光催化的对映选择性的1,4-共轭加成反应

汇报人：游新宇
导师：蔡泉 研究员

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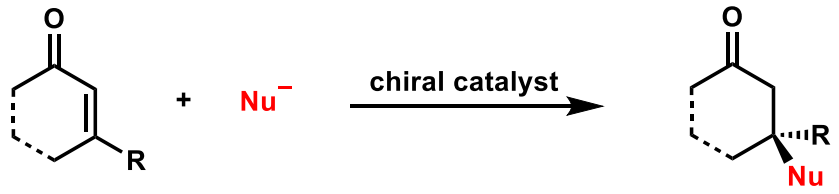
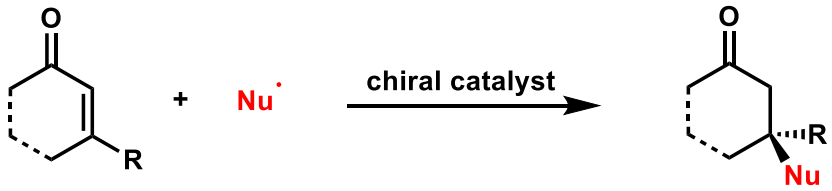
双电子型亲核试剂



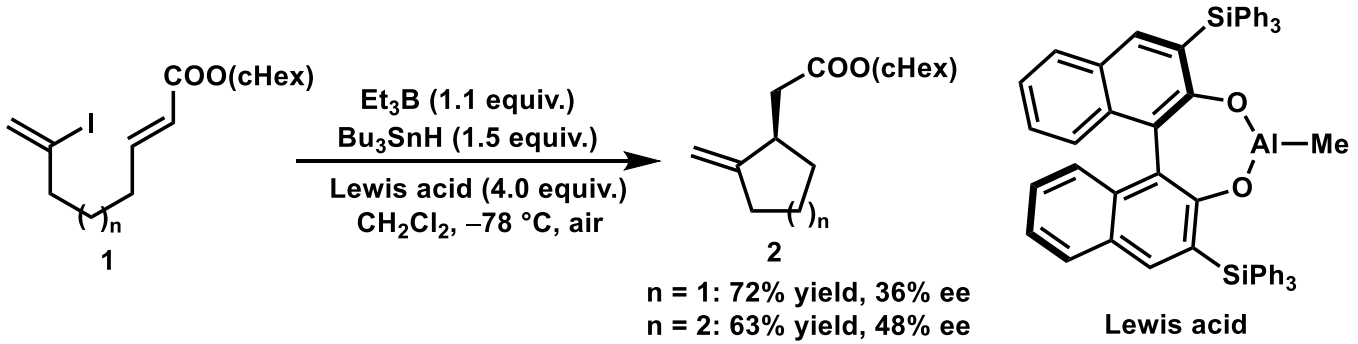
1. 体系发展成熟
2. 构建手性中心及新的化学键最重要的方法之一

单电子型亲核试剂

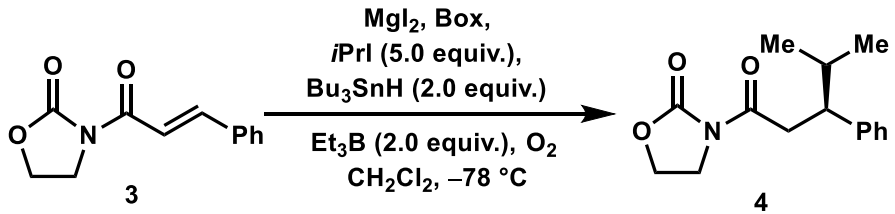


1. 自由基反应活性高，寿命短
2. 存在消旋背景反应

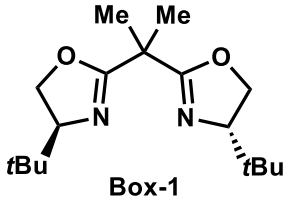
背景介绍



Hayashi, H.; Nishida, A.; Kawahara, N.; Nishida, M. *Chem. Commun*. **1996**, 579.

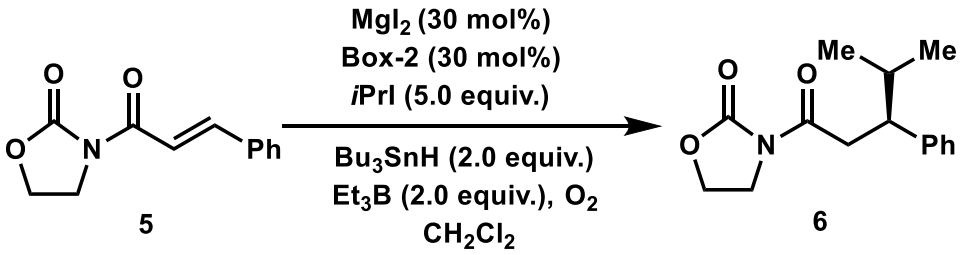


Entry	Lewis acid (equiv.)	Yield (%)	ee (%)
1	1.00	88	82
2	0.50	86	79
3	0.20	86	67
4	0.05	57	40



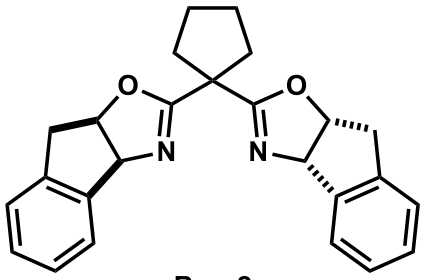
Ji, J.; Sibi, M. P. *J. Am. Chem. Soc*. **1996**, *118*, 9200.

背景介绍

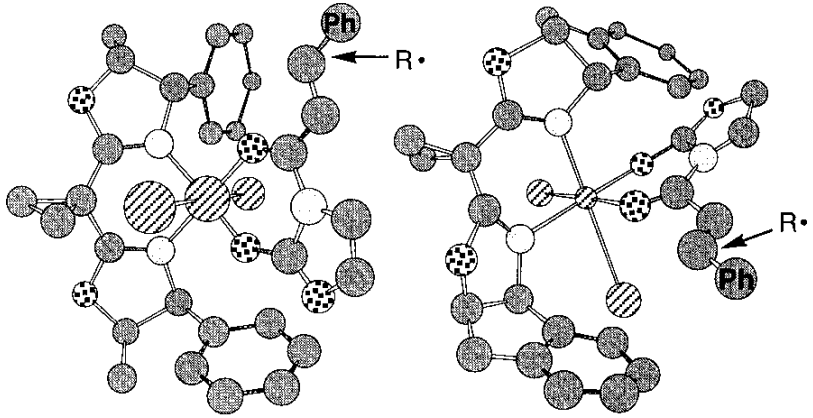


5 6

Entry	T (°C)	Yield(%)	ee(%)
1	–78 °C	91	97
2	–20 °C	93	95
3	0 °C	91	94
4	25 °C	87	93



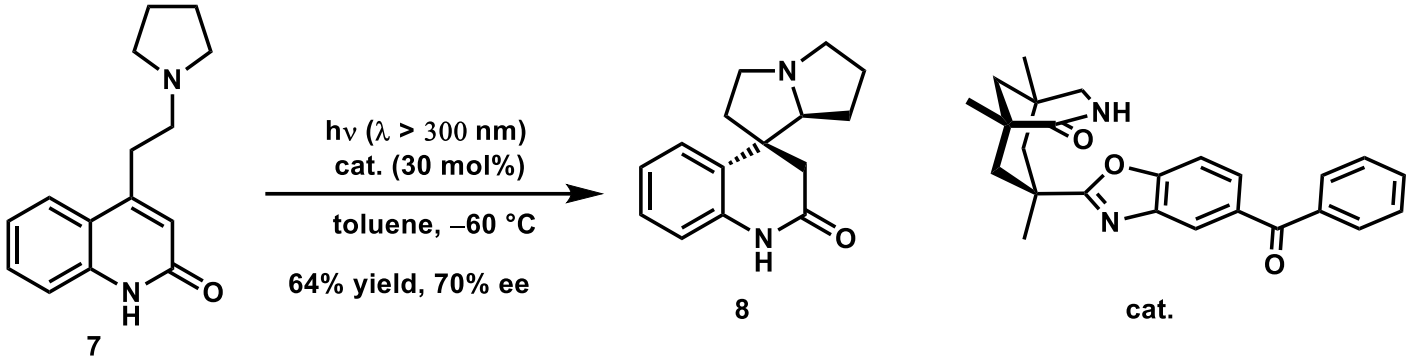
Box-2

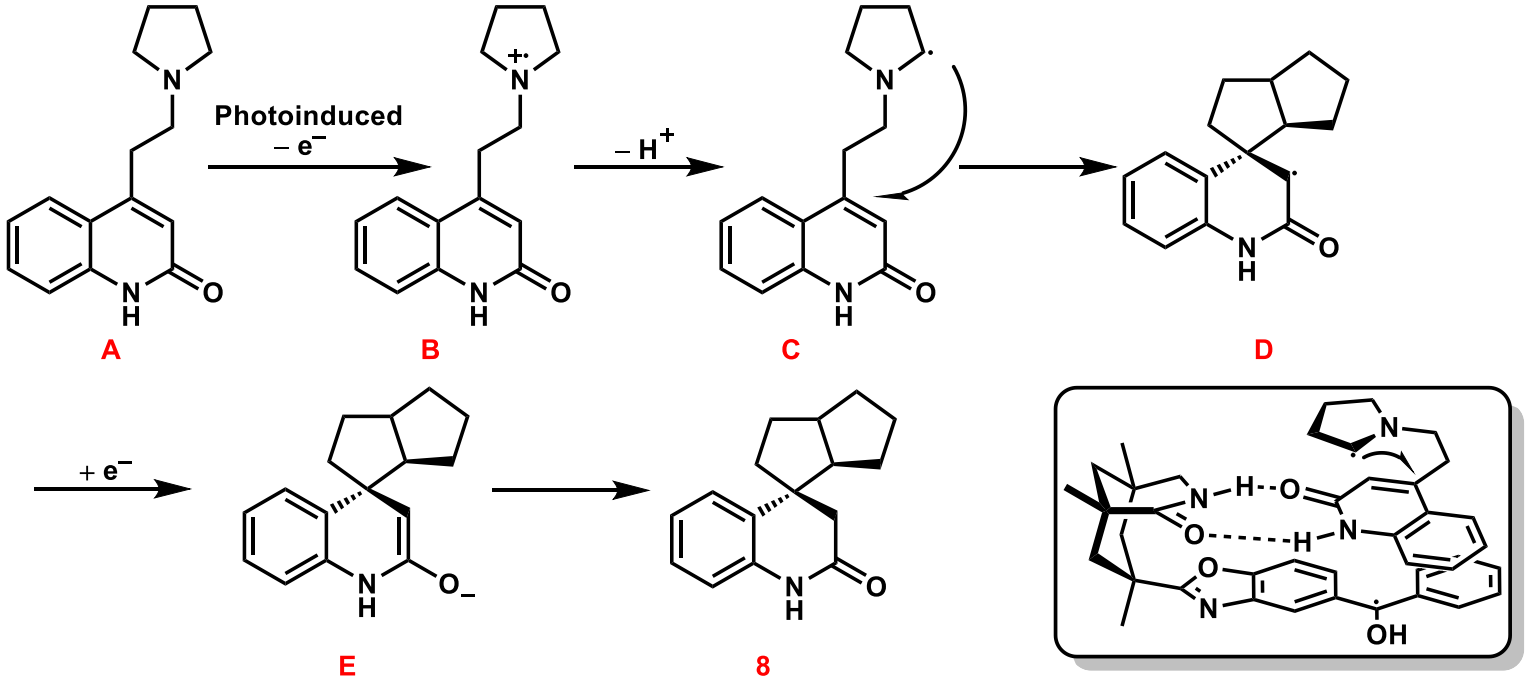


A B

Ji, J.; Sibi, M. P. *J. Org. Chem*. **1997**, *62*, 3800.

背景介绍





Bauer, A.; Westkamper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139.

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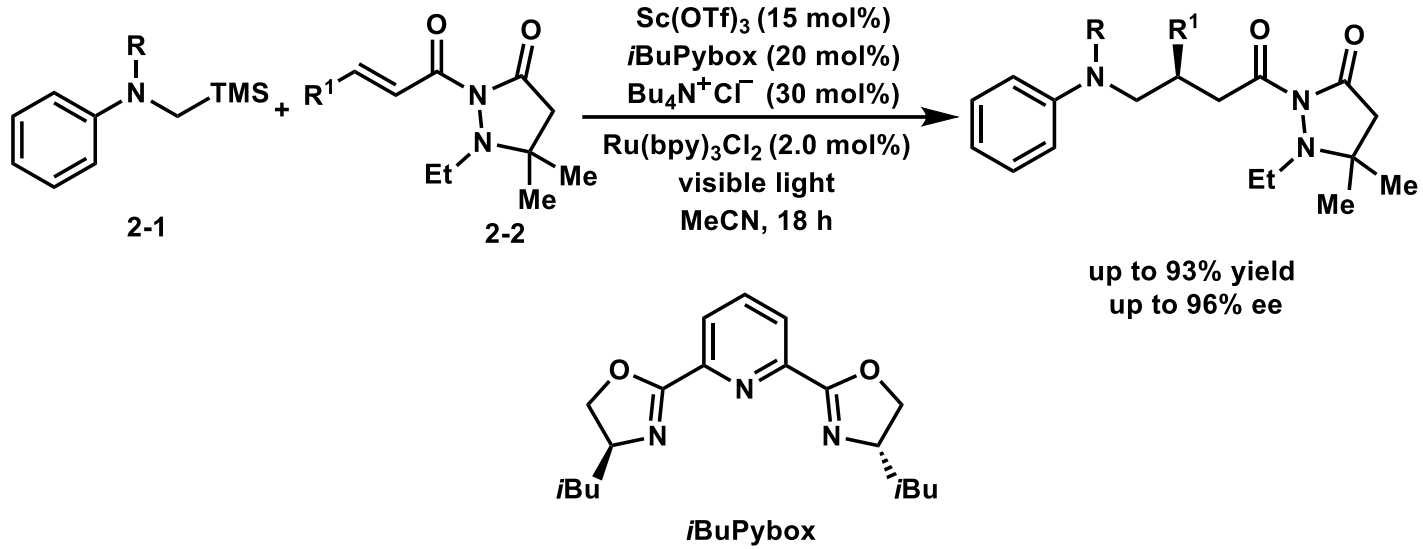
手性路易斯酸催化的共轭加成反应



氯离子效应

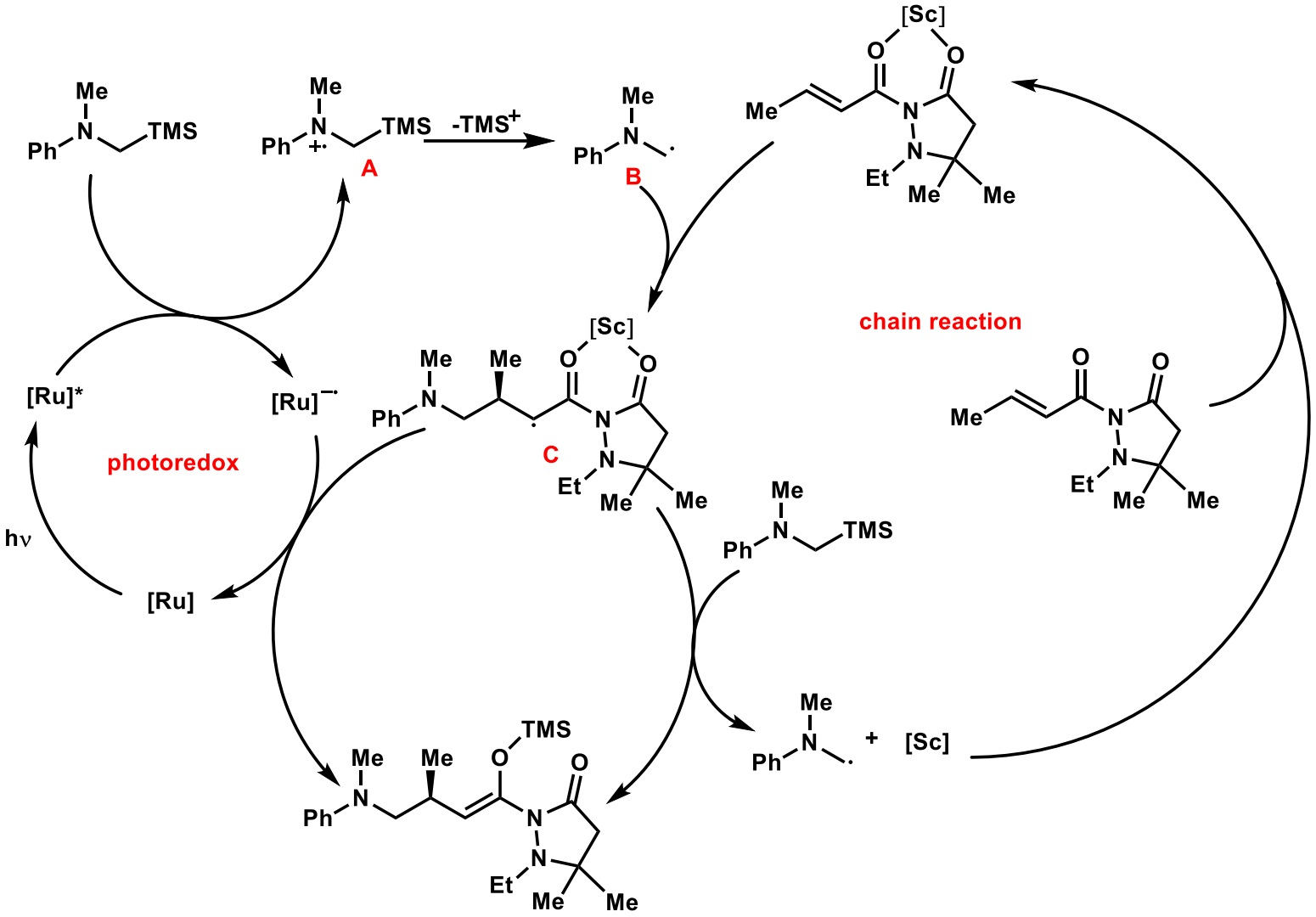
Entry	Lewis acid	Addtive	Time	Yield(%)
1	none	none	3 h	25
2	none	30 mol%$Bu_4N^+Cl^-$	3 h	28
3	sBuPybox·$Sc(OTf)_3$	none	2 h	67
4	sBuPybox·$Sc(OTf)_3$	30 mol%$Bu_4N^+Cl^-$	2 h	98
5	sBuPybox·$ScCl_3$	none	6 h	61

氯离子促进了路易斯酸的催化循环次数

Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc*. **2015**, *137*, 2452.

手性路易斯酸催化的共轭加成反应

反应机理



Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc*. **2015**, *137*, 2452.

