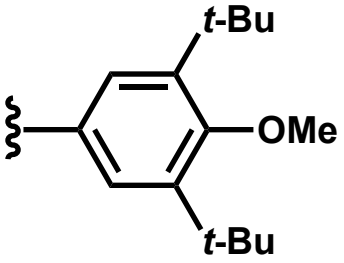


(*R*)-BINAP



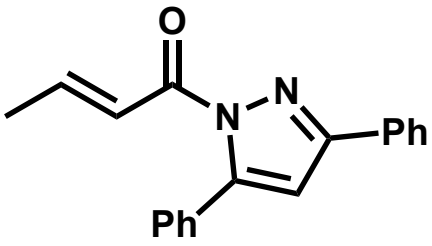
(*R*)-SEGPHOS:Ar = Ph

(*R*)-DTBM-SEGPHOS:Ar =

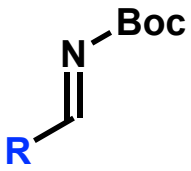


Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55.

Substrate Scope (1)



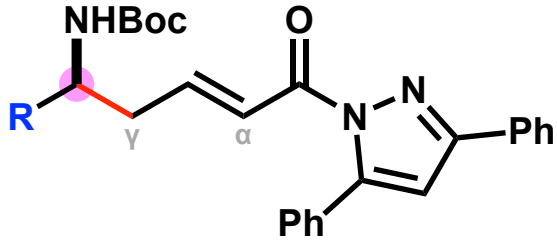
(1 eq.)



(2 eq.)

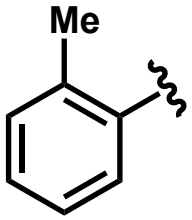
(*R*)-DTBM-SEGPHOS (2 mol%)
$[Cu(MeCN)_4]PF_6$ (2 mol%)
Et_3N (50 mol%)

THF, -20 °C, 24h



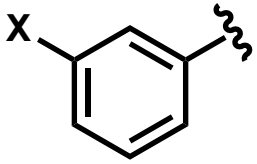
γ/α > 20/1

R =



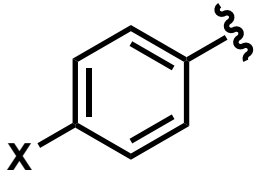
95%, 87% ee

R =



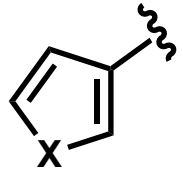
X = Me, 89%, >99% ee
X = OMe, 94%, >99% ee
X = Cl, 70%, 91% ee [a]
X = Br, 81%, 93% ee [a]

R =



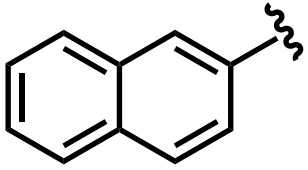
X = Me, 86%, >99% ee
X = *t*-Bu, 95%, 97% ee
X = OMe, 97%, 97% ee
X = F, 89%, 95% ee
X = NO_2, 26%, 39% ee [b]
X = CN, trace [b]

R =



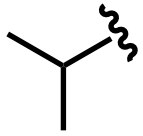
X = O, 77%, 88% ee
X = S, 87%, 93% ee

R =



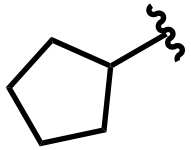
94%, 99% ee

R =



74%, 87% ee [c]

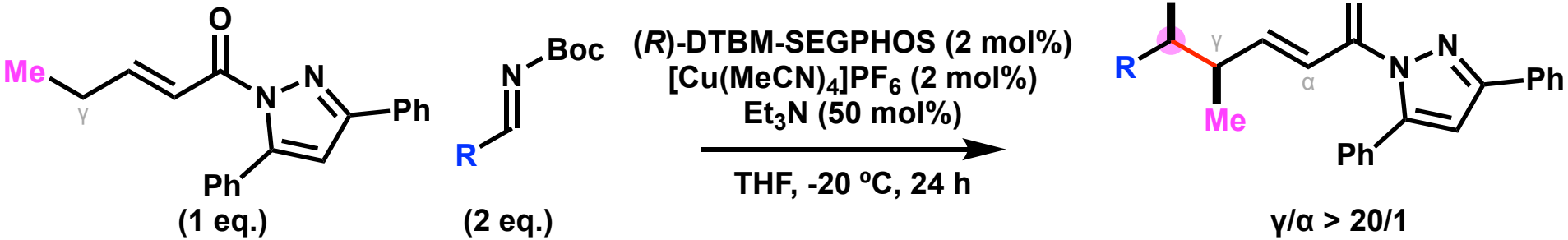
R =

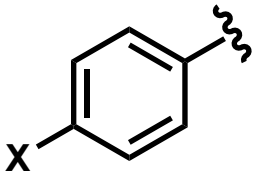


87%, 86% ee [c]

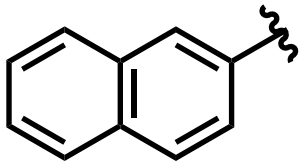
a) 0 °C
b) 12 h
c) 5 eq. *N*-Boc imine employed.

Substrate Scope (2)

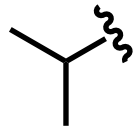


R = 

X = H, 97%, 11/1 dr, >99% ee
X = F, 89%, 10/1 dr, >99% ee

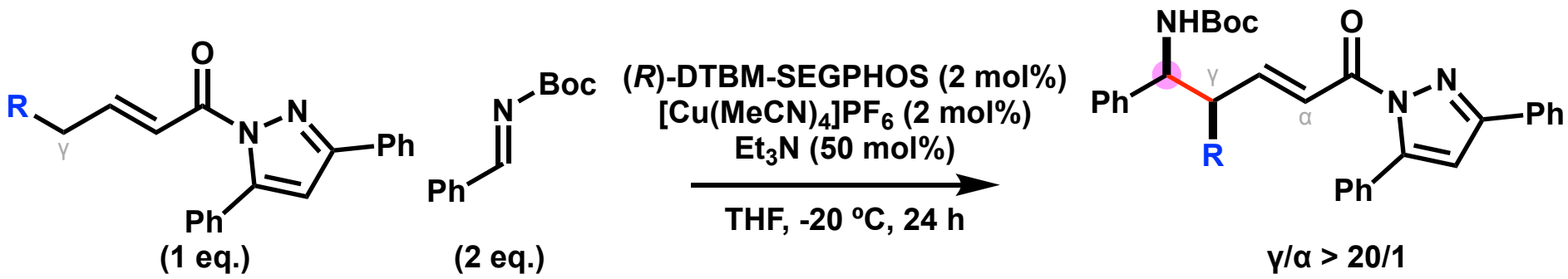
R = 

98%, 10/1 dr, >99% ee

R = 

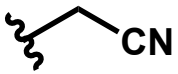
72%, 2.2/1 dr, 77% ee

Substrate Scope (3)



