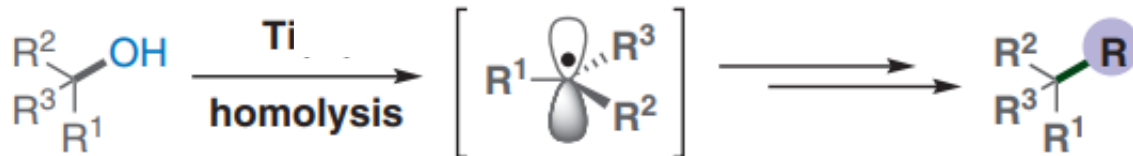




# 镍催化构建C-C键的不对称偶联反应

-----钛介导醇的脱羟基自由基化



汇报人:张利利  
导师:杨泽鹏  
2021年10月15日



# 目录

- 背景
- 镍催化醇衍生物构建C-C键的偶联反应最新进展
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  - 醇的衍生物----醚类
  - 醇的衍生物----硫酸酯类
- 钛配合物介导的醇自由基脱羟基功能化最新进展
  - 化学计量钛配合物介导醇的均裂
  - 催化计量钛配合物介导醇的均裂
- 总结与展望



Richard F. Heck



Ei-ichi Negishi



Akira Suzuki

## 2010年诺贝尔化学奖得主

在钯催化交叉偶联研究领域作出杰出贡献  
研究成果使人类能高效合成复杂有机物



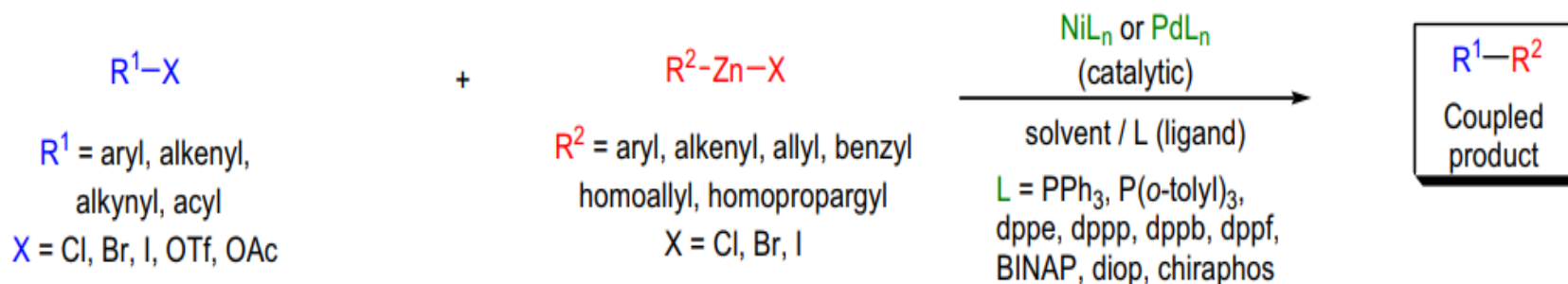
## 经典偶联反应

### Kumada Cross-Coupling Reaction<sup>1972</sup> :



R<sup>1-3</sup> = H, alkyl, aryl, alkenyl; X = F, Cl, Br, I, OTf; R<sup>4</sup> = alkyl, aryl, alkenyl; X = Br, I; L = PPh<sub>3</sub> or L<sub>2</sub> = dppp, dppe, dppb

### Negishi Cross-Coupling Reaction<sup>1976</sup> :

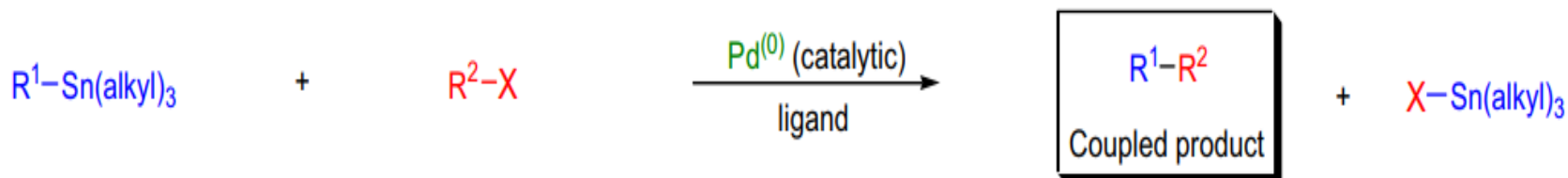




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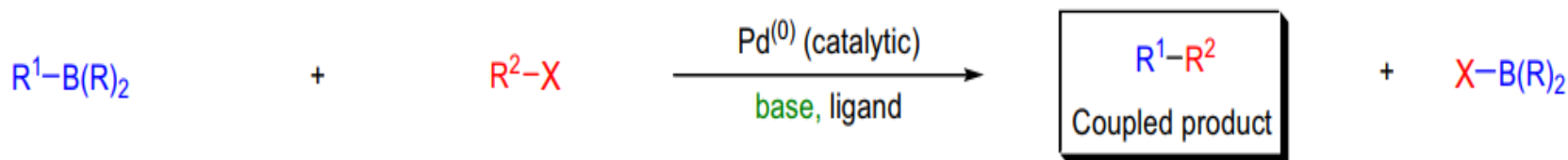
## 经典偶联反应

Stille Cross-Coupling Reaction<sup>1978</sup> :



$\text{R}^1$  = allyl, alkenyl, aryl;  $\text{R}^2$  = alkenyl, aryl, acyl;  $\text{X}$  = Cl, Br, I, OTf, OPO(OR)<sub>2</sub>

Suzuki Cross-Coupling Reaction<sup>1979</sup> :

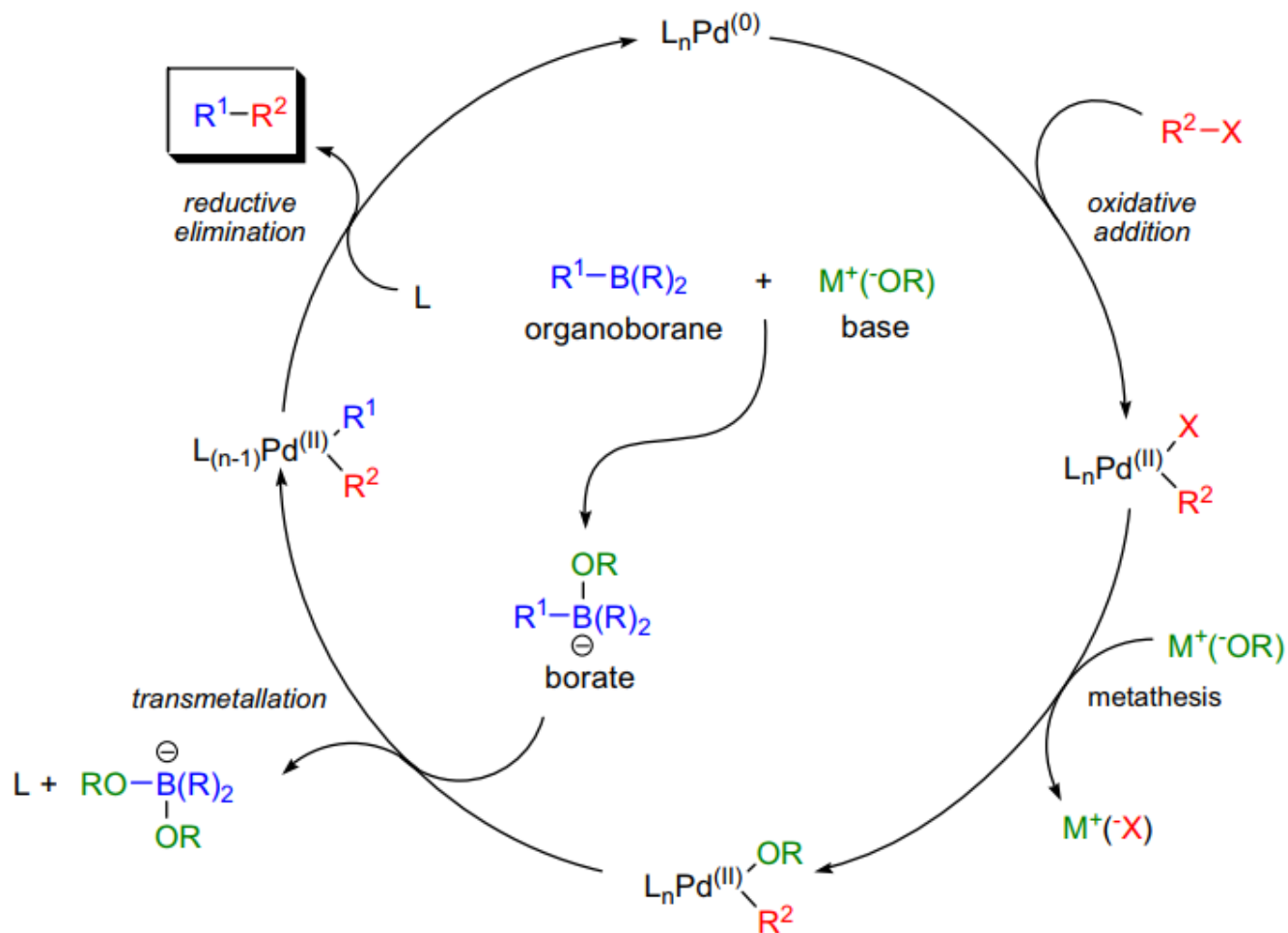


$\text{R}^1$  = alkyl, allyl, alkenyl, alkynyl, aryl;  $\text{R}$  = alkyl, OH, O-alkyl;  $\text{R}^2$  = alkenyl, aryl, alkyl;  $\text{X}$  = Cl, Br, I, OTf, OPO(OR)<sub>2</sub> (enol phosphate);  
base = Na<sub>2</sub>CO<sub>3</sub>, Ba(OH)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, TIOH, KF, CsF, Bu<sub>4</sub>F, NaOH, M<sup>+</sup>(<sup>-</sup>O-alkyl)