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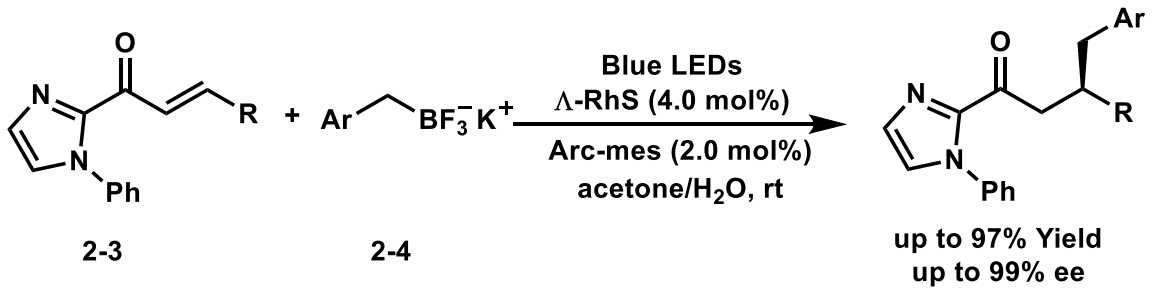
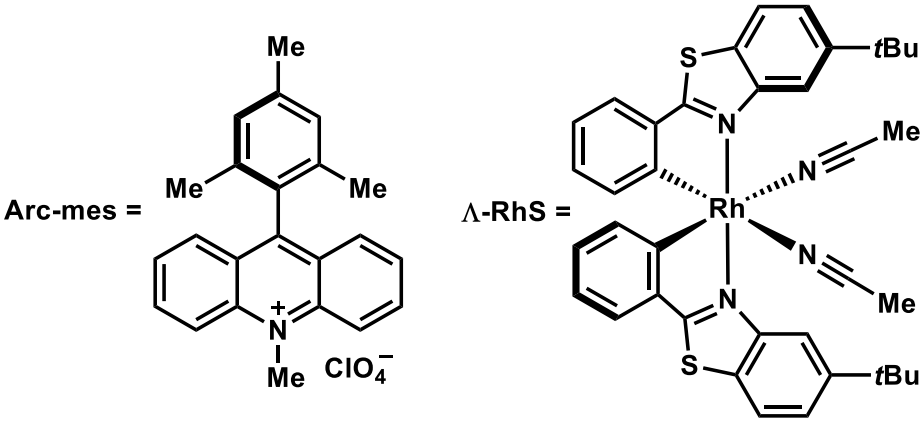
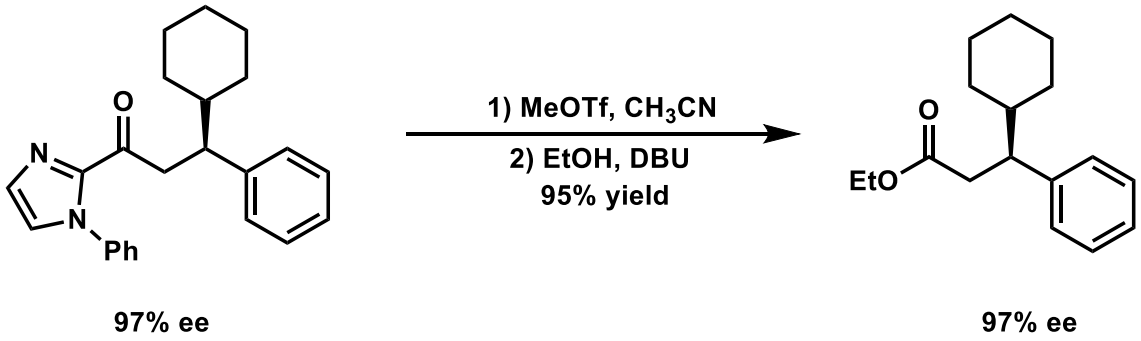


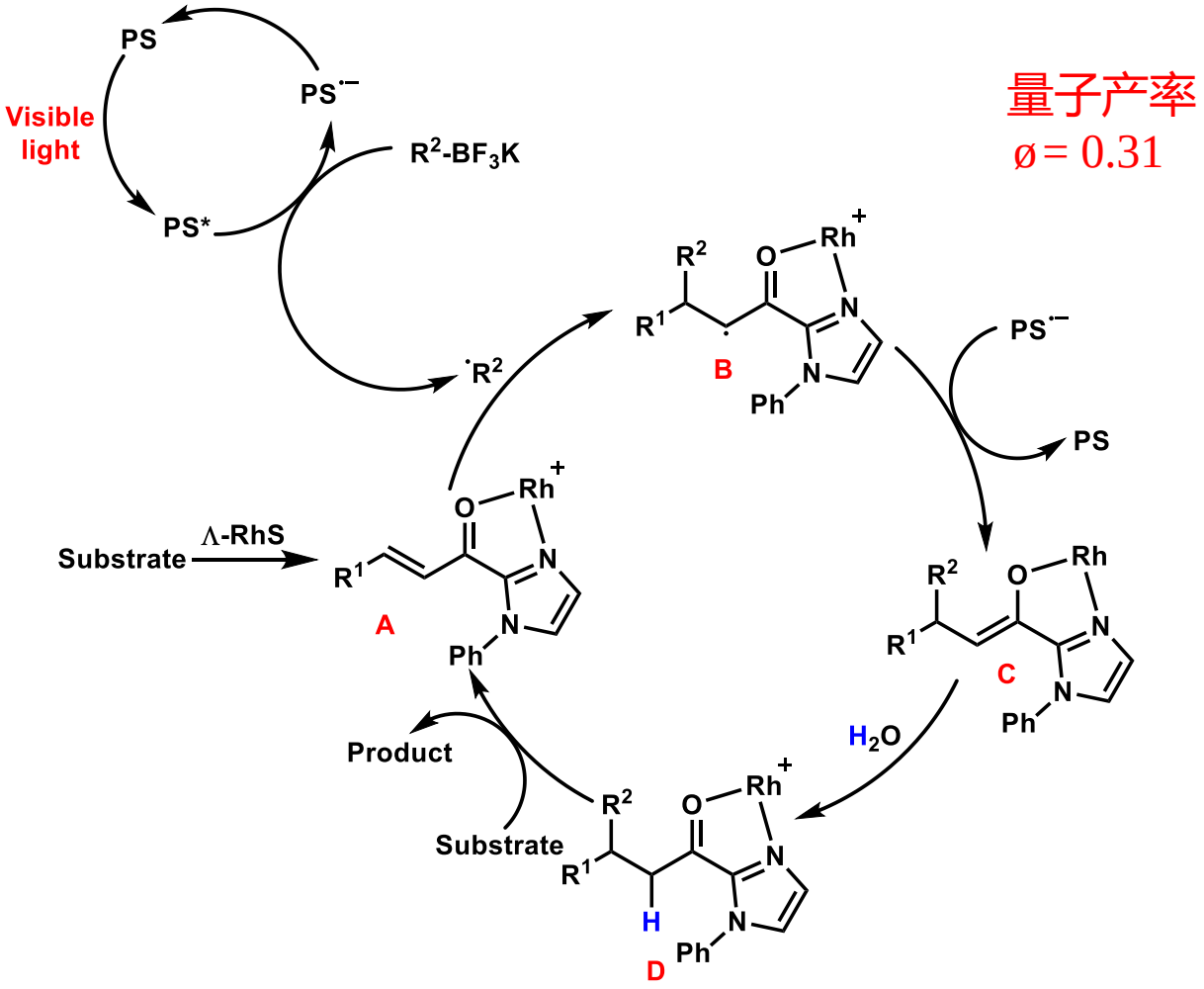




Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc*. **2016**, *138*, 6936.

手性路易斯酸催化的共轭加成反应

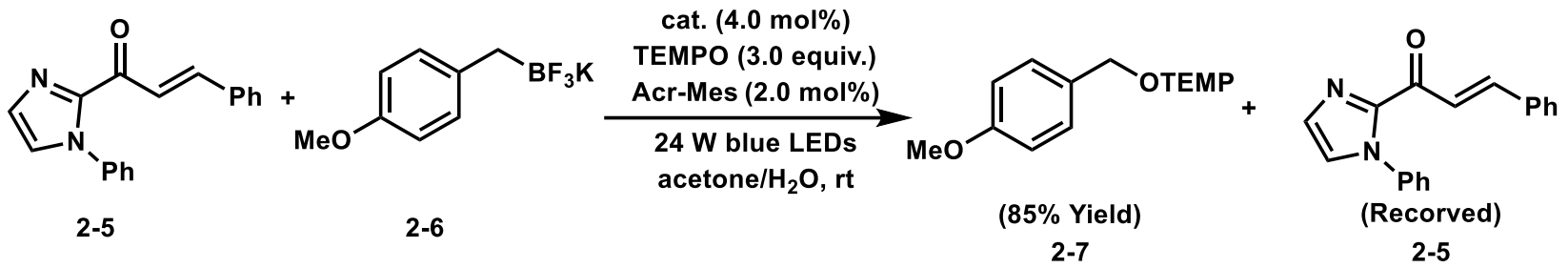
反应机理



Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 6936.

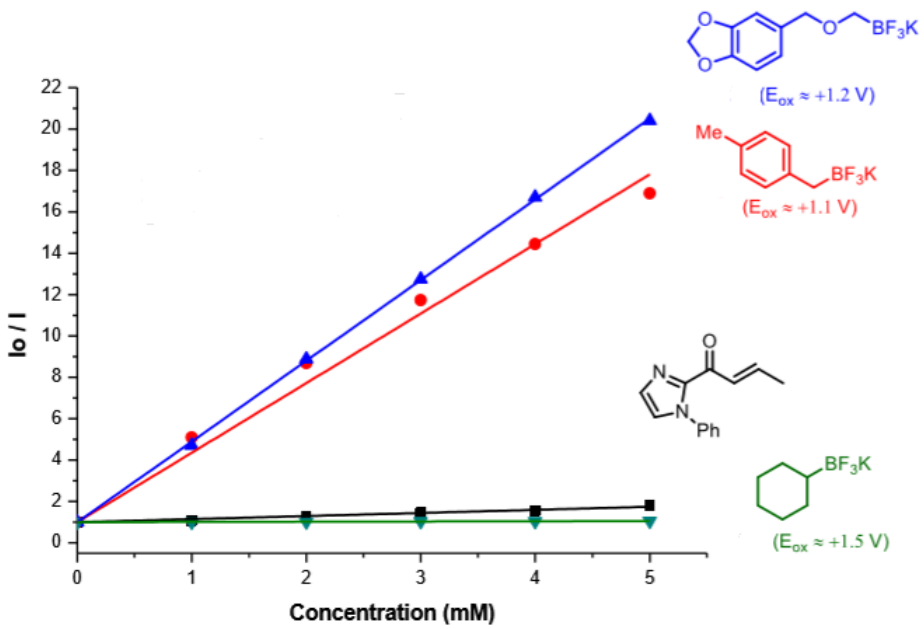
手性路易斯酸催化的共轭加成反应

对照试验



2-5　　2-6　　(85% Yield) 2-7　　(Recored) 2-5

荧光淬灭实验



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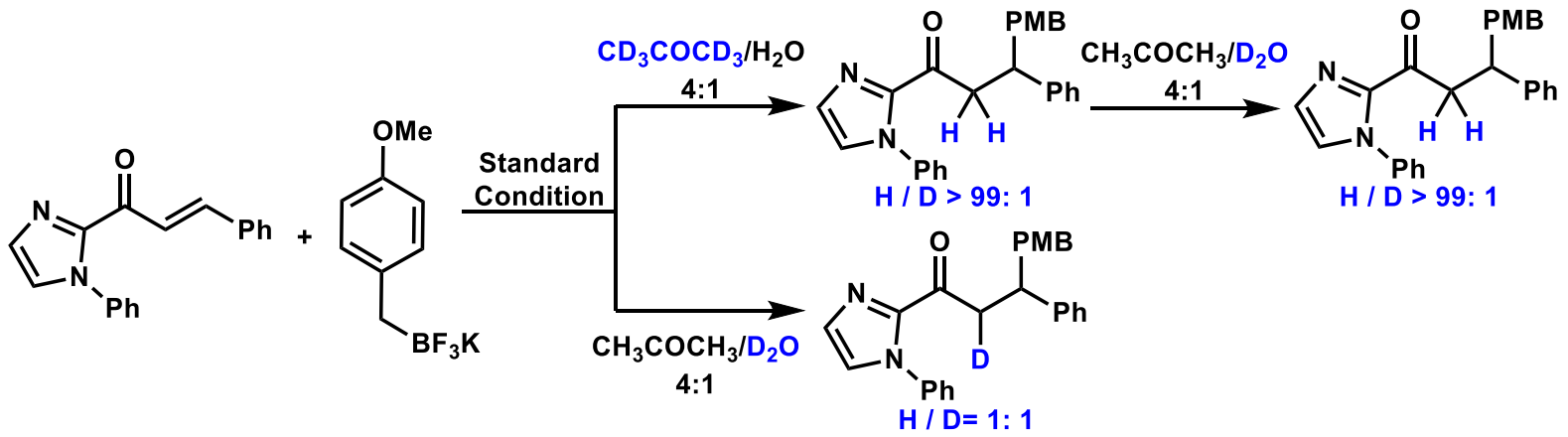
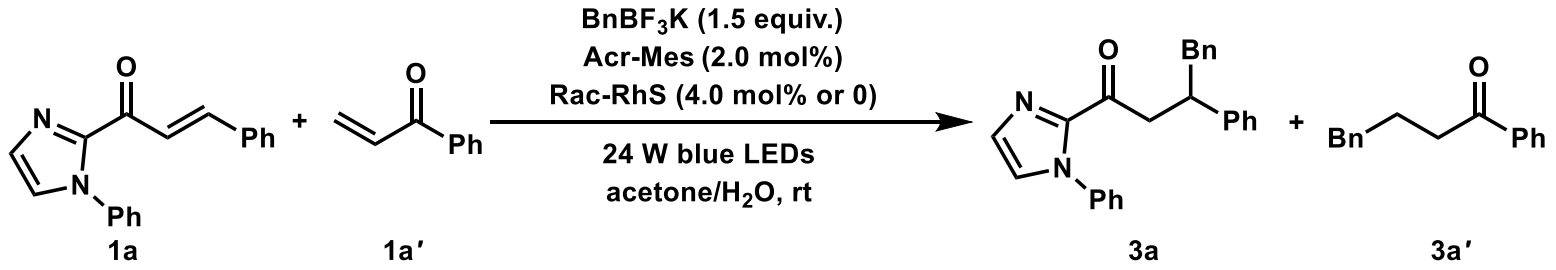
对照试验



竞争试验



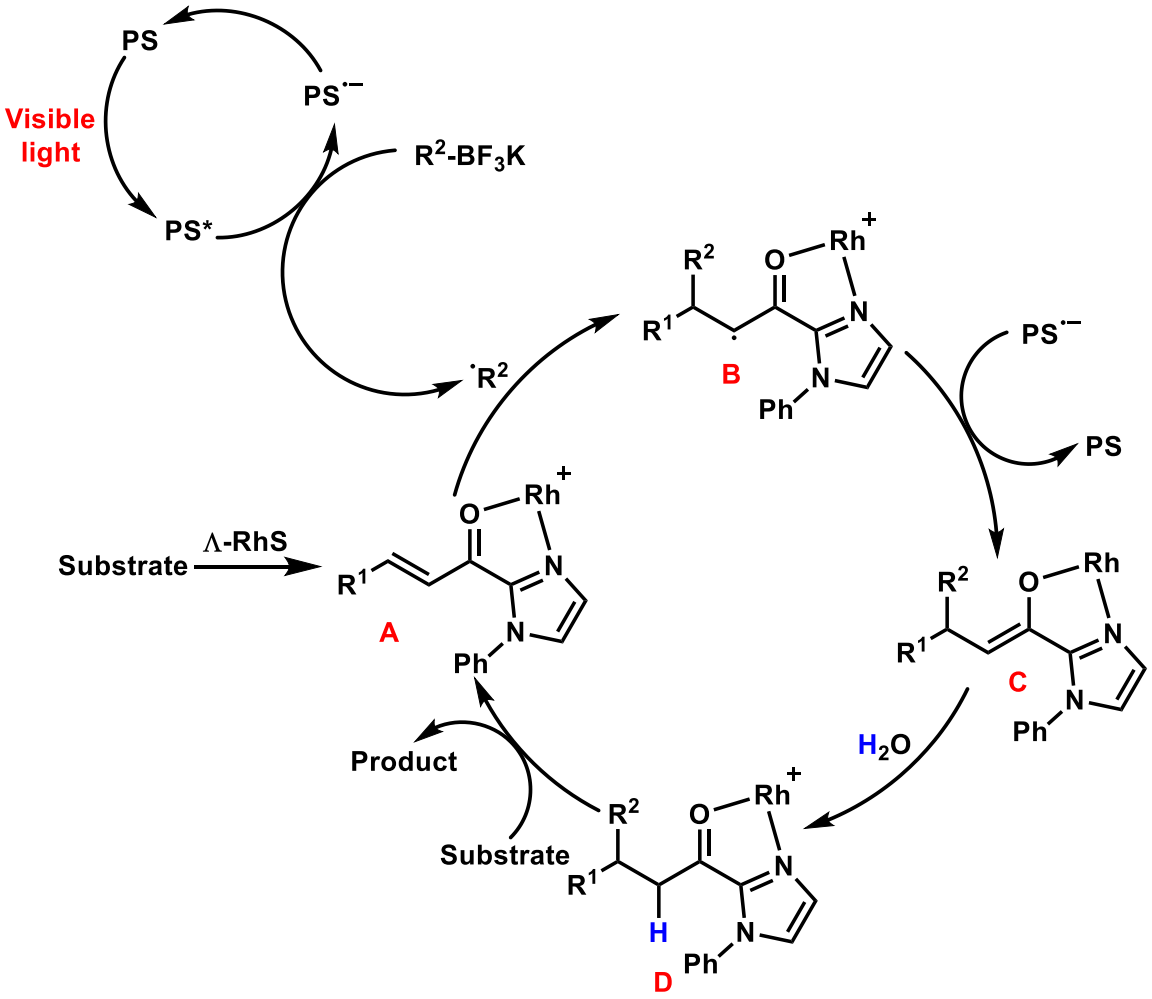
1a　　1a′　　3a　　3a′

RhS (%)	Yield (3a)	Yield (3a′)	3a:3a′
0	8%	20%	0.4: 1
4.0	55%	not observed	> 550: 1

Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 6936.