R = Et

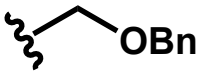
98%, 3/1 dr, >99% ee

R = 

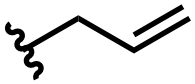
99%, 2.2/1 dr, 98% ee

R = 

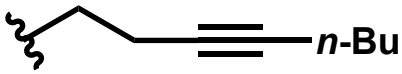
90%, 1.5/1 dr, 99% ee

R = 

89%, 3/1 dr, 95% ee

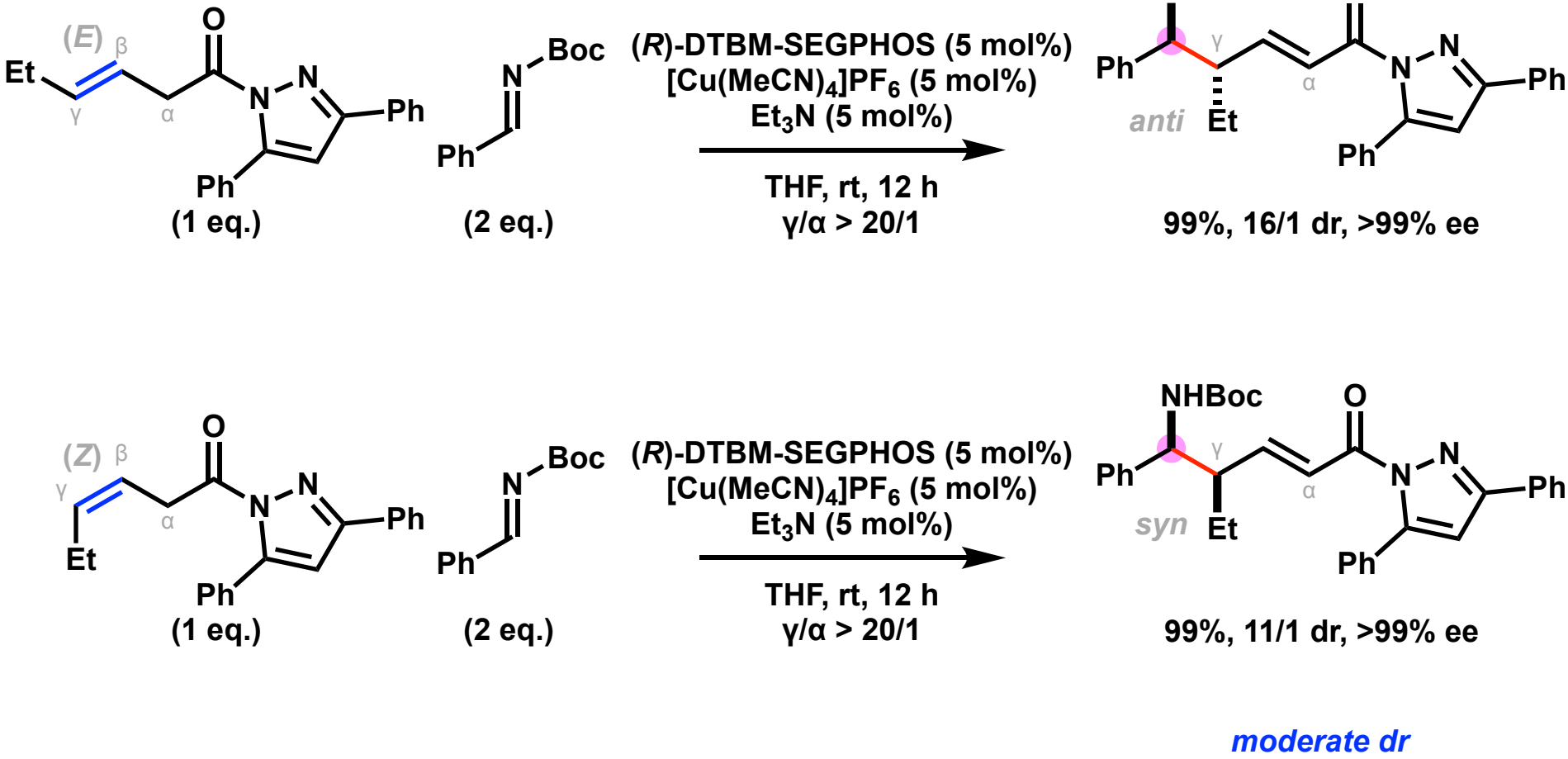
R = 

89%, 3/1 dr, 95% ee

R = 

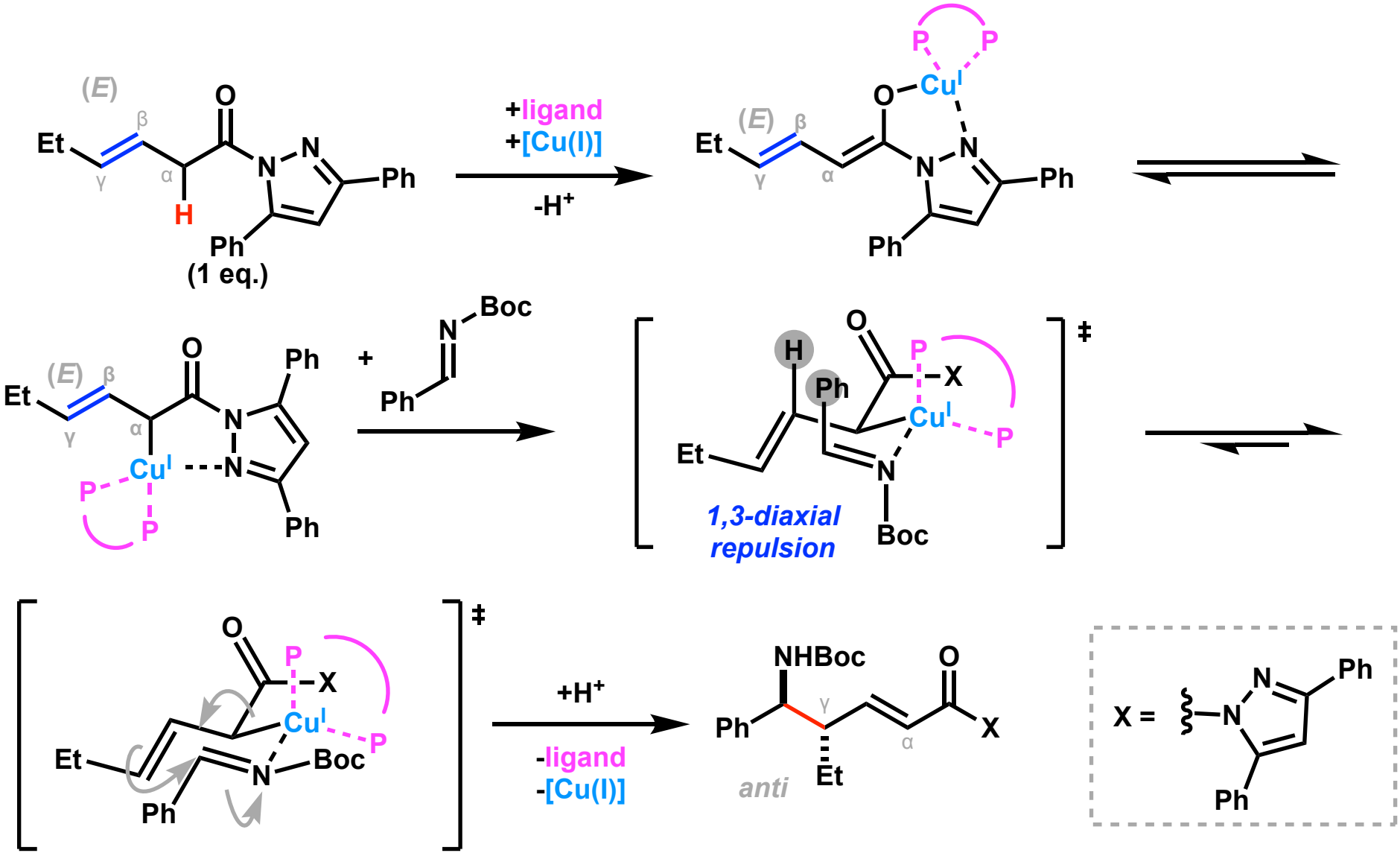
95%, 1.5/1 dr, 99% ee

Stereoselectivity of *syn*/*anti* (1)



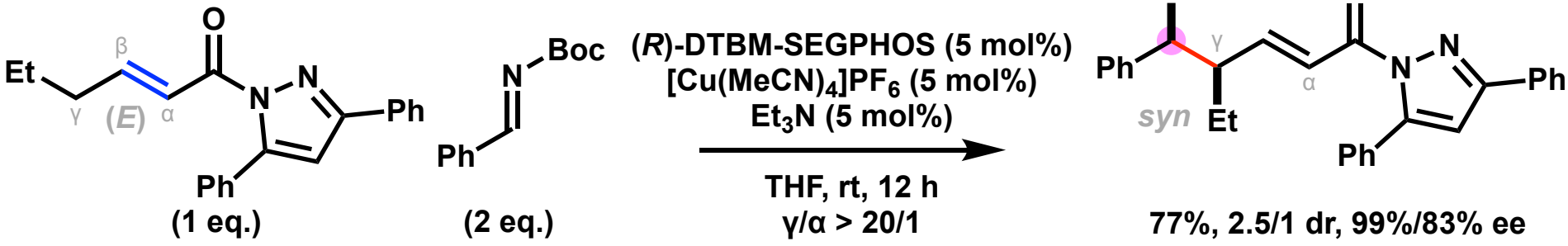
moderate dr

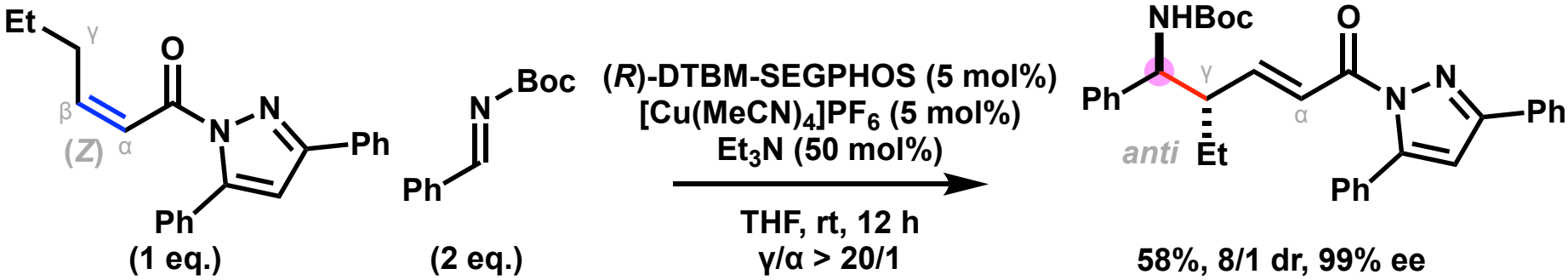
Proposed Mechanism from β,γ-Unsaturated Pyrazoleamide



Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55.

