

钴催化 $C(sp^2)-C(sp^3)$ Suzuki-Miyaura 偶联反应及机理研究

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20231208

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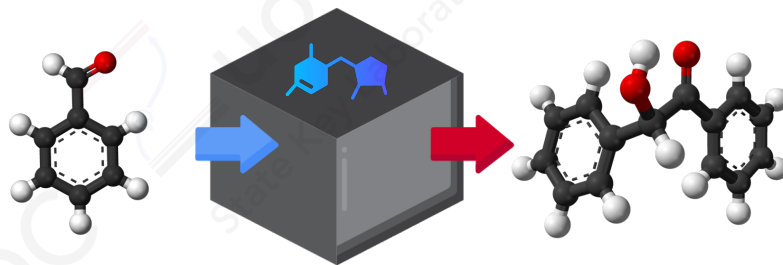
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促进对类似反应的认识

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仅能被证伪不能被证明

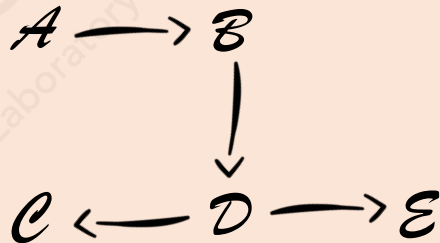
合理的机理可能不止一种



◆ 缺乏表征手段

◆ 分离中间体和副产物

◆ 稳定性的分析和推理



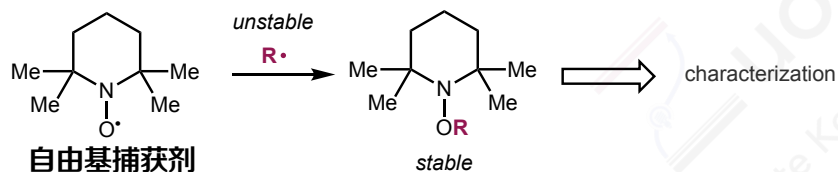
◆ 理论基础的发展

◆ 先进的表征手段

◆ 研究方法形成定式

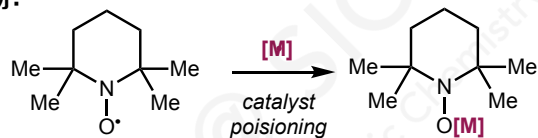


■ 自由基捕获

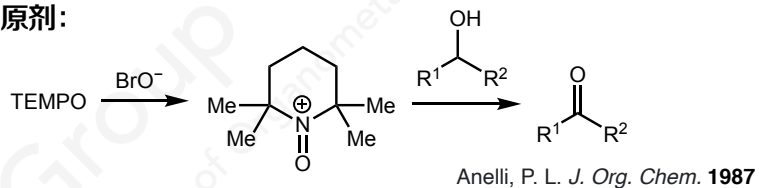


TEMPO抑制反应能否说明为自由基过程?

催化剂毒物:

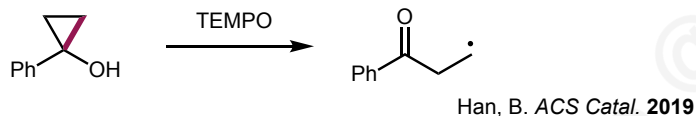


氧化/还原剂:

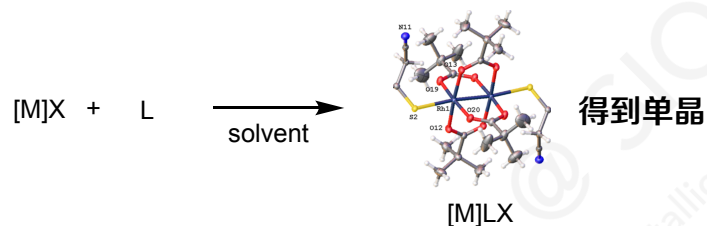


捕获到自由基能否说明由催化体系产生?

自由基引发剂:

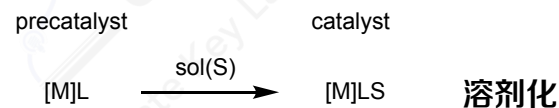


■ 单晶衍射



[M]LX:

催化剂?
 活性物种?
 预催化剂

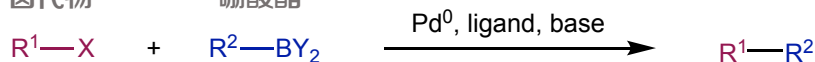


如何进行机理实验的设计? 如何阅读文献中的机理研究?

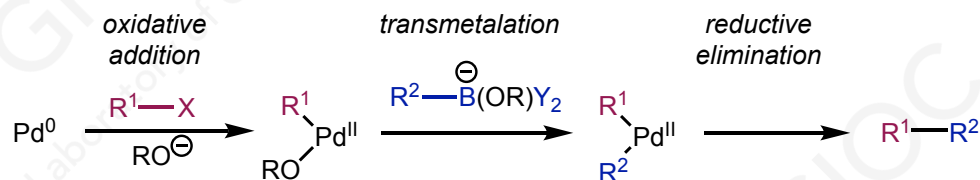
Suzuki-Miyaura偶联反应

全氟磺酸
卤代物

硼酸
硼酸酯



A. Suzuki, 1979.

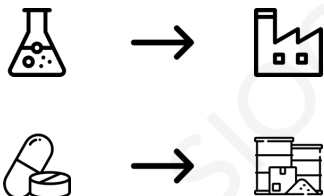


◆ 很好的底物适应性

◆ 很好的官能团容忍性

◆ 对水不敏感

◆ 底物获取非常容易

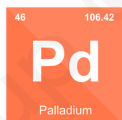


◆ 配体低于3当量容易产生钯黑

◆ 需引入羟基和碱用于活化硼酸

◆ 配体高于4当量降低反应效率

◆ 形成的硼酸盐活性是硼酸的 10^6 倍

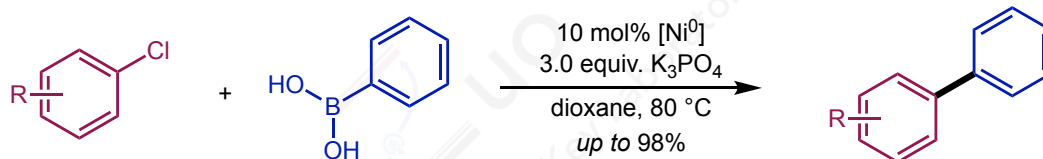


◆ 昂贵、稀缺

◆ 生产带来污染

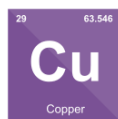
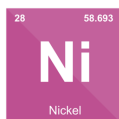
◆ 铂族生物毒性

◆ 监管严格

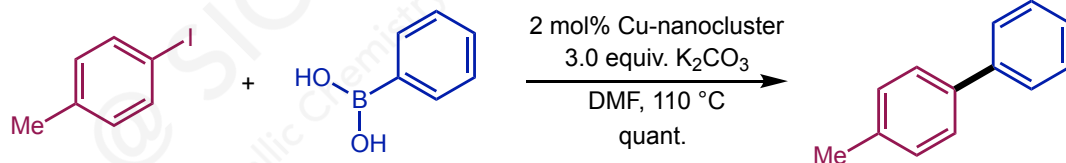


$[Ni^0]$: $NiCl_2(dppf) + 4 \text{ equiv. } ^tBuLi$ *in situ*

N. Miyaura, et al. *Tetrahedron Lett.*, **1996**, 37, 2993.



第一排过渡金属



G. Rothenberg, et al. *J. Am. Chem. Soc.*, **2002**, 11858.

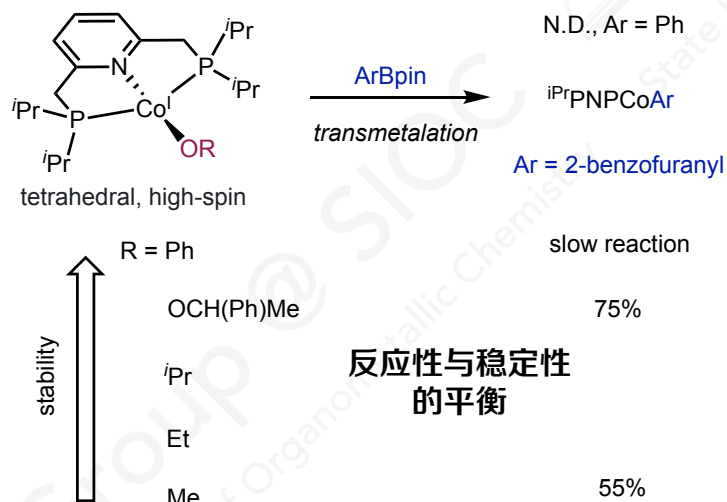
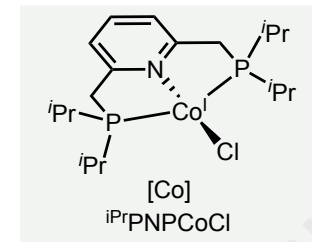
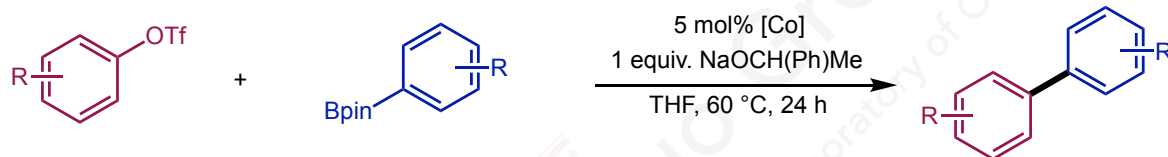
◆ 地壳丰富

◆ 不易发生 β -氢消除

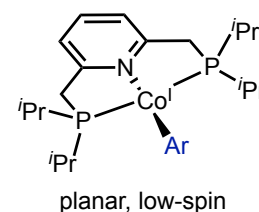
◆ 毒性较小

◆ 转金属化活性低

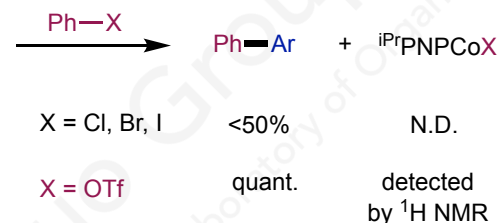
PNP-Pincer-钴配合物催化的Suzuki-Miyaura偶联反应



转金属化产物

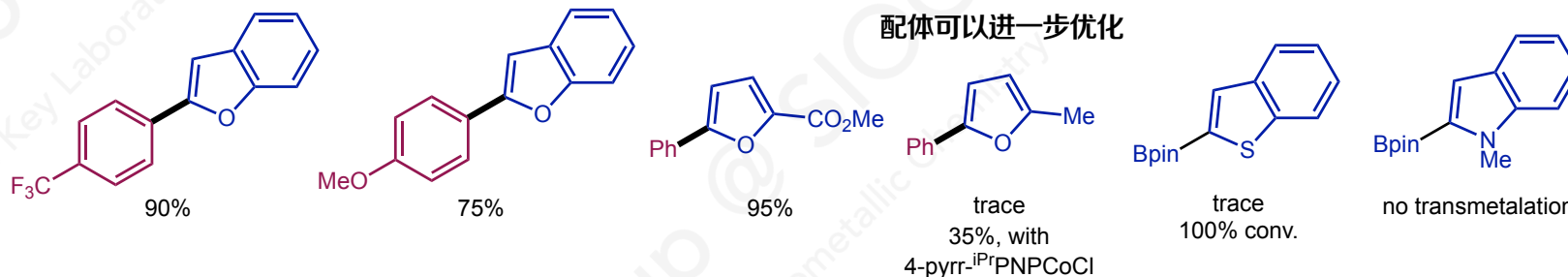


高低自旋态一价钴物种快速相互转化

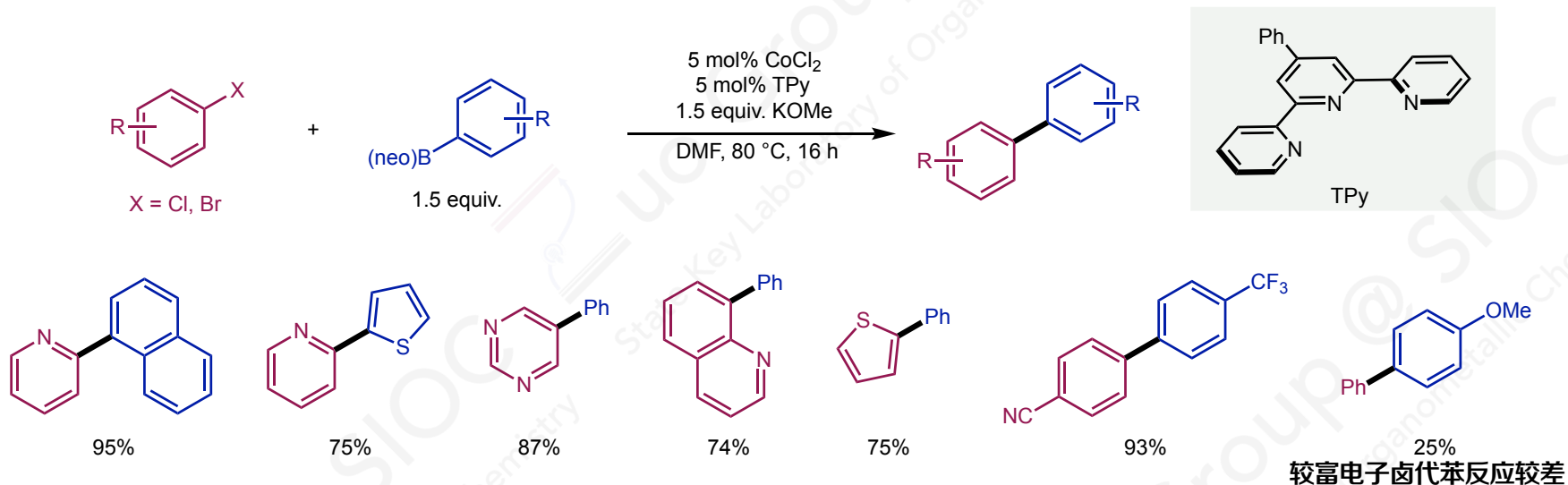


反应性与稳定性的平衡

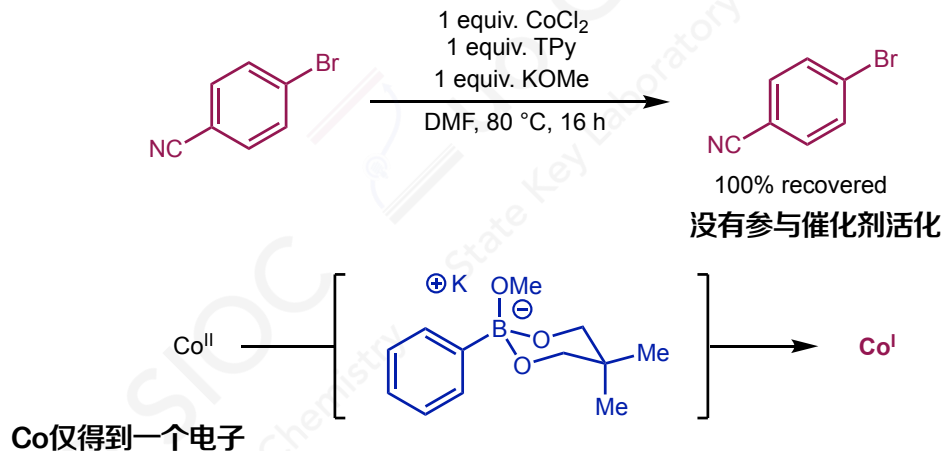
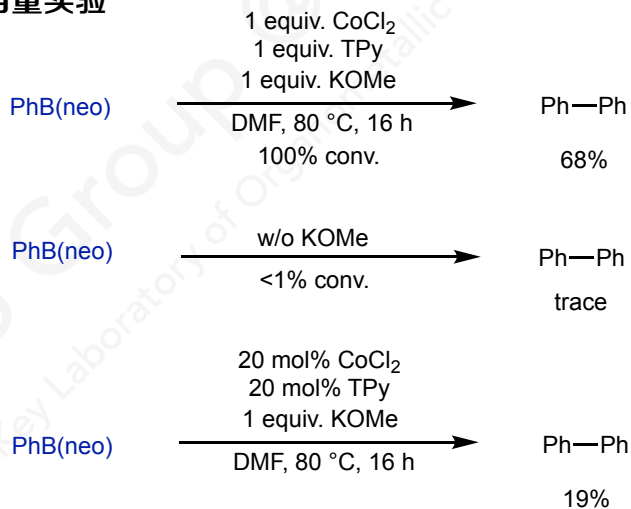
配体可以进一步优化