手性路易斯酸催化的共轭加成反应

反应机理



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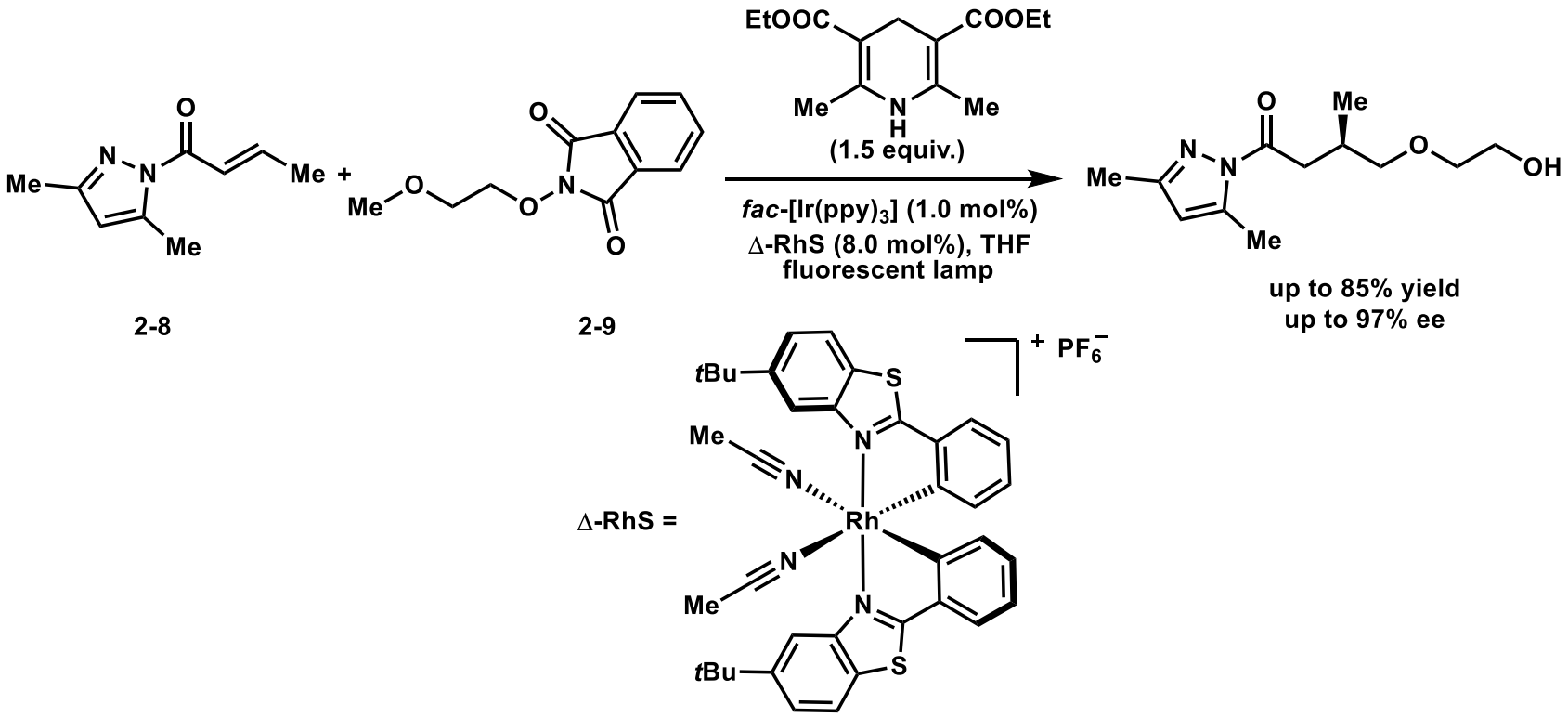
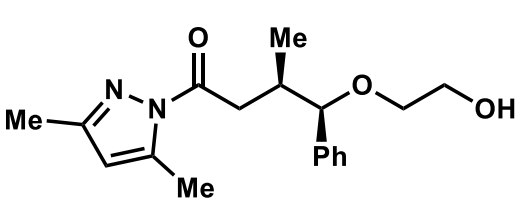
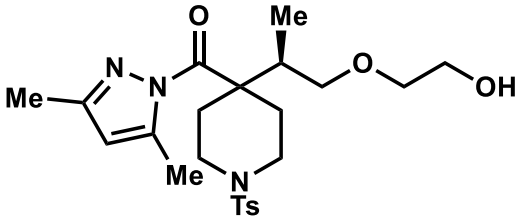
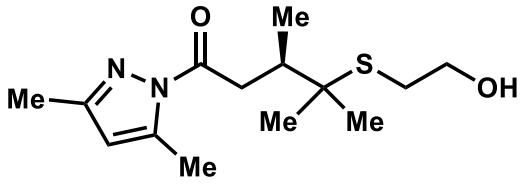




71% yield, 3:1 dr, 97% ee



54% yield, 92% ee

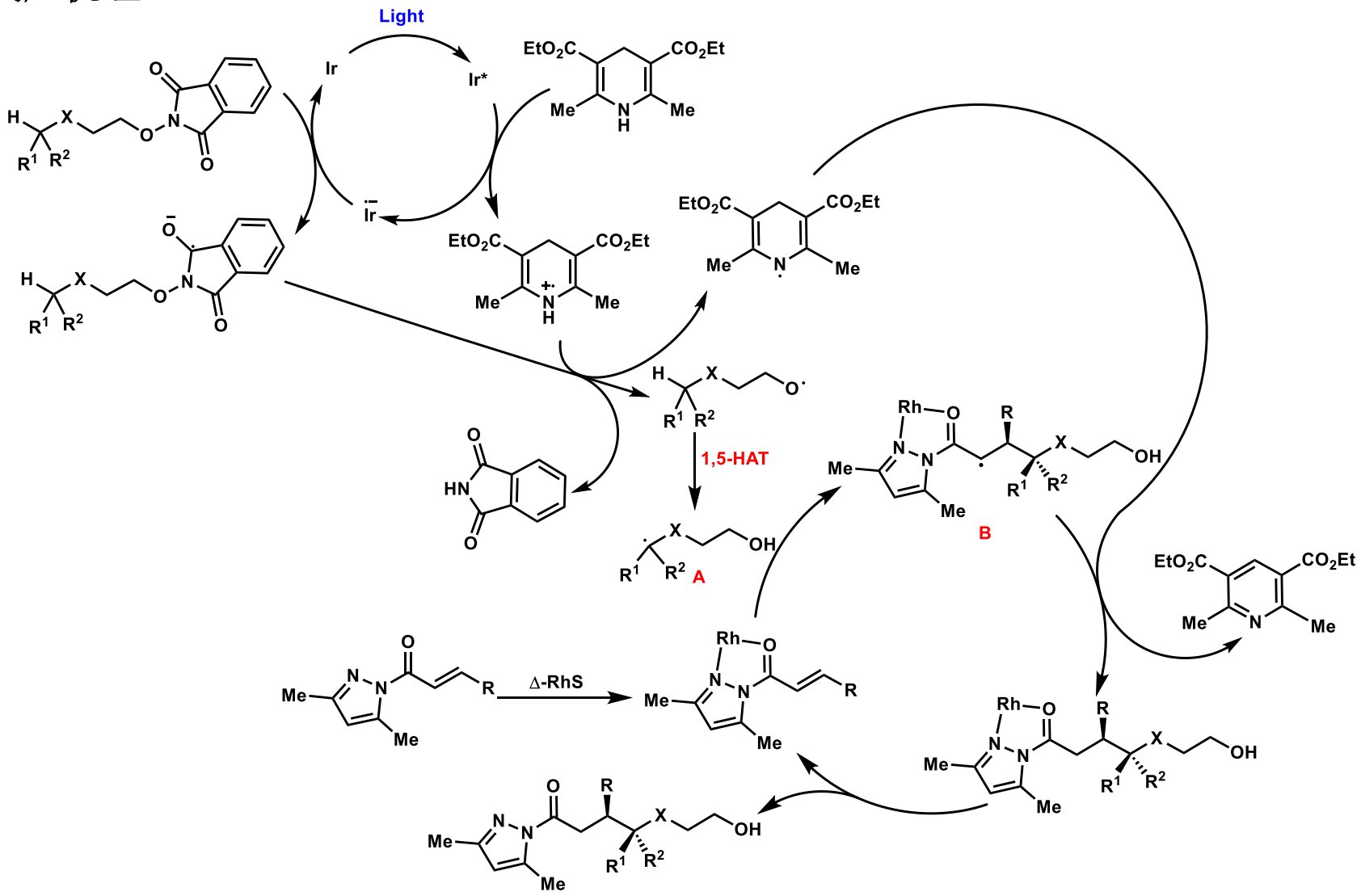


72% yield, 93% ee

Wang, C.; Harms, K.; Meggers, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 13495.

手性路易斯酸催化的共轭加成反应

反应机理



Wang, C.; Harms, K.; Meggers, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 13495.

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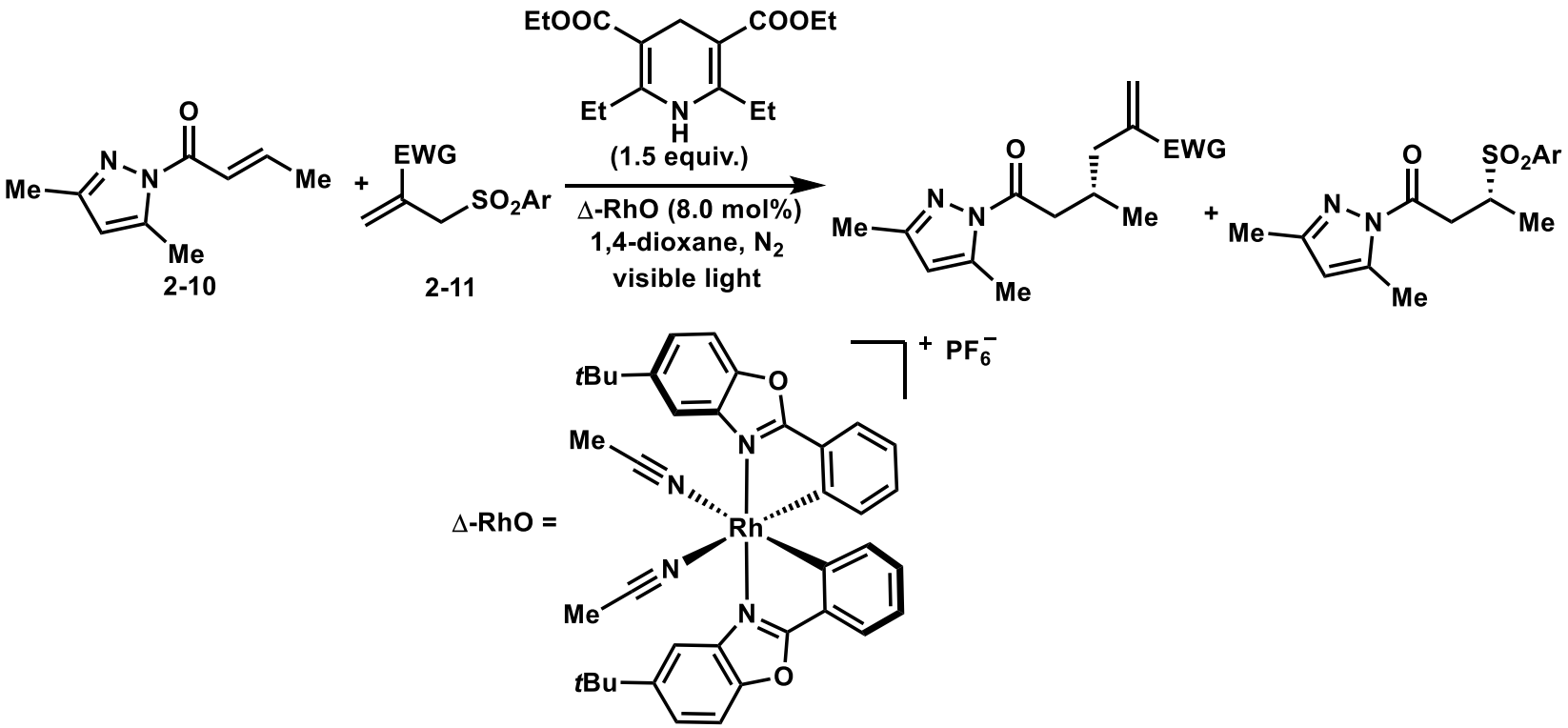
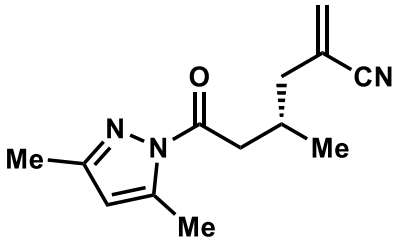
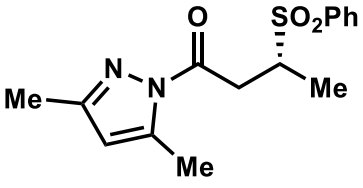
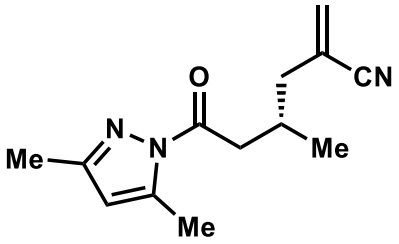




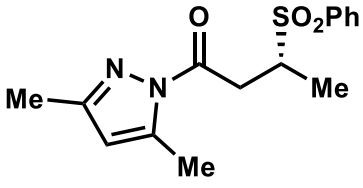
85% yield, 96% ee



92% yield, 85% ee



79% yield, 95% ee

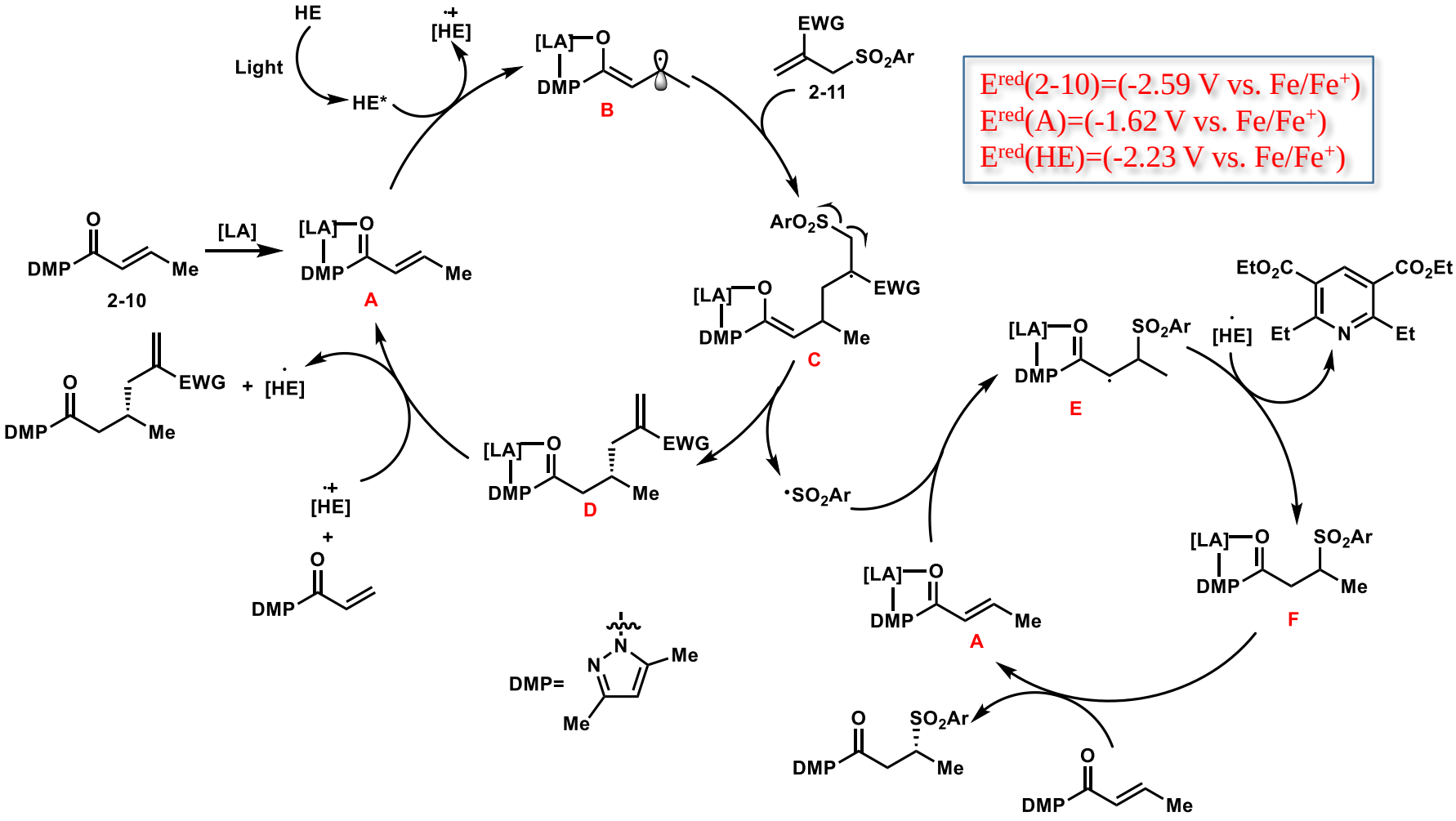


68% yield, 84% ee

Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harmsa, K.; Meggers, E. *Chem. Sci.* **2017**, *8*, 7126.

手性路易斯酸催化的共轭加成反应

反应机理



Huang, X.; Luo, S.; Burghaus, O.; Webster, R. D.; Harmsa, K.; Meggers, E. *Chem. Sci.* **2017**, *8*, 7126.

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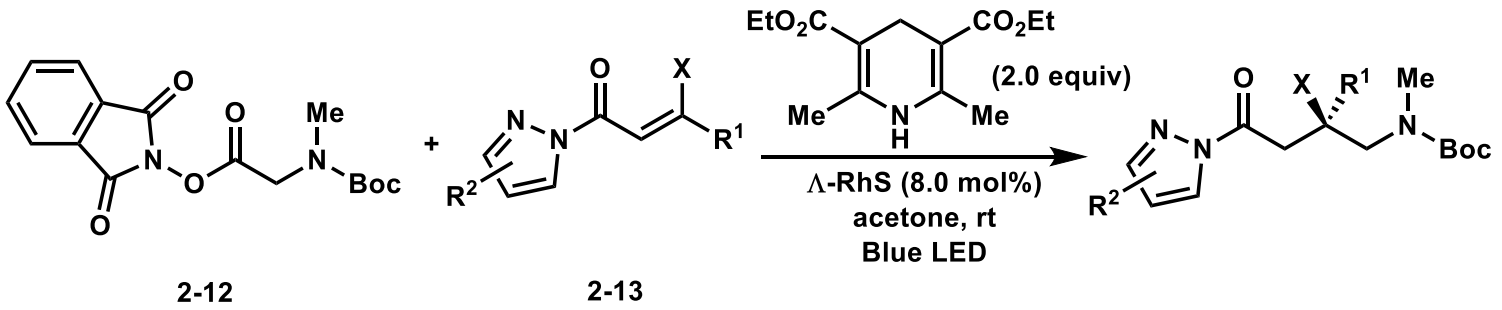
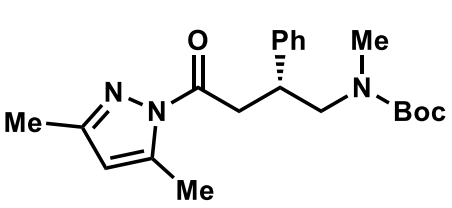
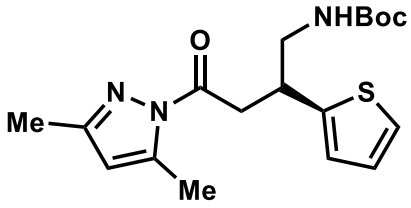
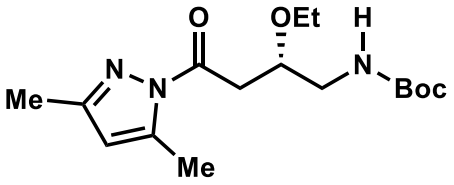