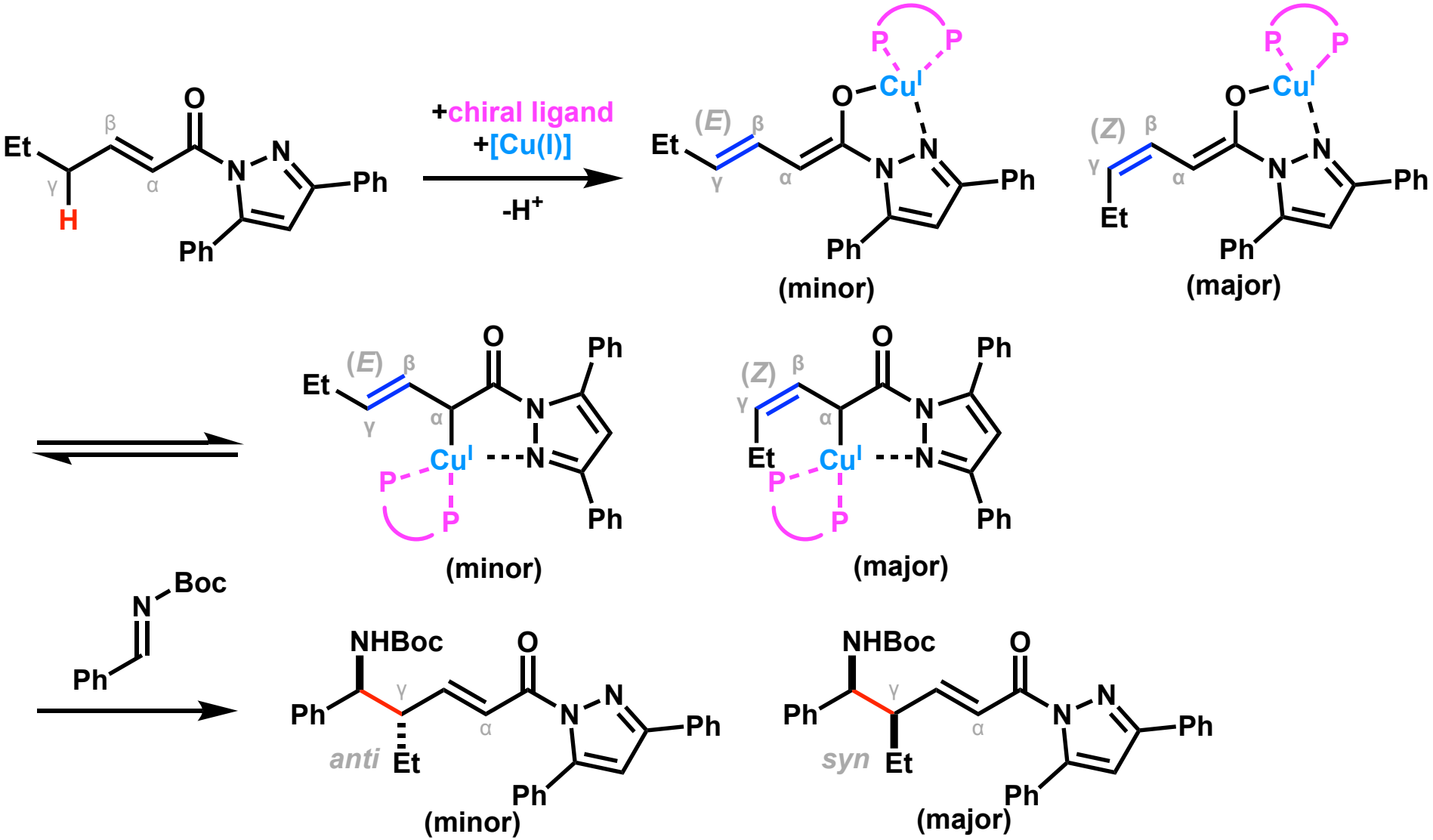
Stereoselectivity of *syn*/*anti* (2)