Tpy-钴配合物催化的Suzuki-Miyaura偶联反应

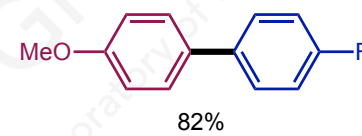
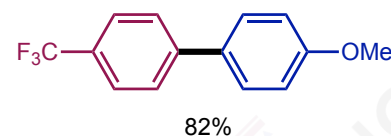
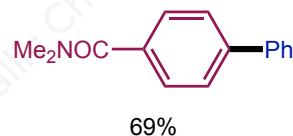
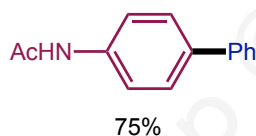
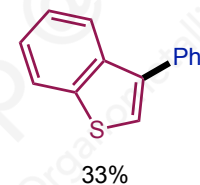
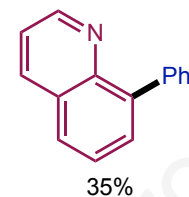
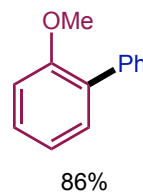
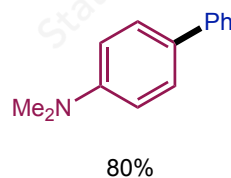
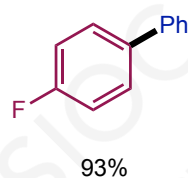
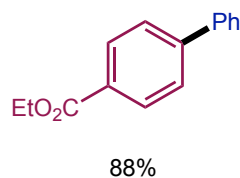
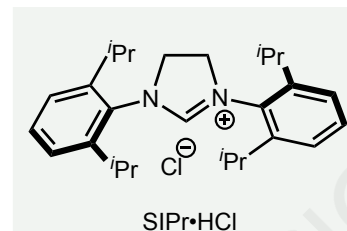
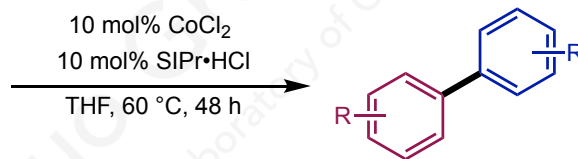
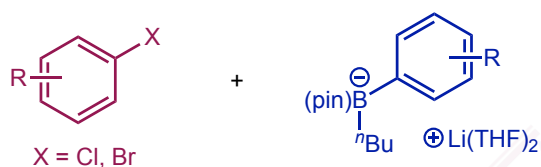


■ 当量实验

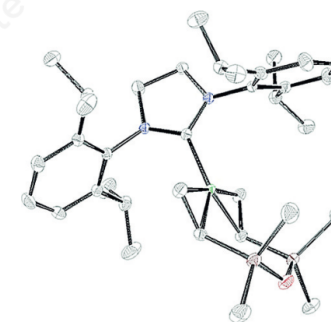
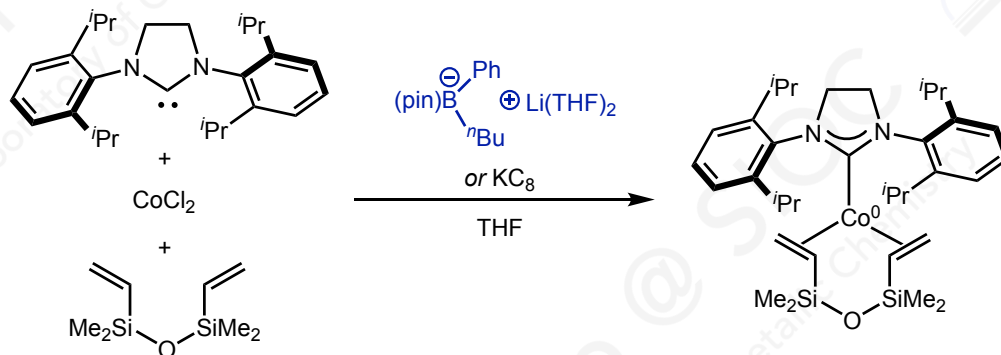


硼酸酯和碱参与催化剂活化步骤，给出一个电子生成Co^I物种

NHC-钴配合物催化的Suzuki-Miyaura偶联反应

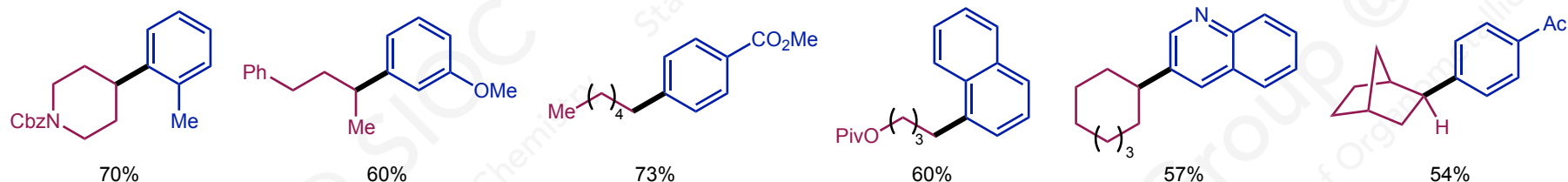
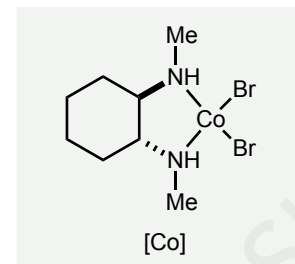
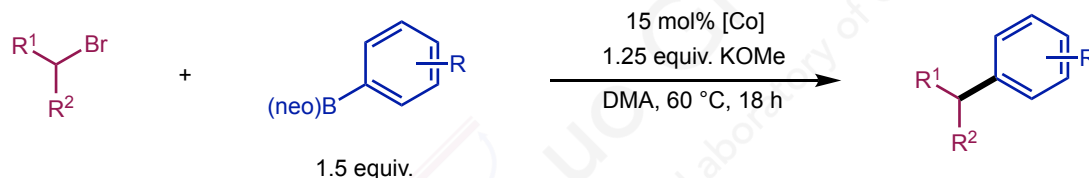


■ 烯基硅氧烷低价钴捕获实验

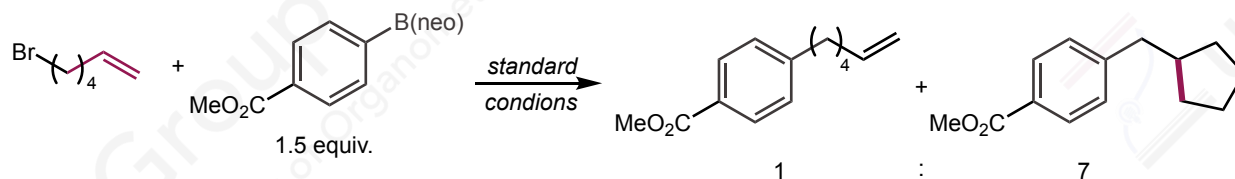


活化的硼酸酯将催化剂还原为 Co^0 物种

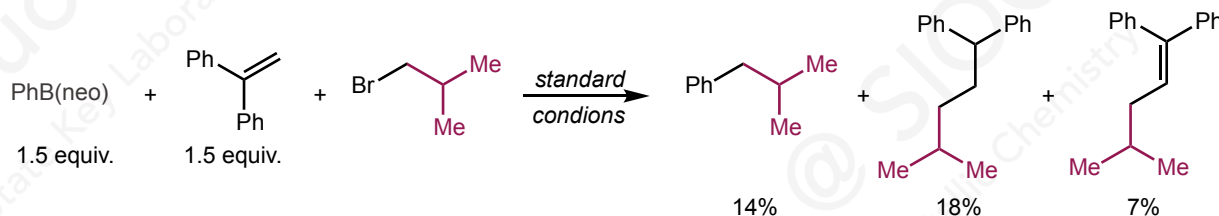
钴催化的C(sp²)-C(sp³) Suzuki-Miyaura偶联反应



■ 自由基捕获实验

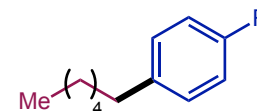


5-己烯基自由基直接偶联与分子内环化速率为相同数量级



支持笼逃逸自由基的生成

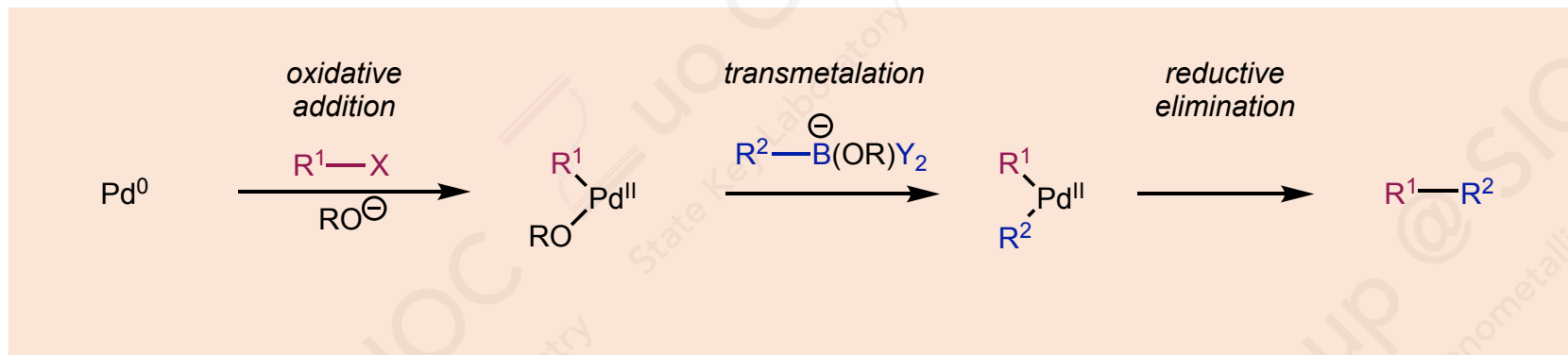
■ 硼酸酯竞争实验



KOMe	R = CO ₂ Me	R = OMe
1.25 eq.	66%	5%
2.5 eq.	34%	20%

反应倾向于路易斯酸性更强的硼中心

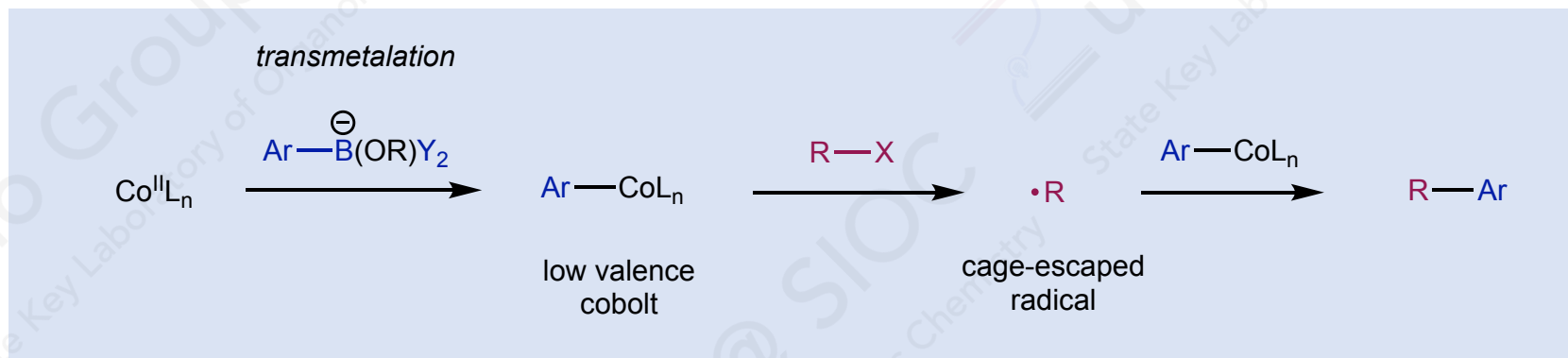
小结：钴催化的Suzuki-Miyaura偶联反应



◆ 反应需要碱的活化

◆ 先氧化加成机理

◆ 转金属化步骤一般氧化还原中性

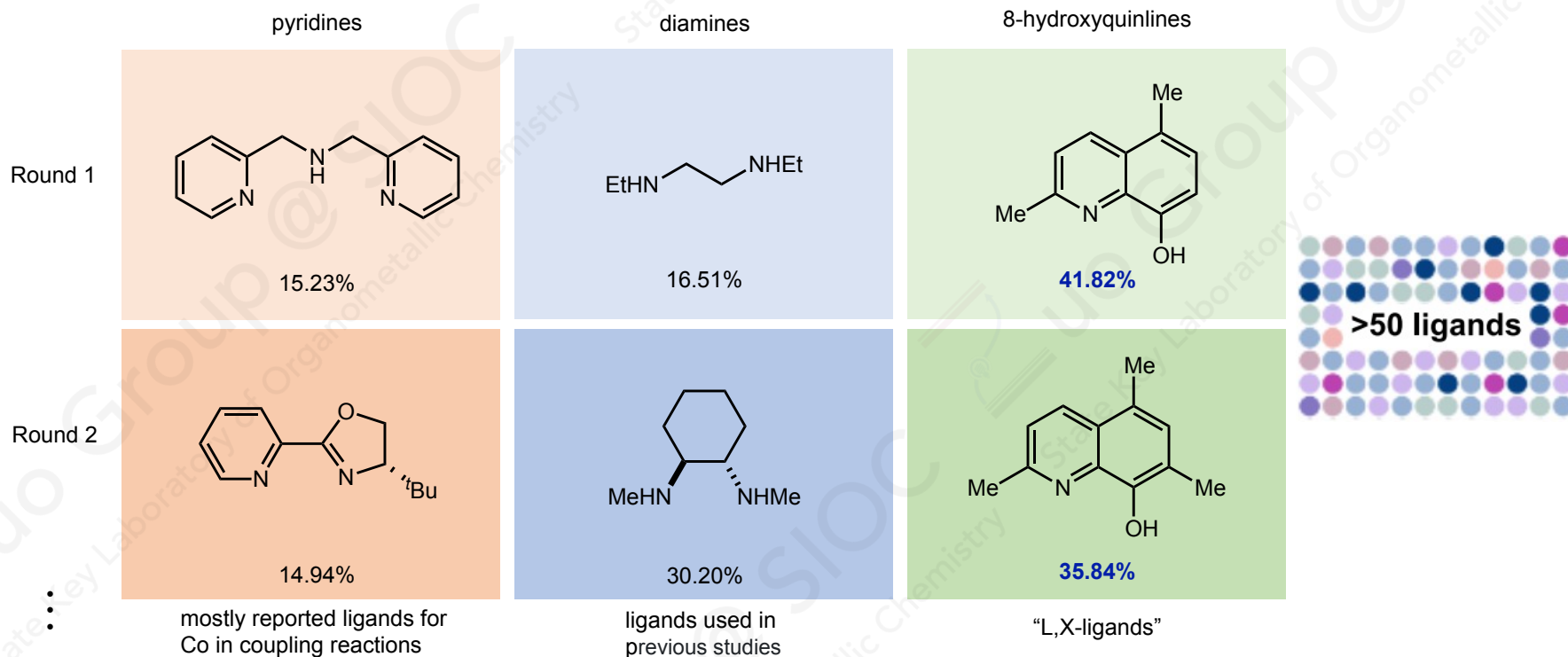
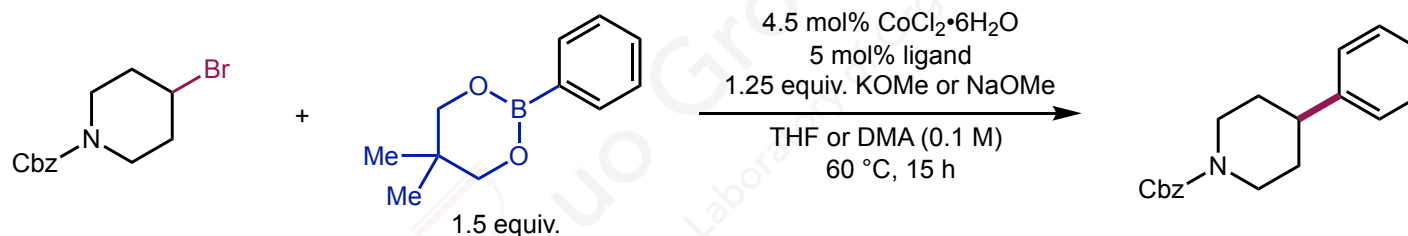