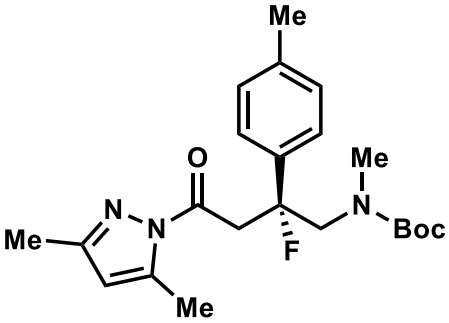
84% yield, 95% ee



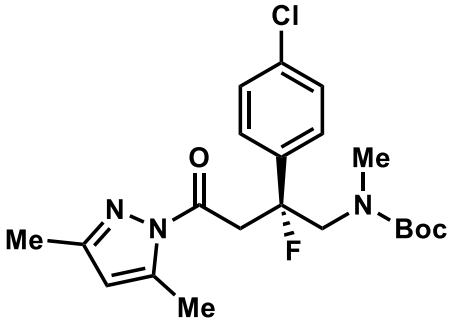
42% yield, 91% ee



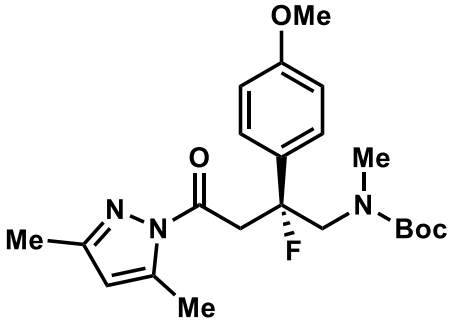
89% yield, 97% ee



71% yield, 94% ee



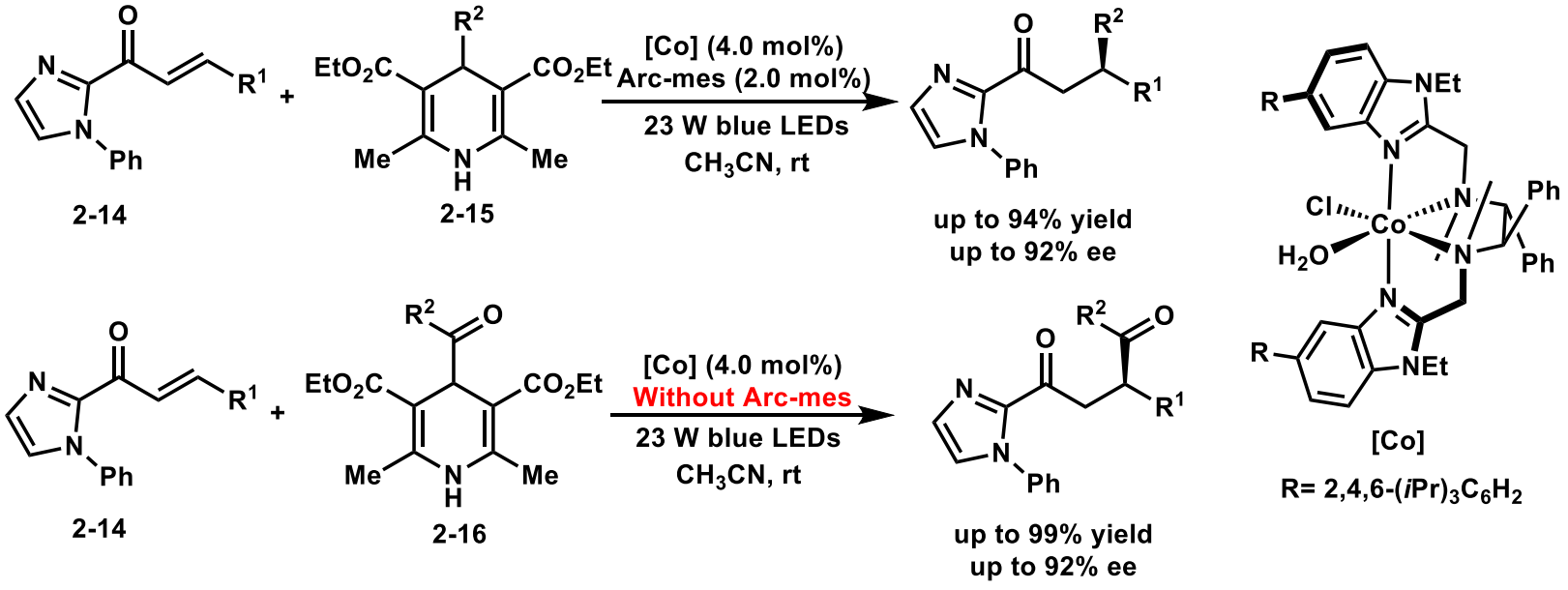
53% yield, 93% ee

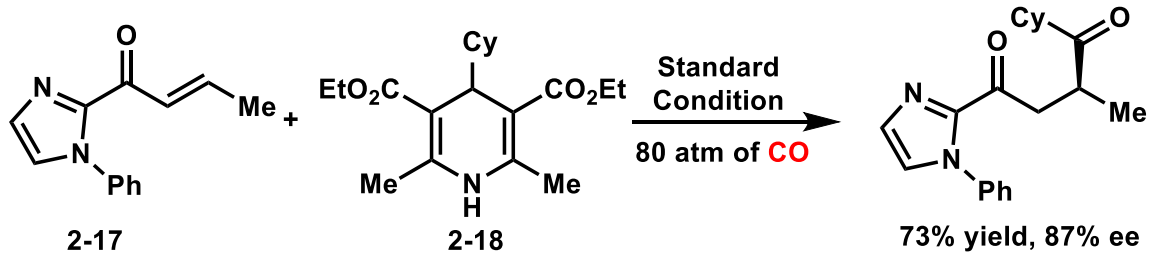


80% yield, 94% ee

Ma, J.; Lin, J.; Zhao, L.; Harms, K.; Marsch, M.; Xie,X.; Meggers, E. *Angew .Chem., Int.Ed.* **2018**, *57*, 11193.

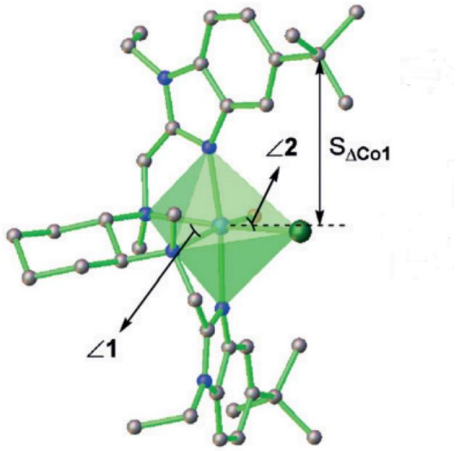
手性路易斯酸催化的共轭加成反应





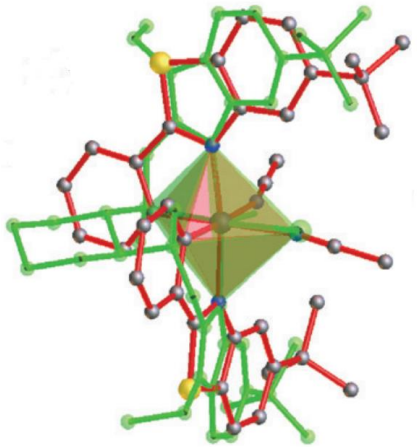
Zhang, K.; Lu, L.; Jia, Y.; Wang, Y.; Lu, F.; Pan, F.; Xiao, W. *Angew. Chem., Int. Ed.* **2019**, *58*, 13375.

手性路易斯酸催化的共轭加成反应



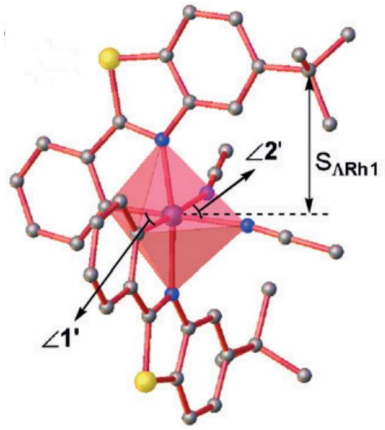
ΛCo1 (green)

$S_{\Lambda Co1}$ = 5.05 Å *vs* $S_{\Lambda Rh1}$ = 4.57 Å



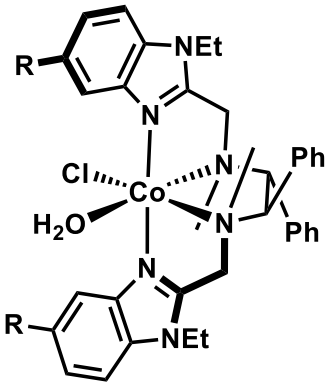
overlay of ΛCo1 and ΛRh1

∠1 = 81.1° *vs* ∠1' = 87.8°



ΛRh1 (red)

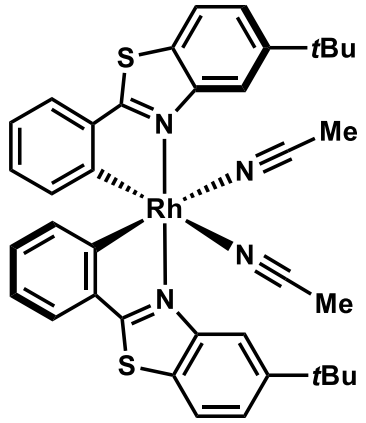
∠2 = 95.8° *vs* ∠2' = 88.3°



[Co]

R= 2,4,6-(*i*Pr)C_6H_2

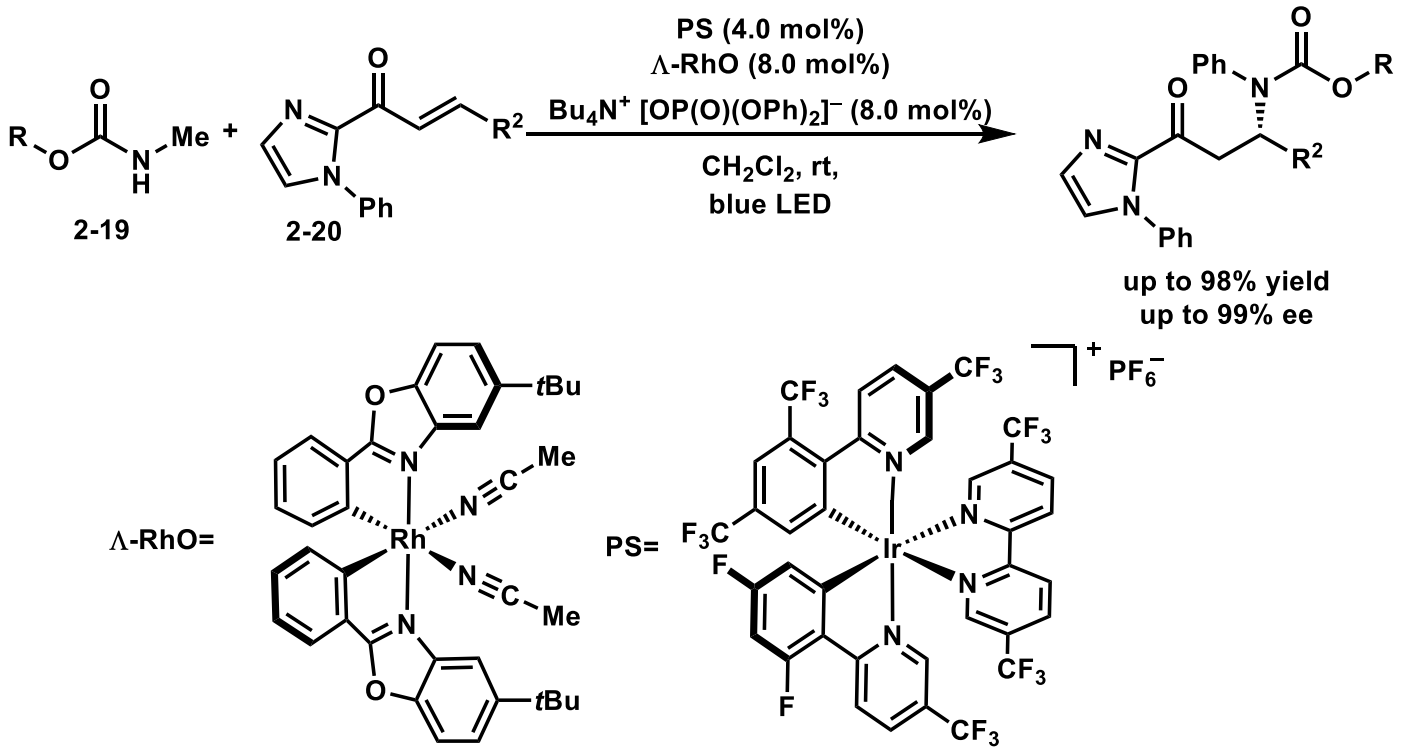
Co cat	yield(%)	ee
R= *t*Bu	80	40
R= 2,4,6-(*i*Pr)$_3C_6H_2$	92	92

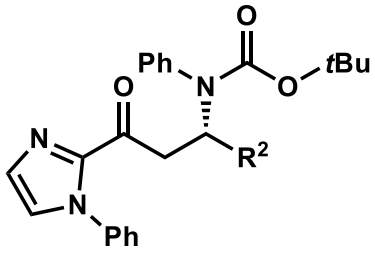


Λ-RhS

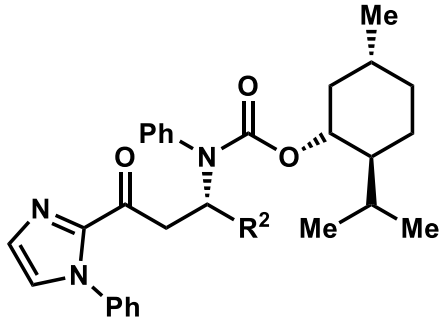
Zhang, K.; Lu, L.; Jia, Y.; Wang, Y.; Lu, F.; Pan, F.; Xiao, W. *Angew. Chem., Int. Ed*. **2019**, *58*, 13375.

手性路易斯酸催化的共轭加成反应

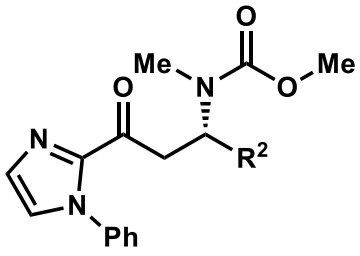




92% yield, 98% ee



85% yield, > 99:1 d.r.

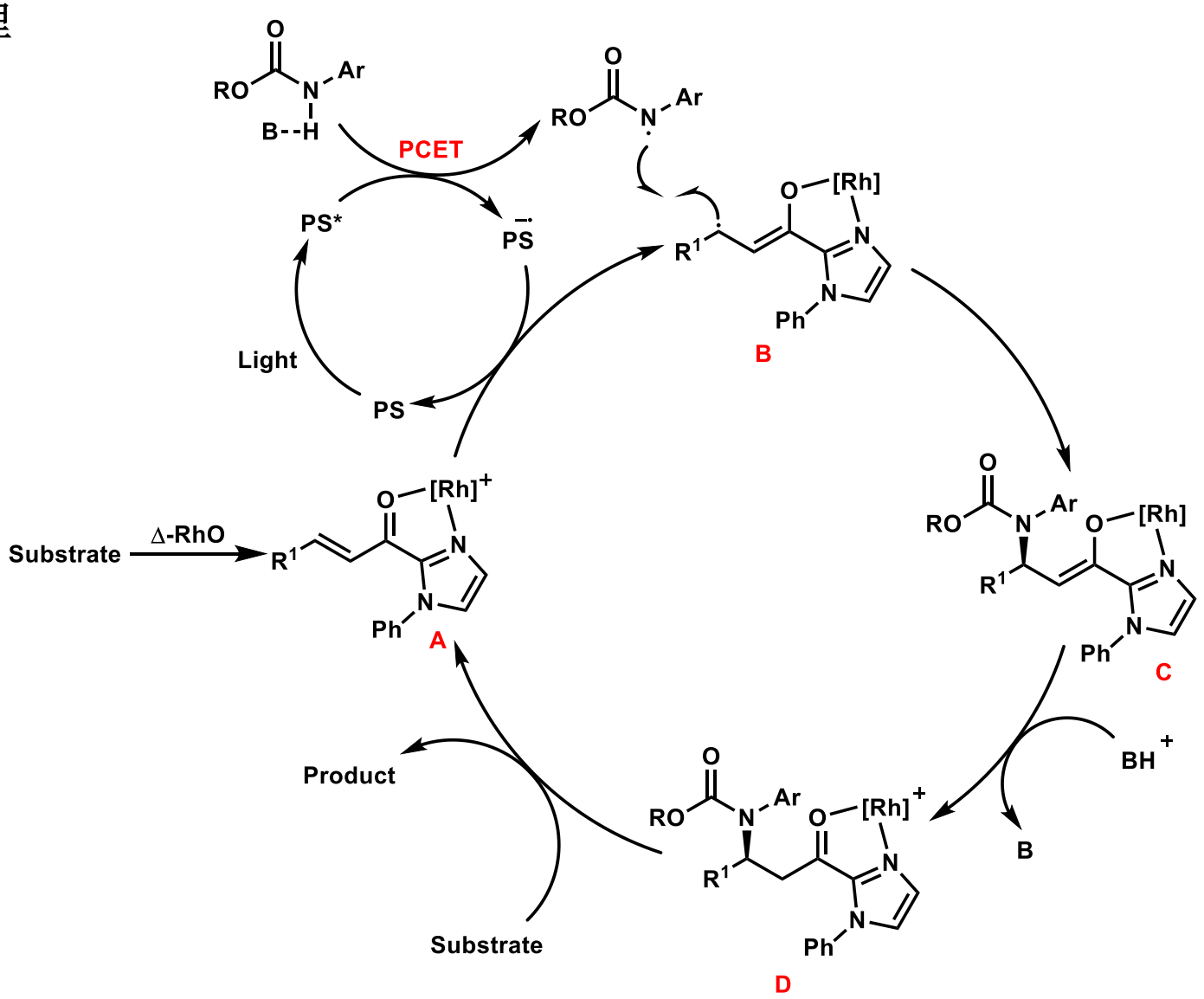


0% yield, 0% ee

Zhou, Z.; Li, Y.; Han, B.; Gong L.; Meggers, E. *Chem. Sci*. **2017**, *8*, 5757.