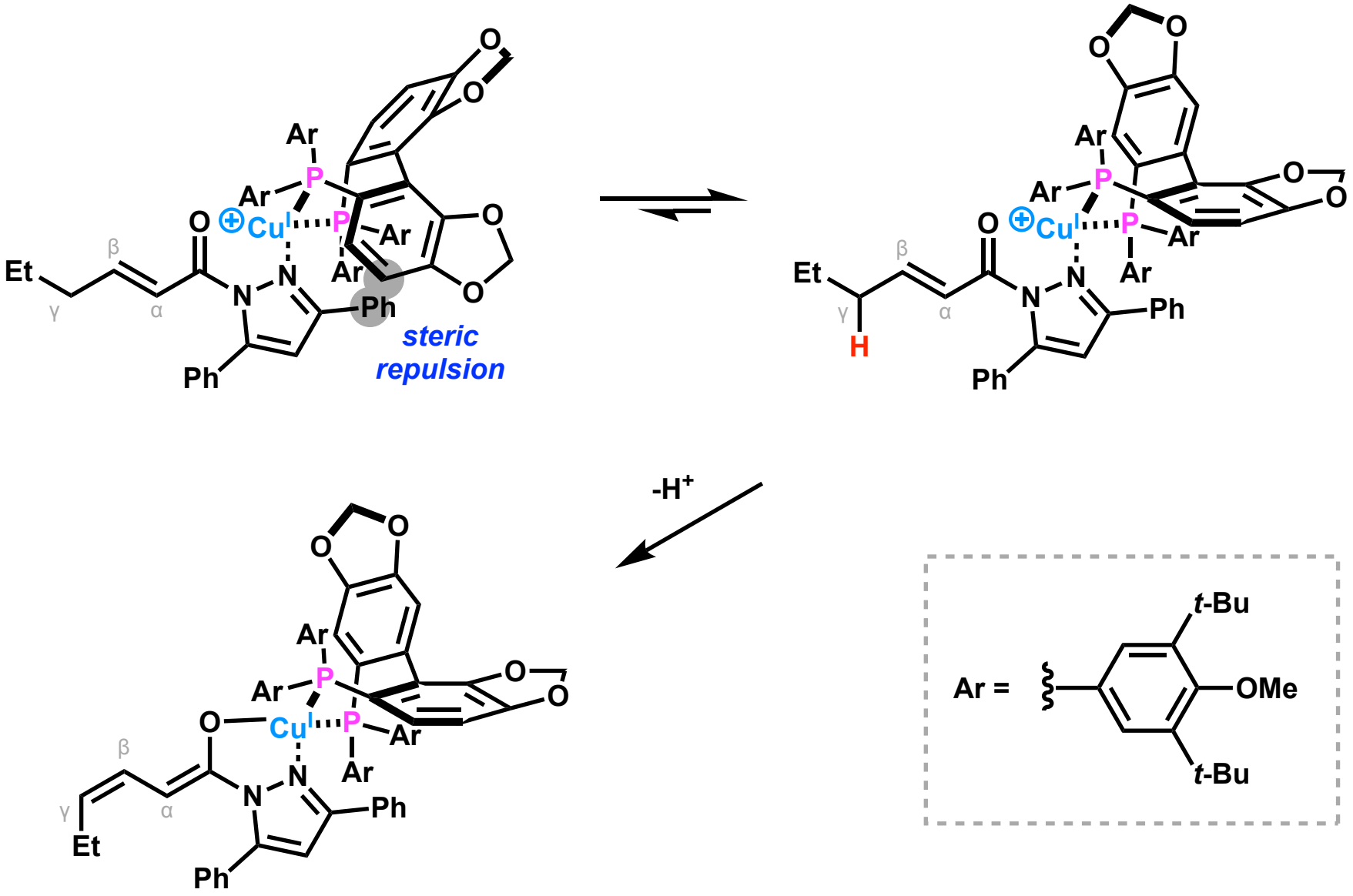
bad dr

Proposed Mechanism from α,β-Unsaturated Pyrazoleamide

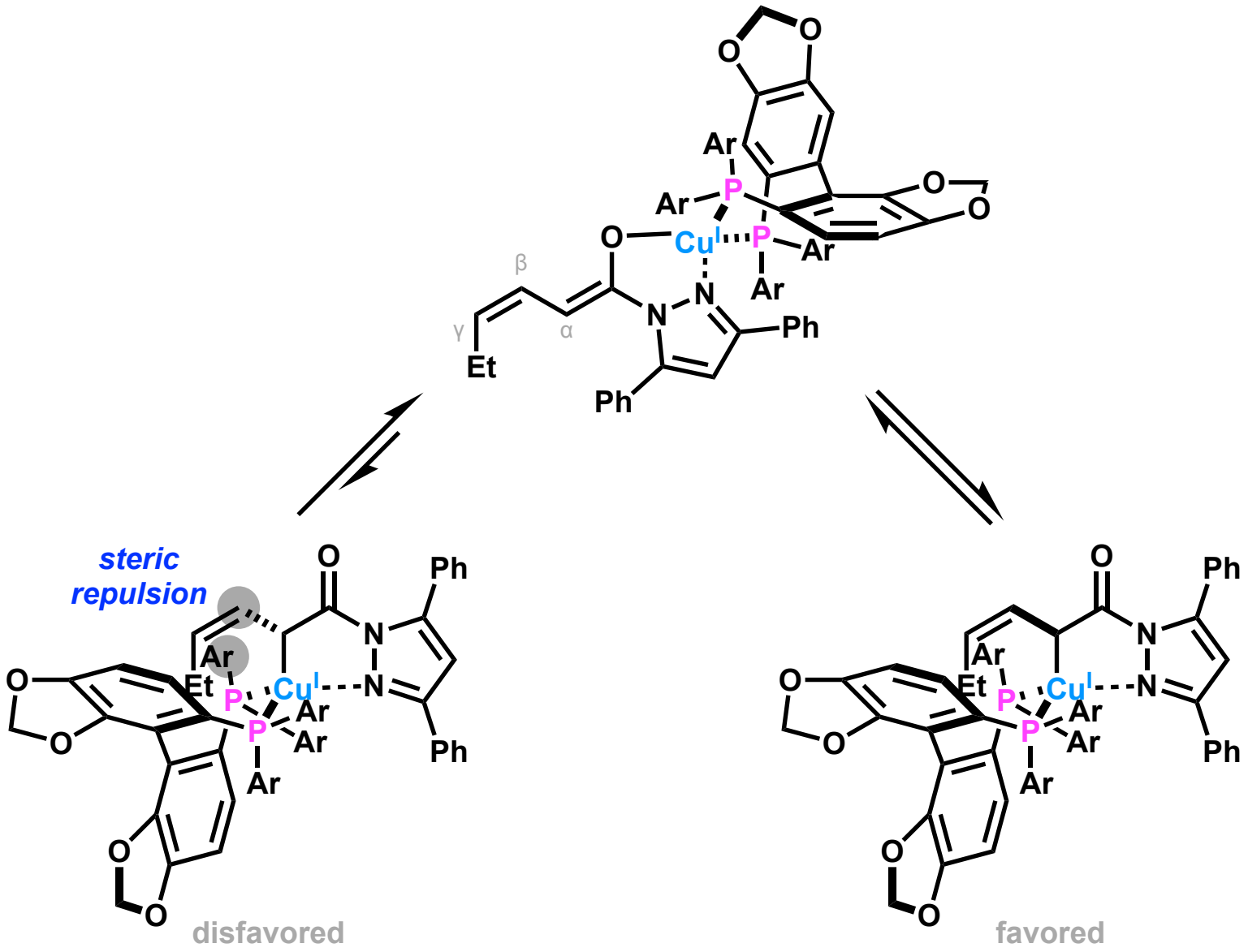


1) Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55. 2) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**. *47*, 163

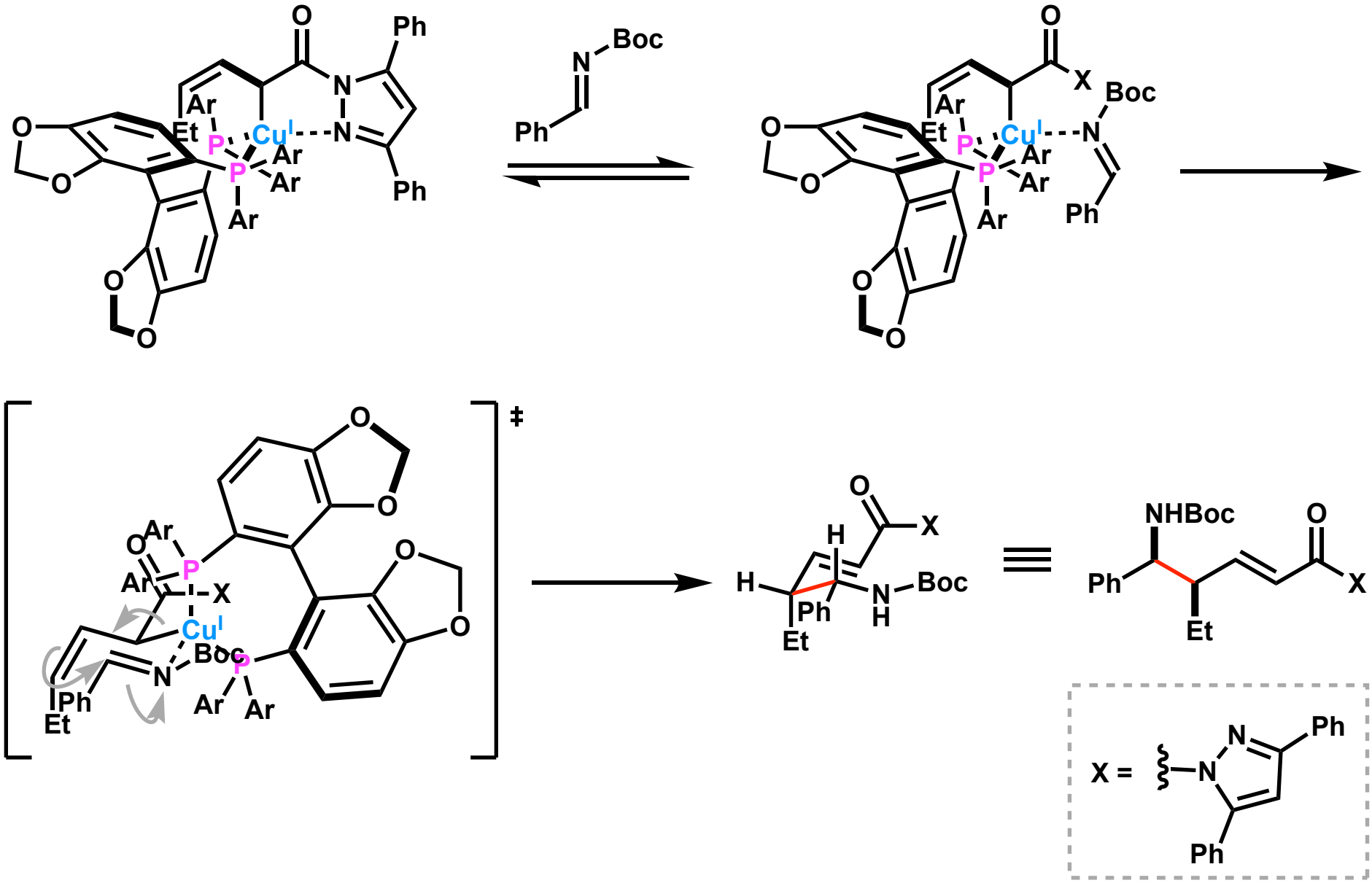
Proposed Enantioselectivity (1)



Proposed Enantioselectivity (2)



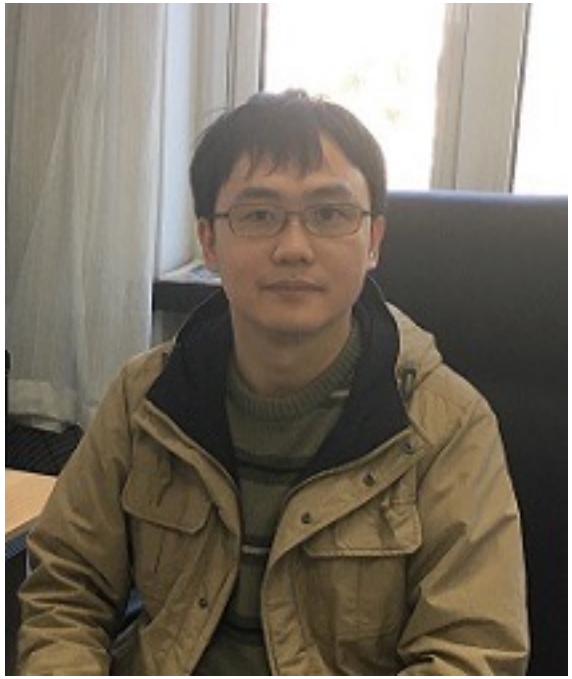
Proposed Enantioselectivity (3)



Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55.