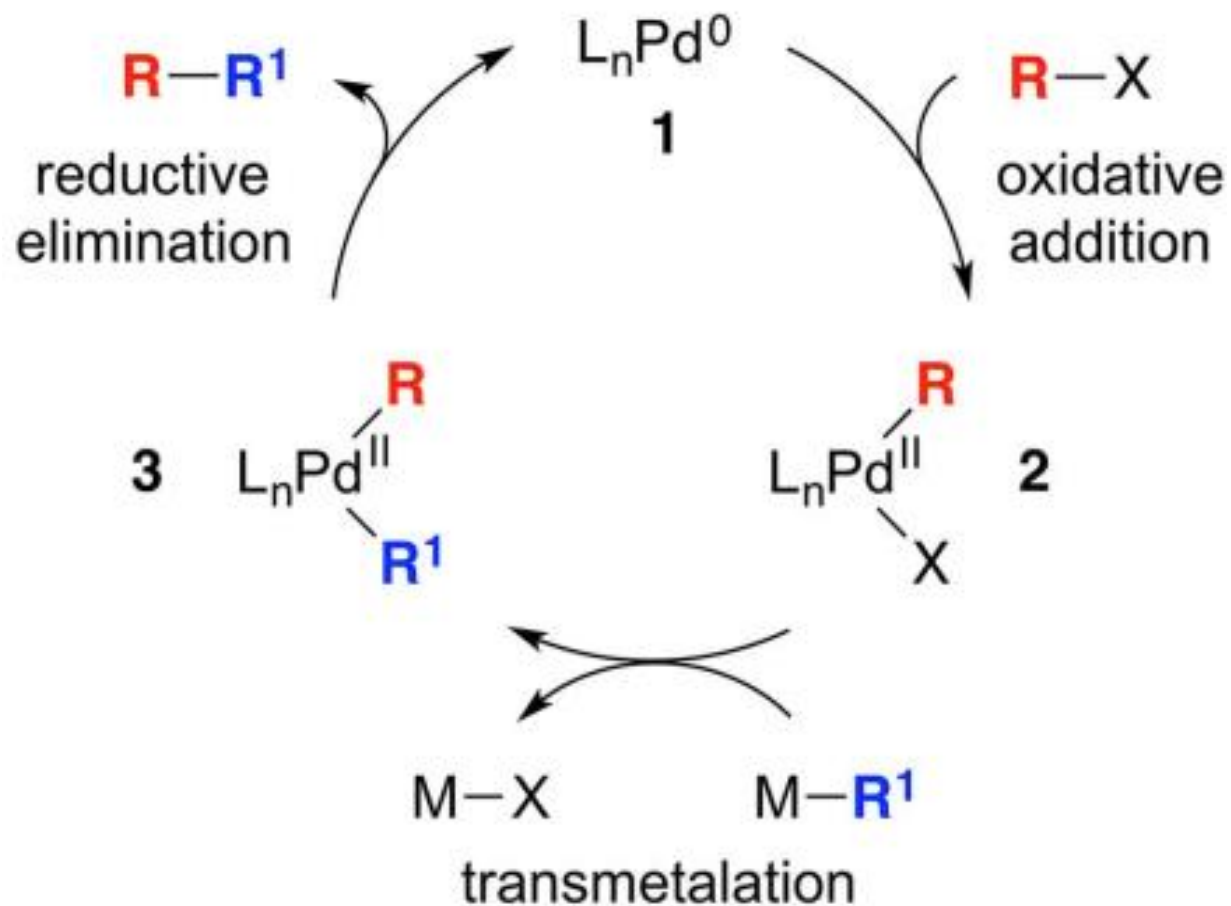
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## Mechanism of Suzuki Cross-Coupling Reaction :



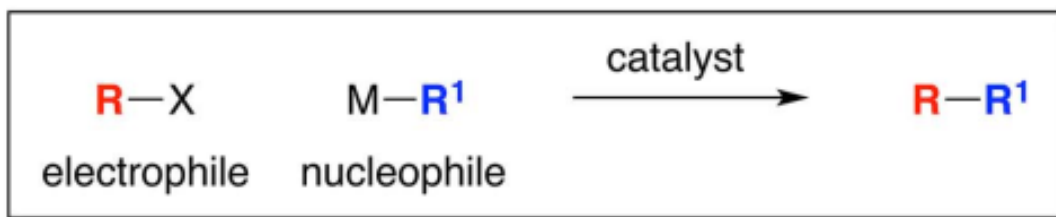


## Mechanism Cross-Coupling Reaction :



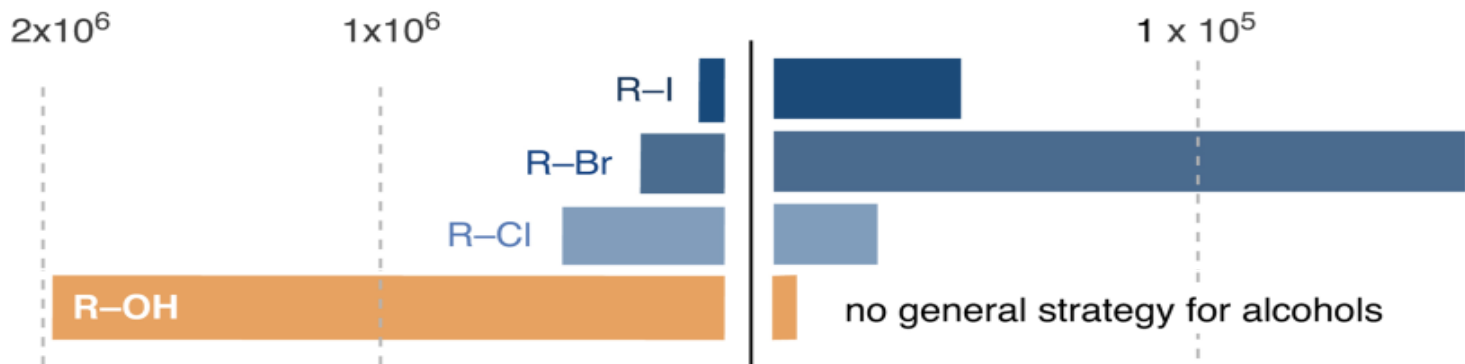


## 偶联反应的关键



亲核试剂：有机镁试剂、有机锌试剂、有机锡试剂、有机硼试剂、有机硅试剂等

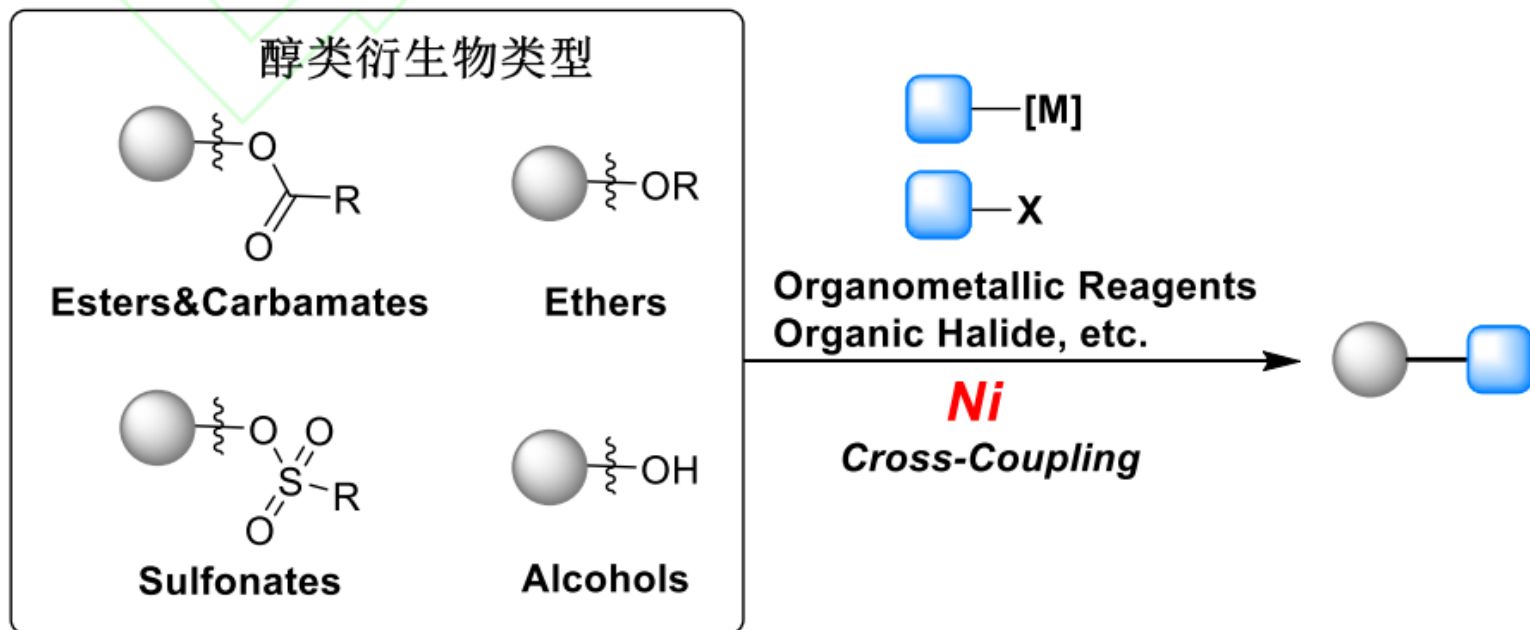
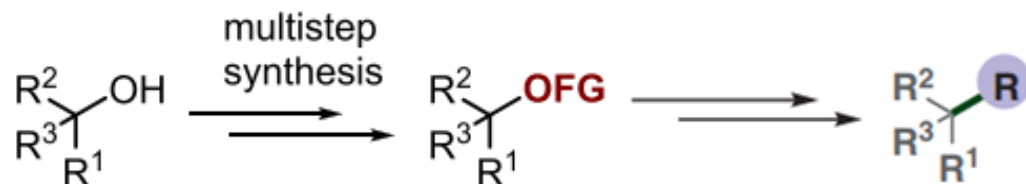
亲电试剂：卤代烃等



能否由醇化合物替代卤代烃？



## 传统醇的碳氧键活化一般策略





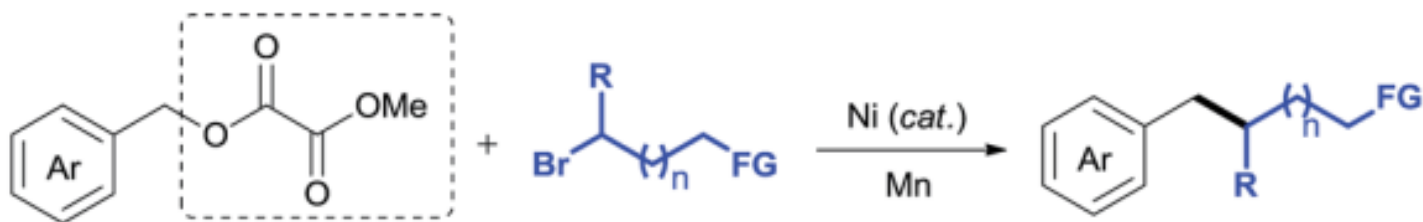
# 镍催化醇衍生物构筑C-C键的最新进展

## ➤ 镍催化剂的特点

- 储量丰富、价格便宜、环境友好；
- 镍原子半径较小，在偶联反应中C-Ni不易发生 $\beta$ -H消除反应，减少了副产物的生成；
- 镍的价态变化丰富，目前已经分离鉴定的镍化合物氧化态包括Ni(0)、Ni(I)、Ni(II)、Ni(III)、Ni(IV)。在催化交叉偶联反应中，既可能存在Ni(0)/Ni(II)双电子转移过程，也可能存在Ni(I)/Ni(II)/Ni(III)单电子转移过程。



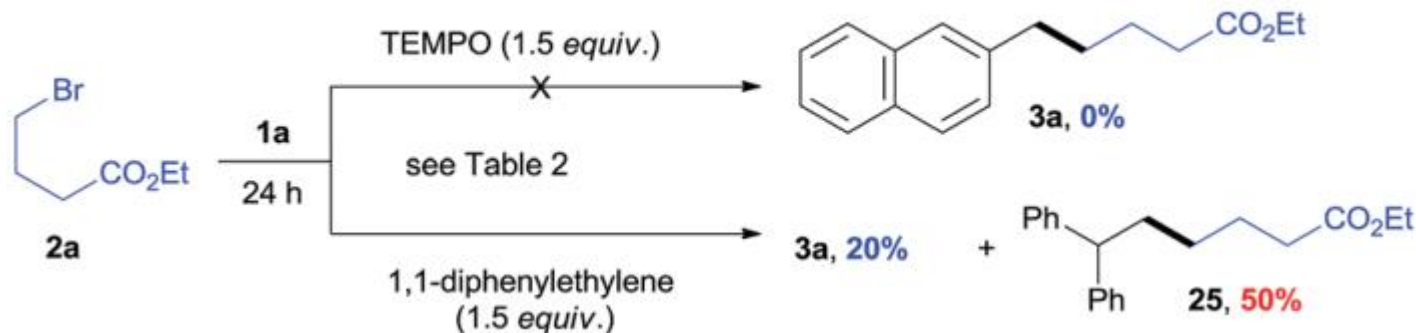
2018年，舒兴中课题组报道了镍催化草酸苄酯与烷基溴的交叉偶联反应



- *New leaving group*
- *Broad substrate scope*
- *1° and 2° alkyl bromides*
- *Highly functionalized alkyl groups (-Bpin, -CO<sub>2</sub>R, -CHO, -NHBoc, -OH etc.)*