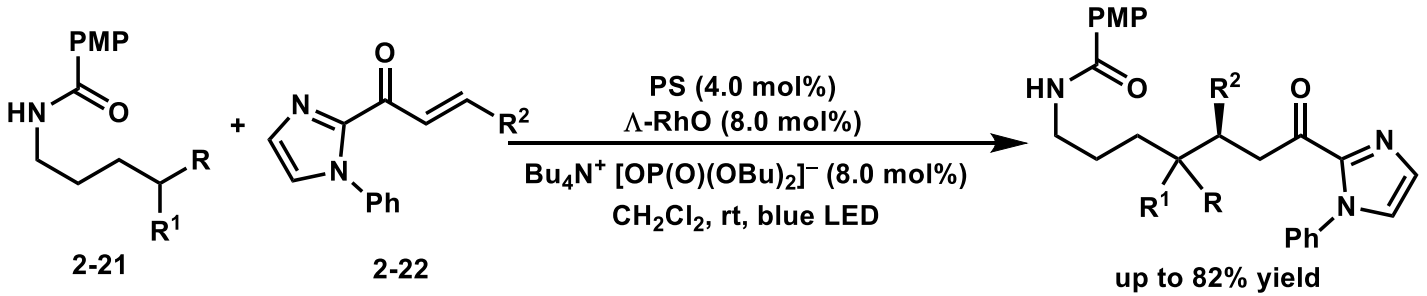
手性路易斯酸催化的共轭加成反应

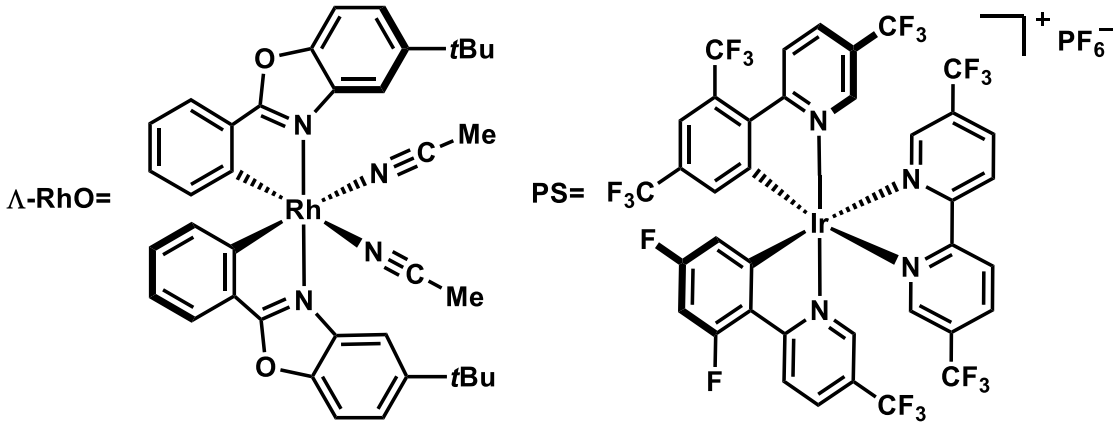
反应机理

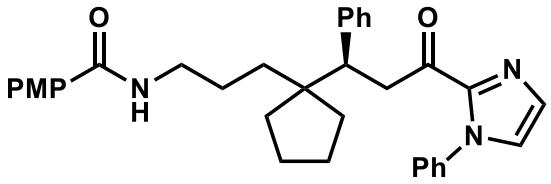


Zhou, Z.; Li, Y.; Han, B.; Gong L.; Meggers, E. *Chem. Sci*. **2017**, *8*, 5757.

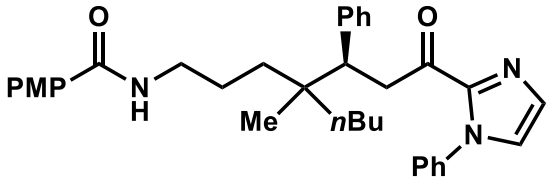
手性路易斯酸催化的共轭加成反应



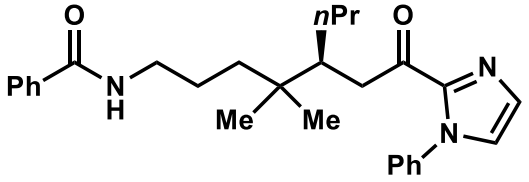




64% yield, 97% ee



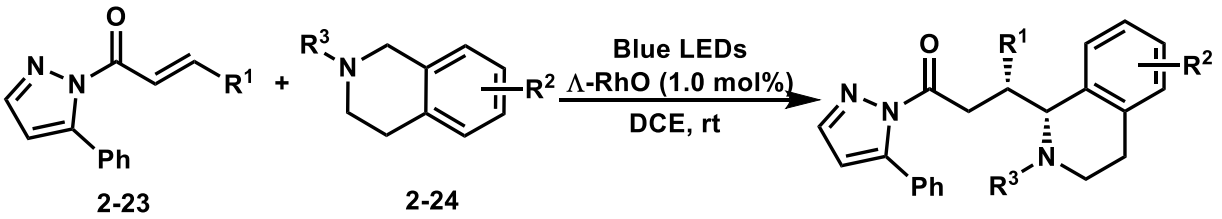
62% yield, 1.2:1, 95% ee, 93% ee

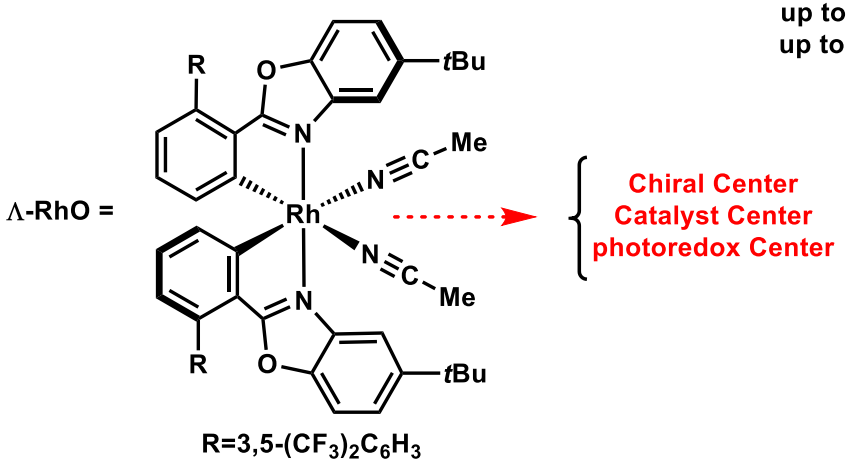


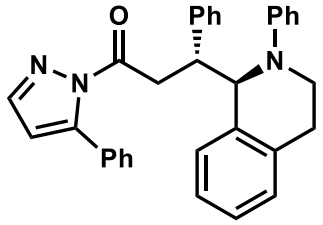
0% yield, 0% ee

Yuan, W.; Zhou, Z.; Gong, L.; Meggers, E. *Chem. Sci*. **2017**, *8*, 5757.

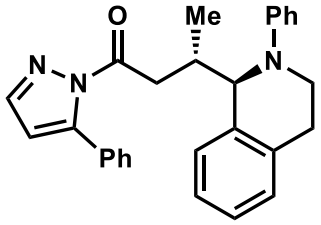
手性路易斯酸催化的共轭加成反应



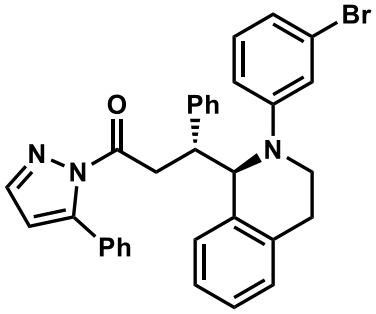




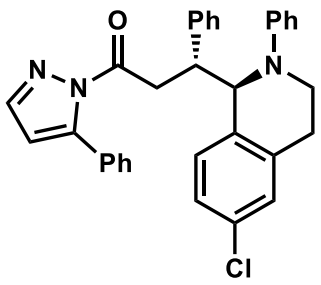
90% yield, 83:17 d.r. 95% ee



54% yield, 66:34 d.r. 97% ee



80% yield, 81:19 d.r. 93% ee

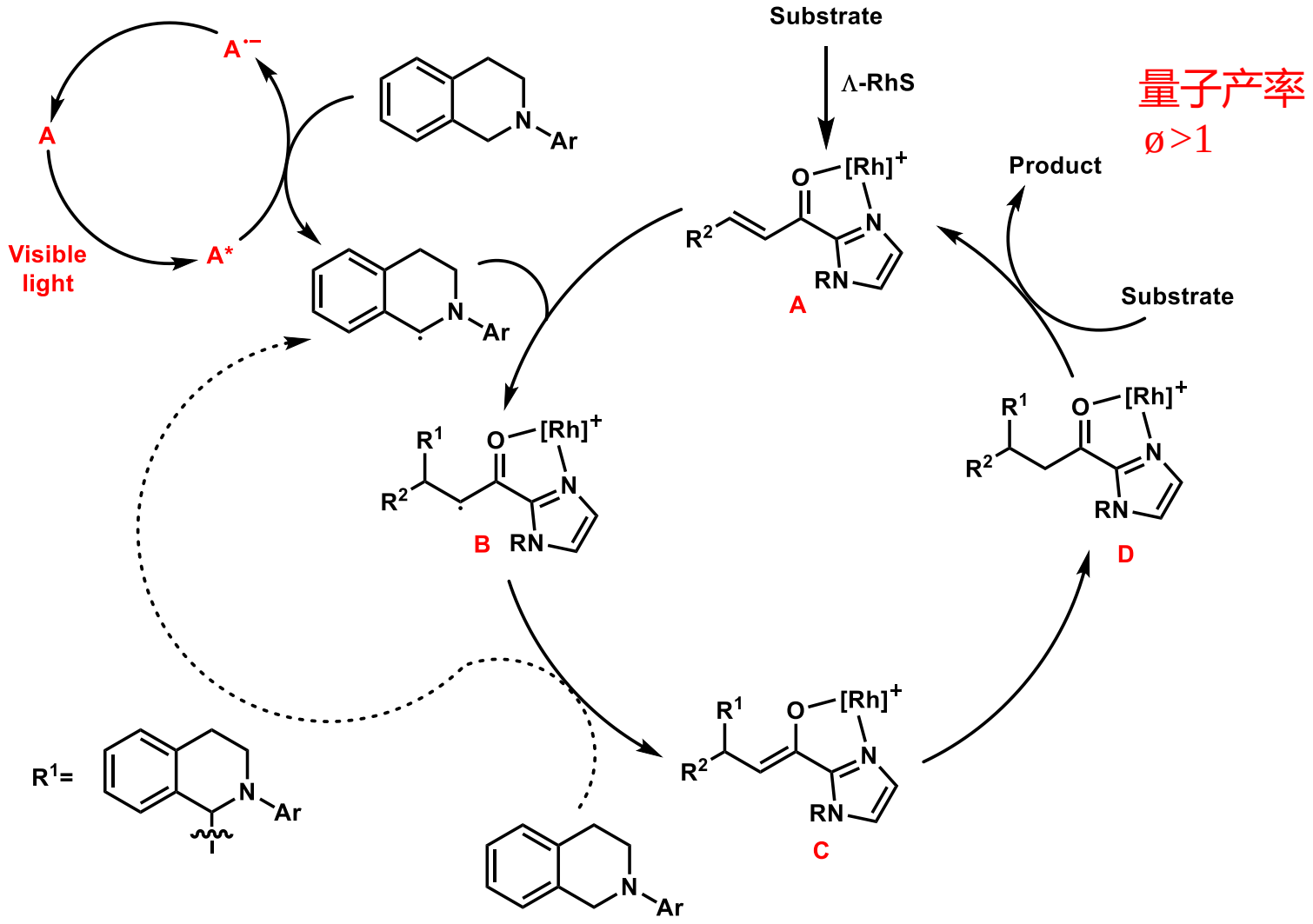


96% yield, 59:41 d.r. 99% ee

Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.; Harms, K.; Marsch, M.; Hilt, M.; Meggers, E. *Nature*, **2014**, *515*, 100.
Lin,S.; Sun, G.; Kang, Q. *Chem. Commun*. **2017**, *53*, 7665.

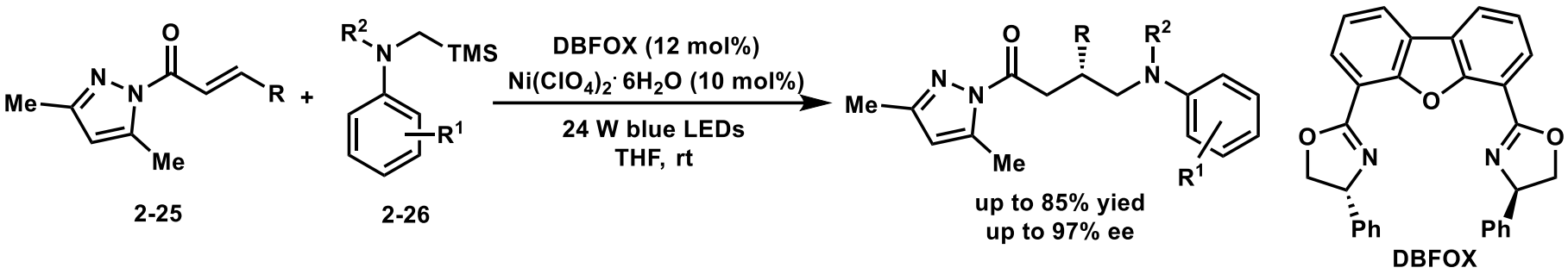
手性路易斯酸催化的共轭加成反应

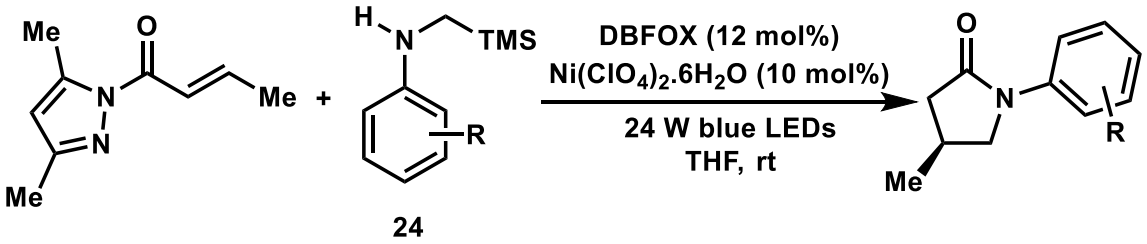
反应机理



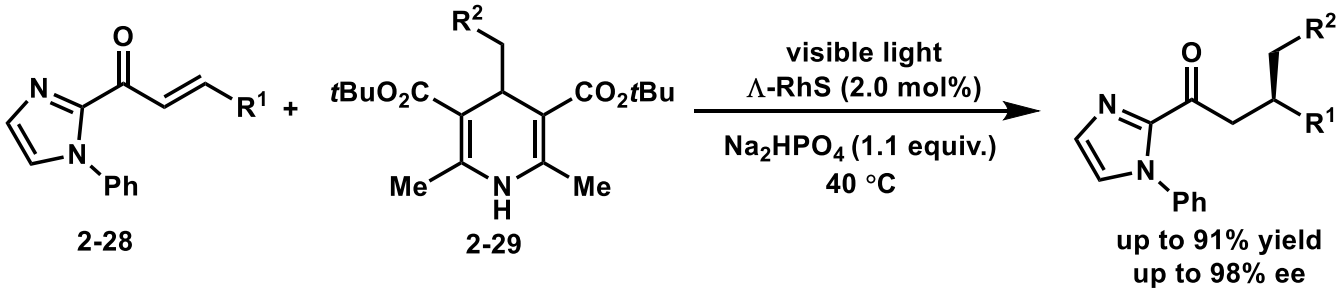
Lin,S.; Sun, G.; Kang, Q. *Chem. Commun*. **2017**, *53*, 7665.

手性路易斯酸催化的共轭加成反应



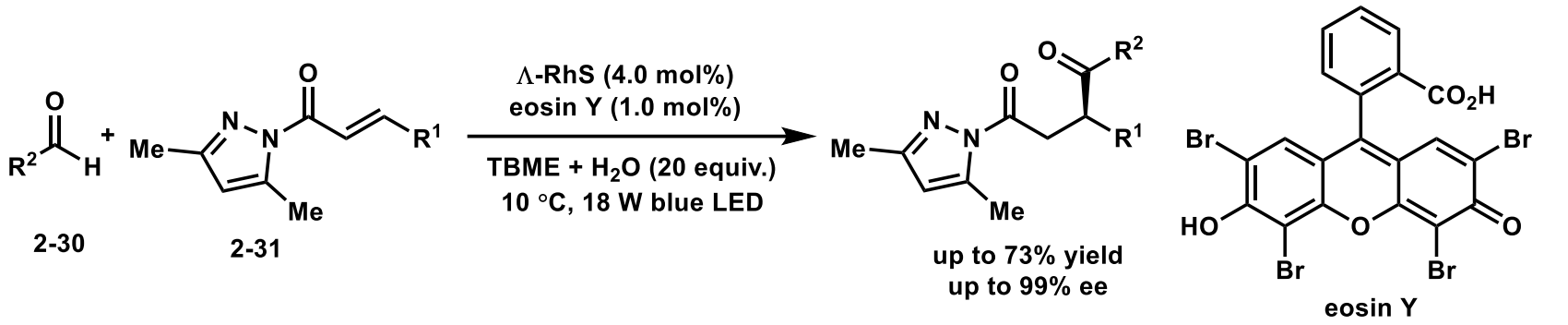


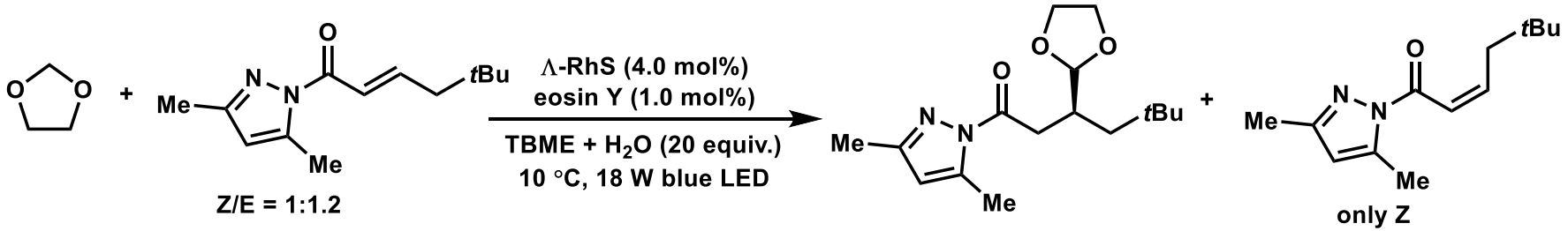
Shen, X.; Li, Y.; Wen, Z.; Cao, S.; Hou, X.; Gong, L. *Chem. Sci*. **2018**, *9*, 4562.

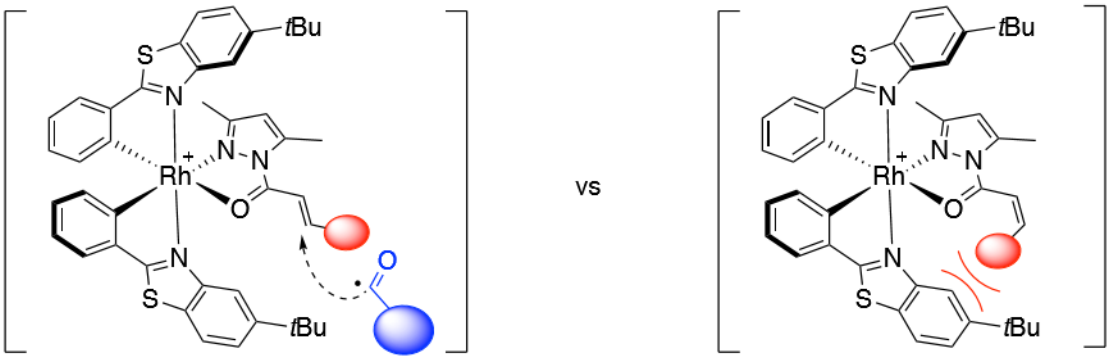


Assis, F. F.; Huang, X.; Akiyama, M.; Pilli, R. A.; Meggers, E. *J. Org. Chem*. **2018**, *83*, 10922−10932.

手性路易斯酸催化的共轭加成反应







Favored Transition state of *E* isomer

Disfavored activation model of *Z* isomer

Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. *Angew. Chem., Int. Ed.* **2019**, *58*, 16859.