Contents

Introduction of Prof. Yin

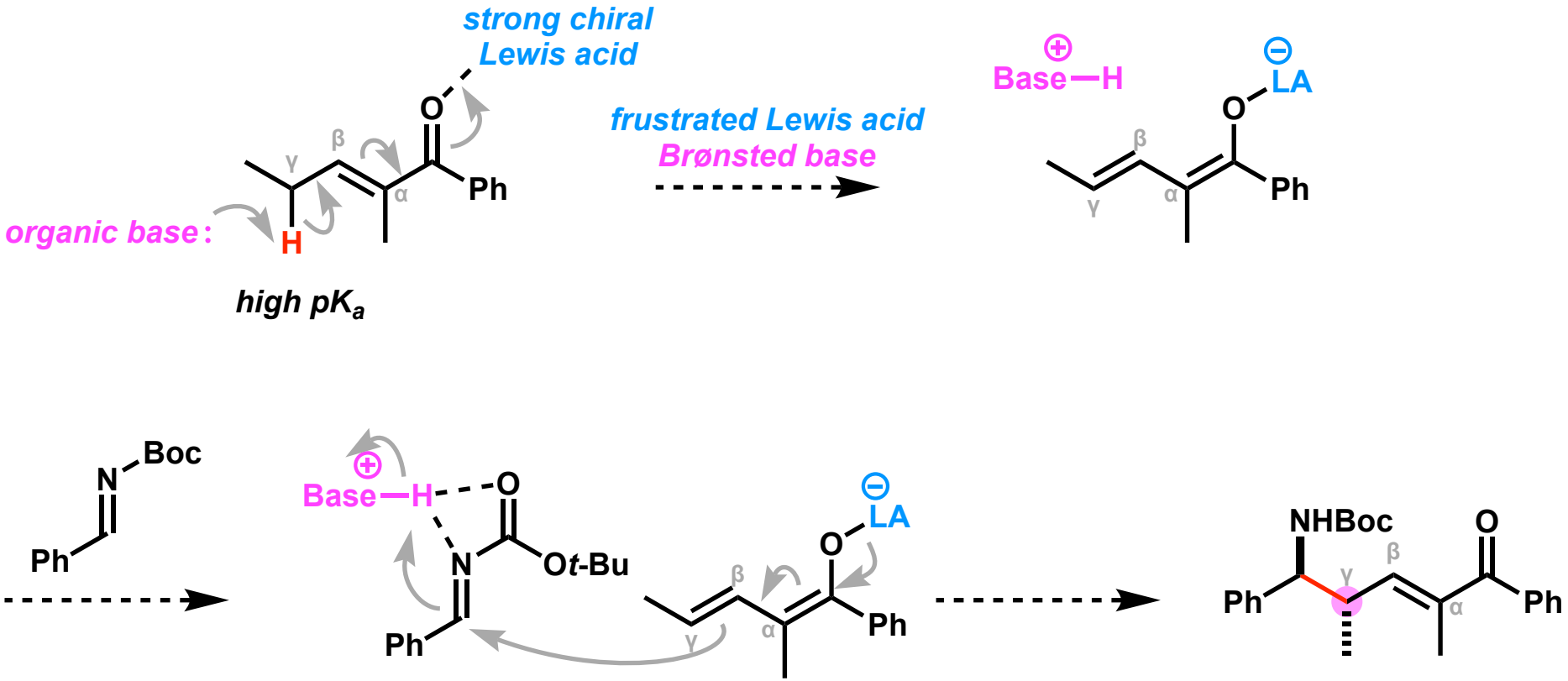


Prof. Xiao-Chen Wang

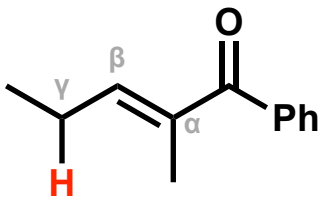
2007 B.S. @ Nankai University (Prof. Qi-Lin Zhou)
2012 Ph.D @ University of Maryland, College Park (Prof. Michael P. Doyle)
2012- Postdoctral fellow
@ The Scripps Research Institute (Prof. Jin-Quan Yu)
2015- Professor @ Nankai University

Research topic: asymmetric catalyst, C-H and C-C bond activation

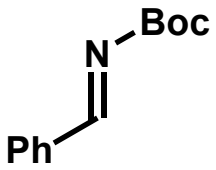
Design of Vinylogous Mannich Reaction



Deprotonation of γ Position



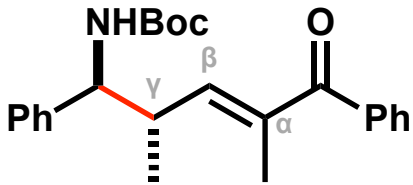
(1 eq.)



(1.5 eq.)

Lewis acid (10 mol%)
Et_3N (20 mol%)

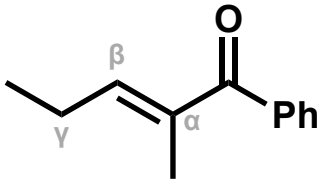
toluene, 10 °C, 24 h



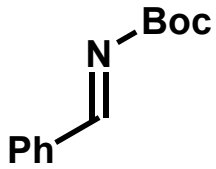
entry	*Lewis acid*	acceptor number	total yield [%]	dr
1	$B(3,4,5\text{-}F_3C_6H_2)_3$	81.7	87	3.0/1
2	$B(C_6F_5)_3$	79.9	91	5.2/1
3		75.7	47	3.2/1
4	$B(2,4,6\text{-}F_3C_6H_2)_3$	70.6	23	4.0/1
5	BPh_3	45.7	no reaction	-

Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Screening of Chiral Borane



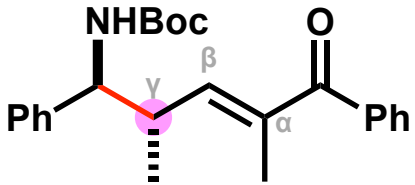
(1 eq.)



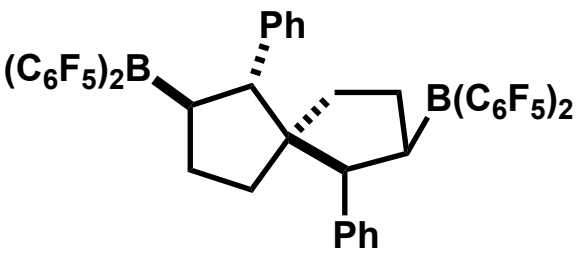
(1.5 eq.)

Lewis acid (5 mol%)
Et_3N (20 mol%)

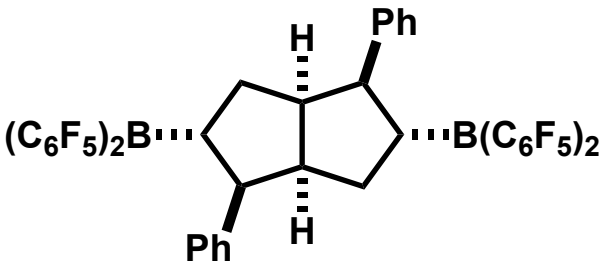
toluene, 10 °C, 24 h



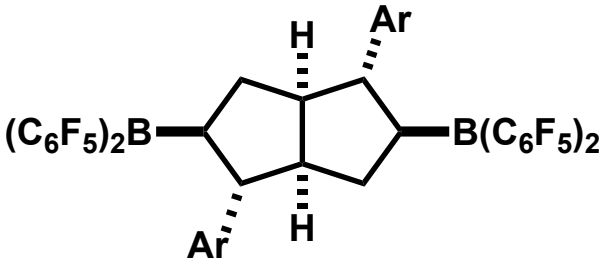
entry	*Lewis acid*	total yield [%]	dr	ee [%]
1	LA1	50	10/1	40
2	LA2	80	5.5/1	82
3	LA3	80	11/1	87



LA1



LA2

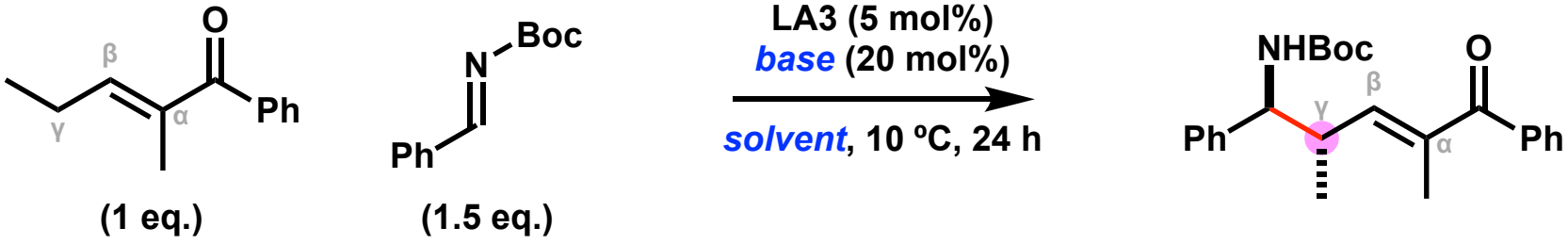


Ar = 4-(*t*-Bu)C_6H_4

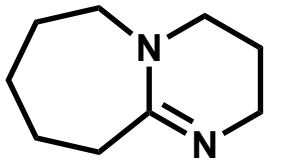
LA3

Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

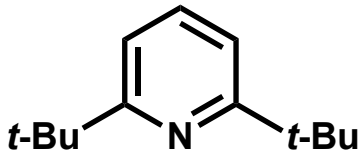
Screening of Base and Solvent



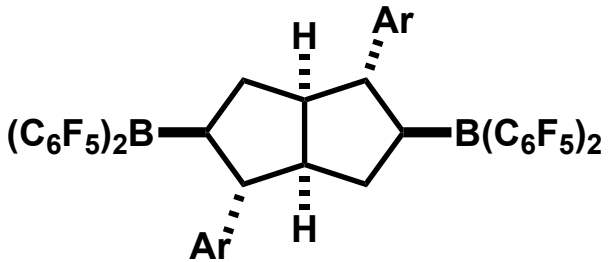
entry	*base*	*solvent*	total yield [%]	dr	ee [%]
1	Et_3N	toluene	80	11/1	87
2	$(i\text{-}Pr)_2NEt$	toluene	11	11/1	85
3	*N*-methylpyperidine	toluene	63	11/1	92
4	DBU	toluene	no reaction	-	-
5	DTBP	toluene	no reaction	-	-
6	*N*-methylpyperidine	$PhCF_3$	94	11/1	92
7	*N*-methylpyperidine	$CHCl_3$	36	9.1/1	88