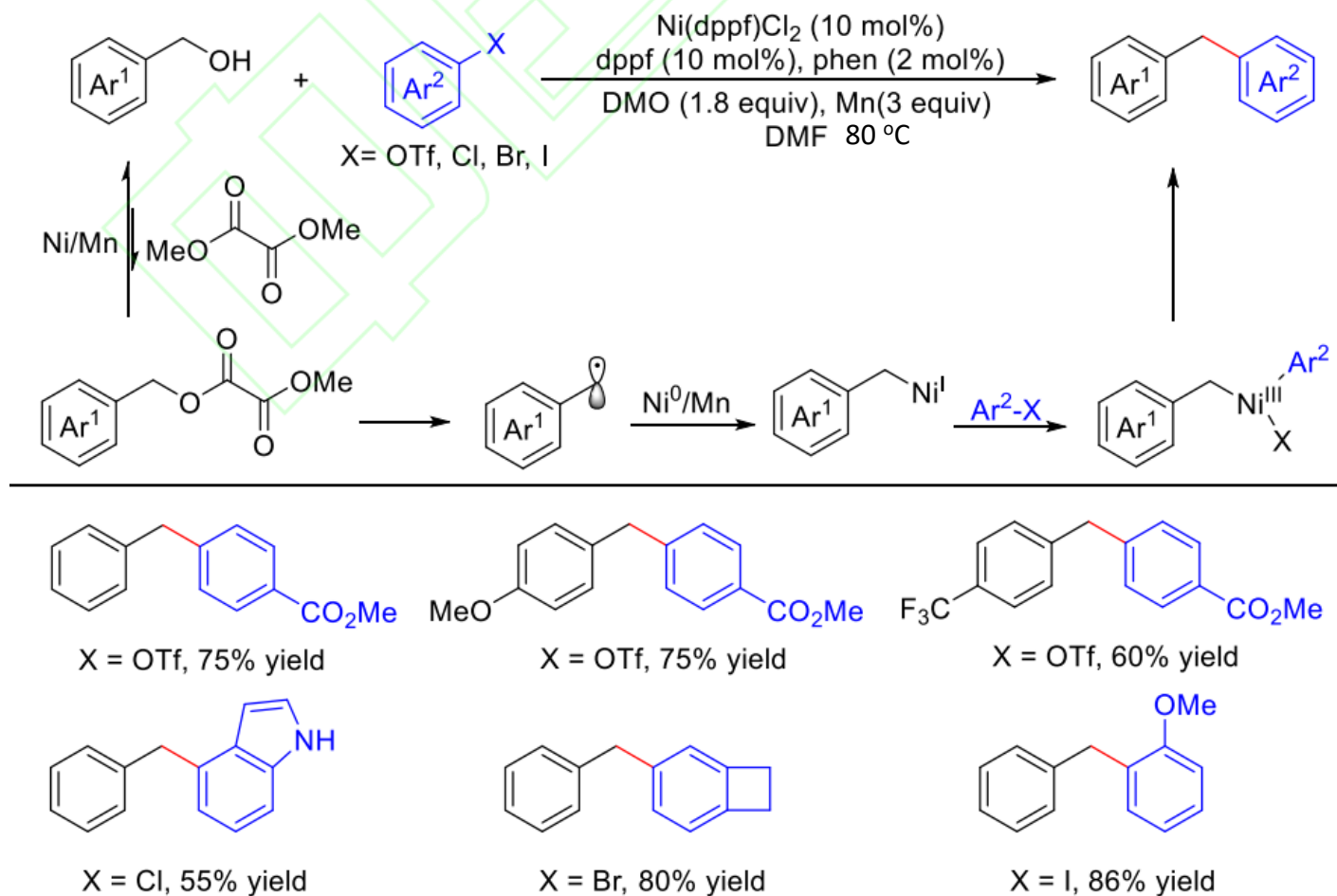
机理研究

Radical inhibition experiments



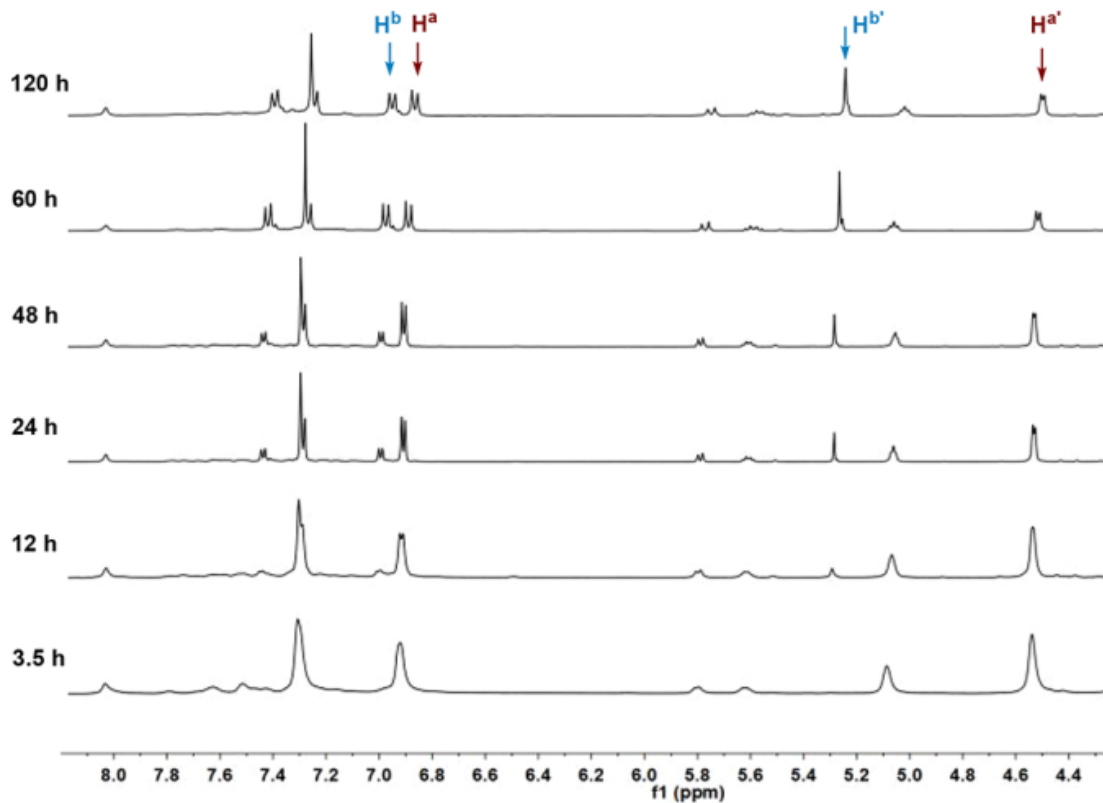
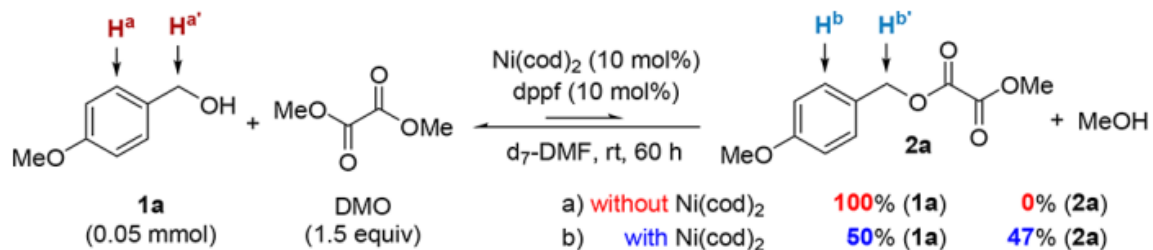


## Shu's work 2021





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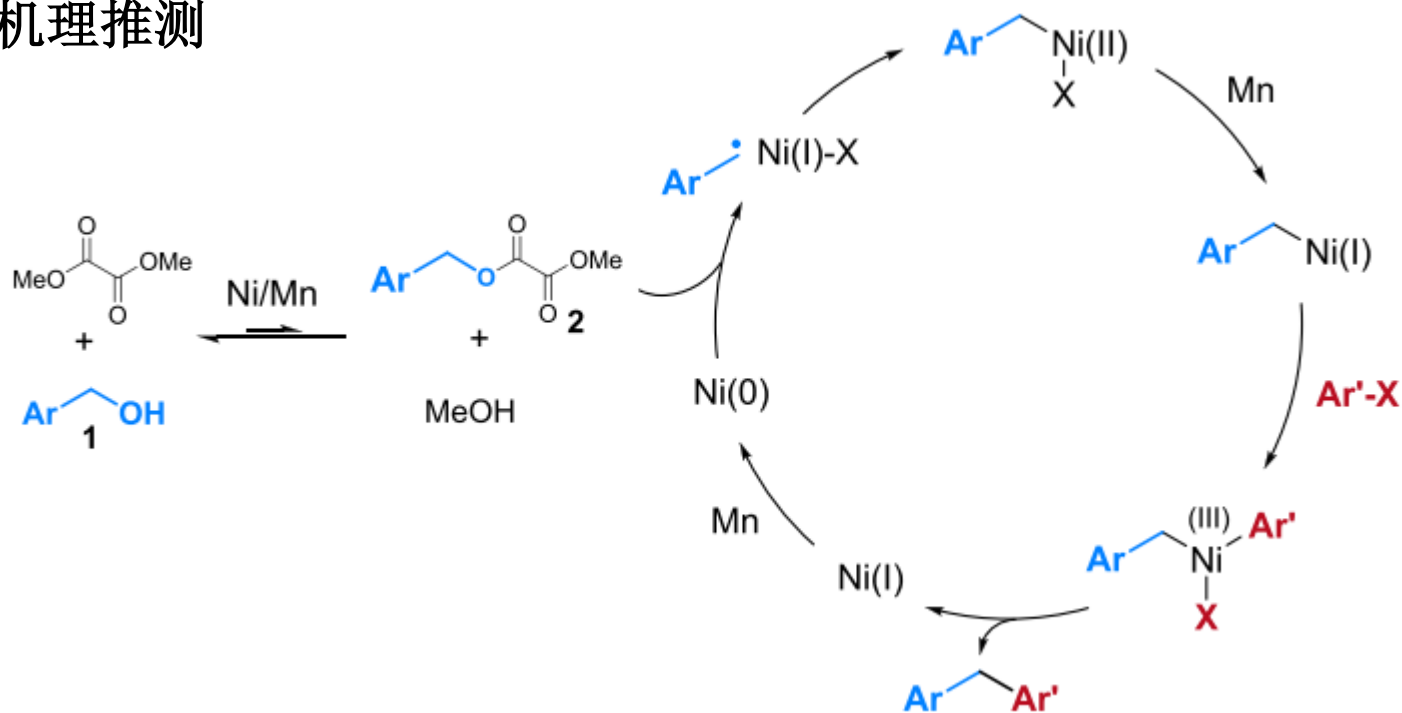