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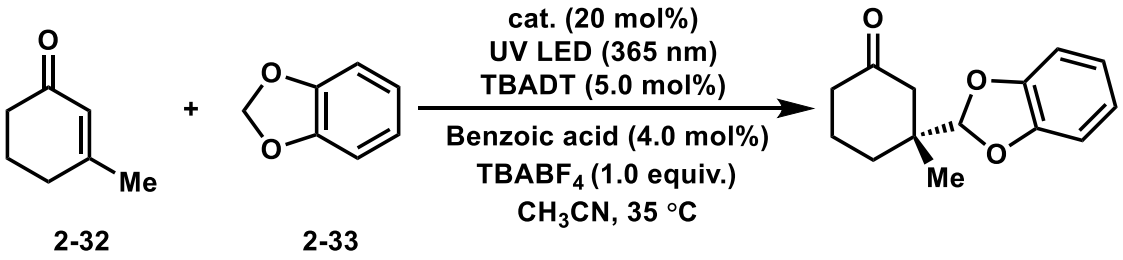
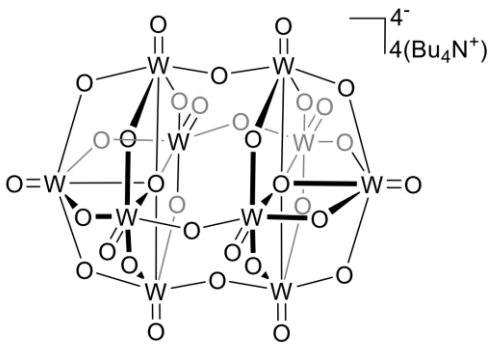
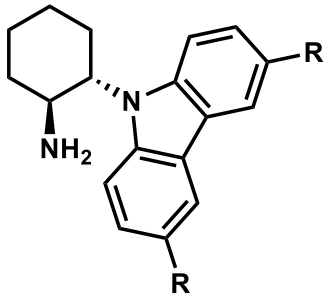
手性胺催化的共轭加成反应

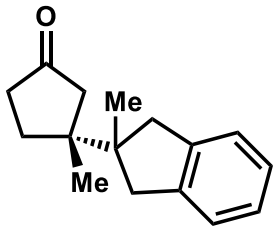




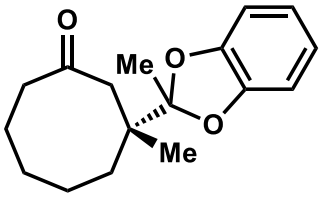
TBADT



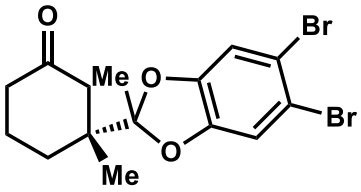
R= 2,4,6-(*i*Pr)$_3$C$_6$H$_2$
cat.



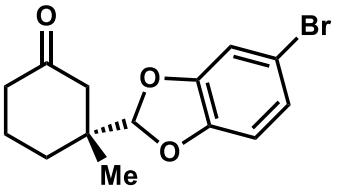
99% Yield,88% ee



63% Yield, 91% ee



67% yield, 1.5:1 d.r., 93% ee

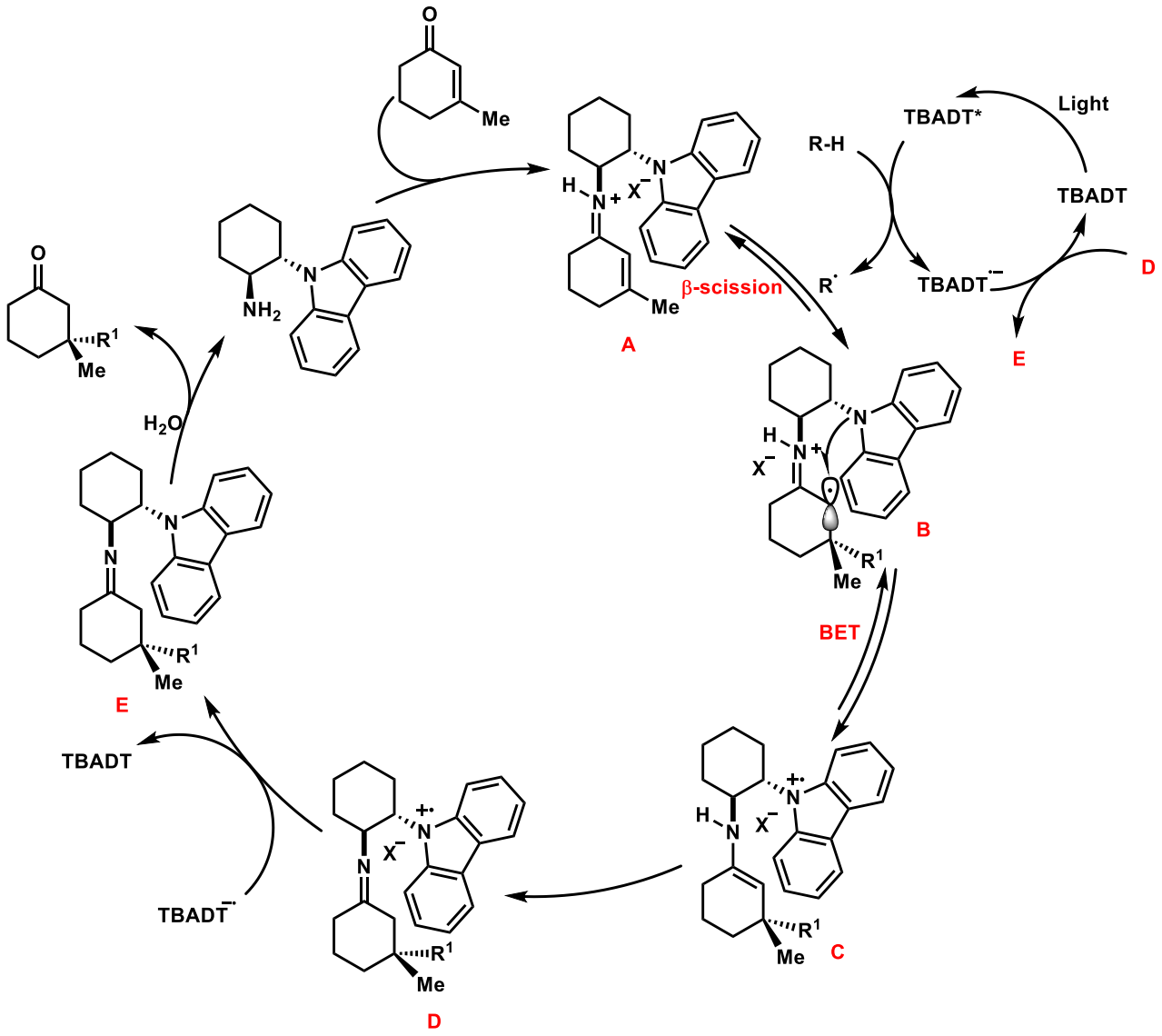


49% Yield, 91% ee

Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature.* **2016**, *532*, 218.

手性胺催化的共轭加成反应

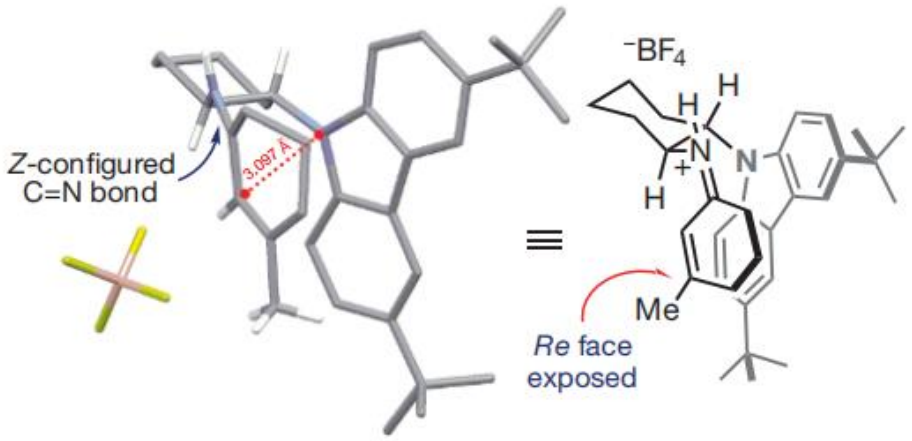
反应机理



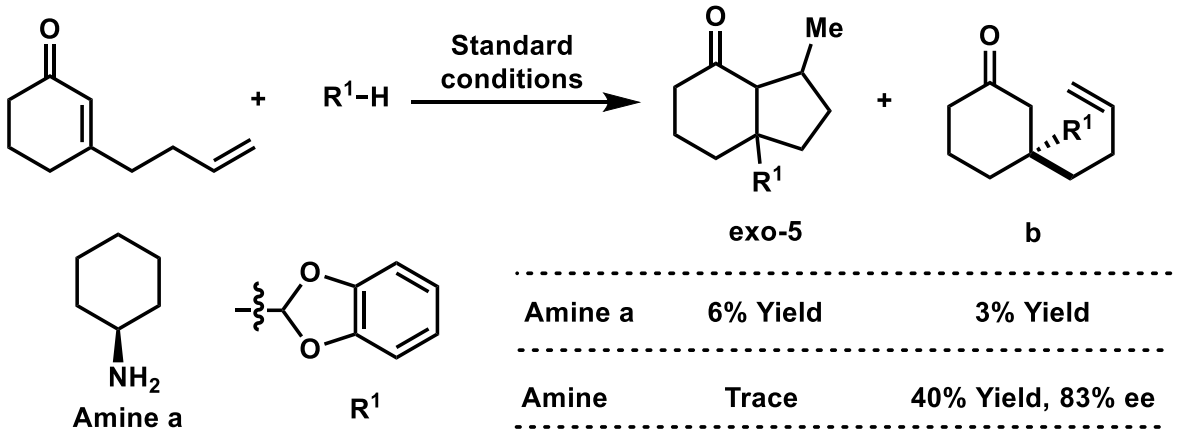
Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature*. **2016**, *532*, 218.

手性胺催化的共轭加成反应

单晶结构

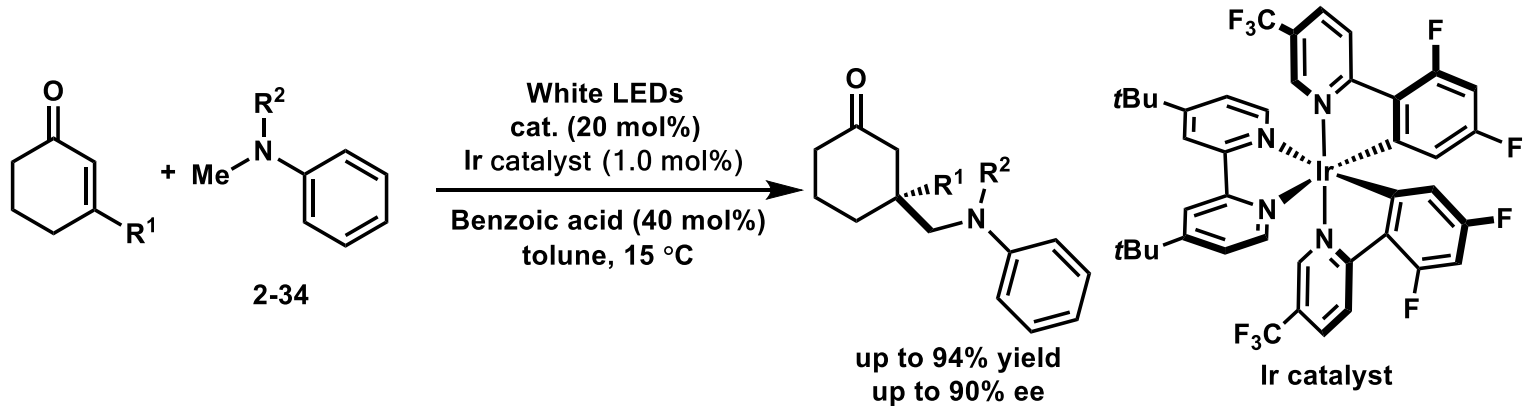


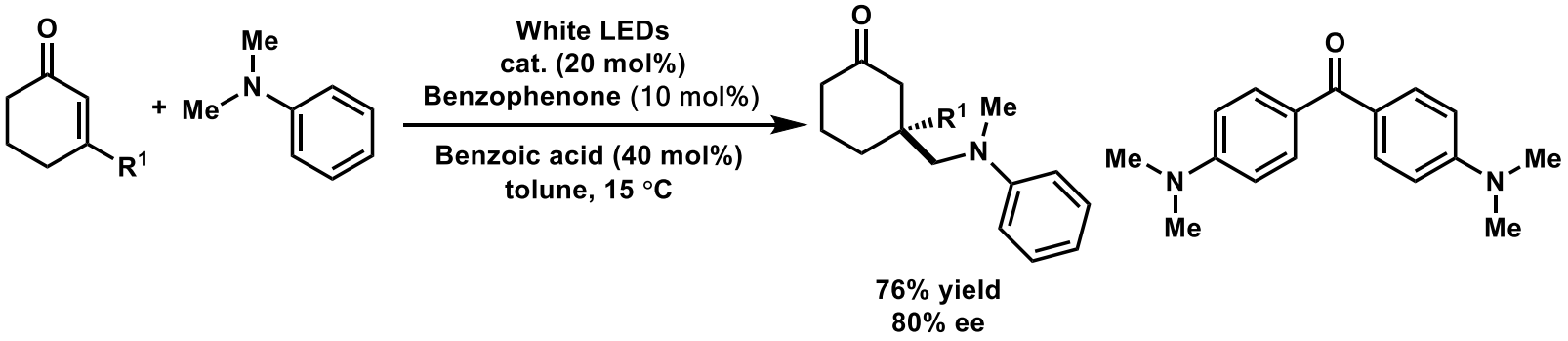
对照试验



Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature*. **2016**, *532*, 218.

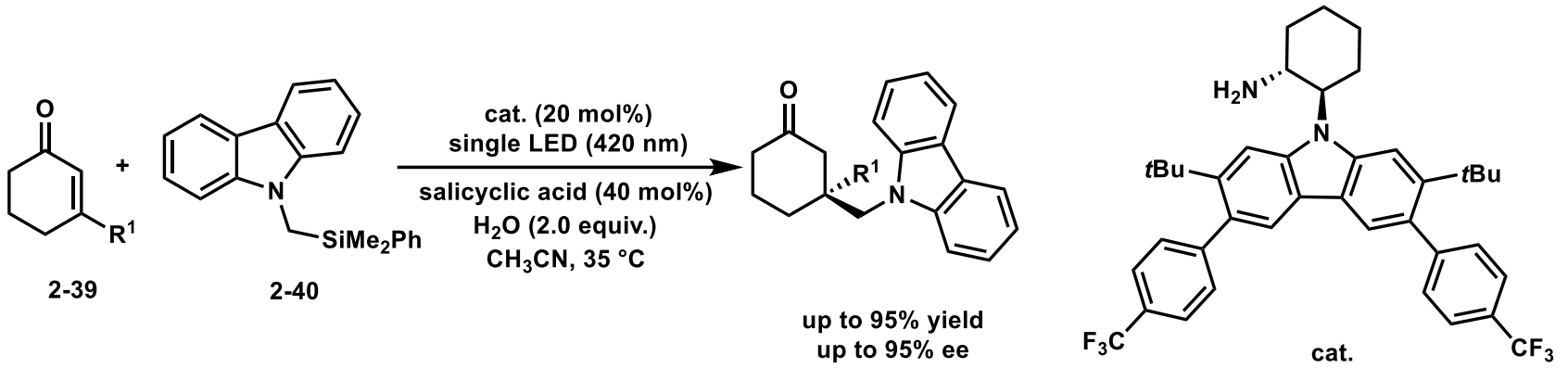
手性胺催化的共轭加成反应



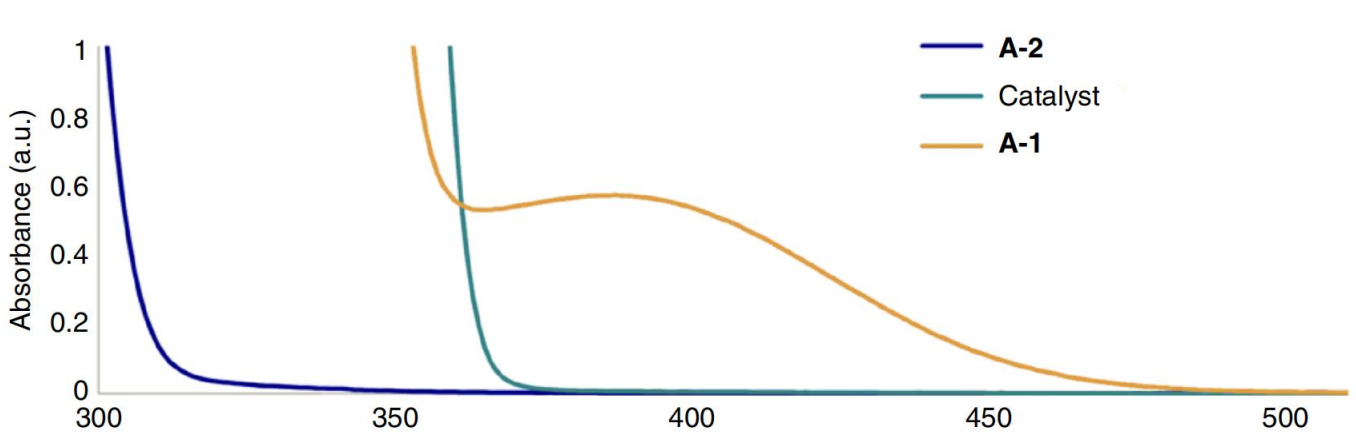


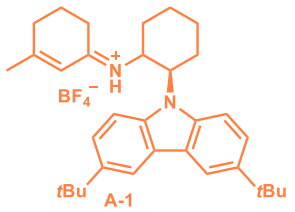
Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature.* **2016**, *532*, 218.