DBU



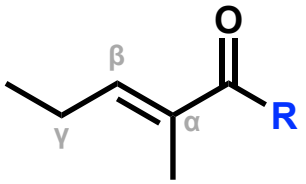
DTBP



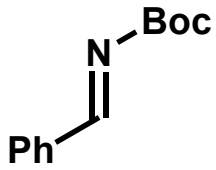
Ar = 4-(*t*-Bu)C_6H_4

LA3

Substrate Scope : Nucleophiles (1)



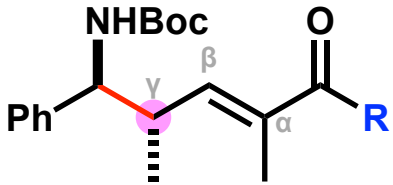
(1 eq.)



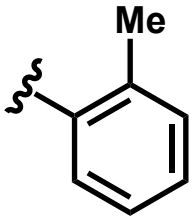
(1.5 eq.)

LA3 (5 mol%)
N-methylpyperidine (20 mol%)

$PhCF_3$, 10 °C, 24 h

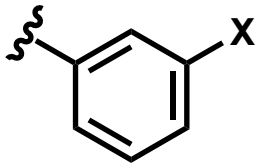


R =



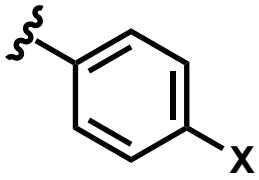
84%, 13/1 dr, 91% ee

R =



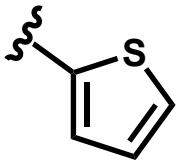
X = Me, 85%, 12/1 dr, 93% ee
X = OMe, 89%, 12/1 dr, 92% ee
X = Cl, 90%, 13/1 dr, 93% ee
X = CF_3, 90%, 14/1 dr, 90% ee

R =



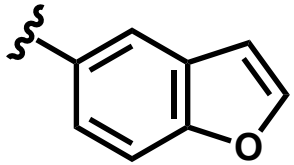
X = Me, 86%, 12/1 dr, 92% ee
X = OMe, 82%, 12/1 dr, 95% ee
X = Br, 88%, 13/1 dr, 91% ee
X = CF_3, 98%, 15/1 dr, 91% ee [a)]

R =



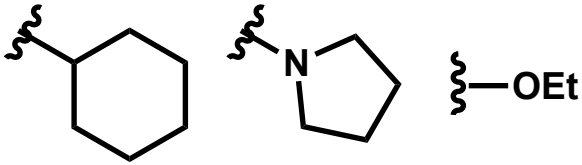
61%, 10/1 dr, 90% ee [a)]

R =



94%, 11/1 dr, 90% ee

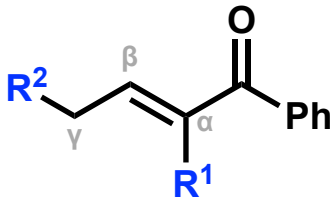
R =



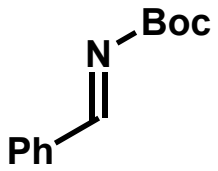
no reaction [b)]

a) 0 °C, b) 25 °C

Substrate Scope : Nucleophiles (2)



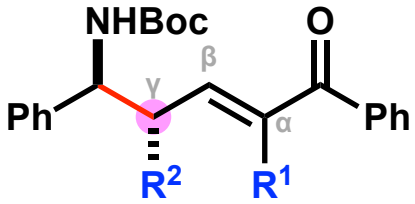
(1 eq.)



(2 eq.)

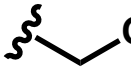
LA3 (5 mol%)
N-methylpyperidine (20 mol%)

$PhCF_3$, 10 °C, 24 h



R^1 = Me

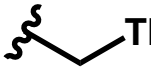
R^2 = Et, 85%, 15/1 dr, 96% ee [a]
R^2 = Bn, 70%, 15/1 dr, 90% ee [b]
R^2 = H, 55%, 85% ee [c] [d]

R^2 =  OTBS

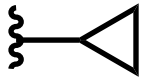
85%, >20/1 dr, 94% ee [c]

R^2 = Me

R^1 = Et, 90%, 16/1 dr, 86% ee* [b] [c]
R^1 = Br, 71%, 10/1 dr, 82% ee* [e]
R^1 = H, 75%, 2.9/1 dr, 78/85% ee [f]

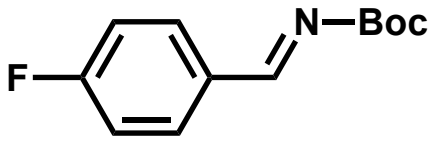
R^1 =  TMS

87%, >20/1 dr, 88% ee* [c]

R^1 = 

84%, 1.7/1 dr, 71/87% ee* [c] [h]

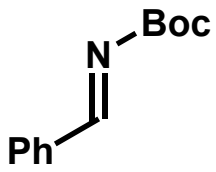
a) 1.5 eq. *N*-Boc imine, b) 0 °C, c) 10 mol% LA3, 40 mol% *N*-methylpypiridine, d) Absolute configuration was not determined. f) -10 °C, g) -20 °C, h) 36 h

* 

was used as an imine.

Unsuccessful Nucleophiles

nucleophiles



(1 eq.)

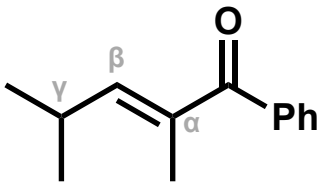
(1.5 eq.)

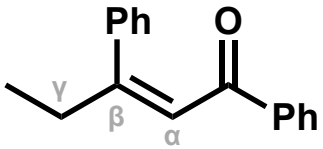
LA3 (5 mol%)
N-methylpyperidine (20 mol%)

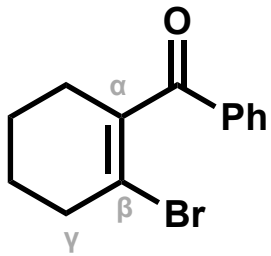
$PhCF_3$, 25 °C, 24 h

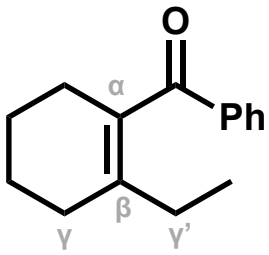
no reaction

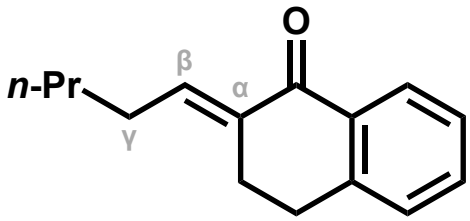
nucleophiles

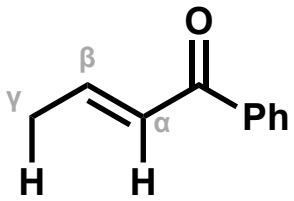




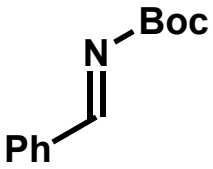








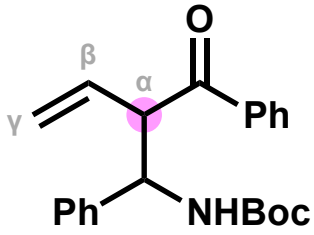
(1 eq.)



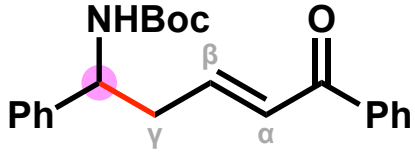
(1.5 eq.)