◆ 反应需要碱的活化

◆ 先转金属化机理

◆ 烷基溴可能产生笼逃逸自由基

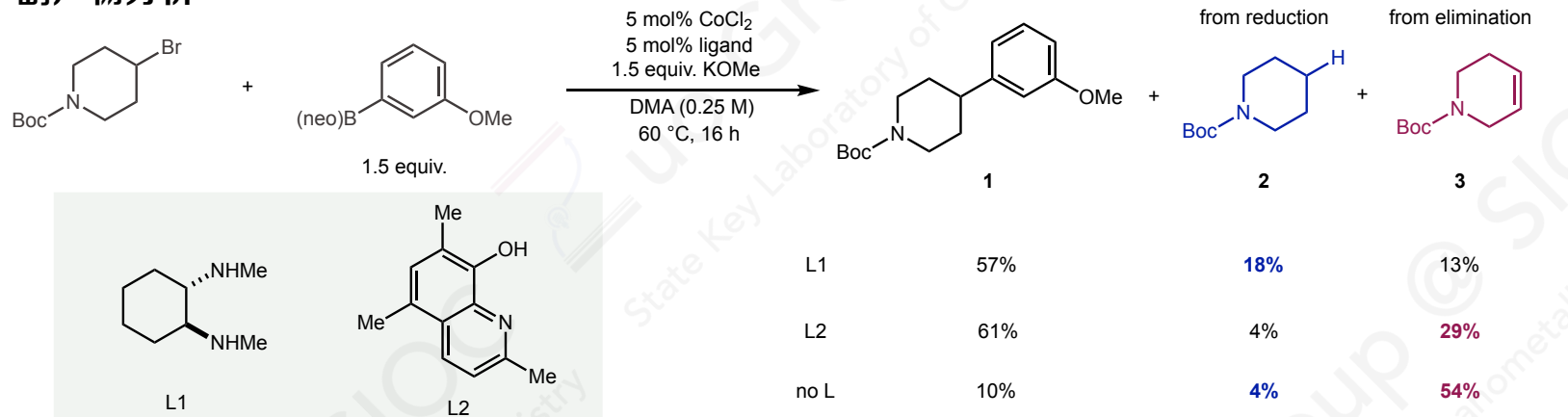
配体的高通量筛选(HTE)——选择配体种类



◆ 可通过去质子化产生离子供体

L,X-配体筛选——选定配体

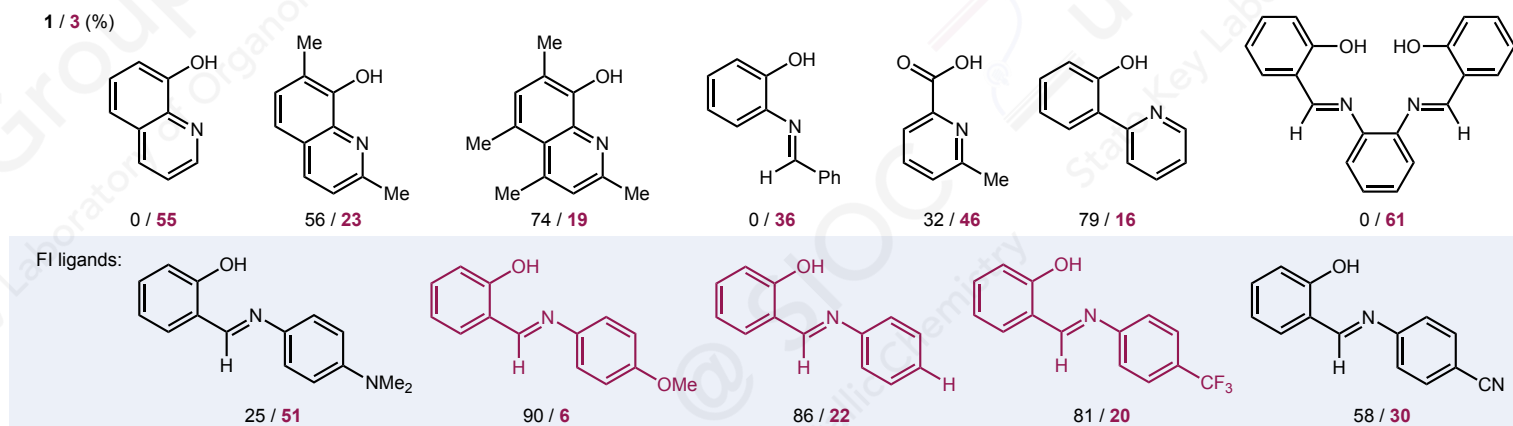
副产物分析



◆ 生成氢化副产物与催化剂种类有关

◆ 生成消除副产物为背景反应，可通过配体加速作用抑制

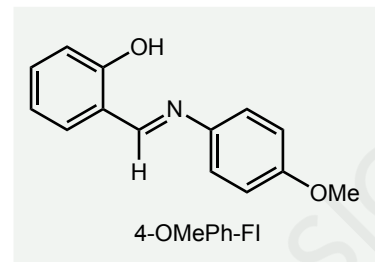
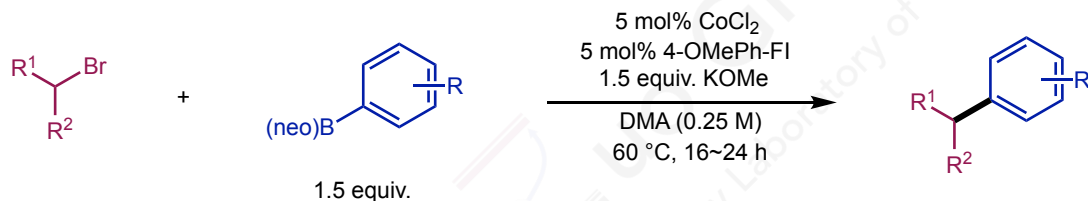
L,X-配体的进一步筛选



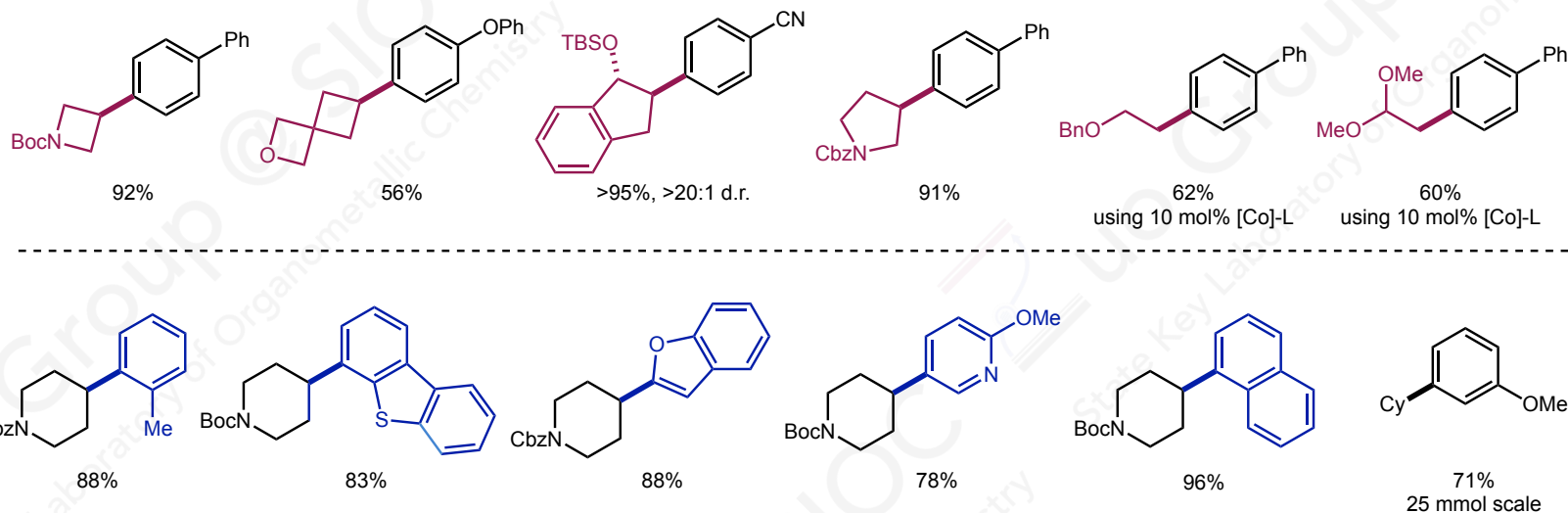
EDG

EWG

底物拓展



选择的底物范围

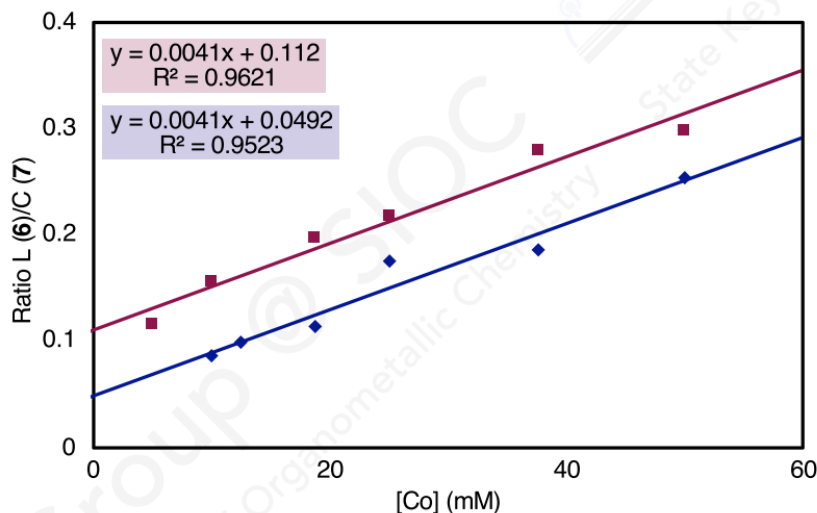
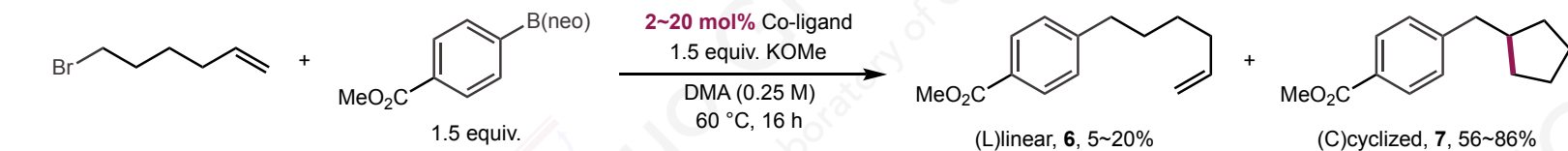


- ◆ 芳基硼酸电性合适时，对不同环上的二级溴代物效果很好
- ◆ 一级溴代物需要提高催化剂当量

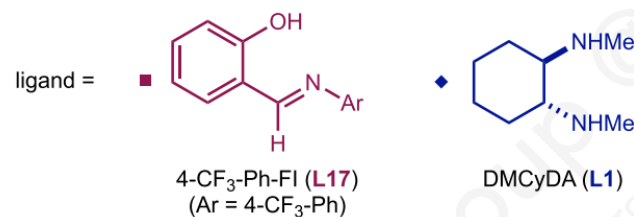
- ◆ 对不同芳基硼酸的适用性较好
- ◆ 可兼容邻位取代或多种杂环等

自由基钟反应——笼逃逸自由基的证据

■ 5-己烯基自由基的5-*exo-trig* 环化



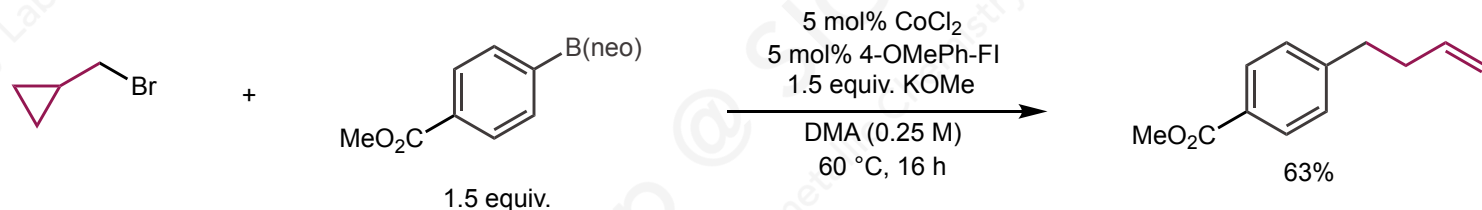
◆ 比例呈线性支持笼逃逸自由基生成



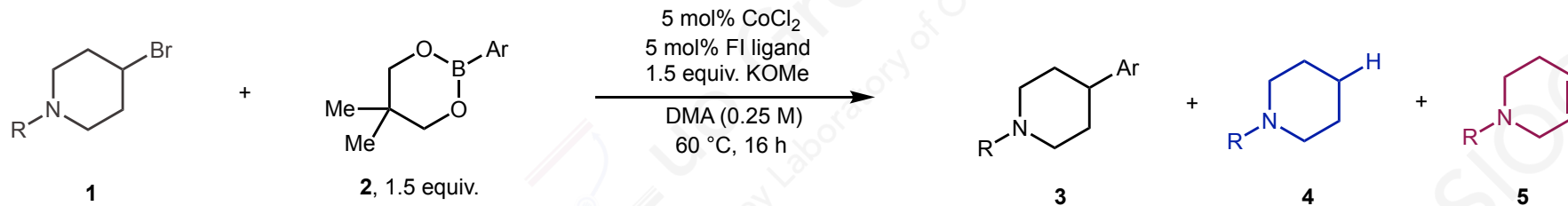
注：根据SI中给出的粗核磁谱图可以确认，原文及SI中均标反了两种产物的产率，但不影响结论

◆ 截距高说明FI配体捕获自由基速率更快

■ α -环丙基自由基的开环



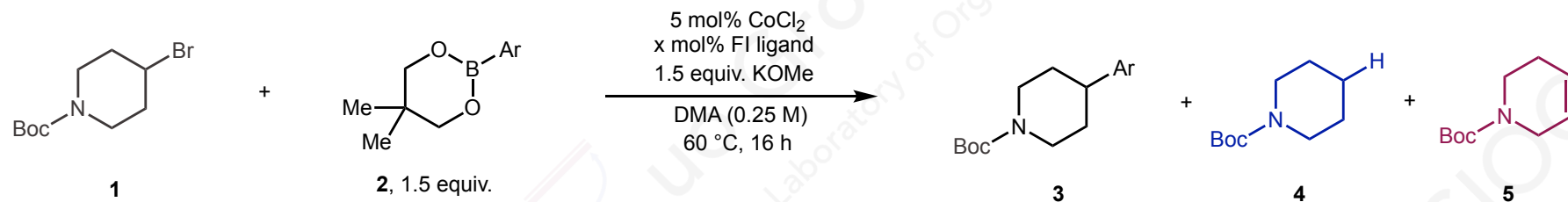
加料顺序的影响



Entry	step	order of addition to DMA solution	1 (%)	3 (%)	4 (%)	5 (%)
1	batch	2 , L, KOMe $\rightarrow$ $\text{CoCl}_2 \rightarrow$ 1	0	83	2	20
2		L, $\text{CoCl}_2 \rightarrow$ 2 , KOMe $\rightarrow$ 1	8	2	0	87
3		2 , L, KOMe, $\text{CoCl}_2 \rightarrow$ 1	27	41	2	44
4		L, KOMe $\rightarrow$ 2 $\rightarrow$ $\text{CoCl}_2 \rightarrow$ 1	8	83	2	11
5	HTE	L, $\text{CoCl}_2 \rightarrow$ 1 , 2 $\rightarrow$ KOMe	4	43	1	23

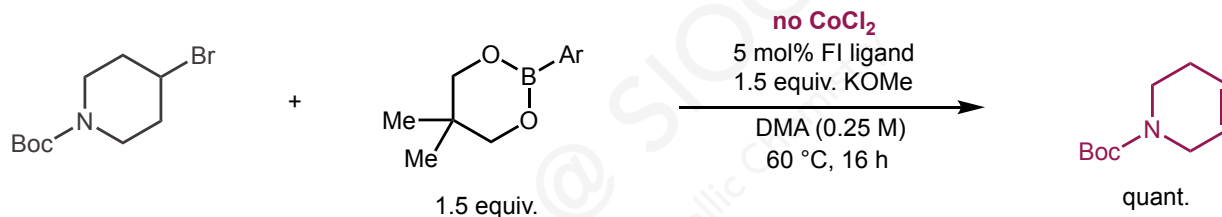
- ◆ **1** 最后加是为了最小化消除反应的竞争。
- ◆ 配体需要预先去质子化，芳基硼酸也需要碱的活化。
- ◆ Co 在芳基硼酸、配体和碱之后加入才能获得较高的偶联效率。

配体过量的影响



Entry	mol% FI ligand	1 (%)	3 (%)	4 (%)	5 (%)
1	1	6	52	4	24
2	5	0	77	2	17
3	7.5	17	25	1	47
4	10	17	9	0	61

◆ 配体的过量会引起大量的消除副产物的增加。

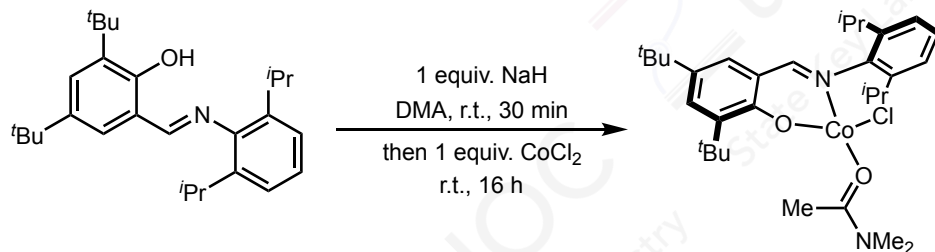


钴和配体的比例关系非常重要，还需要进一步的研究

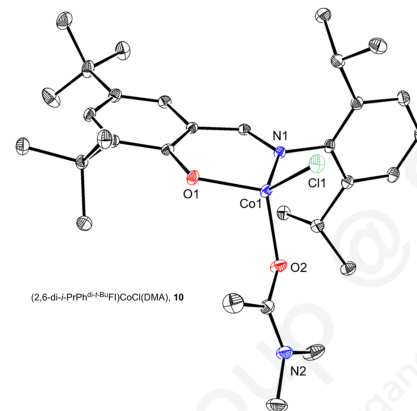
P. J. Chirik, et al. *ACS Catal.* **2022**, 12, 1905.