Ni (0) 催化醇与草酸

酯的酯交换反应



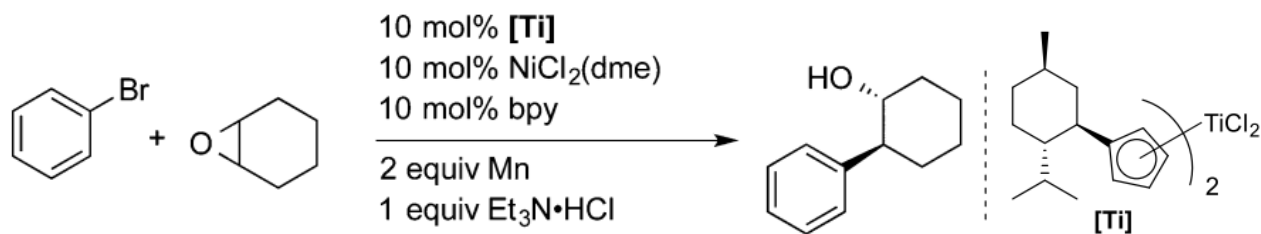
## 机理推测



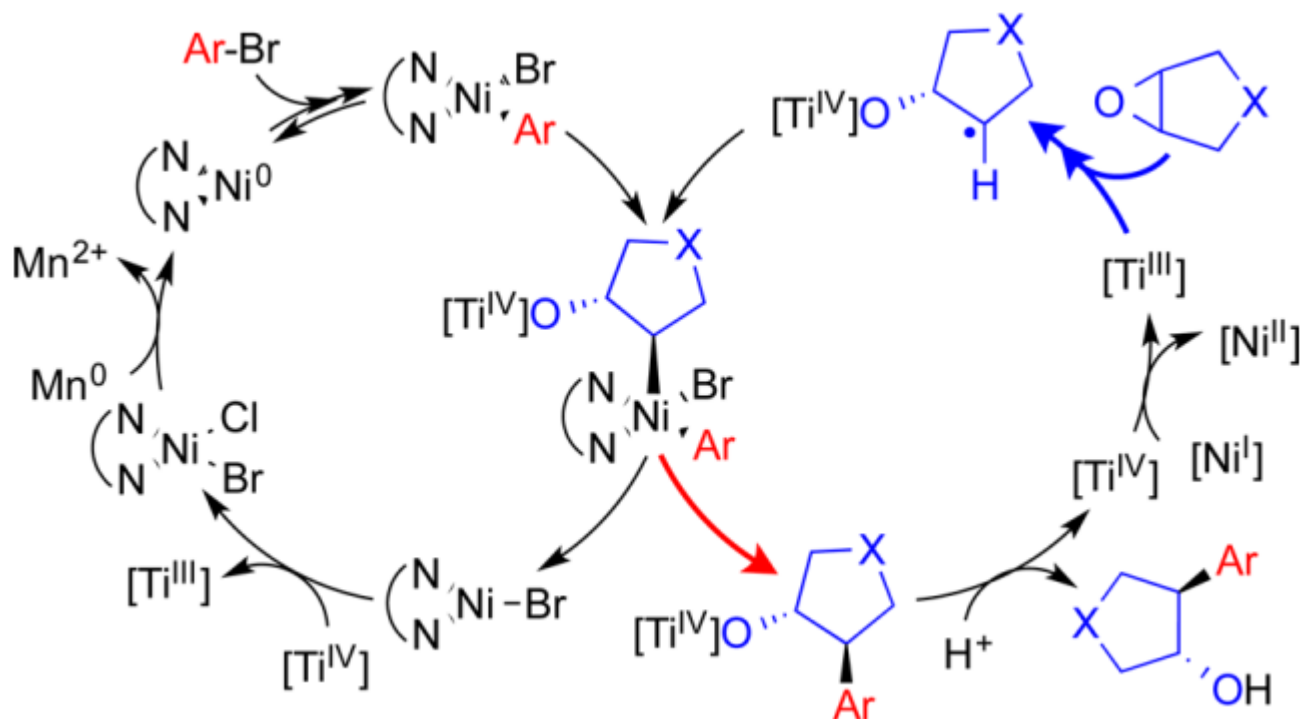
锰镍催化醇与草酸酯发生酯交换反应得到草酸苄酯。草酸苄酯受热分解产生苄基自由基，自由基与Ni(0)反应，然后被Mn还原，得到Ni(I)。Ni(I)中间体与芳基卤化物氧化加成，最后通过还原消除得到所需的偶联产物。



## 2015年, Weix课题组环氧乙烷与芳基卤化物的不对称交叉偶联反应



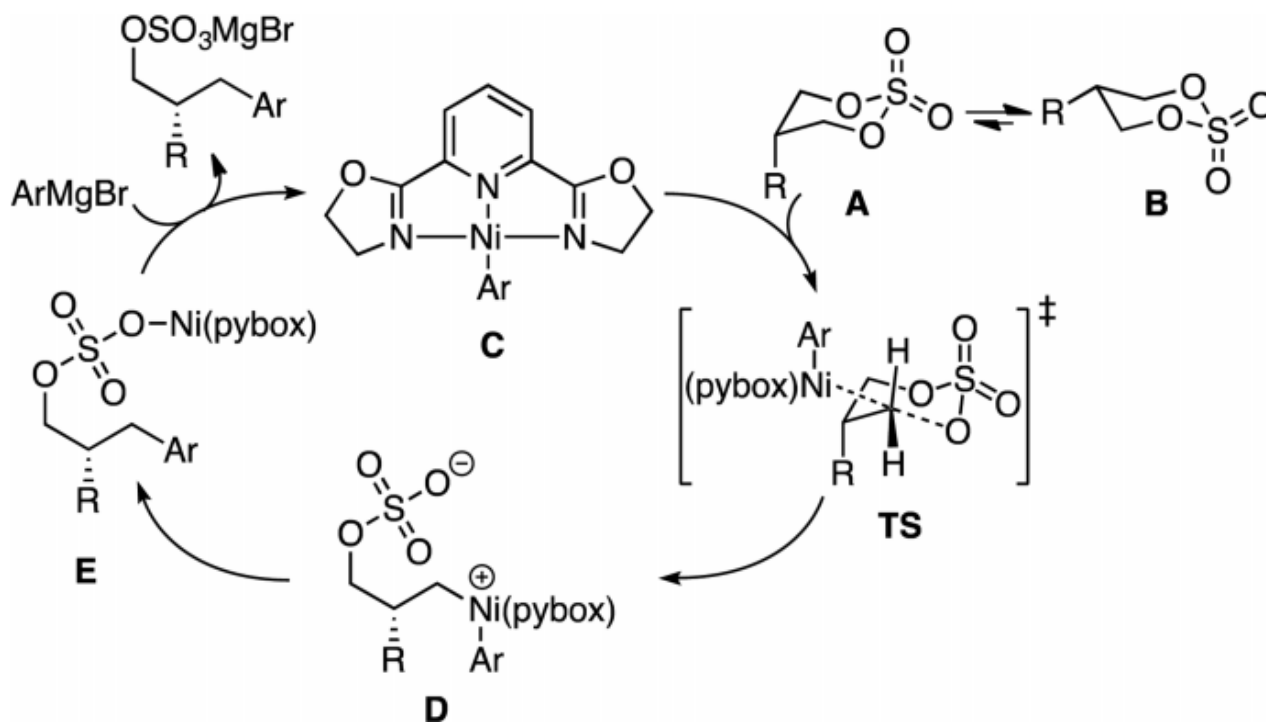
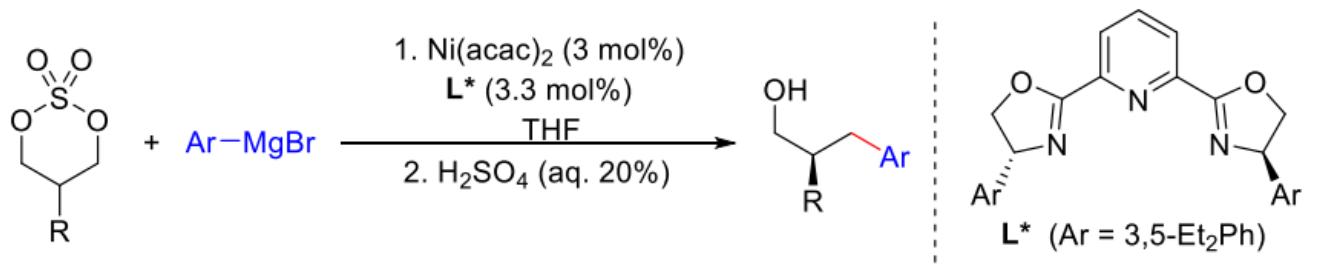
二价镍  
+  
手性茂钛



反应的关键步骤是  
由内消旋环氧化物  
对映选择性地形成  
 $\beta$ -钛氧碳自由基



## 2016年, Morken 课题组报道镍催化环状硫酸酯与格氏试剂的偶联反应







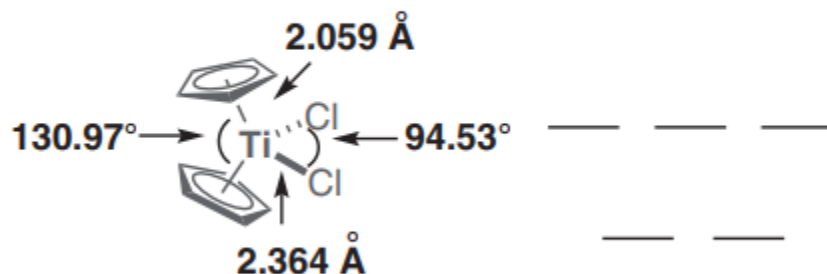
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# 钛配合物介导的醇自由基脱羟基官能化反应

**含量：**地壳中元素排行：氧、硅、铝、铁、钙、钠、钾、镁、氢、钛；  
地壳中钛含量达千分之六，比铜多61倍。

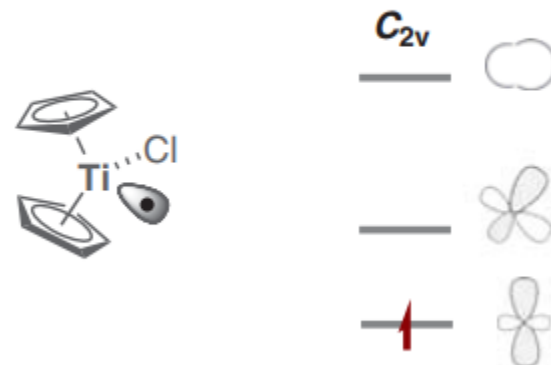
**特点：**钛配合物对氧极其敏感，稳定的有机钛配合物难以分离。1954年，Wilkinson和Birmingham首次制备了 $Cp_2TiCl_2$ 配合物。钛配合物通常以Ti(IV)存在，被还原的Ti(III)配合物极不稳定，反应性强，通常以二聚体和单体的动态平衡状态存在。

**a** Fundamental parameters of  $Cp_2TiCl_2$



16-electron  $d^0$  Ti(IV)

**b** Fundamental parameters of  $Cp_2TiCl$



15-electron  $d^1$  Ti(III)

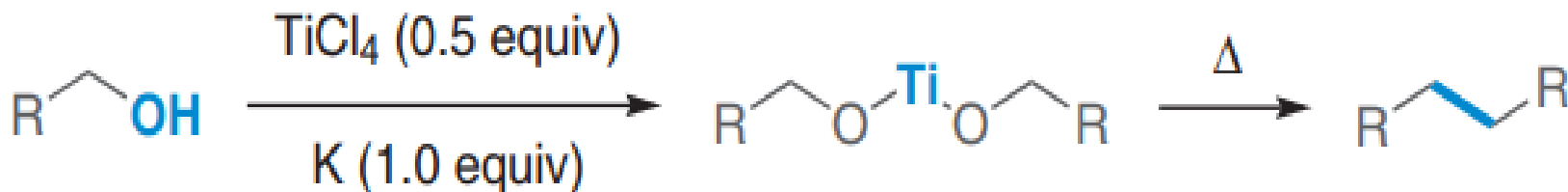
Wilkinson, G.; Birmingham, J. M. *J. Am. Chem. Soc.* **1954**, 76, 4281.