LA3 (5 mol%)
N-methylpyperidine (20 mol%)

$PhCF_3$, 10 °C, 24 h



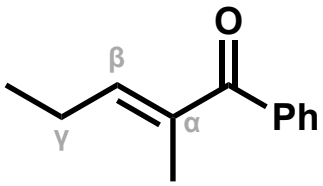
37%, 1.3/1 dr, 83/43 % ee



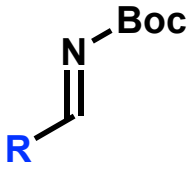
16%, 68 % ee

Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Substrate Scope : Imine



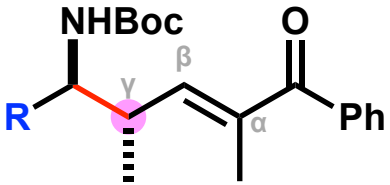
(1 eq.)



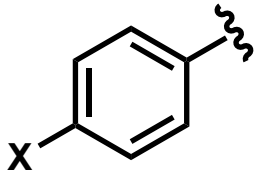
(1.5 eq.)

LA3 (5 mol%)
N-methylpyperidine (20 mol%)

$PhCF_3$, 10 ºC, 24 h



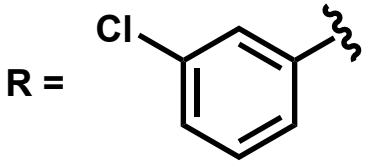
R =



X = Me, 87%, 10/1 dr, 90% ee [a)]
X = F, 94%, 12/1 dr, 90% ee
X = Cl, 93%, 12/1 dr, 90% ee
X = CF_3, 95%, 11/1 dr, 92% ee

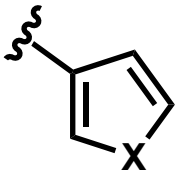
X = CO_2Me, 93%, 11/1 dr, 91% ee
X = SMe, 88%, 9.3/1 dr, 89% ee
X = OCF_3, 82%, 10/1 dr, 90% ee

R =



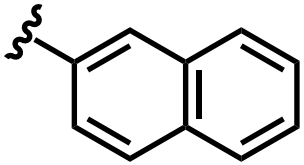
96%, 11/1 dr, 91% ee

R =



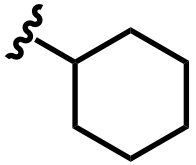
X = O, 70%, 11/1 dr, 92% ee
X = S, 81%, 10/1 dr, 91% ee

R =



93%, 13/1 dr, 90% ee [b)]

R =

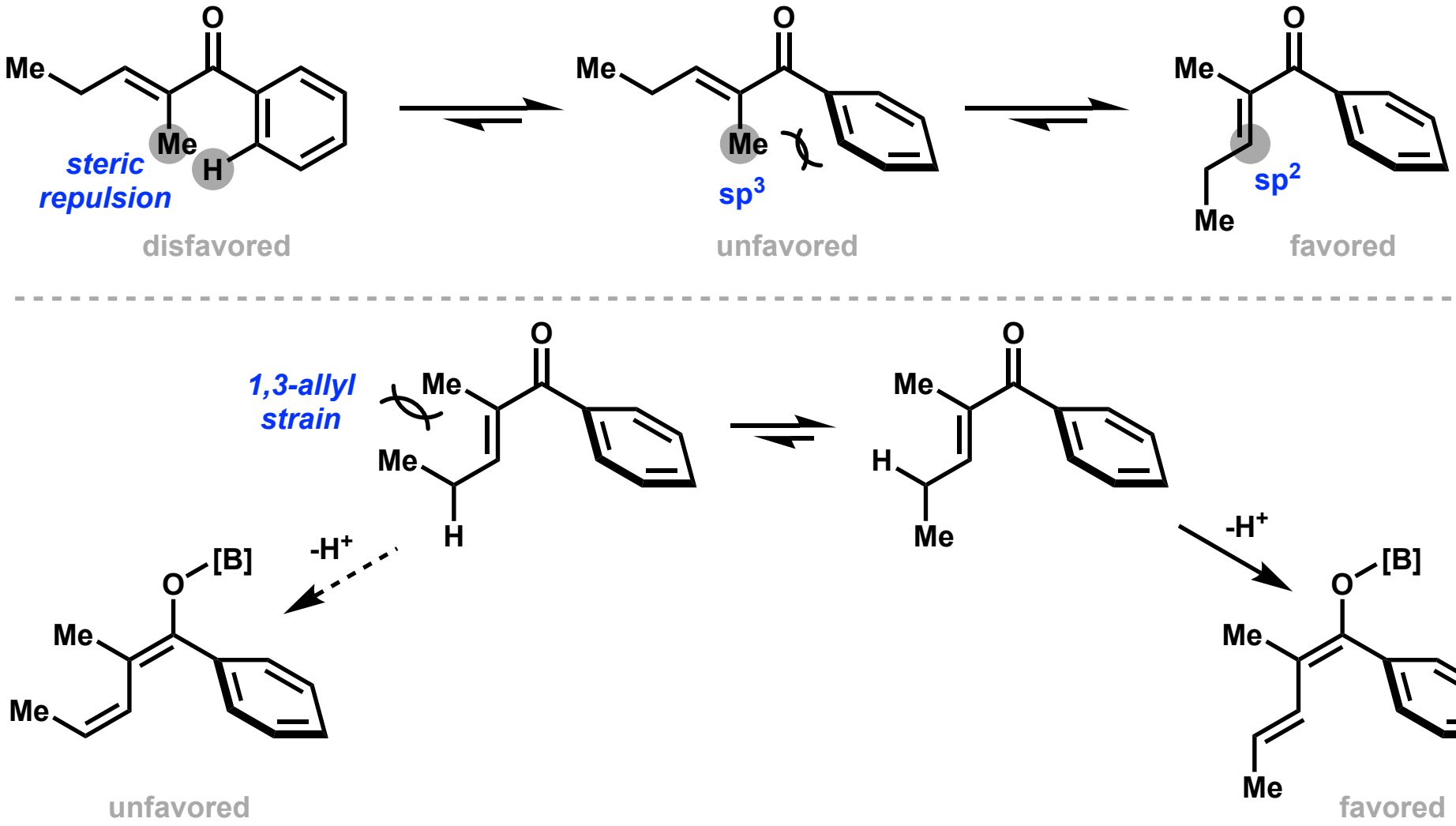


no reaction [c)]

a) -10 ºC, b) 0 ºC, c) 25 ºC

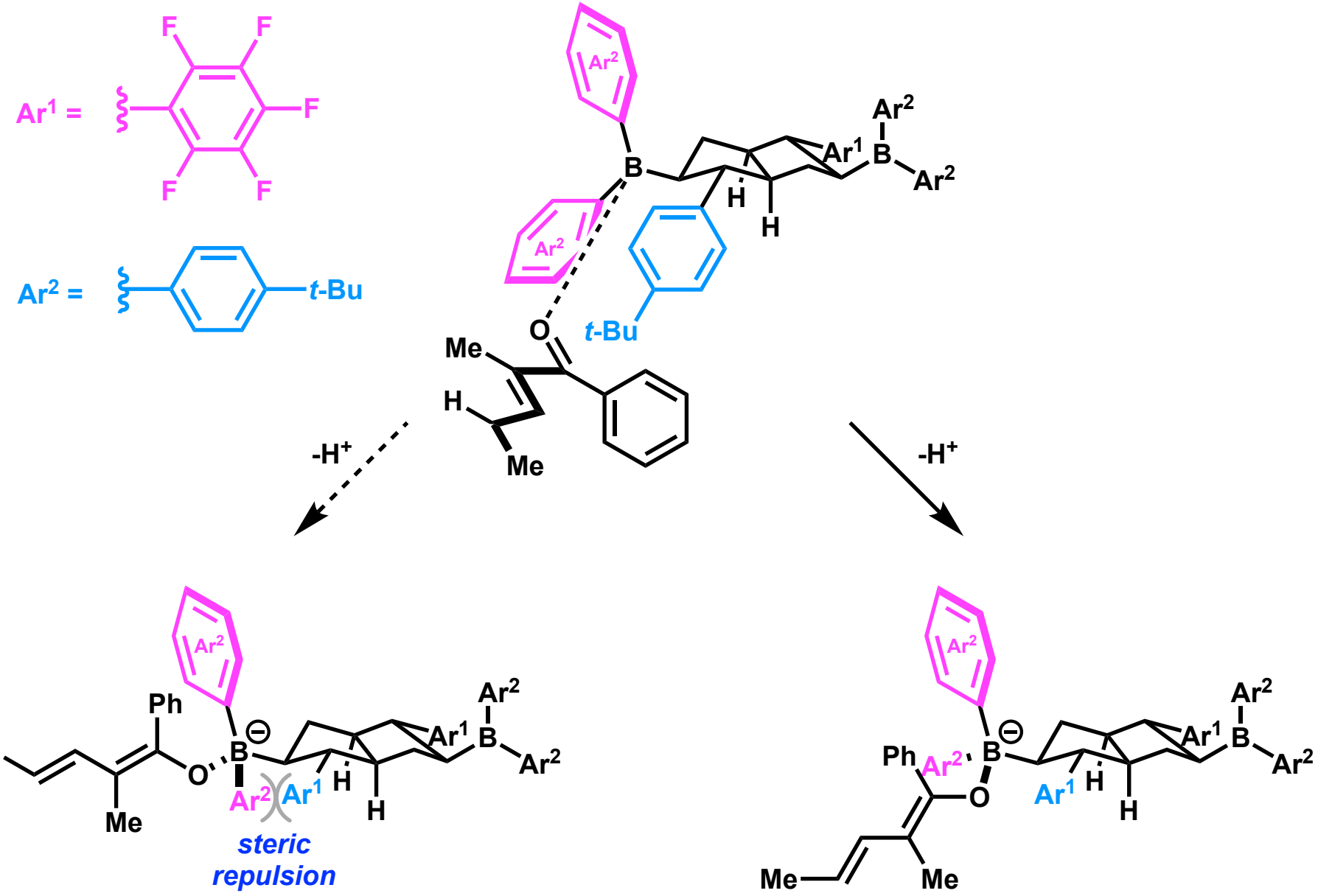
Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Proposed Enantioselectivity (1)