Co-FI 配合物的制备

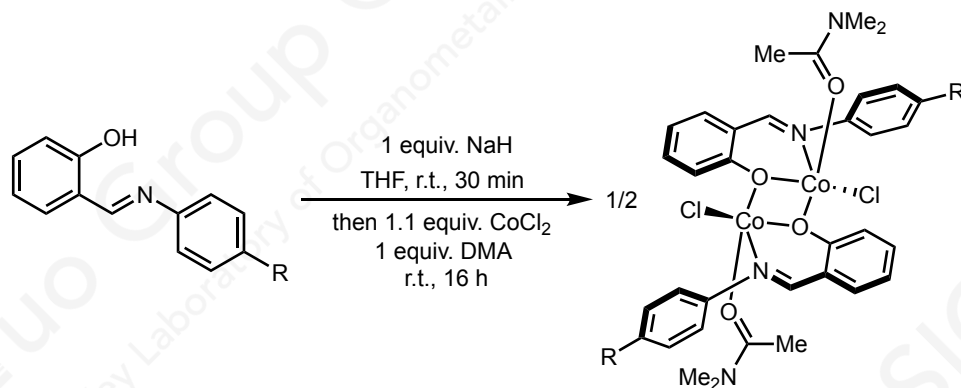
■ Co:FI = 1:1



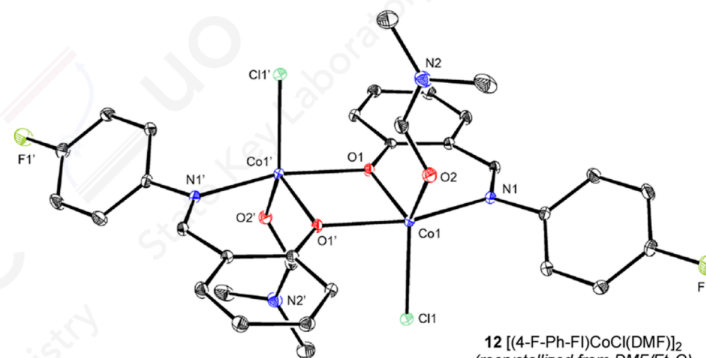
溶剂稳定的大位阻配体与钴的1:1配合物单体



(2,6-di-*i*-PrPh^{di-t-BuFI})CoCl(DMA)



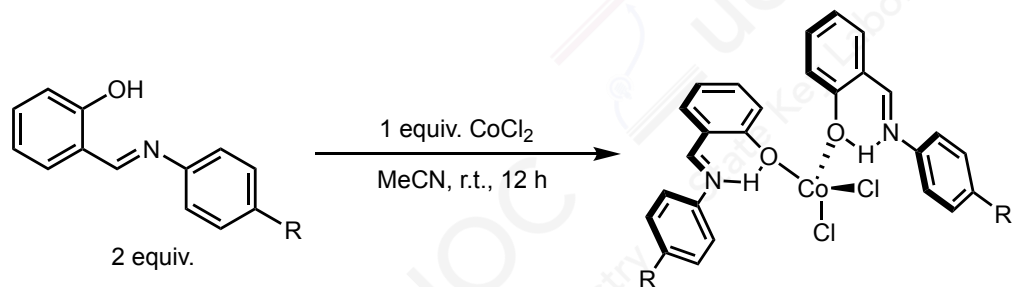
溶剂稳定的配体与钴的1:1配合物二聚体



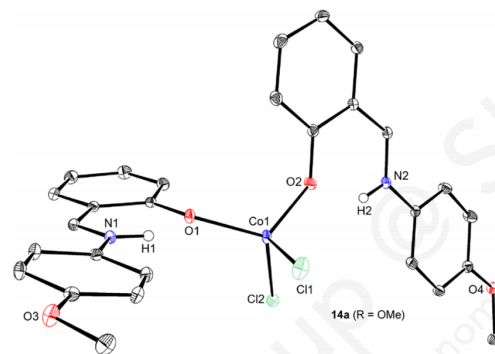
12 [(4-F-Ph-FI)CoCl(DMF)]₂
(recrystallized from DMF/Et₂O)

Co-FI 配合物的制备

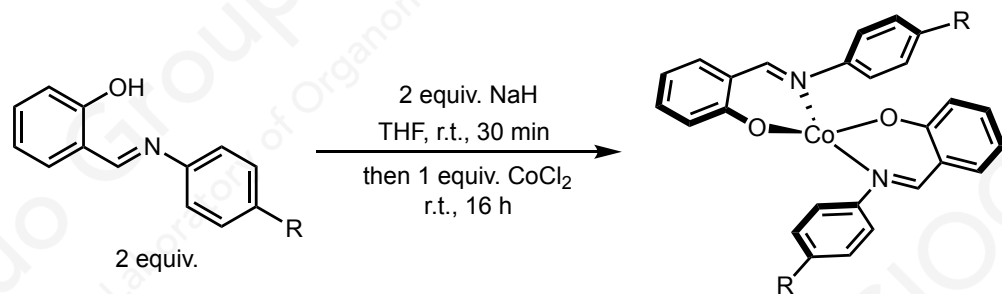
■ Co:FI = 1:2



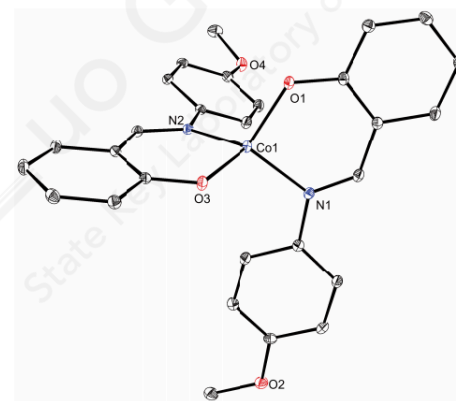
未去质子化的配体与钴的2:1配合物



$(\text{H-4-OMePhFI})_2\text{CoCl}_2$

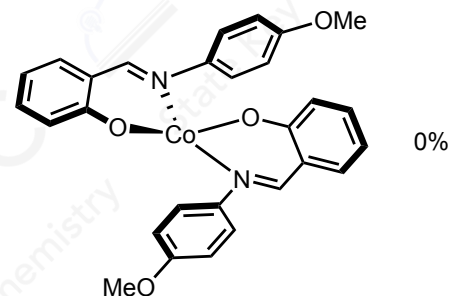
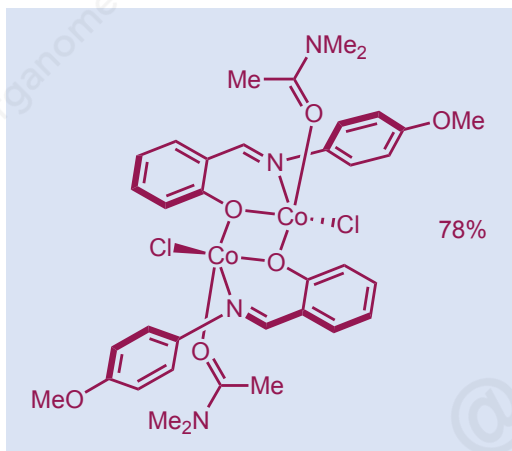
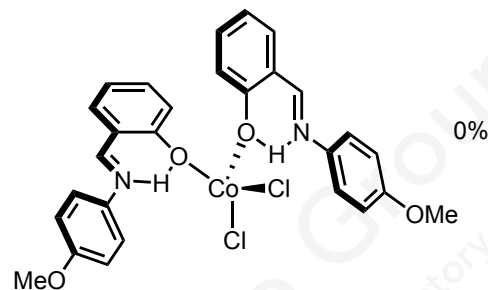
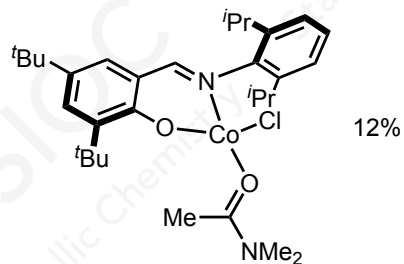
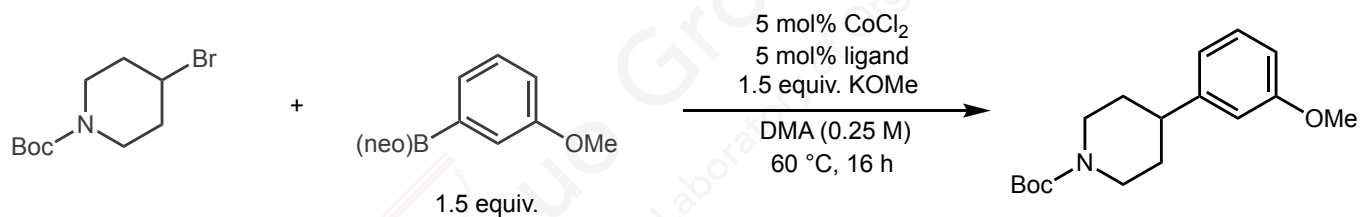


去质子化的配体与钴的2:1配合物



$(4\text{-OMePhFI})_2\text{Co}$

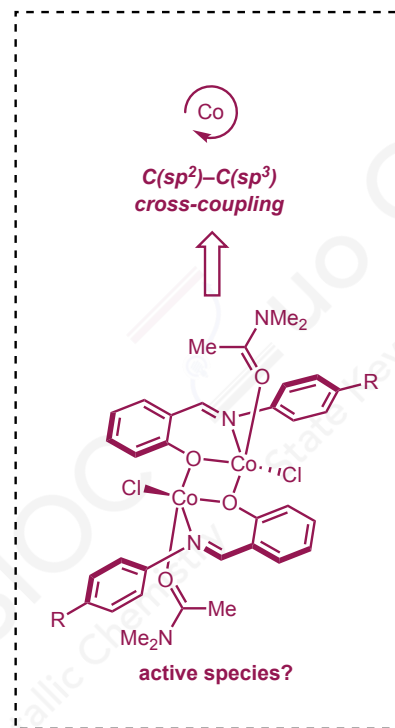
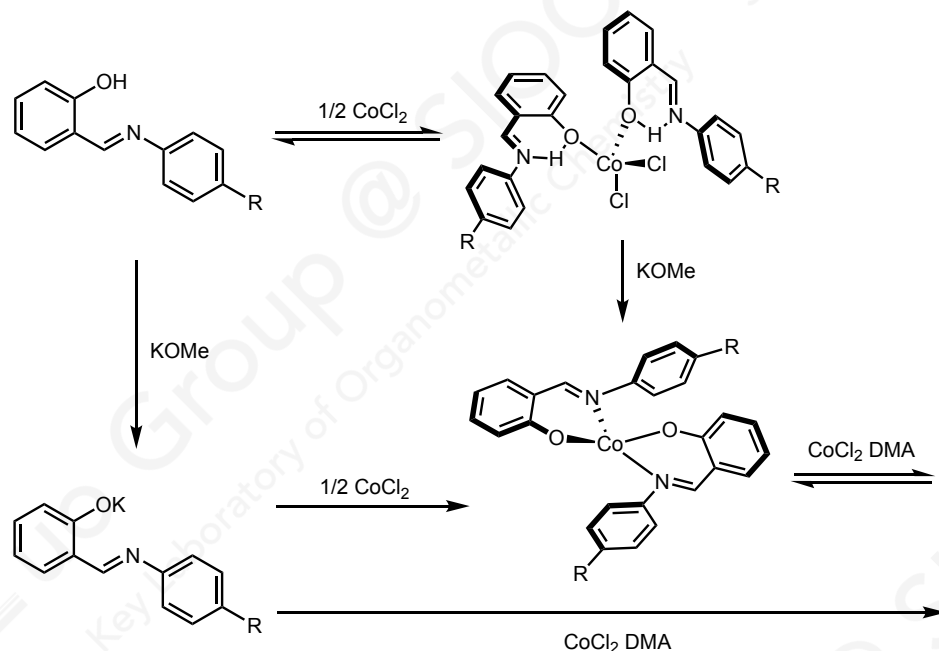
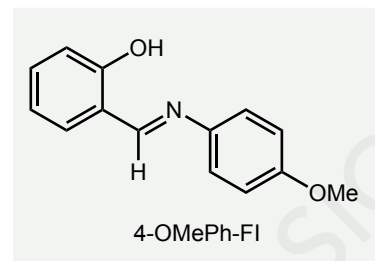
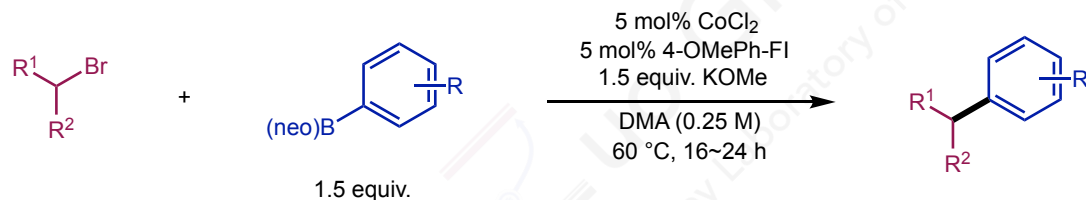
Co-FI 配合物的催化相关性



1:1的二聚体 $[\text{FiCoCl}(\text{DMA})]_2$ 是一种有效的预催化剂

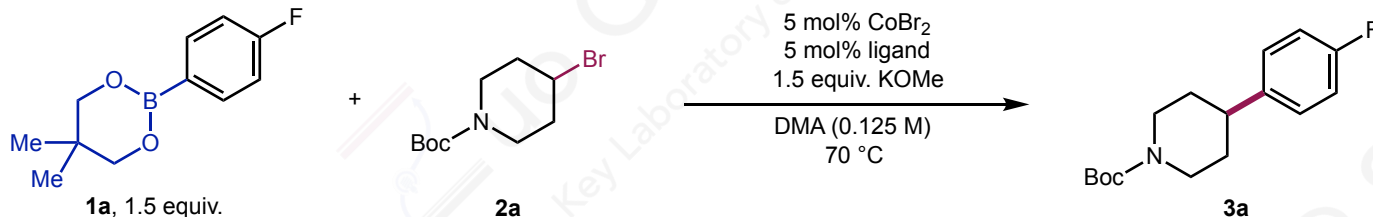
P. J. Chirik, et al. *ACS Catal.* **2022**, 12, 1905.

小结: Co 催化的 C(sp²)-C(sp³) 偶联反应

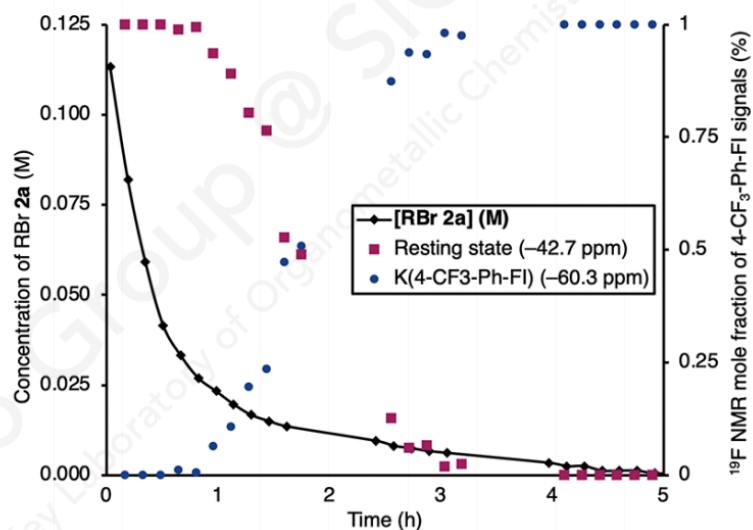


- ◆ 配体易于合成，产物收率较高
- ◆ 说明了Co-FI化学计量比例的重要性
- ◆ 确定了一些活性与非活性的 Co-FI 预催化剂结构
- ◆ 氧化还原物种
- ◆ 催化剂静息态
- ◆ 转化限制步骤
- ◆ 未阐明的问题