Enemærke, J. R.; Larsen, J.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, 126, 7853.



## 化学计量钛配合物介导醇的均裂

1965年，Schwartz首次报道钛活化醇类化合物的反应

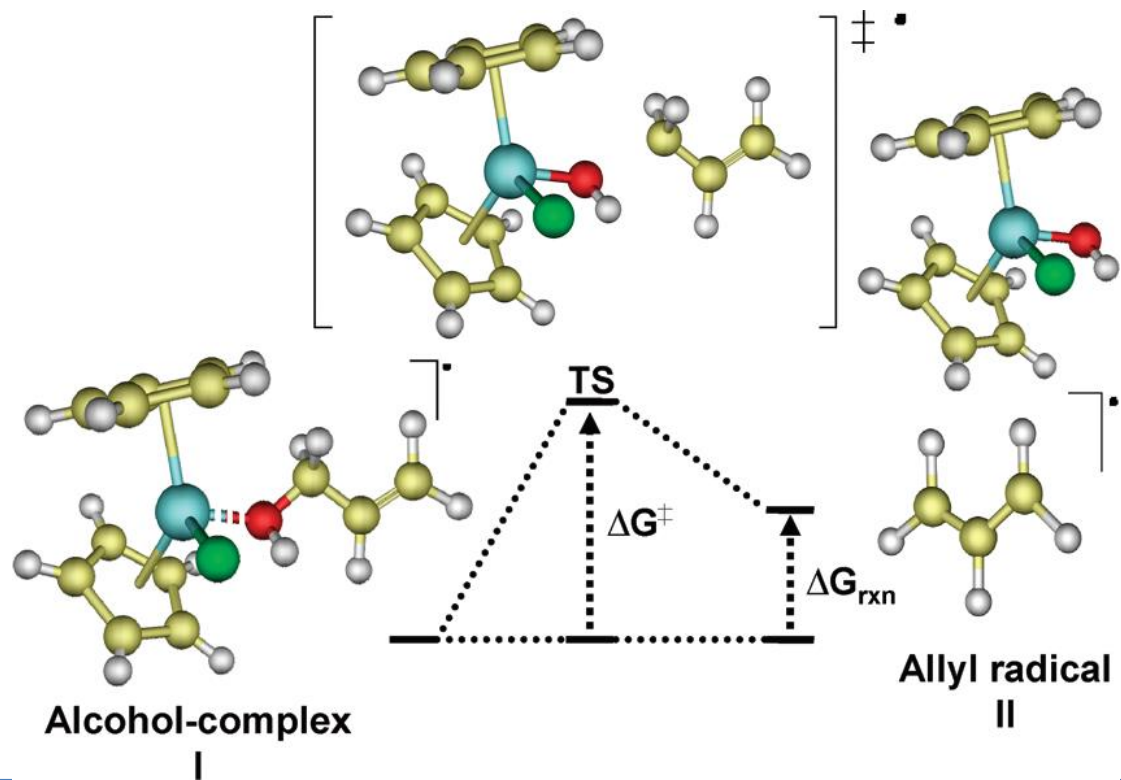
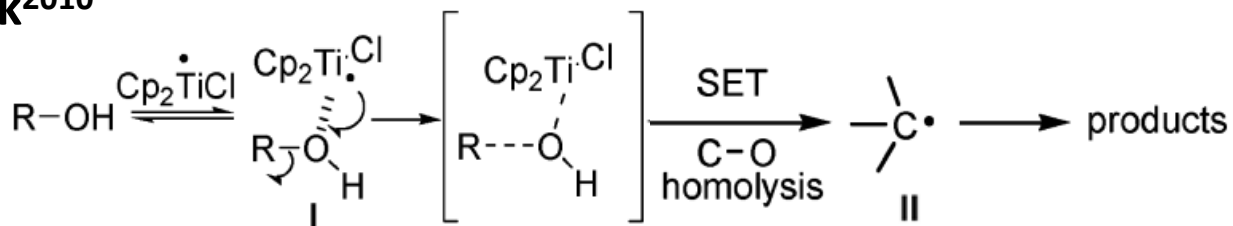


- Benzylic alcohol: 51% yield; allylic alcohol: 38% yield

可能涉及自由基类型的分解

# 化学计量钛配合物介导醇的均裂

Barrero's work<sup>2010</sup>



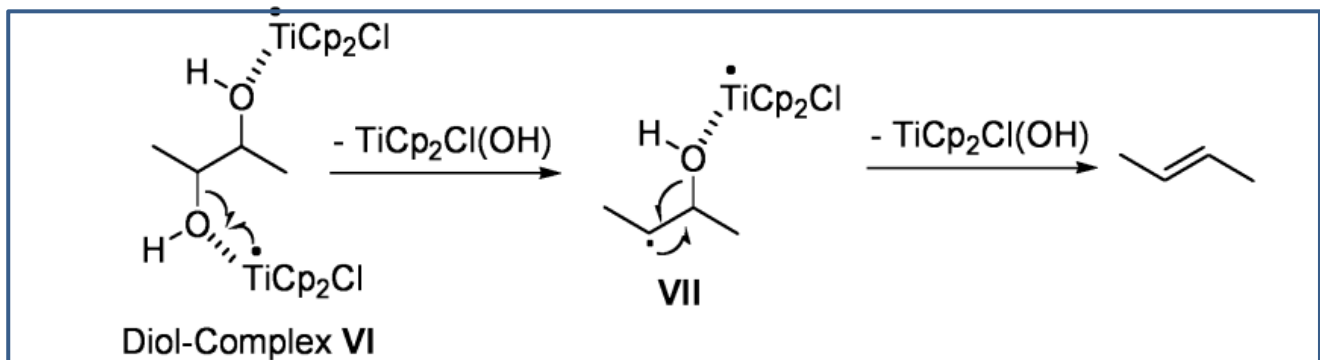
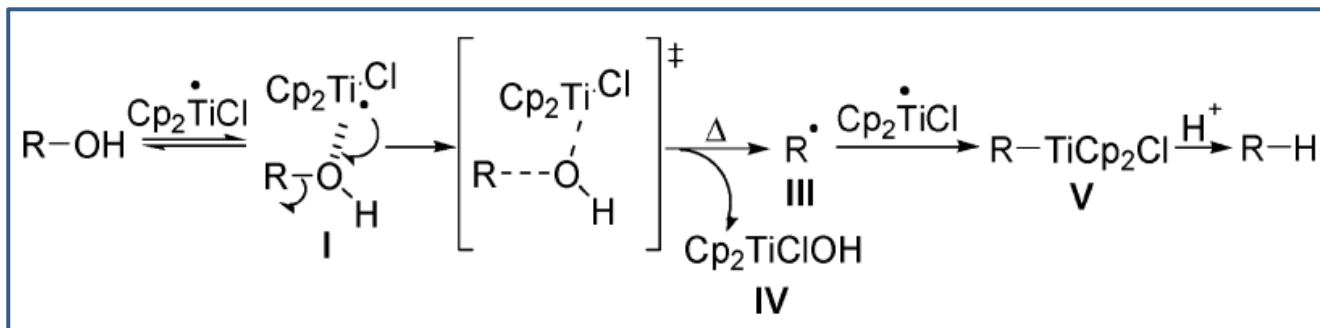
**Ti(III)配合物可有效地降低C-O键均裂的活化能**



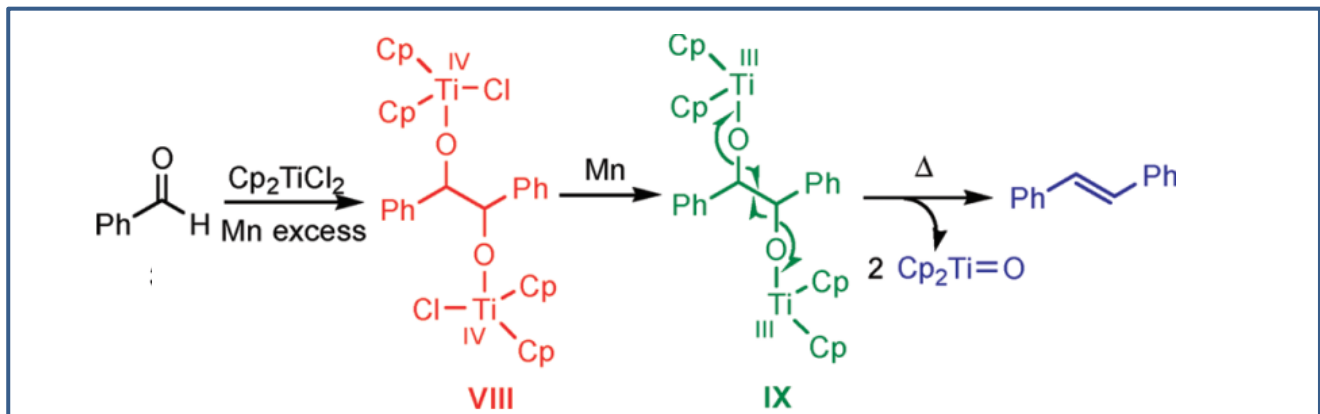
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➤ 脱羟基还原:

- 苕基醇
- 烯丙基醇
- 频哪醇

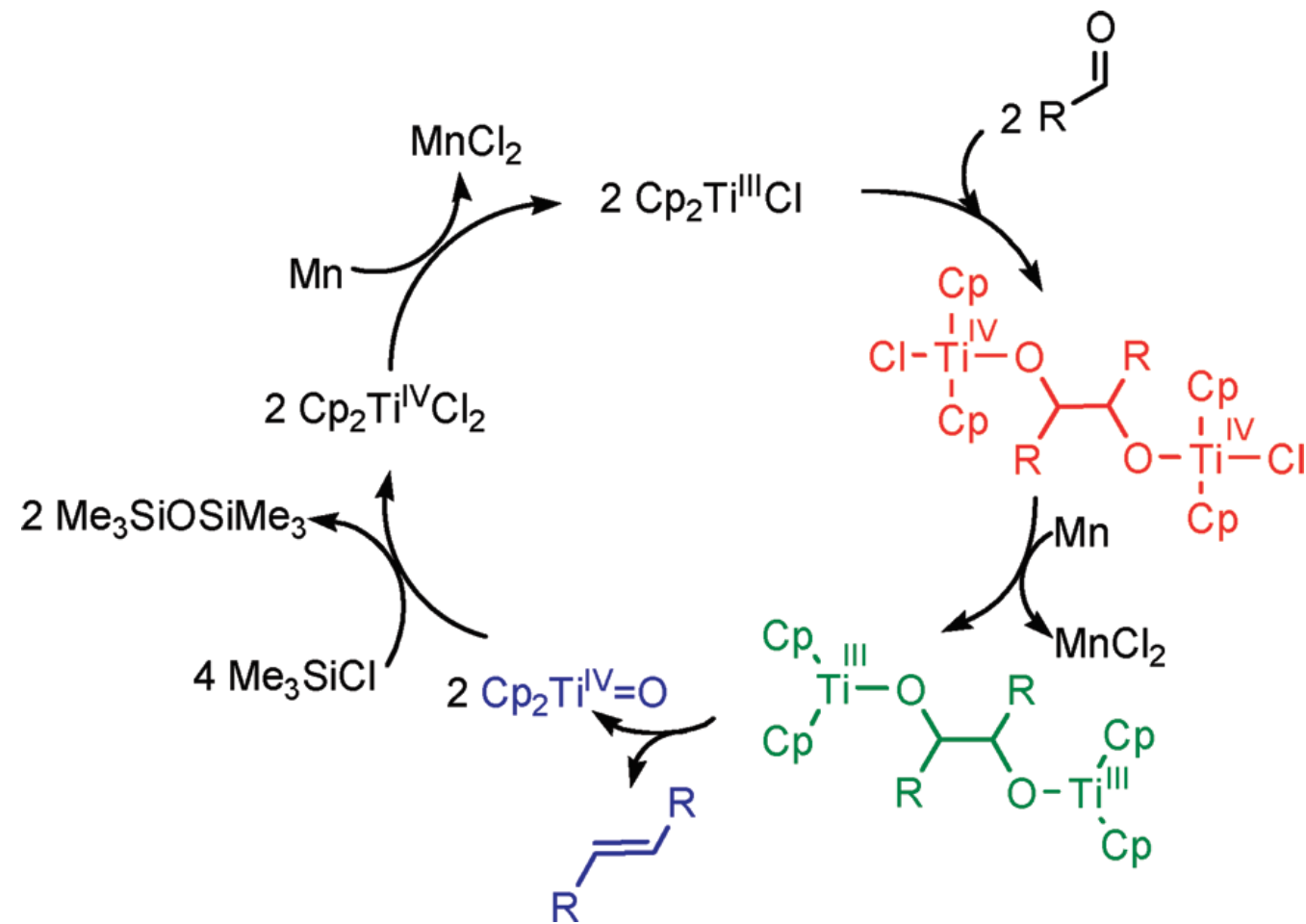


➤ 羰基偶联成烯:





# 如何使用催化量的钛完成该反应？



**TMSCI**

添加比例:

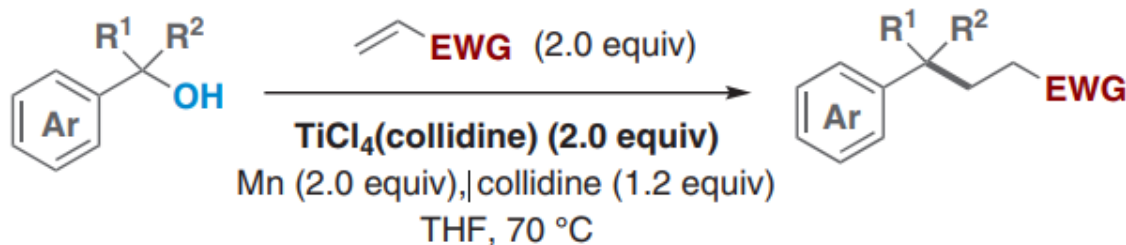
Ti (0.3 eq)

TMSCI (0.3 eq)

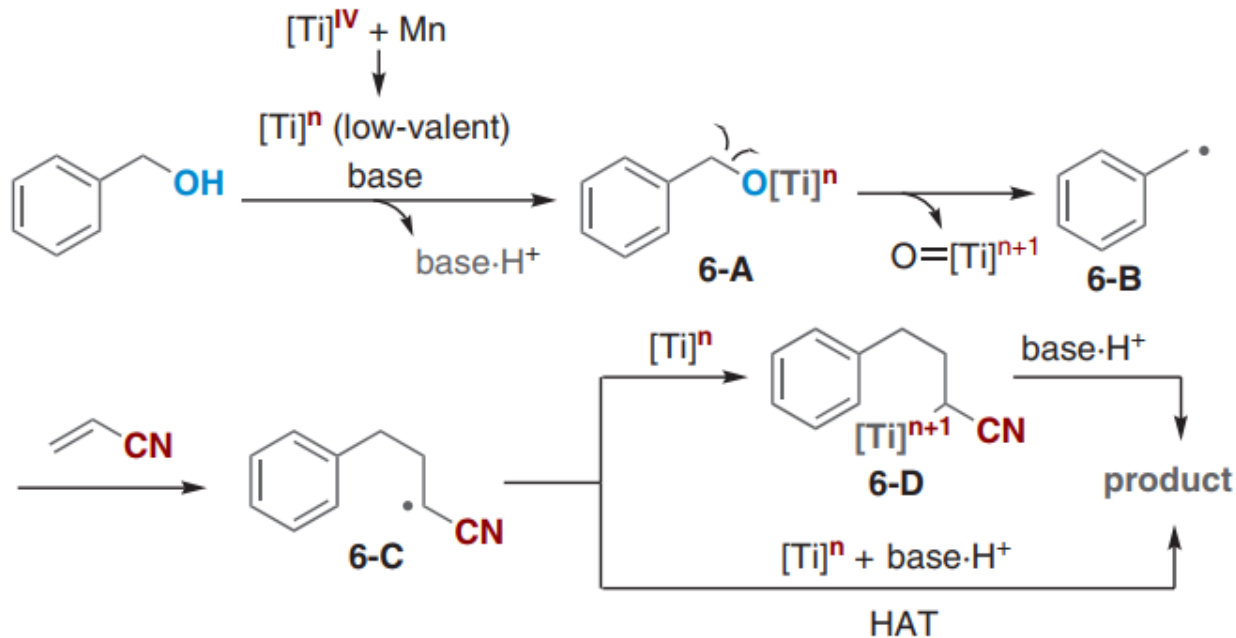


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# 化学计量钛配合物介导醇的均裂



## Proposed mechanism

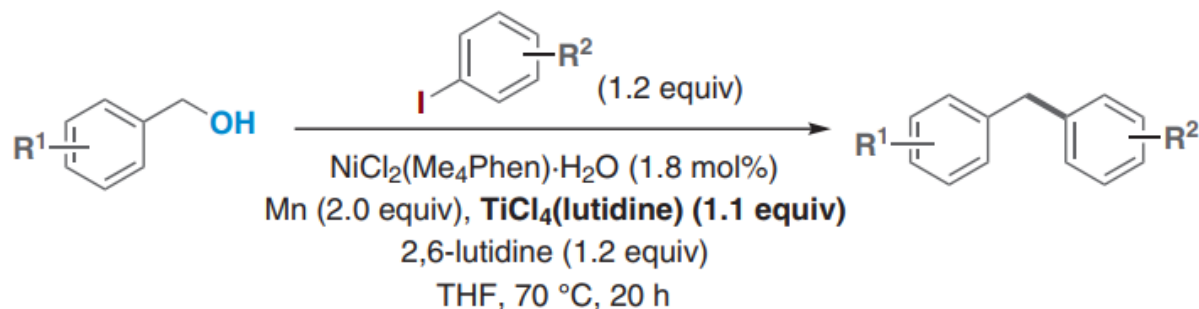


质子化途径:

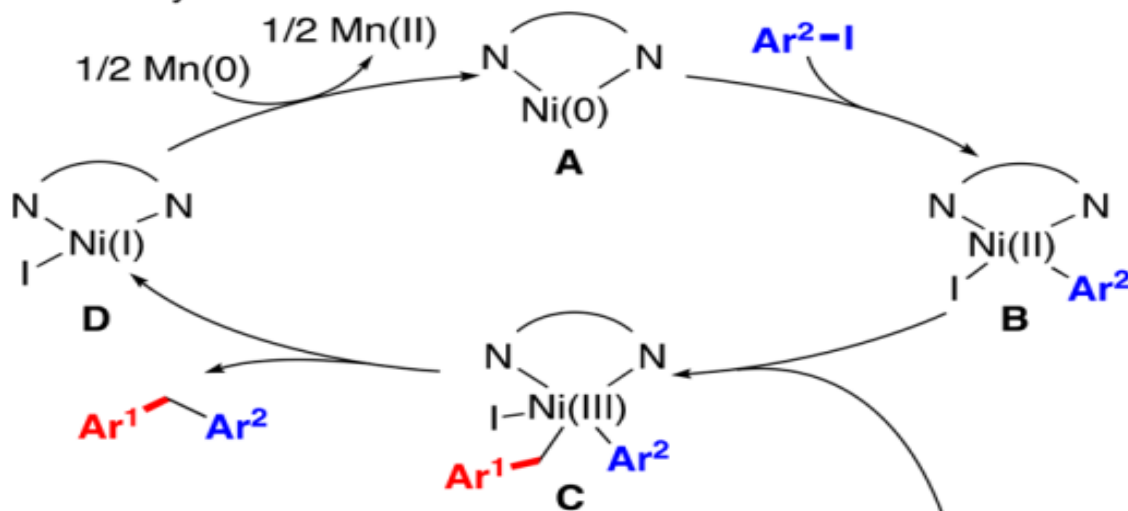
- 低价钛辅助质子化;
- 直接氢原子转移 (HAT)



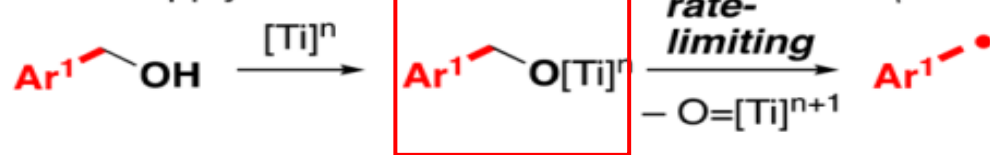
# 化学计量钛配合物介导醇的均裂



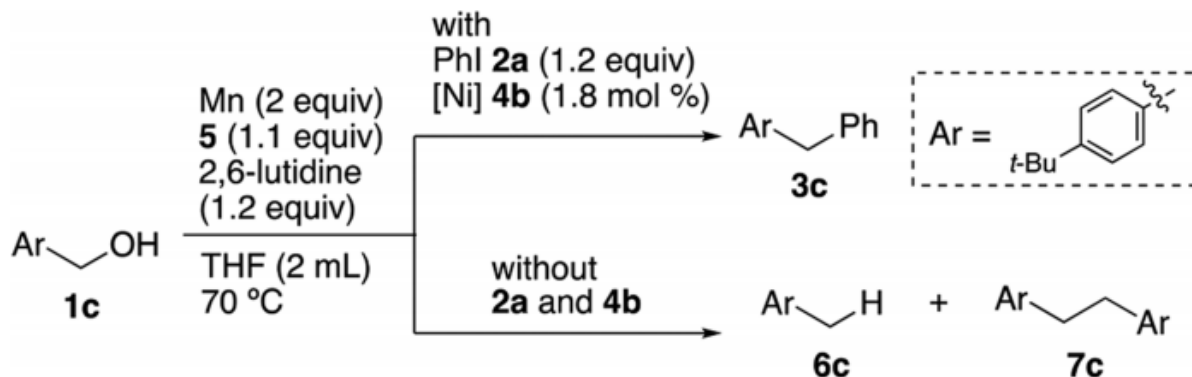
Ni catalysis:



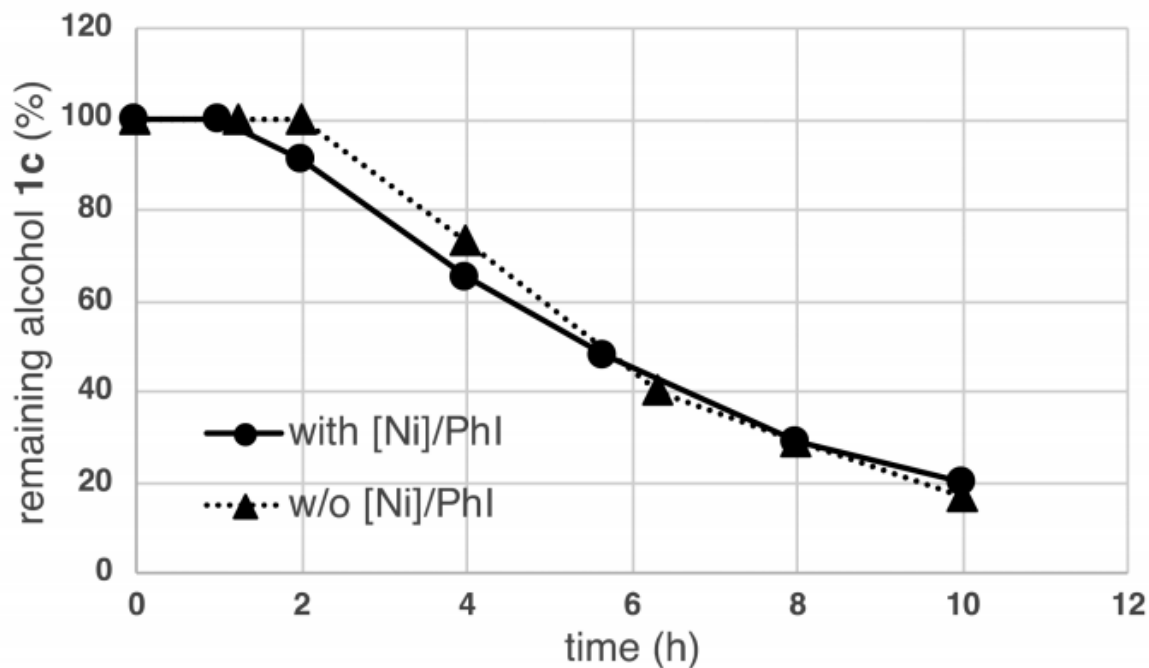
Radical supply:



ArCH<sub>2</sub>O[Ti] 是否有可能以氧化加成的方式参与催化循环中?



[Ni]	NMR yield (%)	
	<b>1c</b>	<b>3c</b>
1.8	65	40
9	65	35

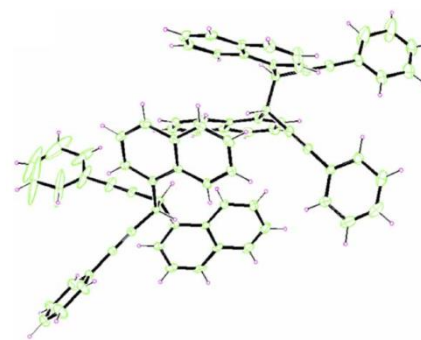
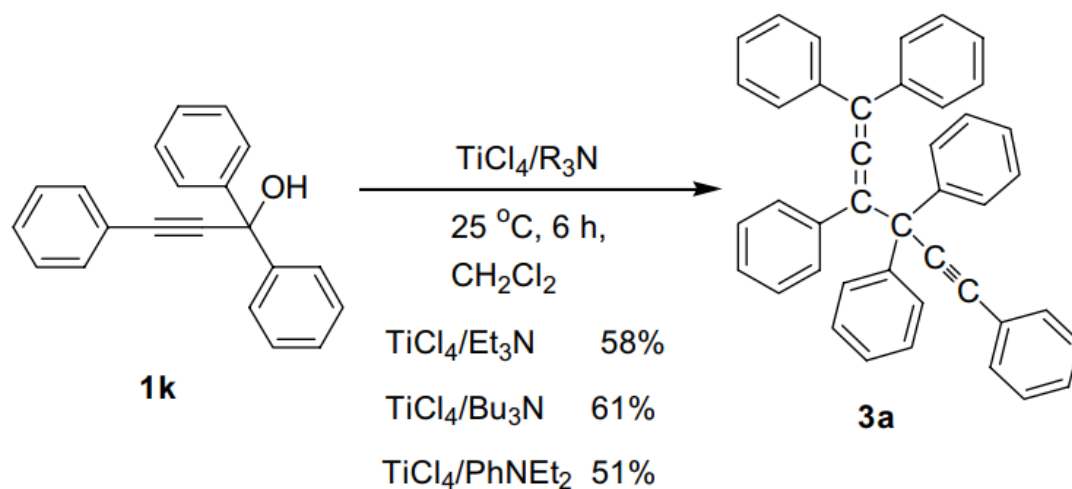
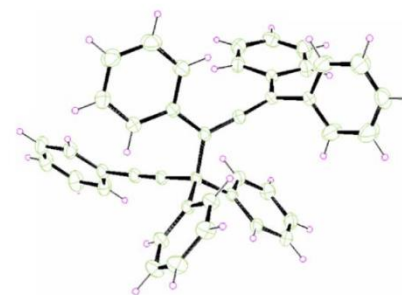
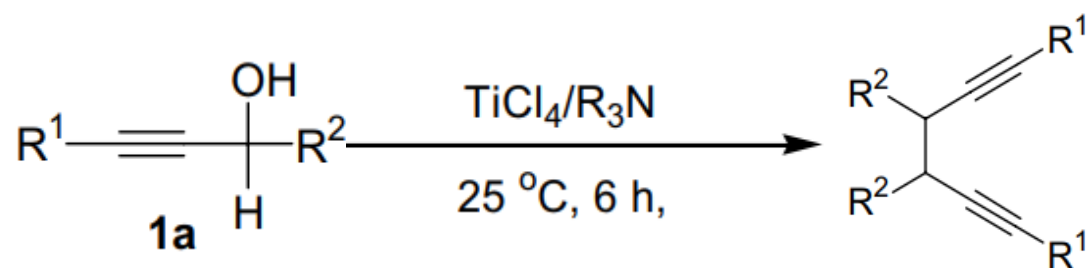


Ni催化剂的有无既不影响反应的速率，也不影响反应的收率，表明反应速率仅取决于 $\text{ArCH}_2\text{O}[\text{Ti}]$ 的自分解，Ni不参与CO键断裂步骤。