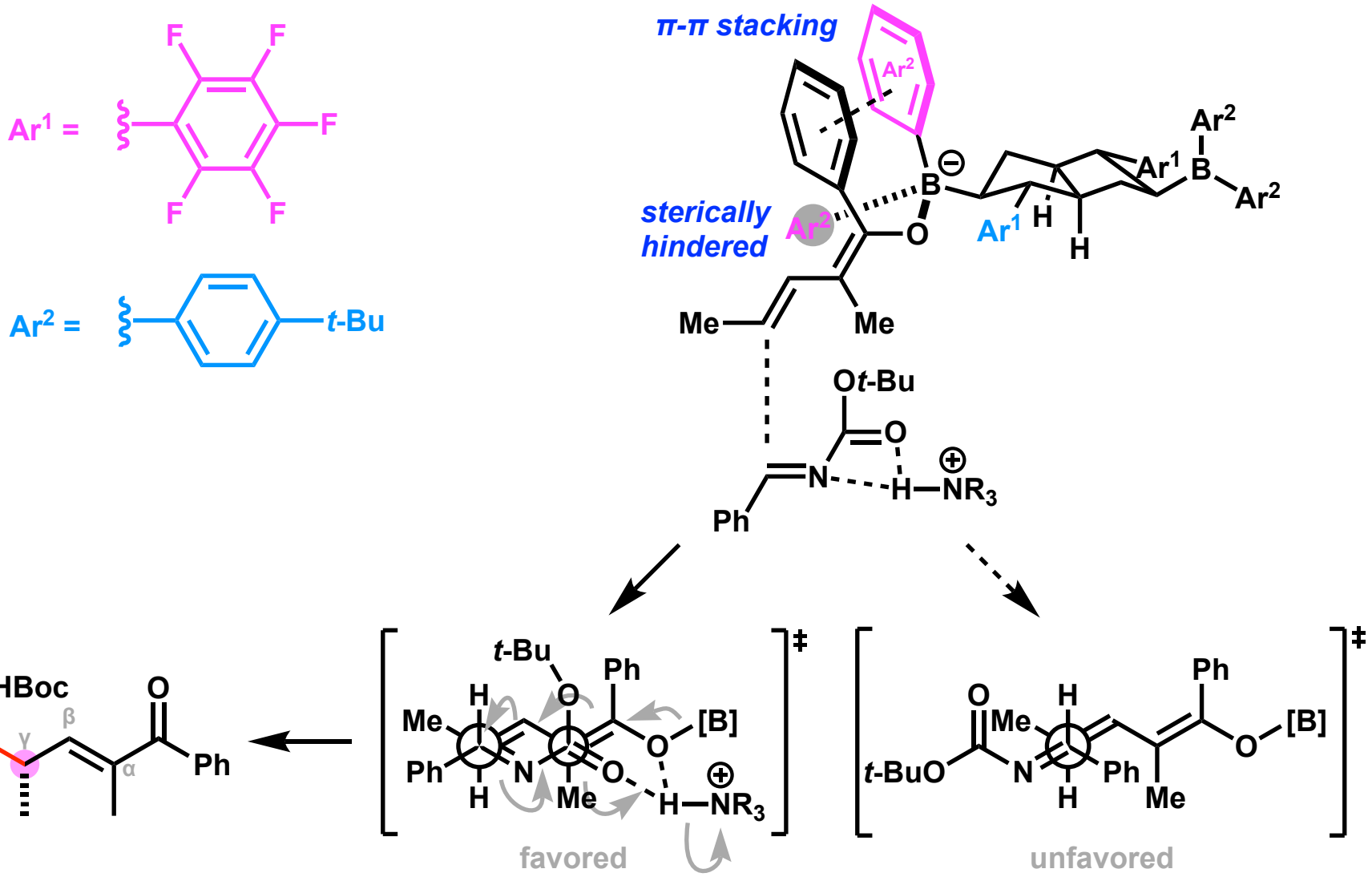
Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Proposed Enantioselectivity (2)



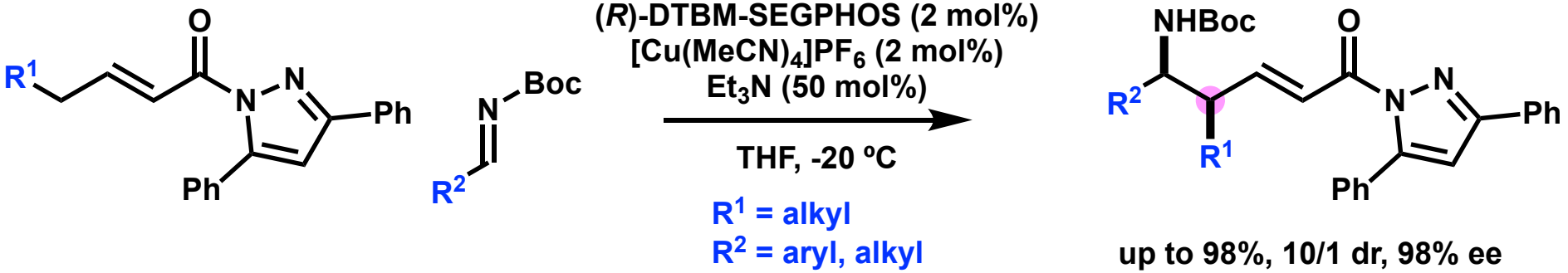
Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Proposed Enantioselectivity (3)

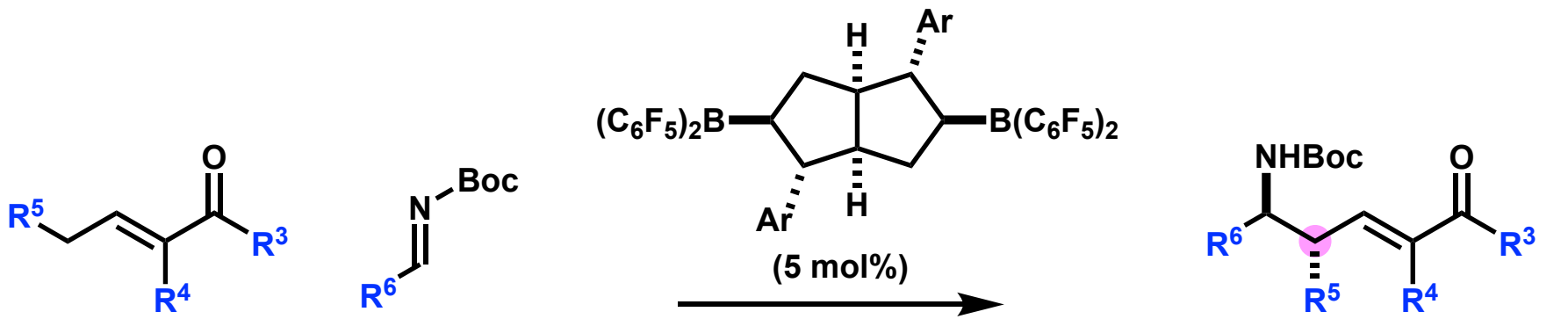


Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.

Summary



up to 98%, 10/1 dr, 98% ee



up to 98%, 15/1 dr, 91% ee

1) Zhan, H.-J.; Zhong, F.; Xie, Y.-C,; Yin, L. *Chin. J. Chem.* **2021**, *39*, 55. 2)Tian, J.-J.; Liu, N.; Liu, Q.-F.; Sun, W.; Wang, X.-C. *J. Am. Chem. Soc.* **2021**, *143*, 3054.