^{19}F NMR 测定静息态催化剂和游离配体含量变化

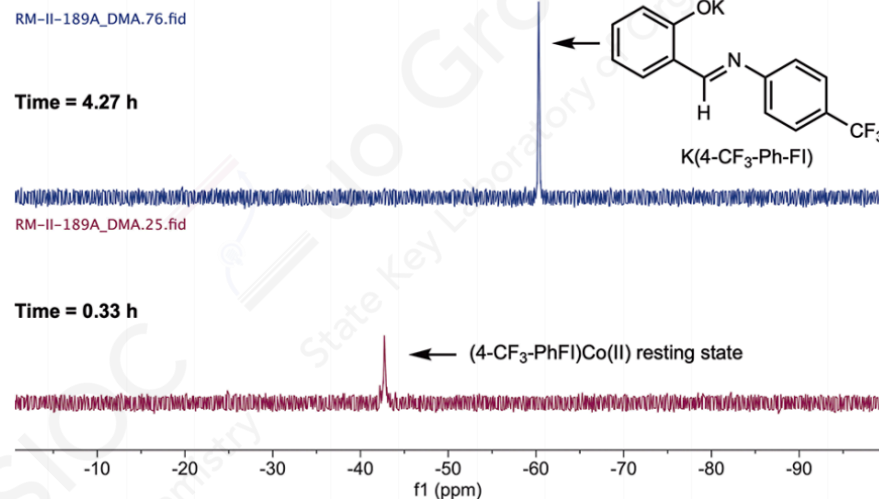


B. Reaction Timecourse^b



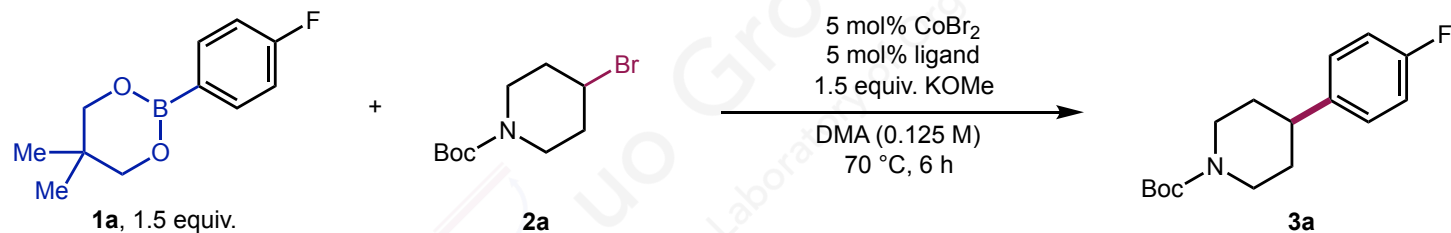
◆ 配体随反应进行逐渐解离

C. ^{19}F NMR analysis of 4- CF_3 -Ph-FI signals (470 MHz)

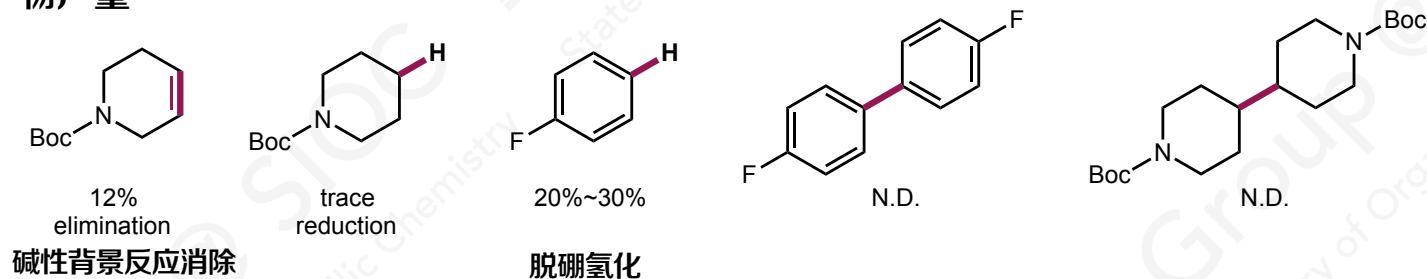


◆ 仅观察到该两组 ^{19}F 信号

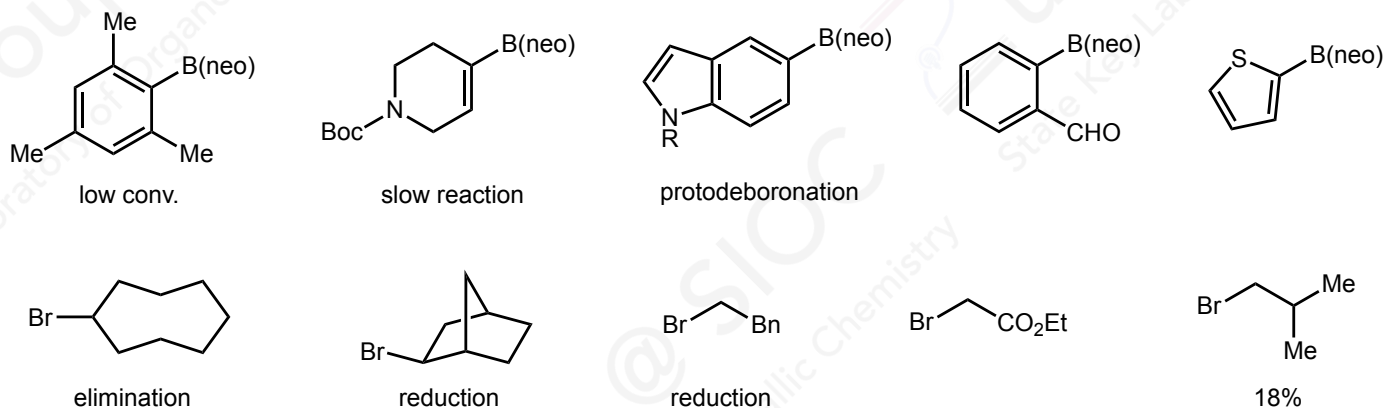
副反应分析



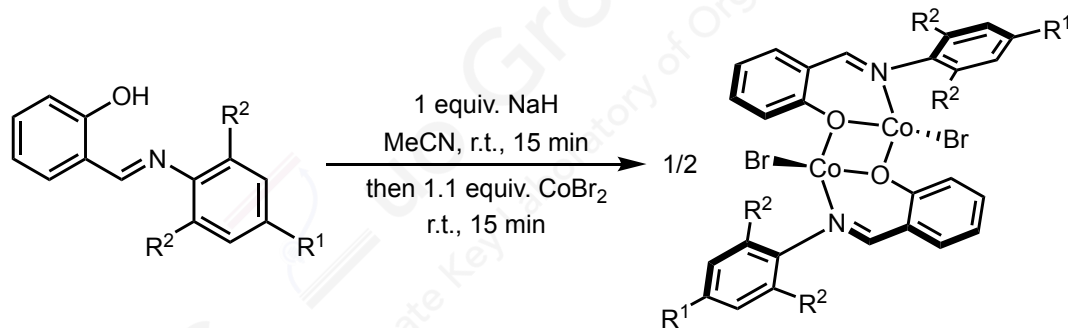
副产物产量



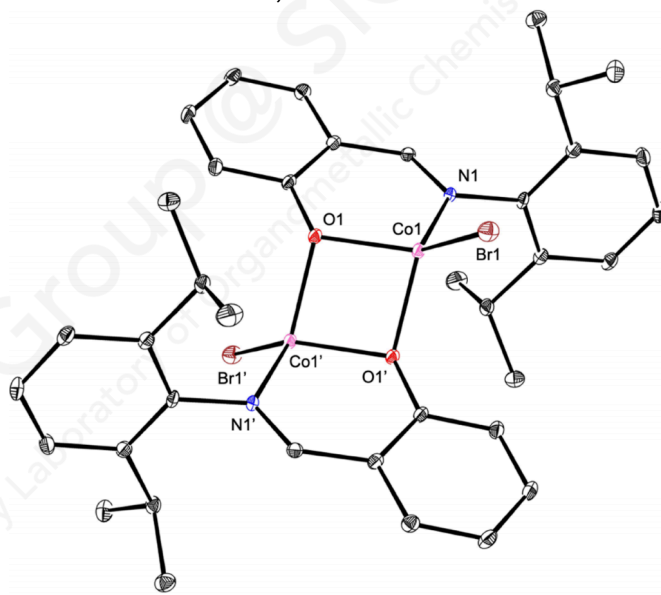
尝试失败的底物



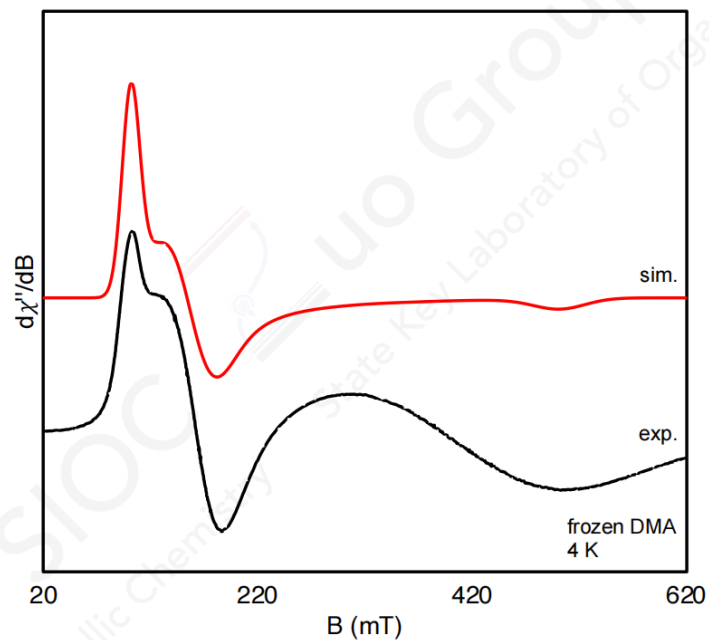
非溶剂稳定的 Co-FI 1:1 配合物的制备



$R^1 = \text{H}$, $R^2 = i\text{Pr}$



$[(2,6\text{-di-}i\text{-PrPhFI})\text{CoBr}]_2$

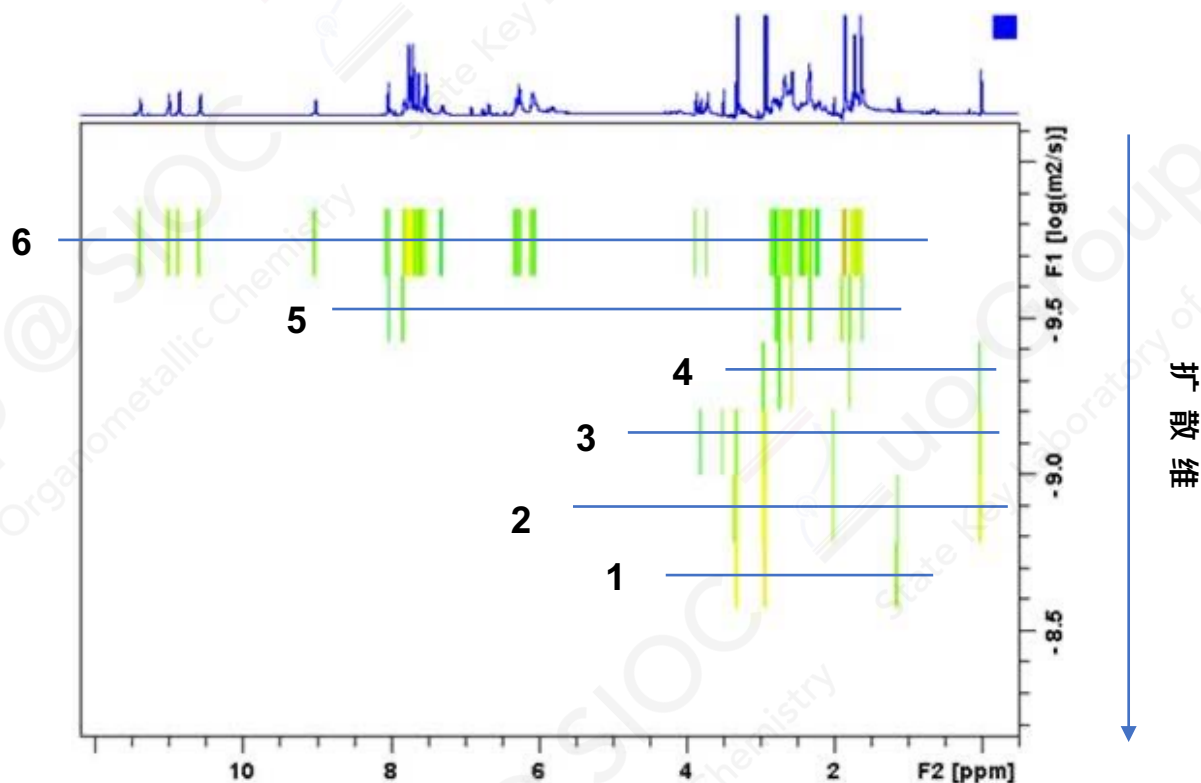


◆在溶液中也以二聚体形式存在么？

Diffusion-Ordered NMR Spectroscopy, 扩散序谱

一种利用脉冲梯度场核磁共振对溶液中具有不同扩散系数的成分进行虚拟分离的一种伪二维核磁技术

通过特殊的脉冲序列，使得不同分子在不同梯度强度下因扩散导致的信号衰减不同，从而实现虚拟分离



图片来源:cpam.iccas.ac.cn

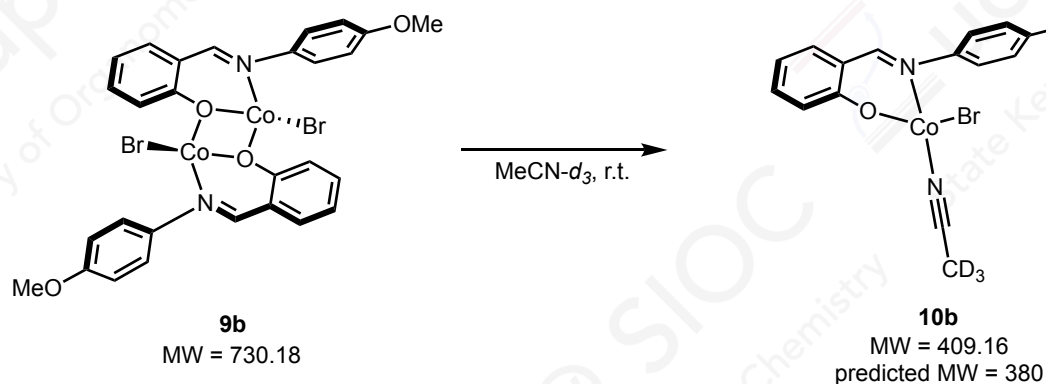
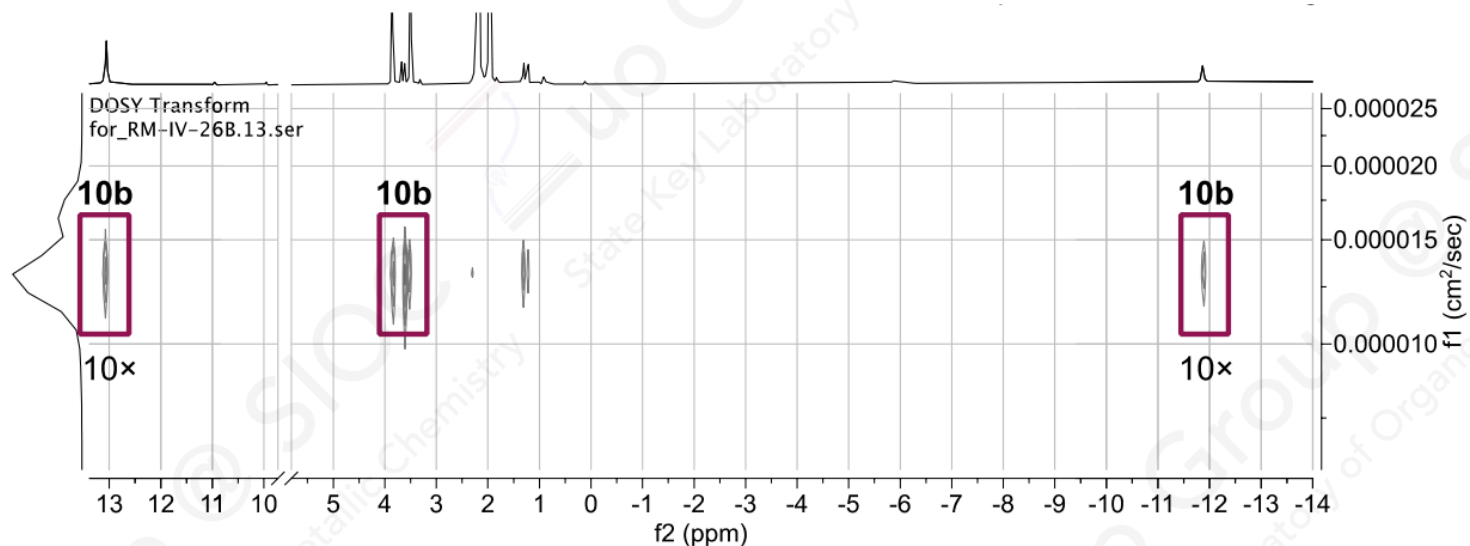
◆ 复杂混合物成分分析