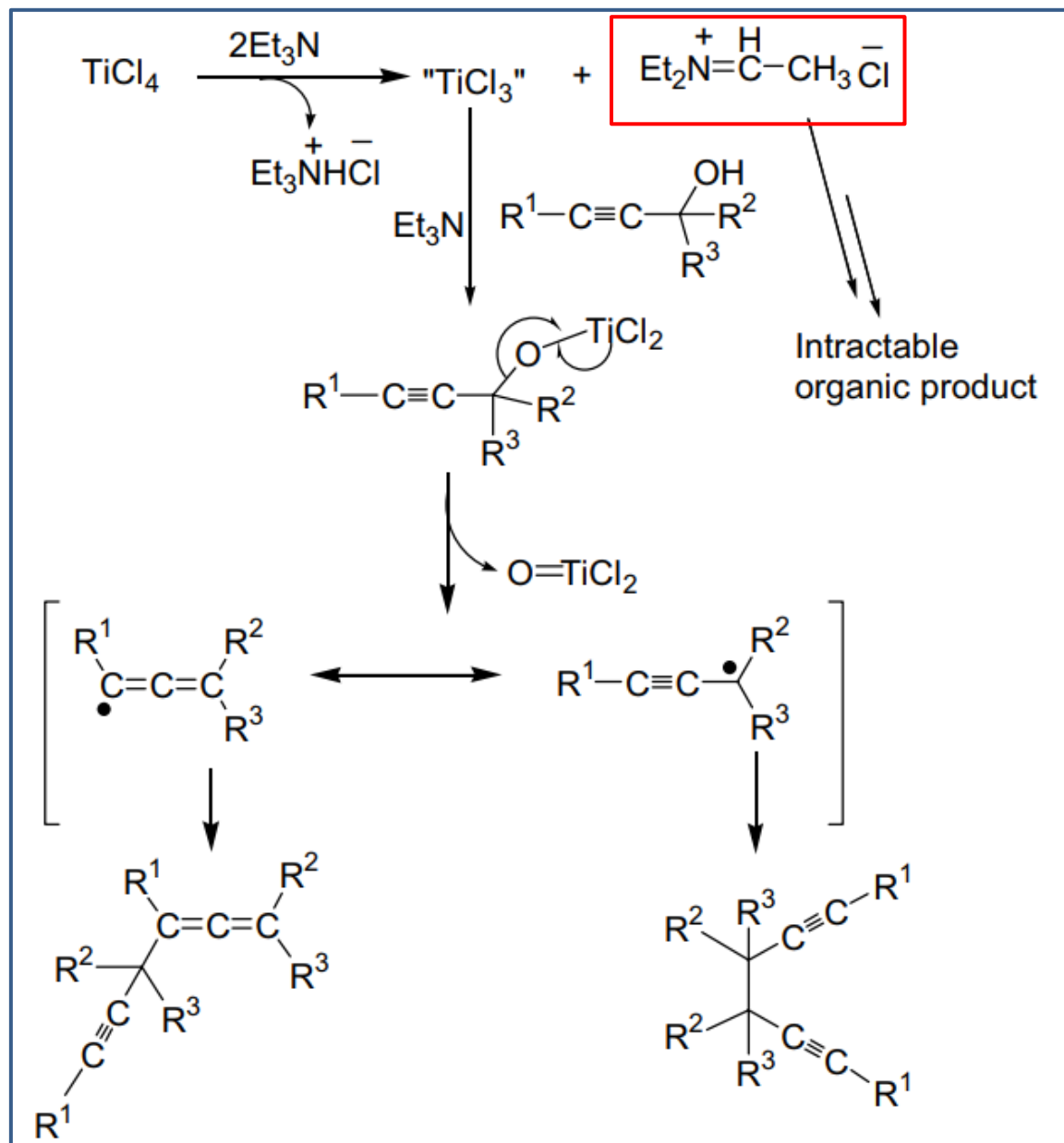


2006年, Periasamy 用  $\text{TiCl}_4/\text{Et}_3\text{N}$  体系将炔丙醇转化为对称的1,5-二炔化合物





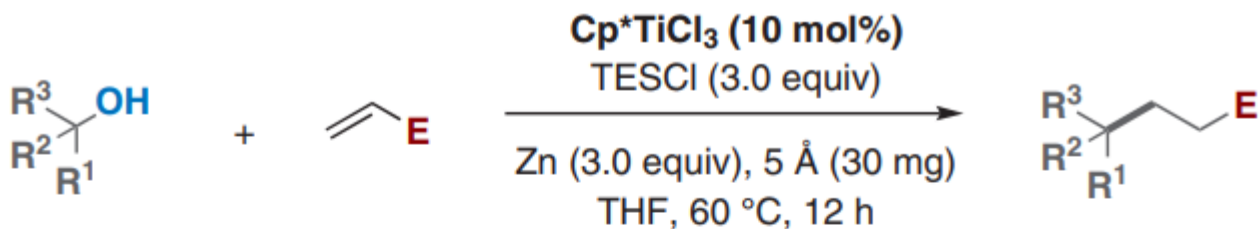
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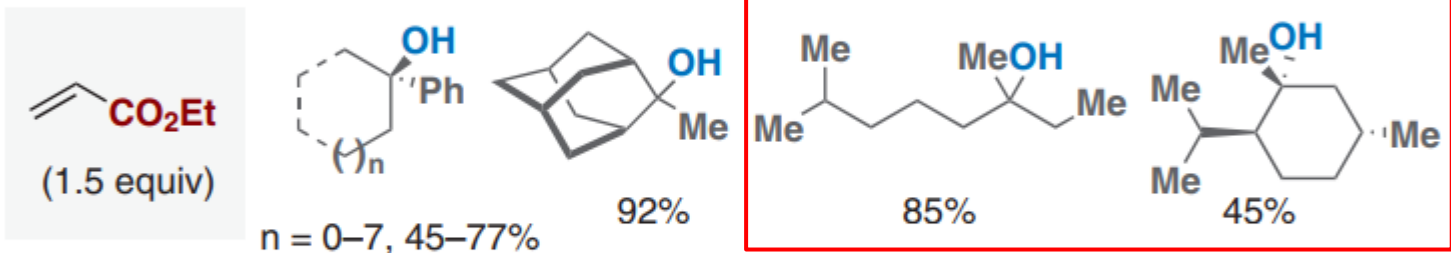


# 催化计量钛配合物介导醇的均裂

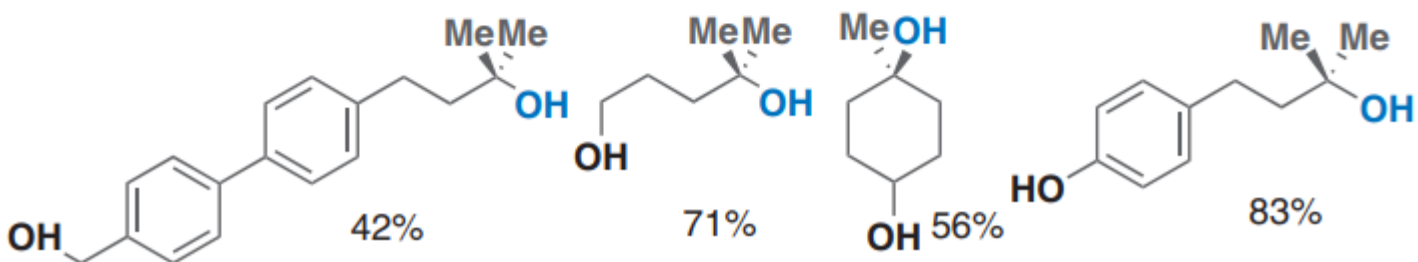
2021年，舒兴中组报道了钛催化叔醇自由基脱羟基烷基化

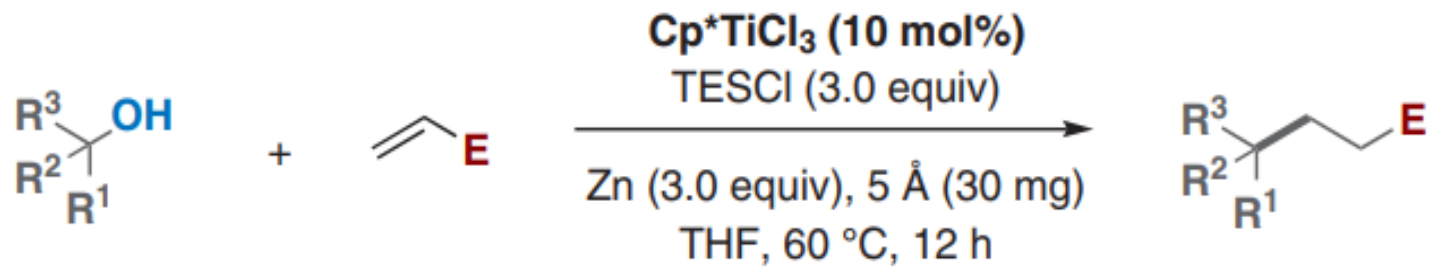


## Tertiary alcohols

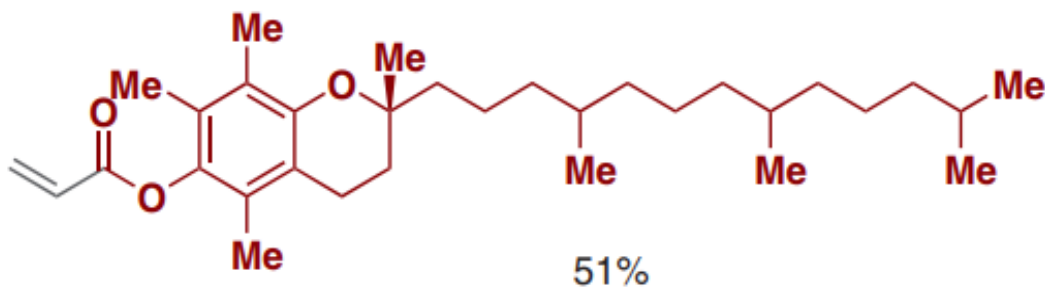
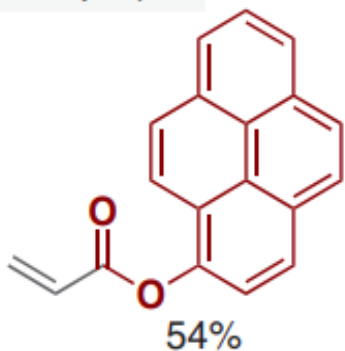
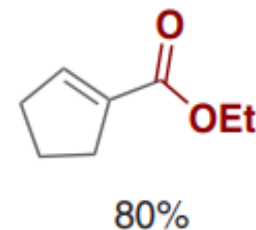
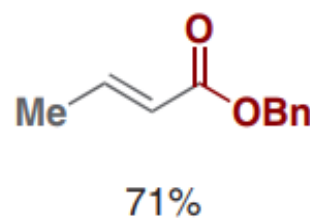
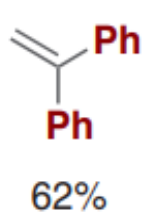
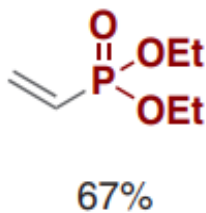
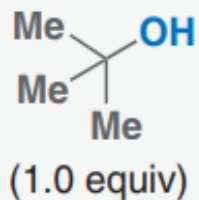


## Selective alkylation of diols





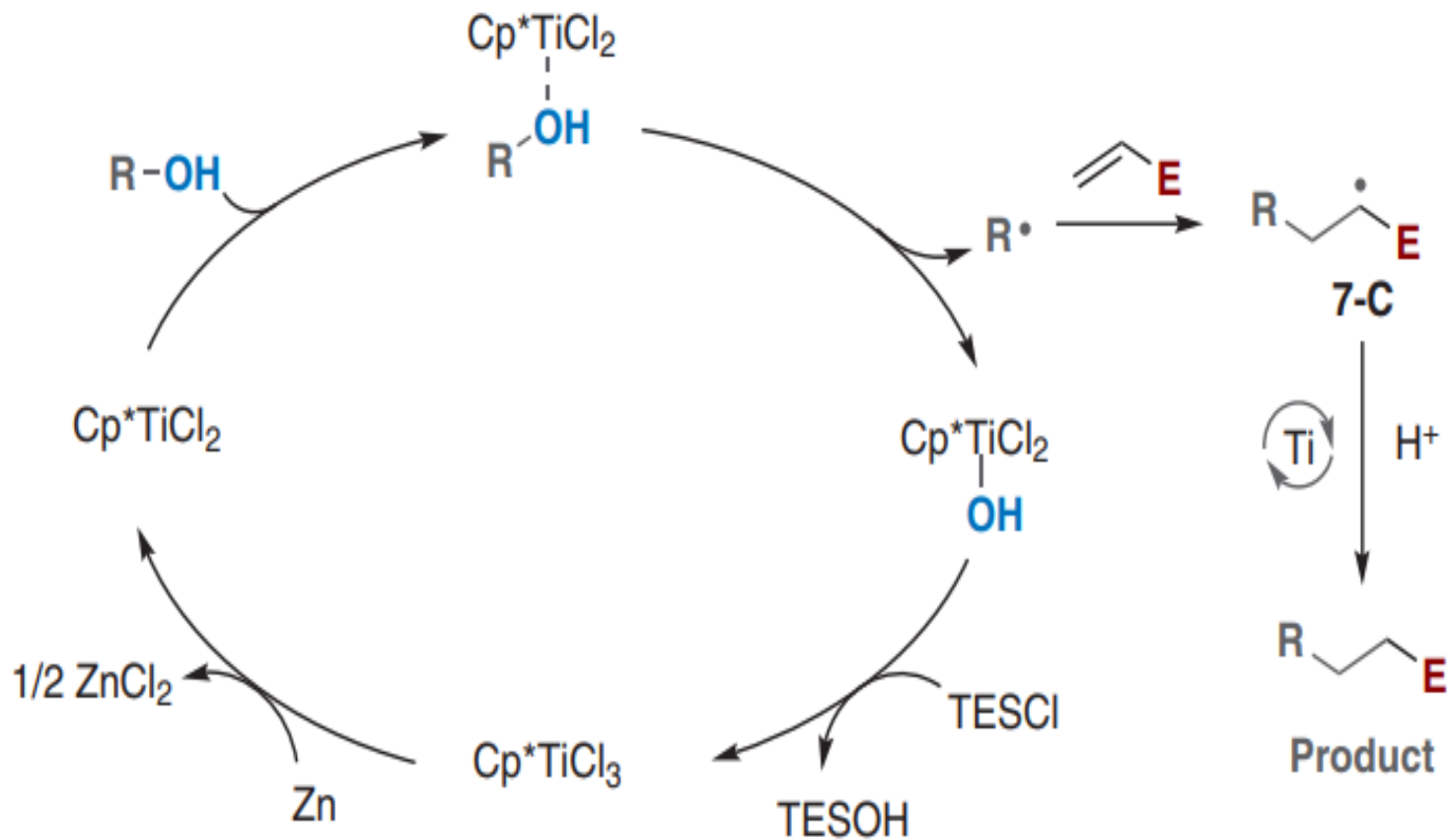
## Activated alkenes





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## ■ Proposed mechanism





# 总结与展望

## ➤ 总结

- 镍催化醇衍生物构筑C-C键已经实现各种官能化反应（芳基化、烷基化、烯基化等）；
- 低价钛配合物在醇自由基脱羟基反应中具有独特的应用价值（还原反应和迈克尔加成反应）。

## ➤ 展望

- 开发新的催化体系（新型还原试剂、通用的钛配合物、温和的反应温度）；
- 拓展醇的底物范围，尝试未活化烯烃；
- 醇的自由基脱羟基官能化仍需探索。



Thanks for your attention!