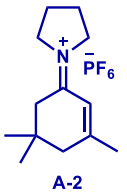
手性胺催化的共轭加成反应



紫外可见光谱



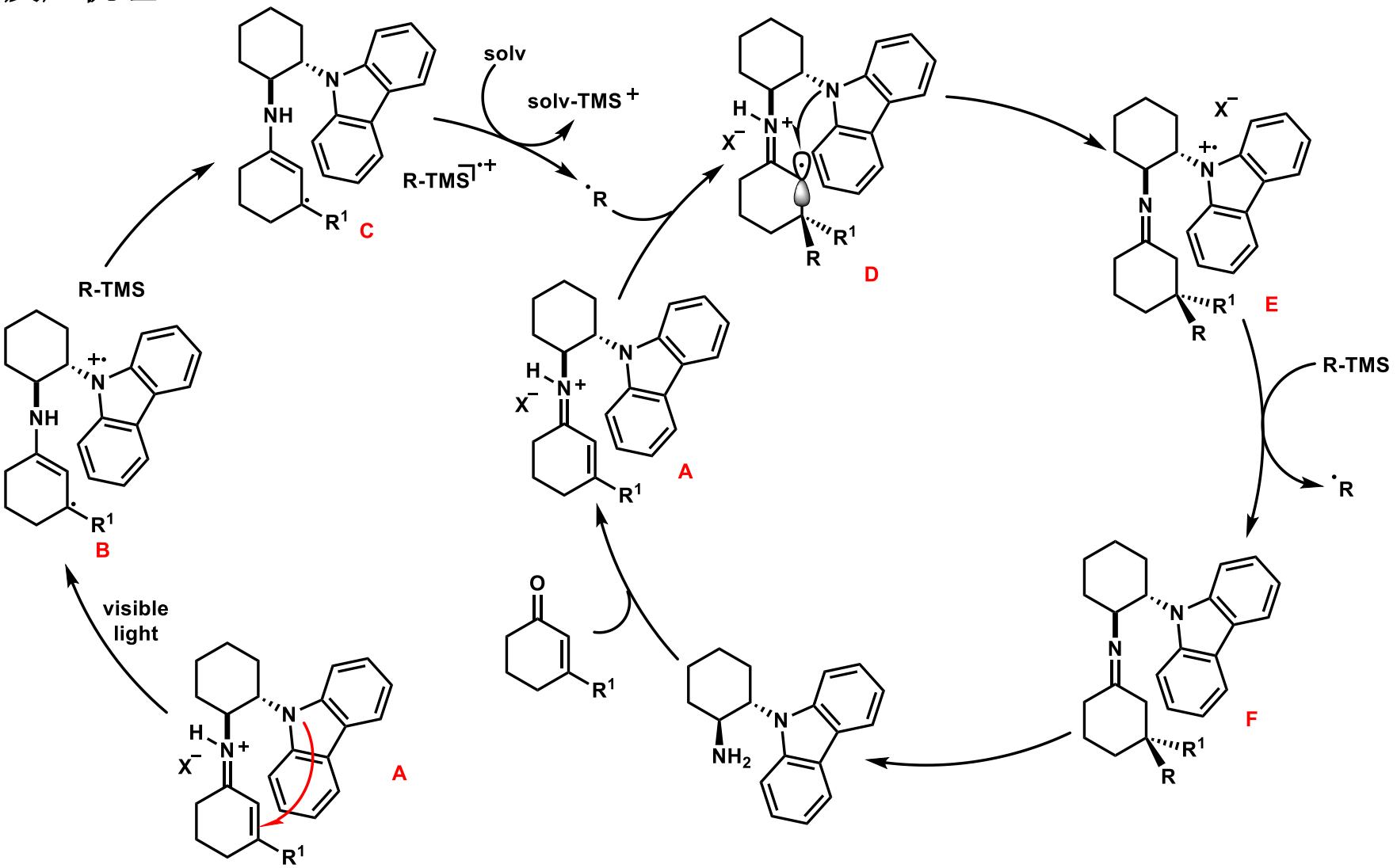




Cao, Z.; Ghosh, T.; Melchiorre, P. *Nat Commun.* **2018**, *9*, 3274.

手性胺催化的共轭加成反应

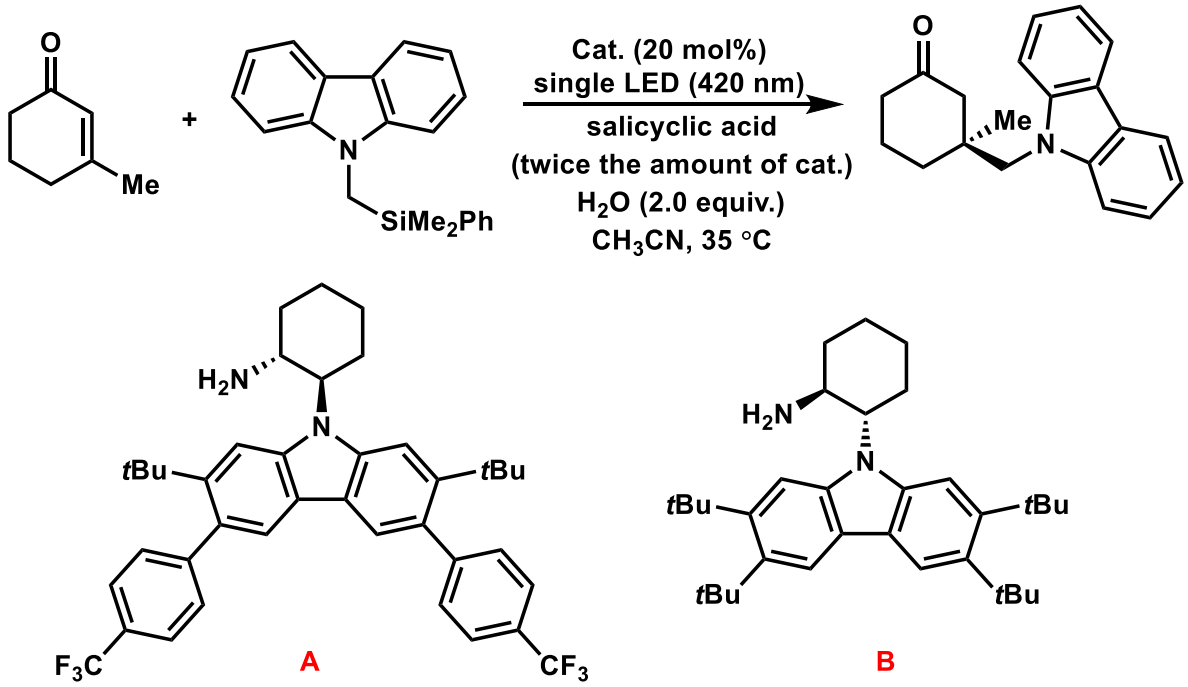
反应机理



Cao, Z.; Ghosh, T.; Melchiorre, P. *Nat Commun.* **2018**, *9*, 3274.

手性胺催化的共轭加成反应

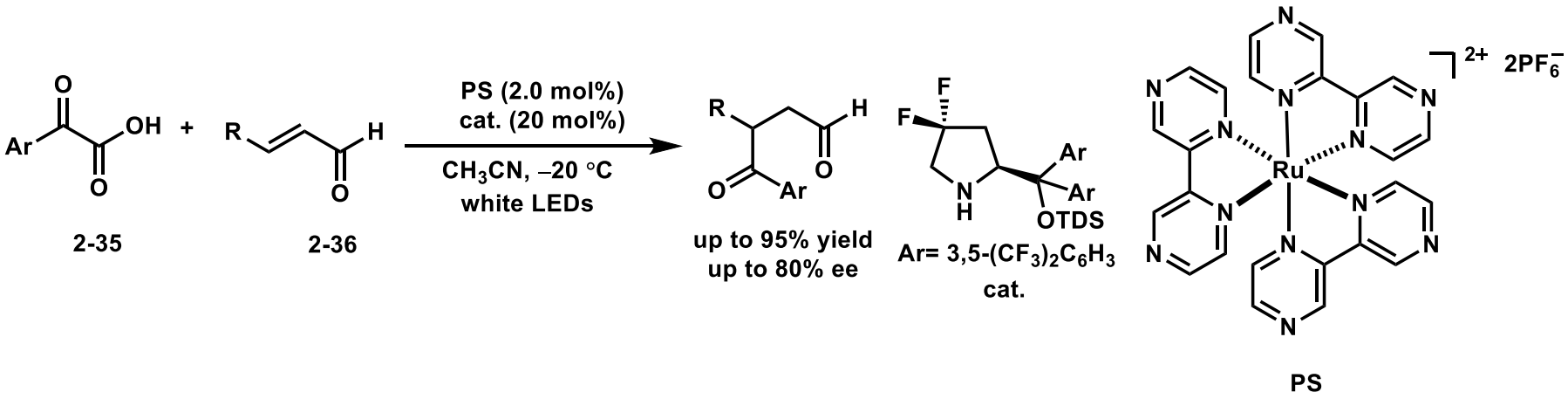
对照试验



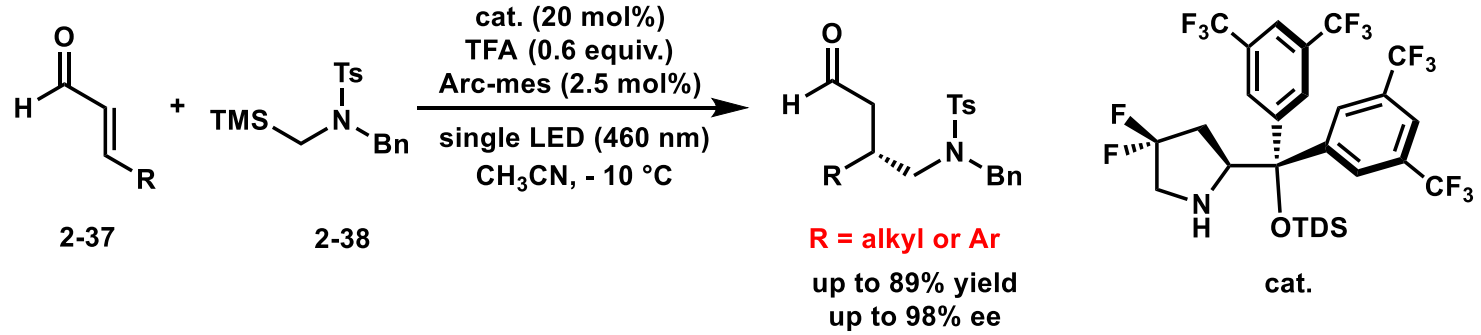
Cat.	Yield(%)	ee(%)
A (R, R) (15 mol%)	44	80
B (S, S) (5 mol%)	-	-
A (R, R) (15 mol%)+ B (S, S) (5 mol%)	40	42

Cao, Z.; Ghosh, T.; Melchiorre, P. *Nat Commun.* **2018**, *9*, 3274.

手性胺催化的共轭加成反应

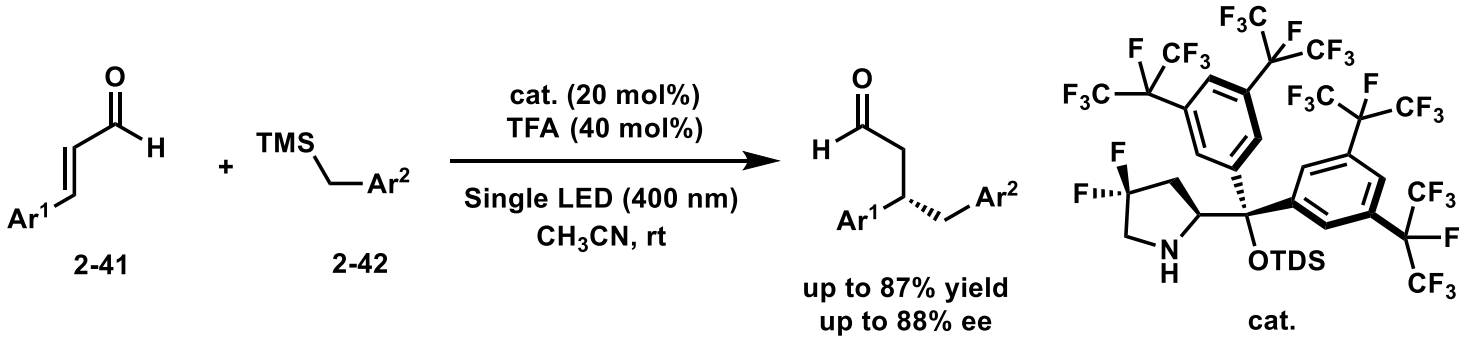


Zhao, J.; Zhang, H.; Shen, X.; Yu, S. *Org. Lett*. **2019**, *21*, 913.

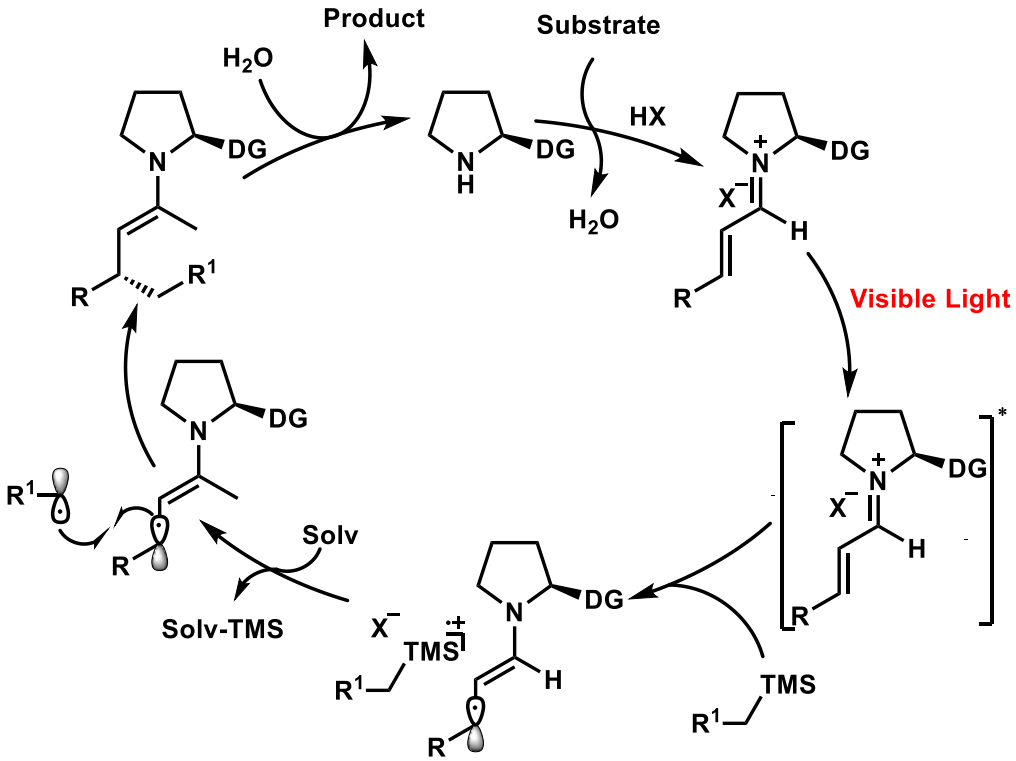


Saux, E. L.; Ma, D.; Bonilla, P.; Holden, C. M.; Lustosa, D.; Melchiorre, P. *Angew .Chem., Int. Ed*. DOI:10.1002/anie.202014876.

手性胺催化的共轭加成反应

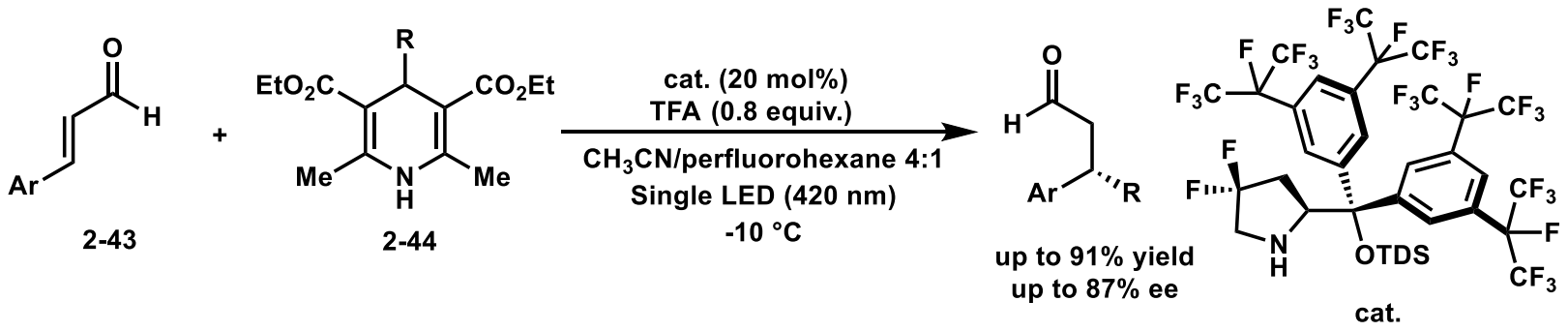


反应机理

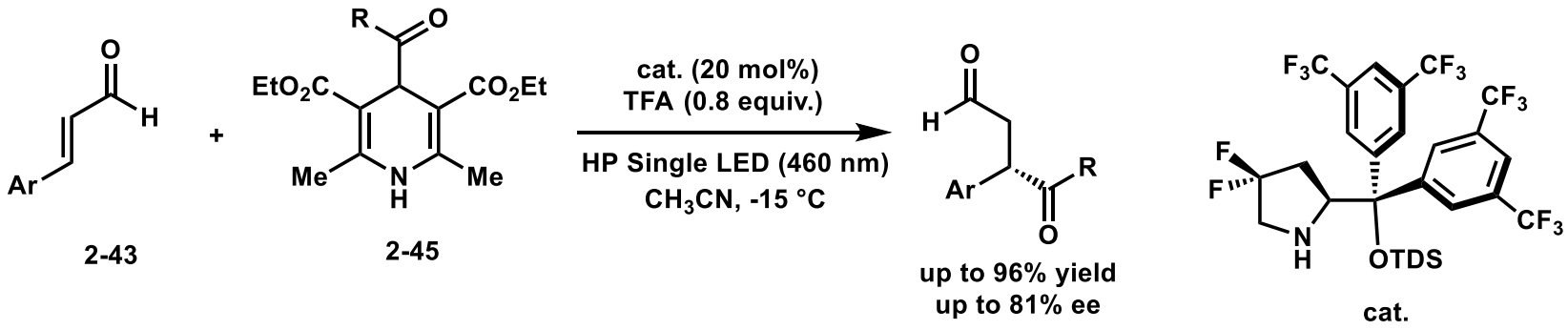


Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868.

手性胺催化的共轭加成反应



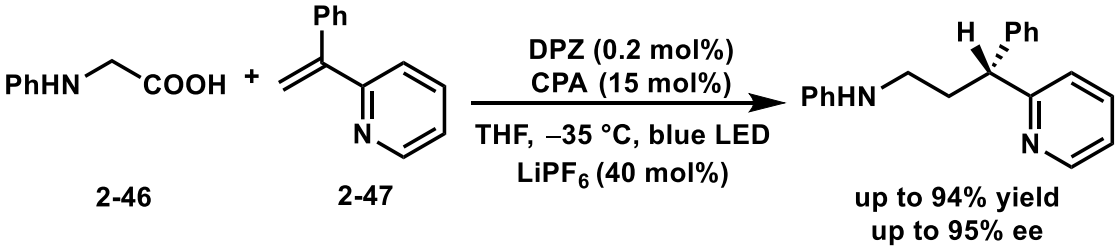
Melchiorre, P et al. *ACS Catal*. **2018**, *8*, 1062.



Goti, G.; Bieszczad, B.; Vega-PeCaloza, A.; Melchiorre, P. *Angew .Chem., Int. Ed.* **2019**, *58*, 1213.