◆ 测定分子大小和分子量

◆ 研究溶液中的分子间相互作用

DOSY 谱预测催化剂在溶液中的分子量

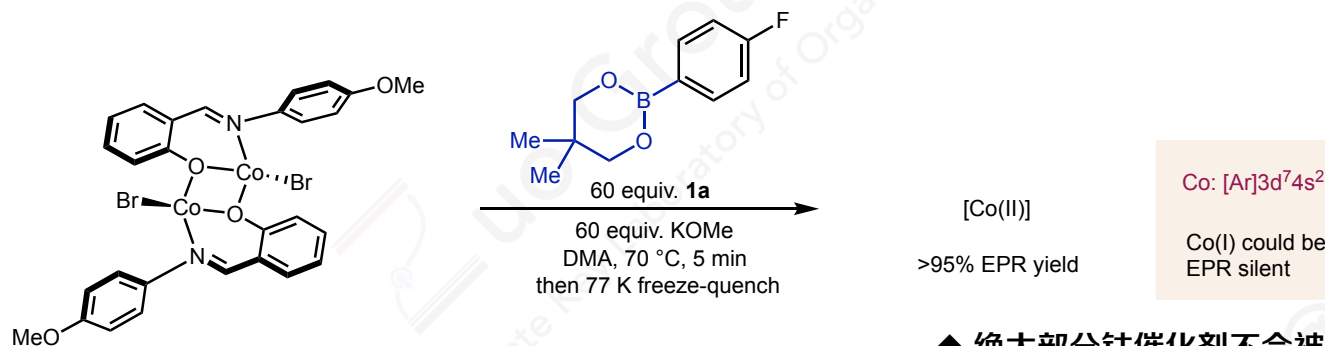
■ 溶液相分子量预测



◆ 溶液中大部分钴催化剂以单体存在

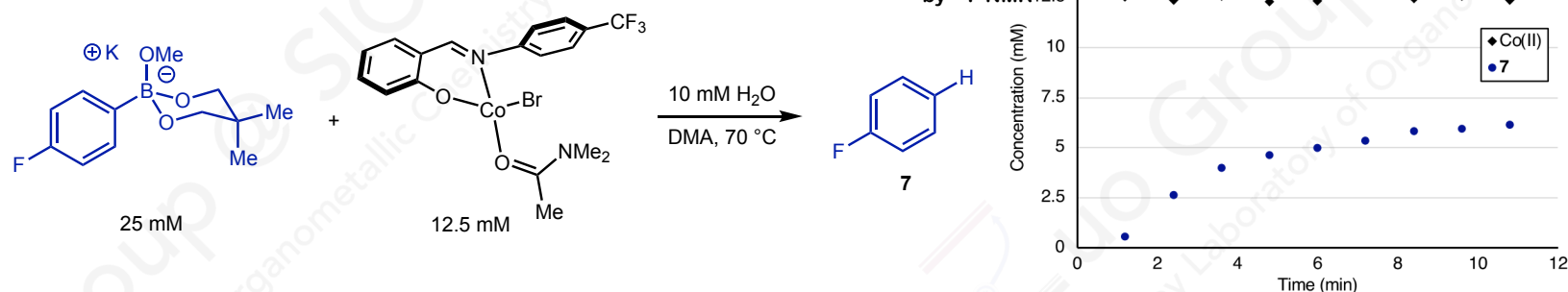
对 Co(I) 的生成的检测

■ EPR

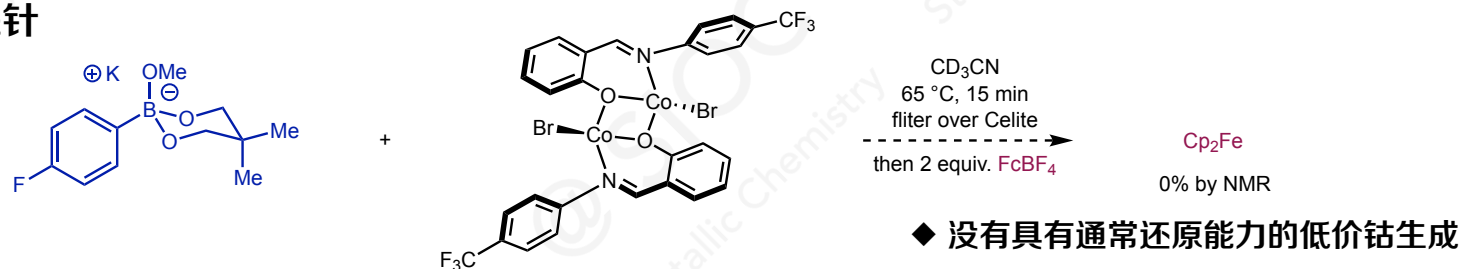


◆ 绝大部分钴催化剂不会被硼酸盐还原

■ 原位NMR



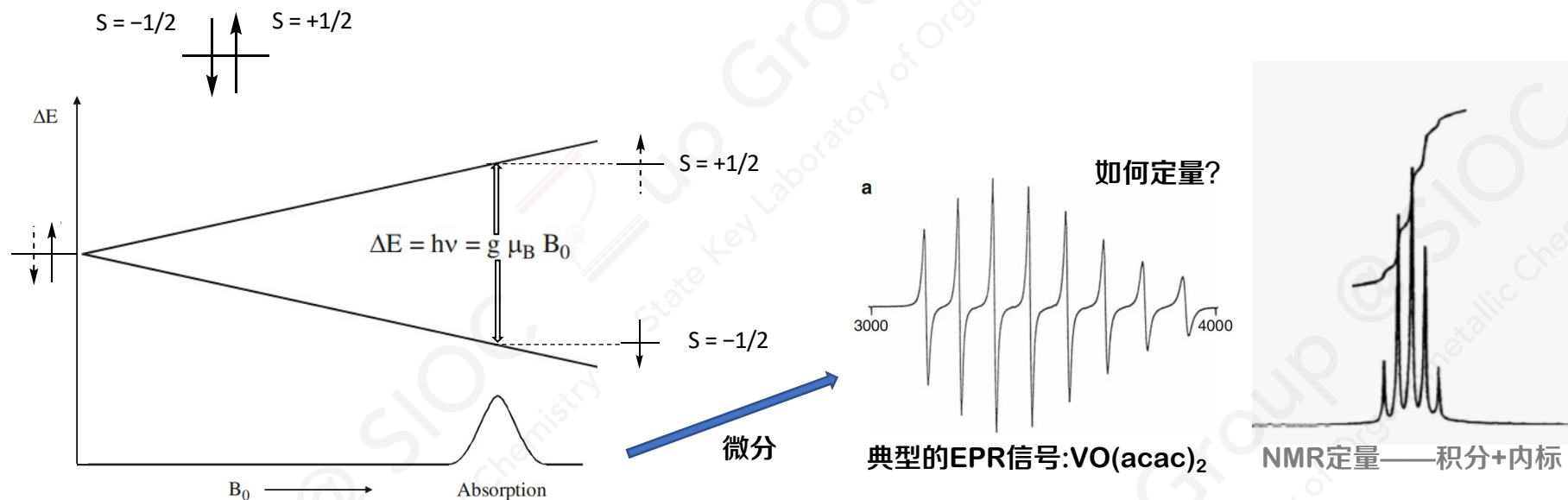
■ 氧化性探针



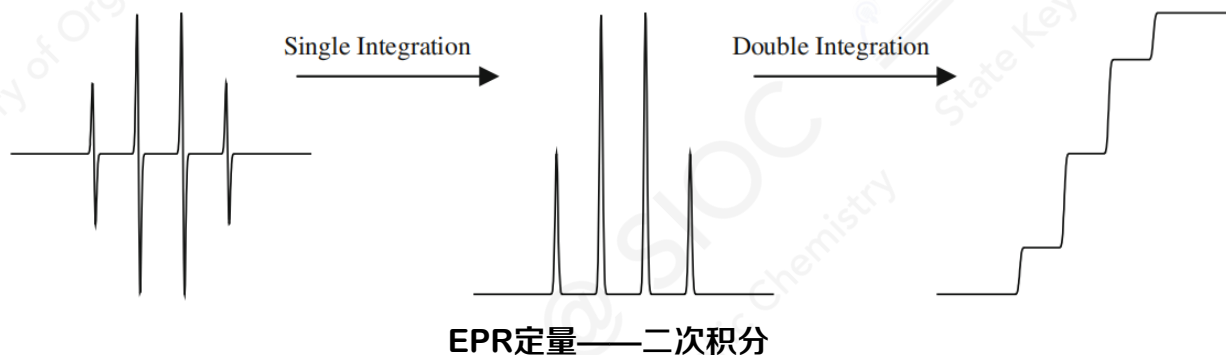
在可检测尺度上，催化剂的活化没有生成低价钴物种

L,X-配体阴离子有利于钴保持高氧化态

Electron Paramagnetic Resonance, 电子顺磁共振及定量



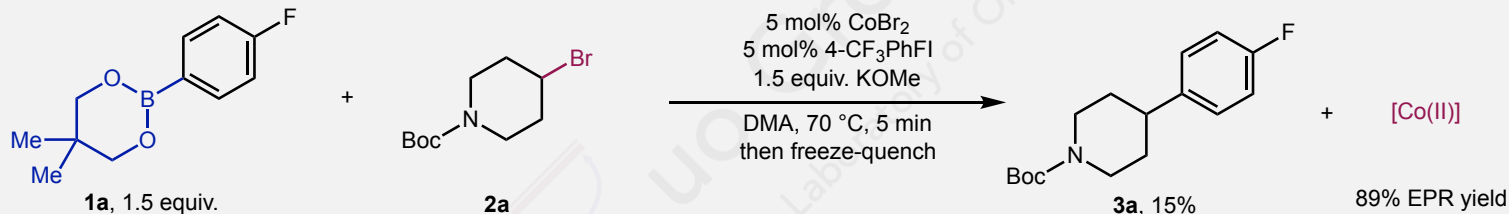
- ◆ 信号受到外界因素、单电子产生的局部磁场和临近的偶极子(具有自旋的原子核)影响顺磁性物种的“指纹”，但仅能获得近程的耦合信息



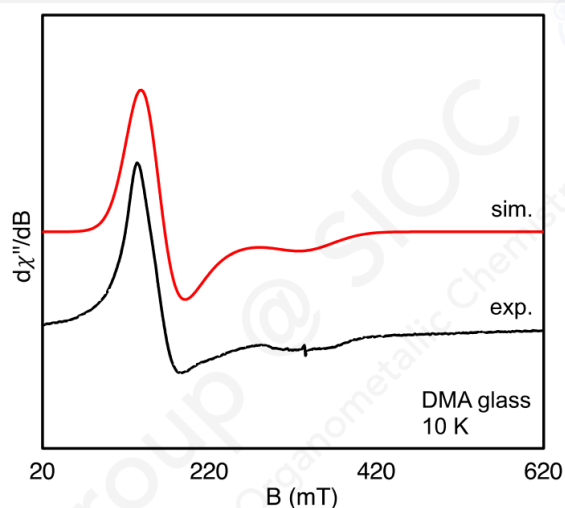
- ◆ 积分面积与自旋数成正比，通常需要使用已知自旋数的外标

催化剂静息态分析

■ 原位检测



◆ 大部分钴配合物都处于静息态



C. ^{19}F NMR spectra (470 MHz, 343 K)

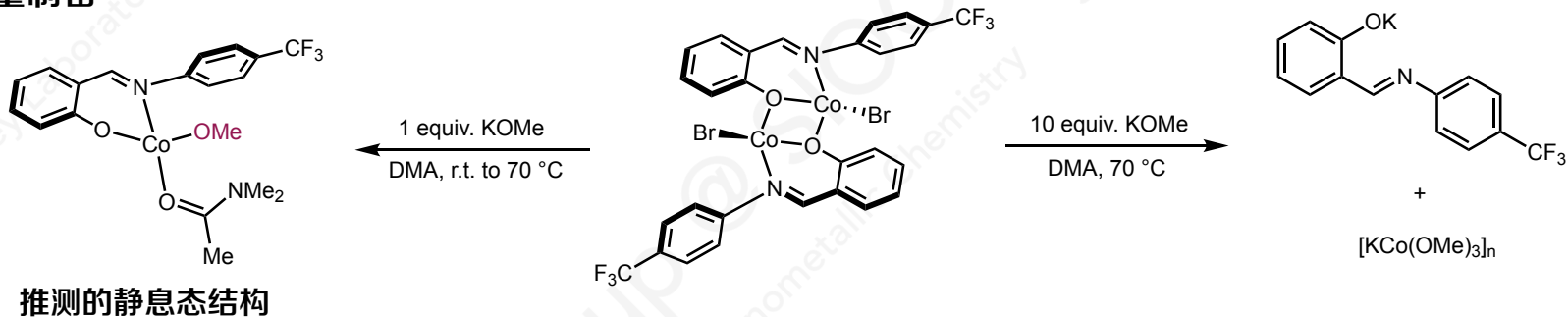
(iii) **9a** + 10 equiv KOMe

(ii) **9a** + 1 equiv KOMe

(i) **9a**

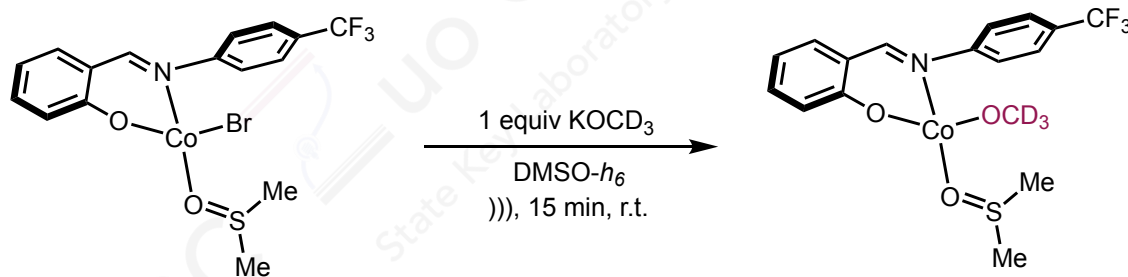
◆ 新的位移与被认为是静息态的位移吻合

■ 当量制备

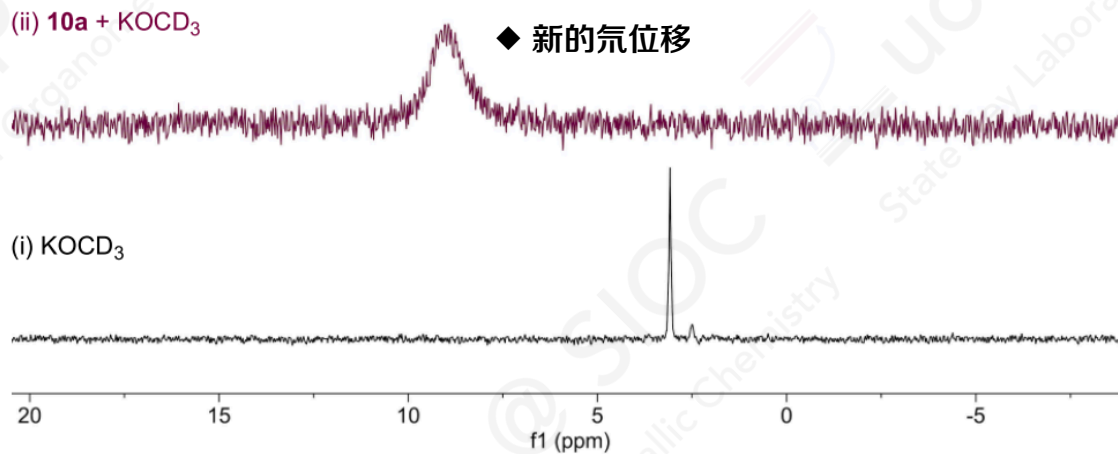


催化剂静息态结构验证

■ 结构验证



B. ²H NMR spectra (61.4 MHz, DMSO-*h*₆, 298 K)



^2H in NMR

◆ “ ^2H 没有 NMR 信号”

核磁共振：具有磁性(整体自旋)的核在外加磁场作用下产生能级分裂

质子和中子都在作自旋运动，奇数个的质子和中子对核的整体自旋都有贡献

$I = 0$: ^{12}C , ^{16}O 质子中子均为偶数

$I = 1/2$: ^1H , ^{13}C , ^{15}N , ^{19}F , ^{31}P

$I = 3/2$: ^7Li , ^{11}B 质子中子一奇一偶

$I = 1$: ^2H , ^{14}N 质子中子均为奇数

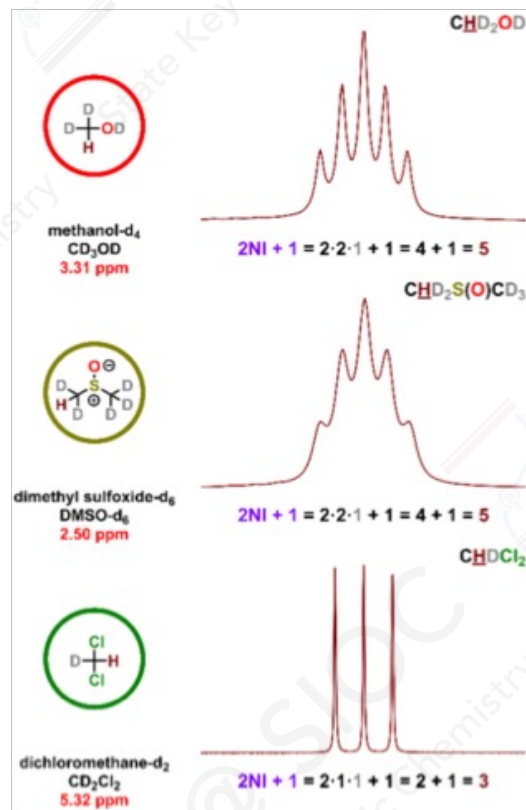
各核的磁矩不同，磁旋比不同，在相同磁场中共振频率也不同，故测氢谱时不会受到其他核共振的干扰

^1H 400 MHz, ^{13}C 100 MHz, ^2H 61.4 MHz

^1H 500 MHz, ^{13}C 125 MHz

◆ “ ^2H 有 NMR 信号, 氘代溶剂会出峰”

氢谱中出峰的是氘代溶剂中未完全氘代的氢产生的裂分是由于氘对氢的耦合



图片来源: cheminfographic.wordpress.com

◆ 为什么要用氘代溶剂?