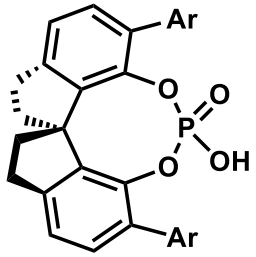
目录

手性磷酸催化的共轭加成反应

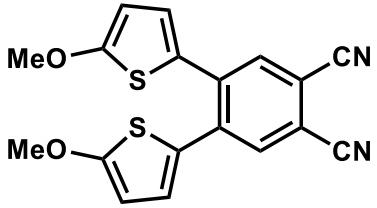


2-46　　2-47

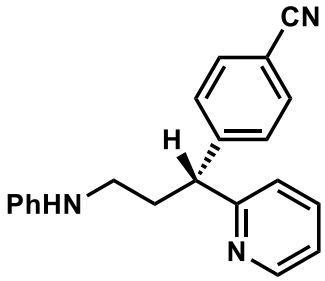
up to 94% yield
up to 95% ee



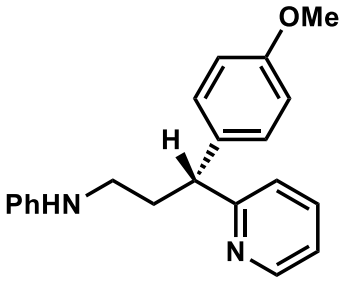
Ar= 2-CF_3Ph



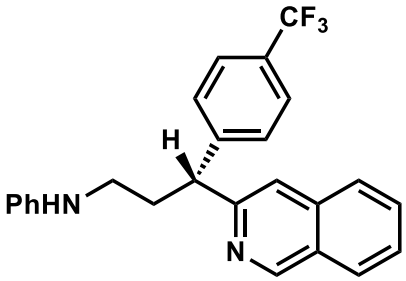
DPZ



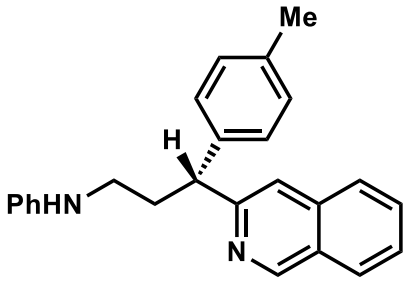
86% yield, 88% ee



82% yield, 90% ee



72% yield, 97% ee

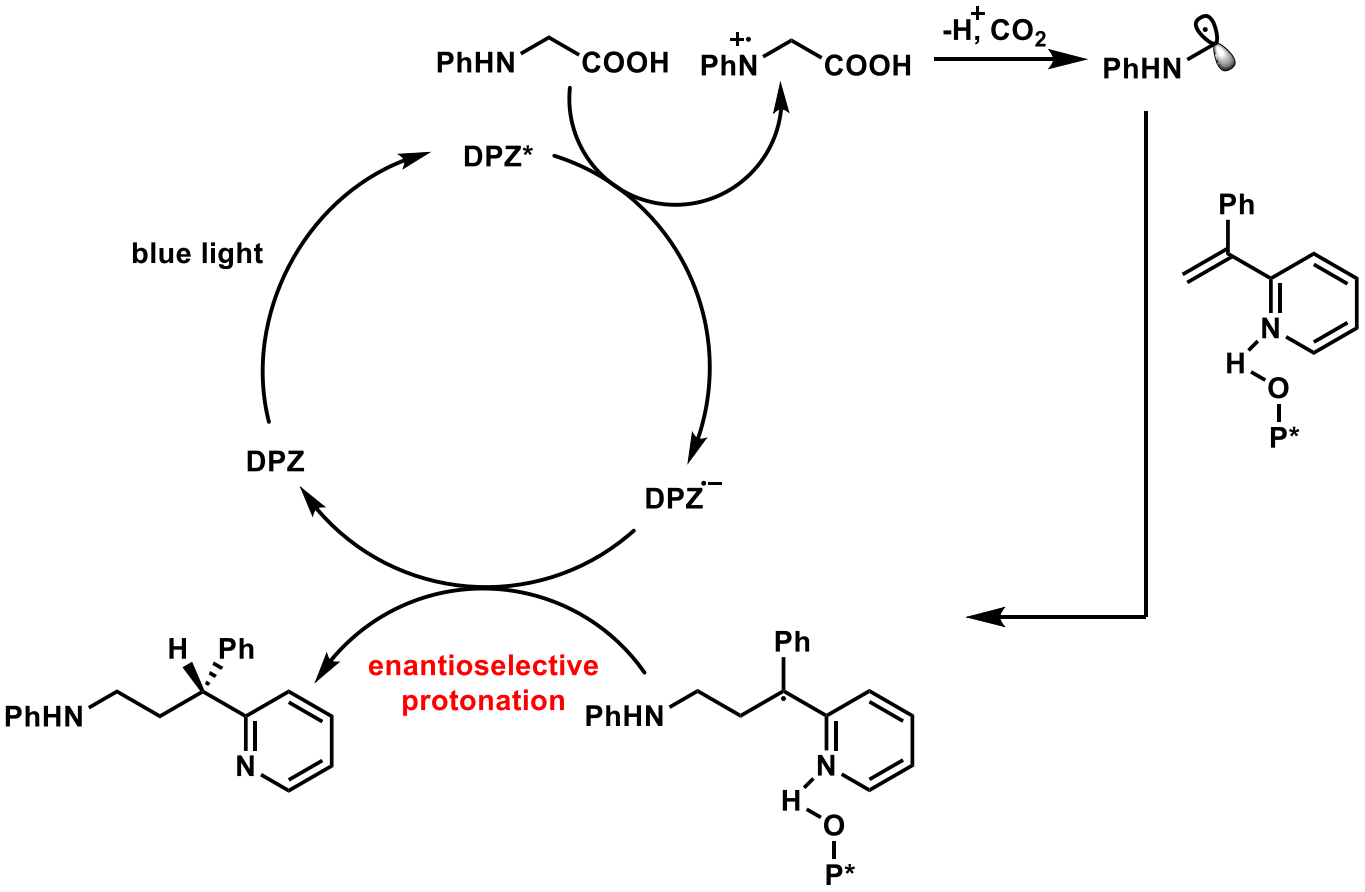


72% yield, 97% ee

Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc*. **2018**, *140*, 6083.

手性磷酸催化的共轭加成反应

反应机理



Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc*. **2018**, *140*, 6083.

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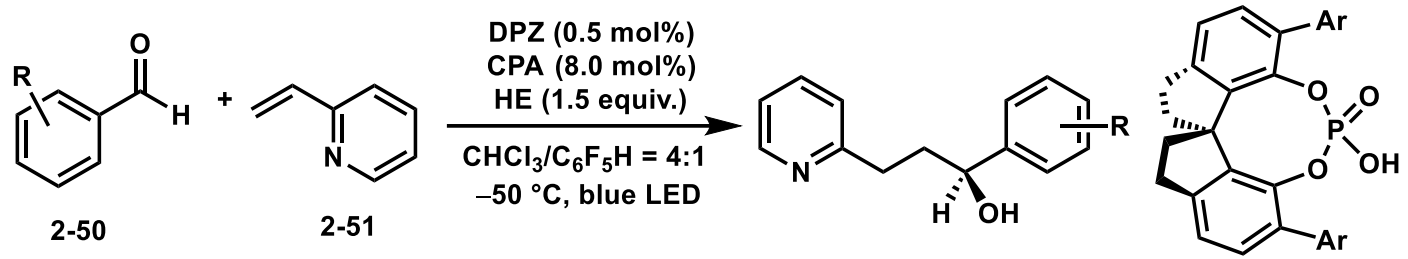
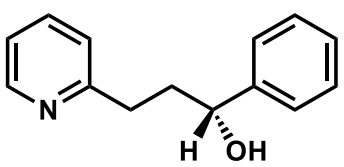
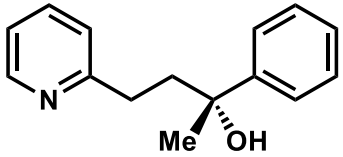
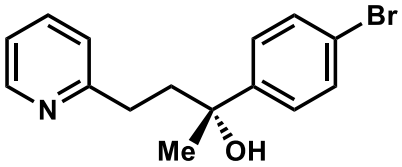




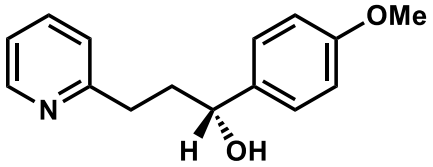
90% yield, 90% ee



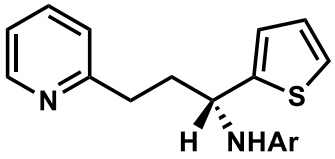
89% yield, 94% ee



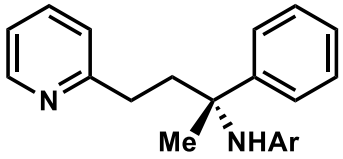
63% yield, 93% ee



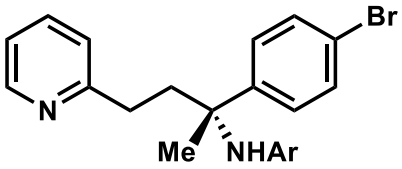
79% yield, 95% ee



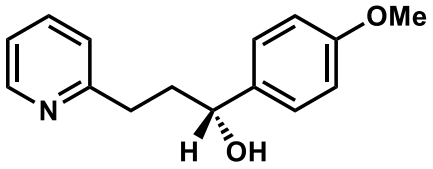
50% yield, 91% ee



65% yield, 92% ee



62% yield, 92% ee

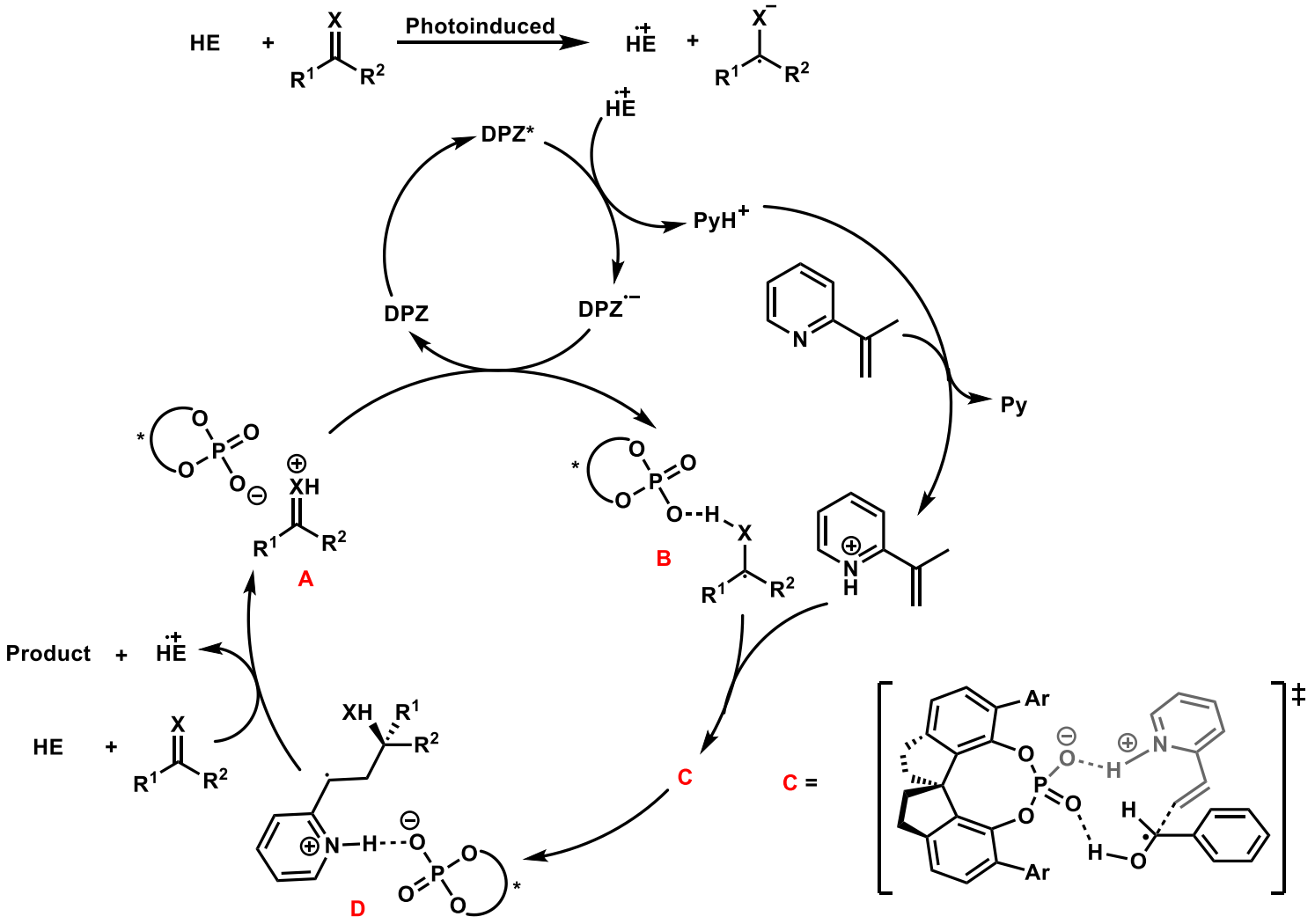


55% yield, 96% ee

Cao, K.; Tan, S.; Lee, R.; Yang, S.; Jia, H.; Zhao, X., Qiao, B., Jiang, Z. *J. Am. Chem. Soc*. **2019**, *141*, 5437.

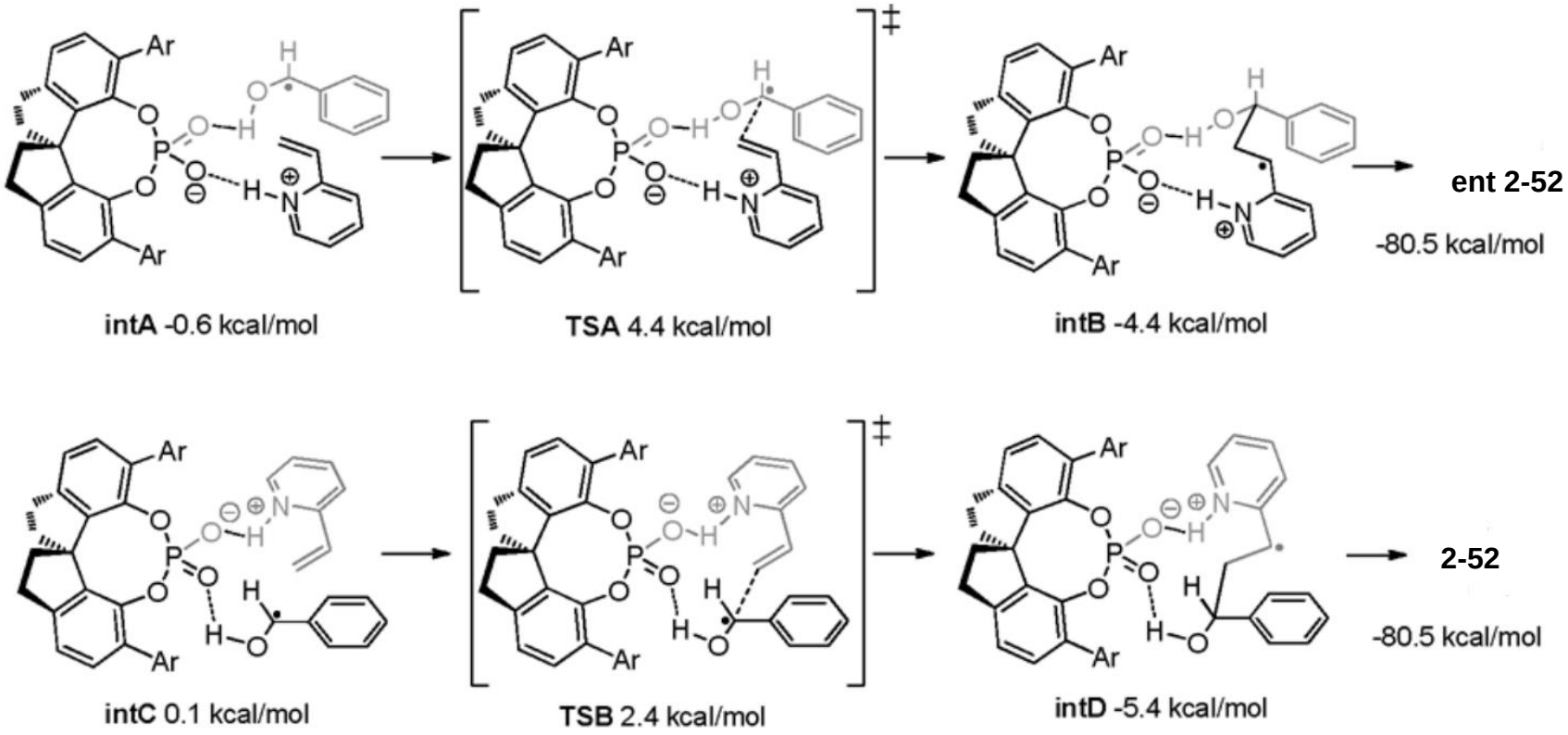
手性磷酸催化的共轭加成反应

反应机理



Zhiyong Jiang et al. *J. Am. Chem. Soc.* **2019**, *141*, 5437−5443.

手性磷酸催化的共轭加成反应



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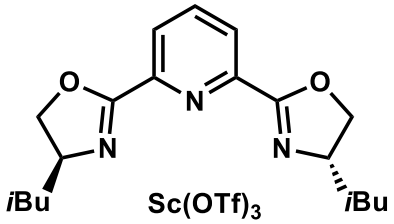
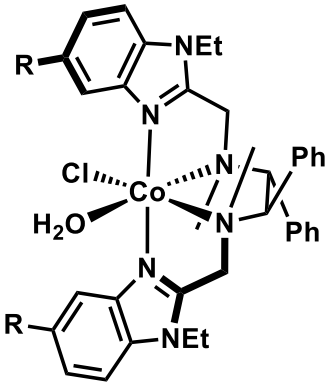
目录

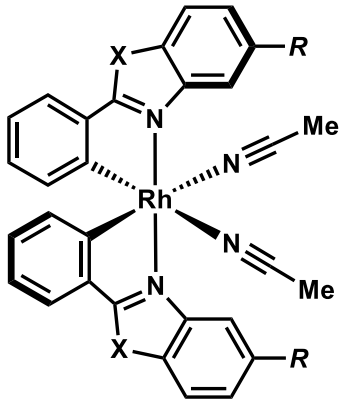
总结

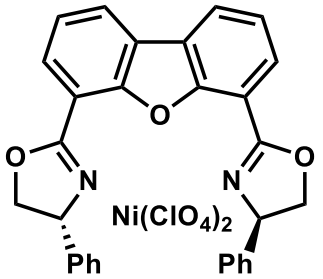
手性路易斯酸





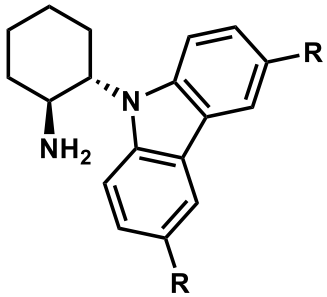
只控制手性



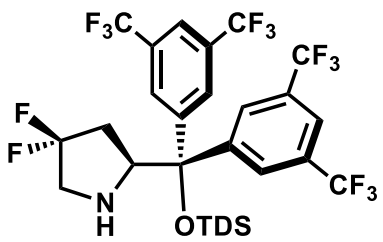


既控制手性，又有光化学性

手性胺

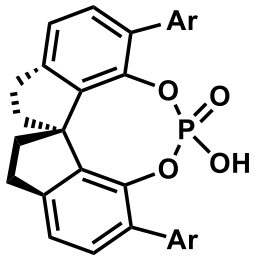


只控制手性，
EDA复合物



只控制手性，
亚胺中间体强氧化性

手性磷酸



对映选择性质子化，
氢键螯合底物控制手性

谢谢大家！
希望大家批评指正！