氘代溶剂不会干扰氢谱，少量氢出峰可以作为参考

氘代溶剂与对应非氘代溶剂化学性质相似，对样品的溶解度相似

核磁仪器需要使用氘信号

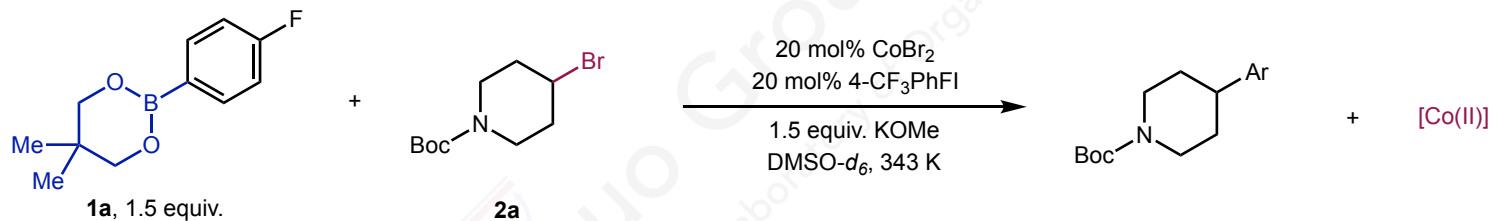
均一、稳定的磁场

匀场和锁场

氘信号

具有锁场功能的NMR仪器一般都有接收氘信号的通道。

催化剂静息态原位核磁分析



■ 氢谱检测顺磁性中心

B. ^1H NMR spectra (DMSO- d_6 , 343 K)

催化剂单体

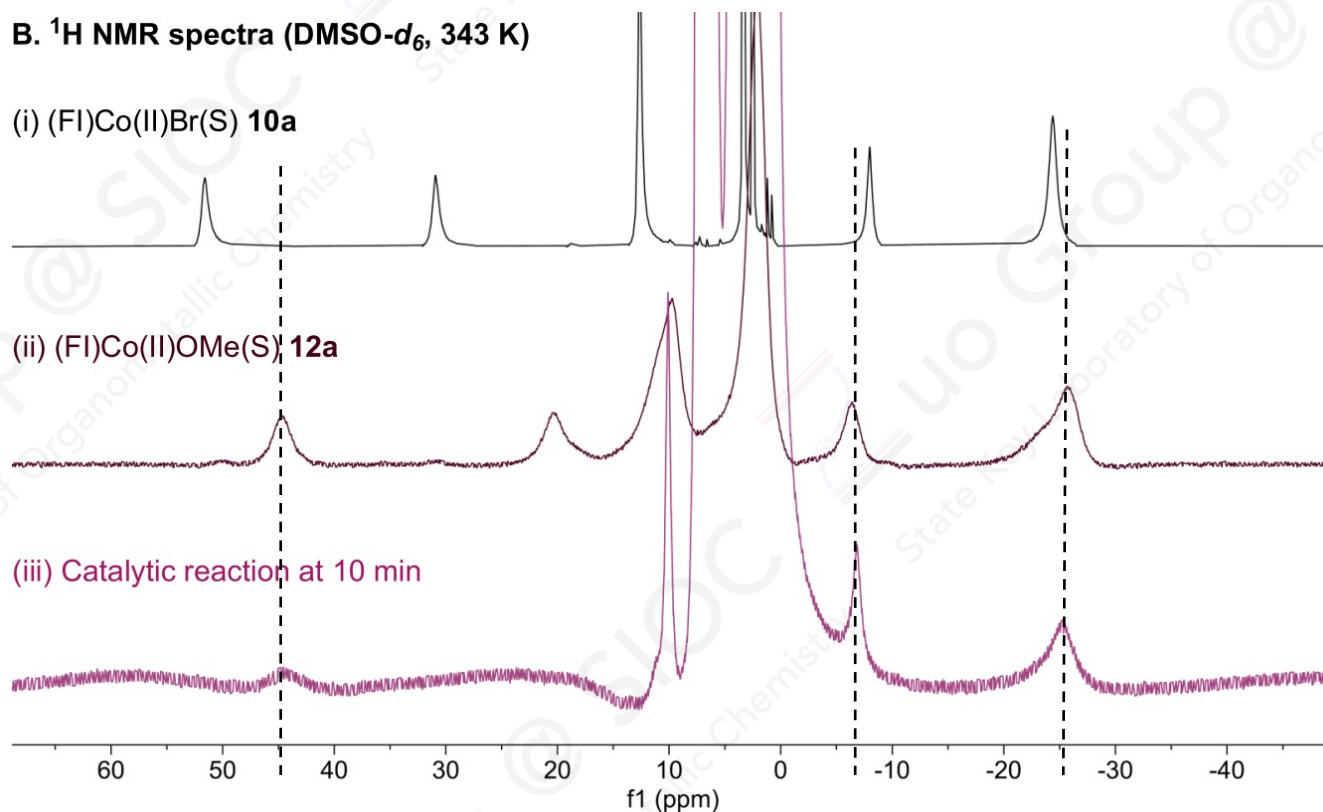
(i) (FI)Co(II)Br(S) 10a

催化剂静息态

(ii) (FI)Co(II)OMe(S) 12a

反应体系

(iii) Catalytic reaction at 10 min



◆ 没有观察到新的顺磁性中心造成的位移

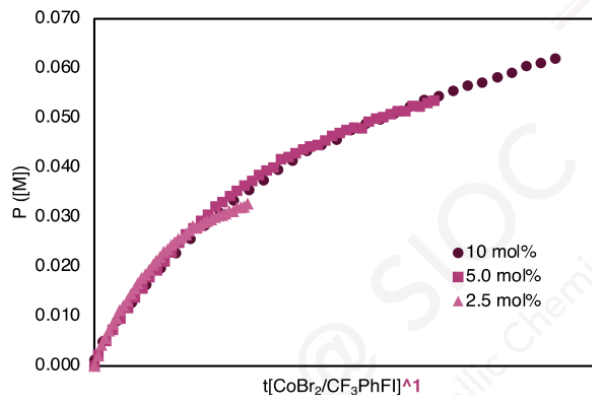
◆ 验证了反应过程中催化剂静息态的结构和单一性

动力学实验：催化剂与底物

反应级数的测定——时间变量归一化分析(VTNA)

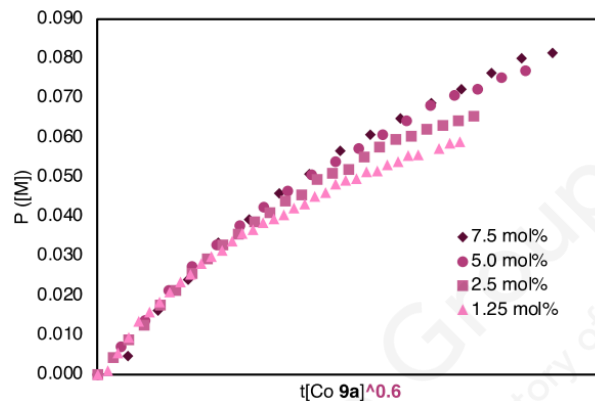
VTNA：一种仅需少量实验便可得到反应级数的图形化数据处理方法

仅改变待测物浓度，用产量对不同级数的时间变量归一化函数作图，不同浓度曲线重合时，该级数即为反应级数



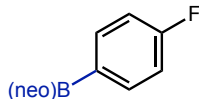
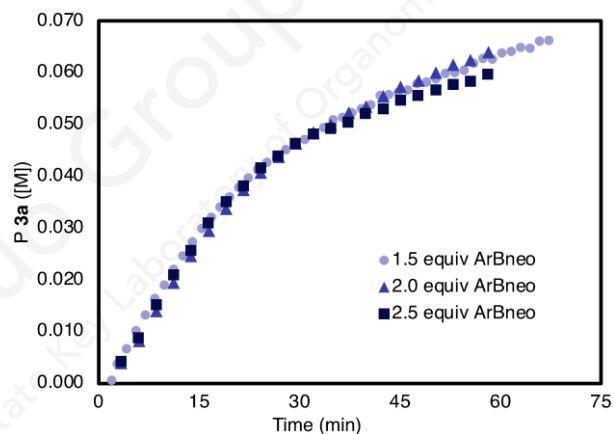
$\text{CoBr}_2 + \text{L}$

1st order

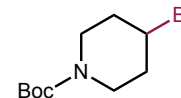
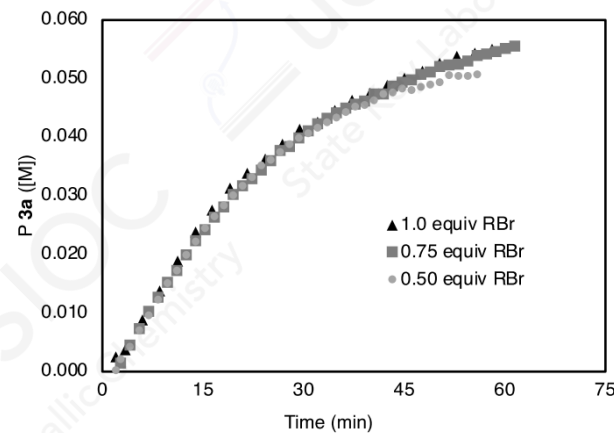


$[(4\text{-FPhFI})\text{CoBr}]_2$

partial order



0th order



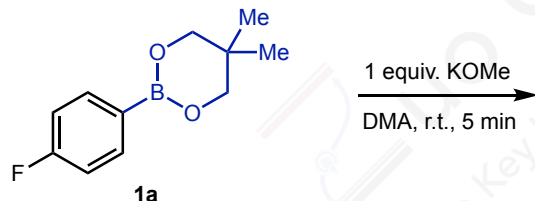
0th order

◆ 催化剂单体参与到反应的转化限制步骤

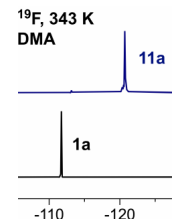
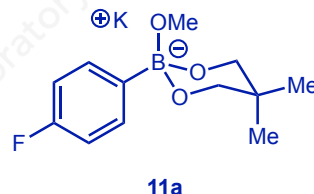
◆ 反应倾向于先转金属化而不是先氧化加成的机理

动力学实验：活化的亲核试剂

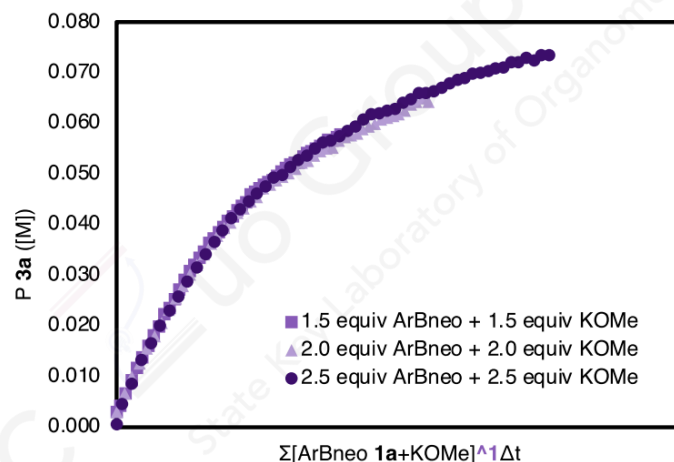
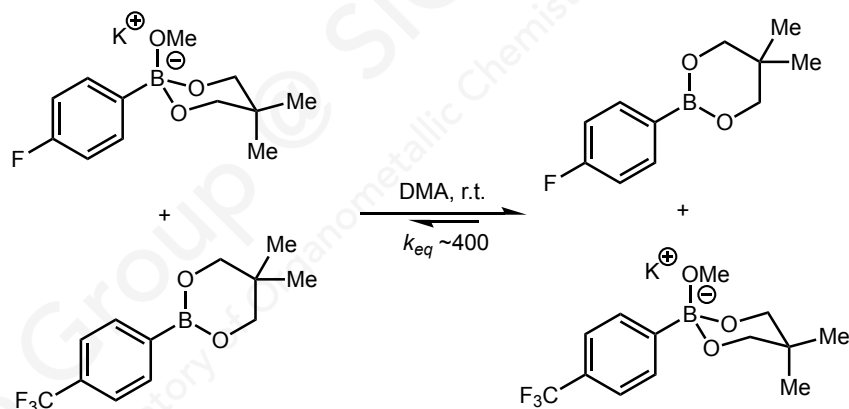
■ 硼酸盐及其反应级数的测定



活化的亲核试剂

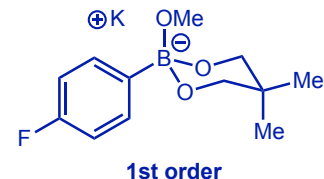


完全转化



◆ 平衡转化为电性更有利的硼酸盐

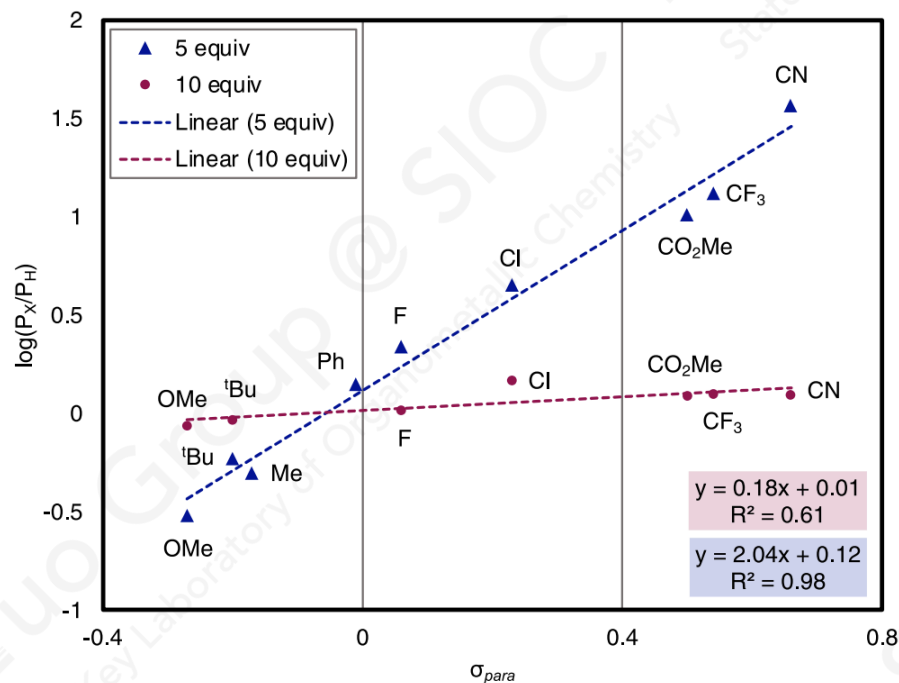
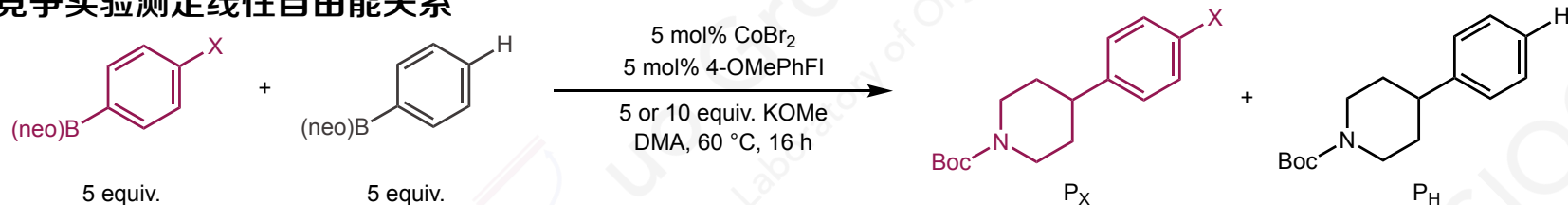
◆ 该硼酸盐的形成是可逆的



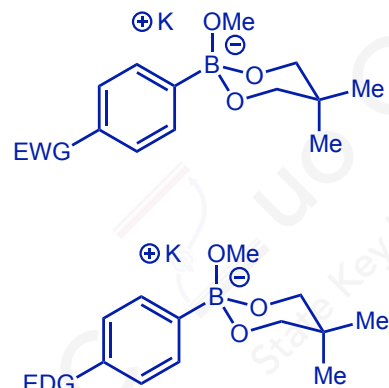
◆ 硼酸盐参与到了反应的转化限制步骤

线性自由能关系和碱的过量效应

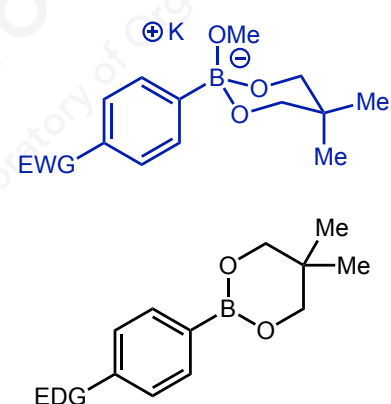
■ 竞争实验测定线性自由能关系



excess KOMe:



limiting KOMe:

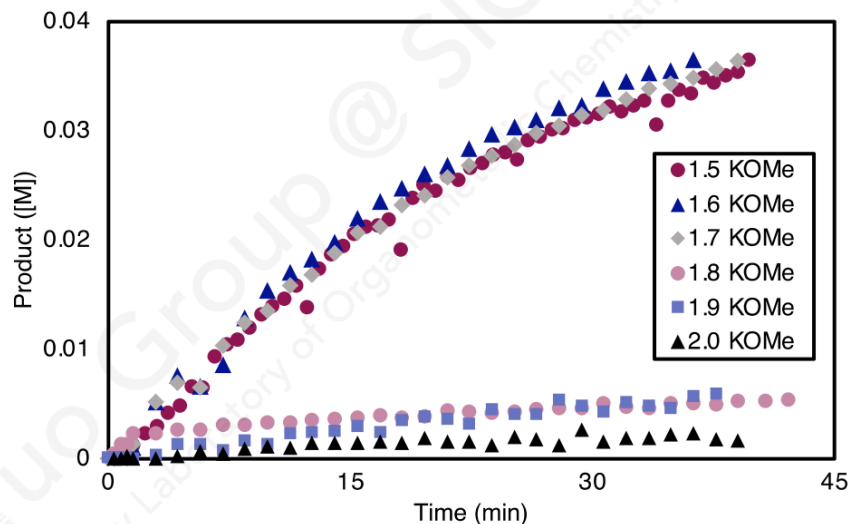
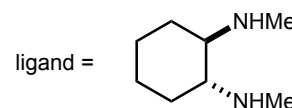
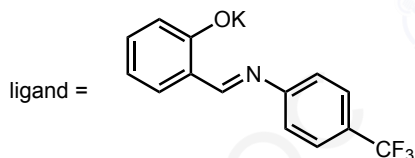
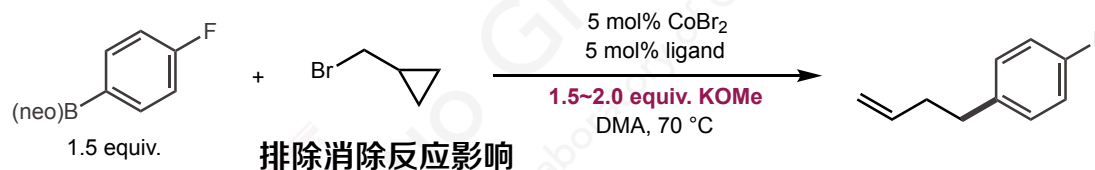


- ◆ 决速步是负电荷积累的过程
- ◆ 碱的量有限时不同电性的差异更为显著

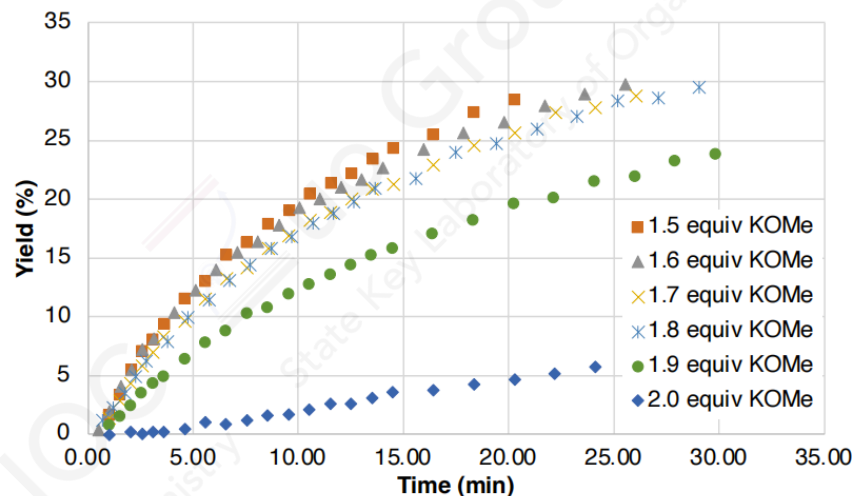
◆ 碱不足量时更缺电子硼酸盐的形成更为有利

略过量的碱对反应有什么影响？

碱的过量效应——L,X-配体的优势



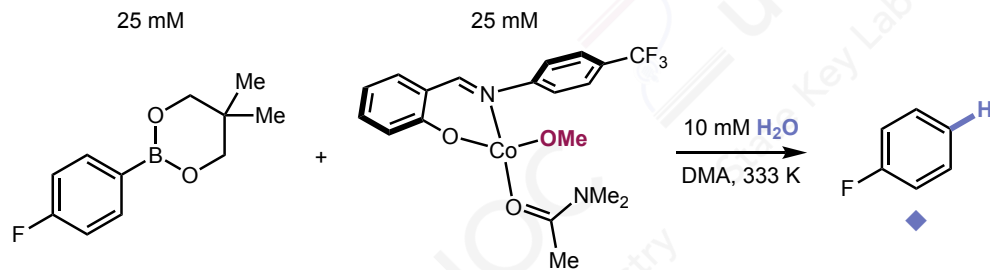
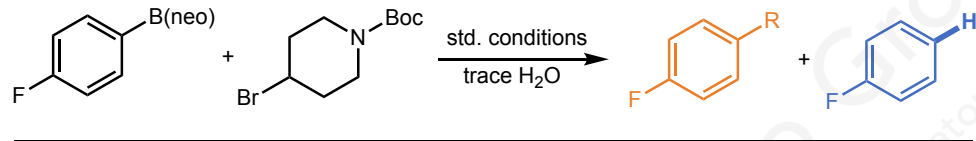
- ◆ 略过量的碱不影响产物生成速率
- ◆ 1.8倍及更高当量的碱有显著的抑制作用



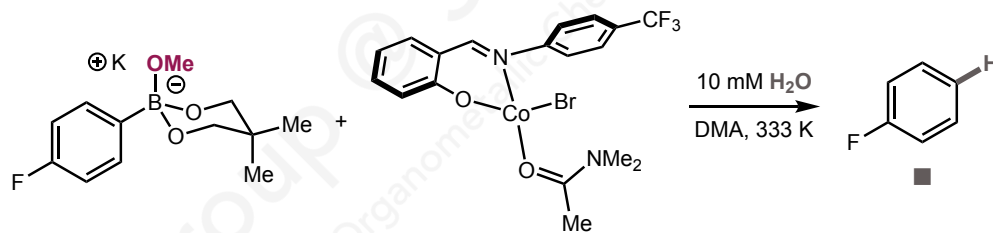
- ◆ 略过量的碱即可观察到反应速率下降

L,X-型配体不会简单解离可能还包含了钴到钾的转金属化过程

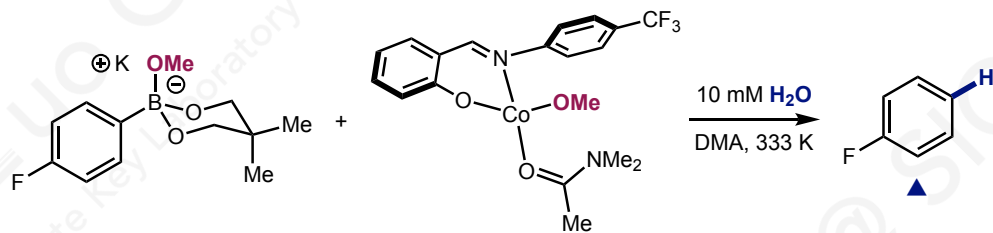
单循环脱硼氢化实验——钴和亲核试剂的作用模式



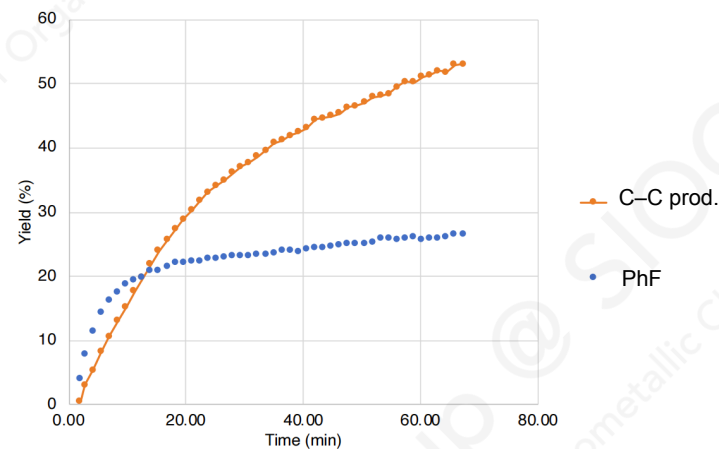
◆ 具有最低脱硼氢化效率，存在 5 min 的诱导期，动力学不利



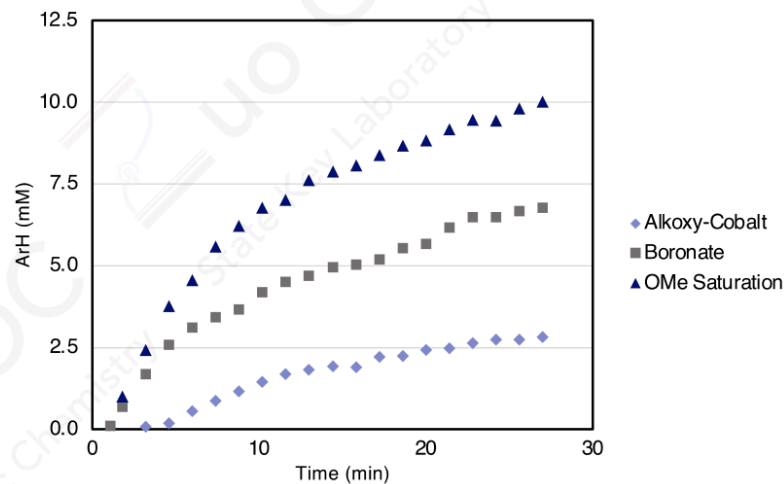
◆ 脱硼氢化效率更高，无需诱导期



◆ 脱硼氢化效率最高，动力学最有利



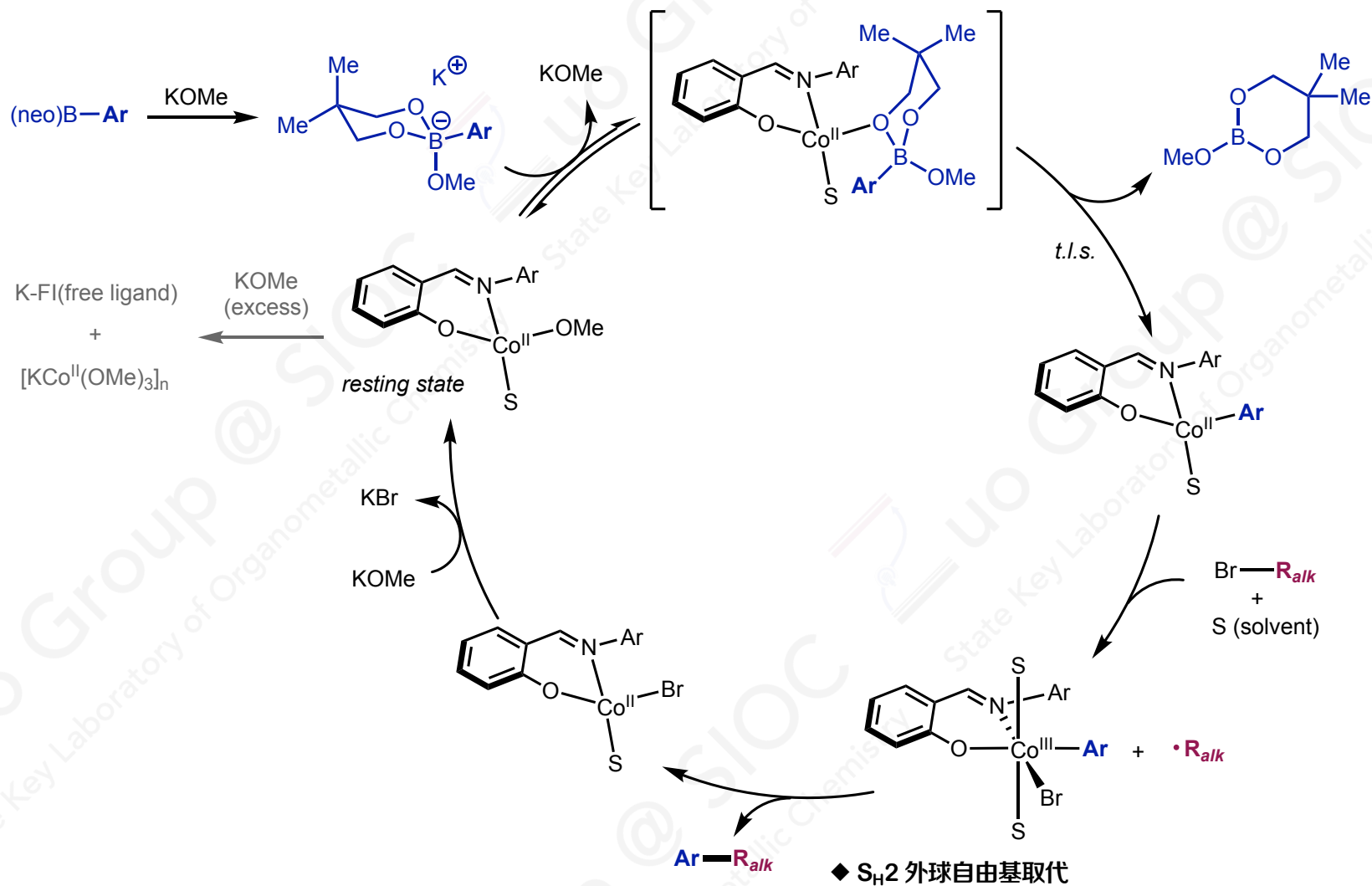
◆ 反应初期脱硼氢化速率快于碳碳键形成故将氟苯的形成作为转金属化的探针



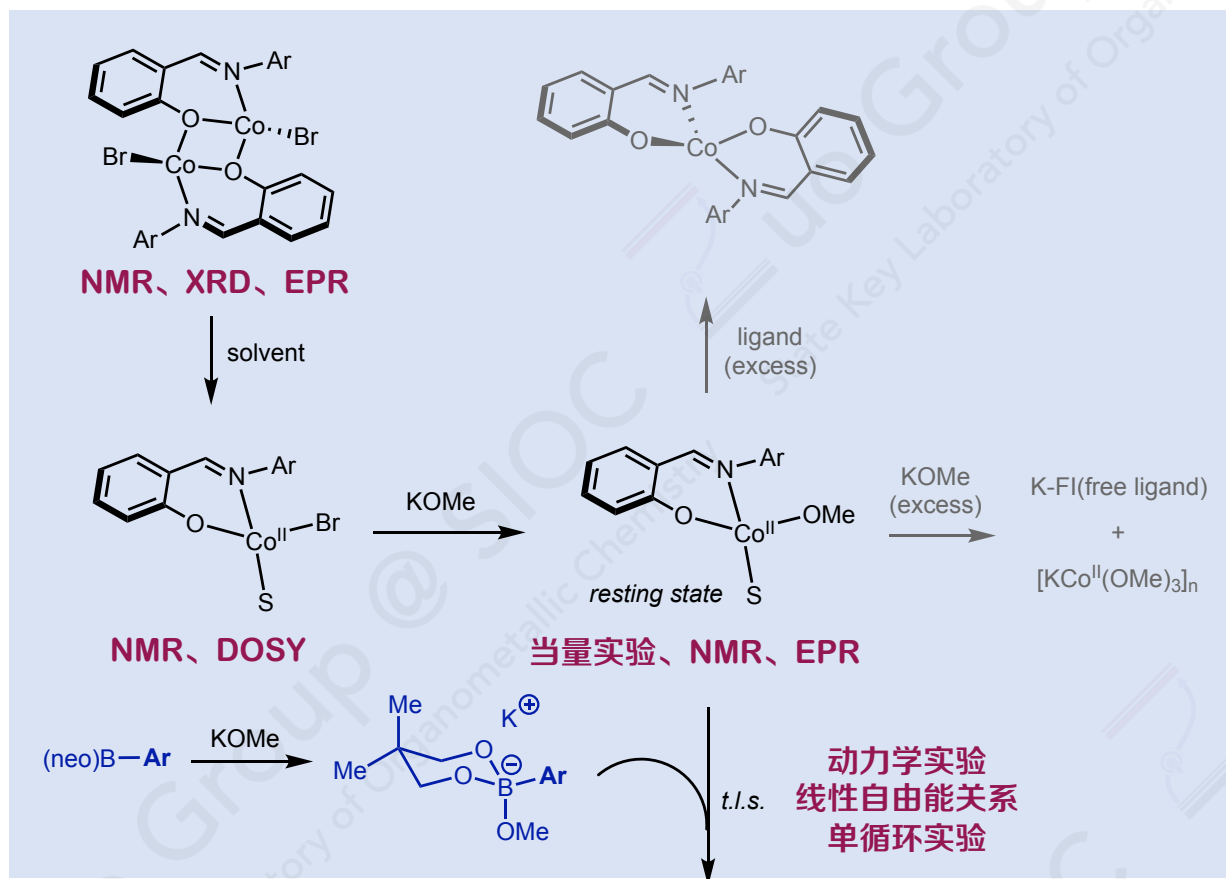
进一步说明甲氧基钴和硼酸盐与转金属化步骤的动力学相关性

P. J. Chirik, et al. *J. Am. Chem. Soc.* **2023**, 145, 17029.

推测的机理



机理研究总结

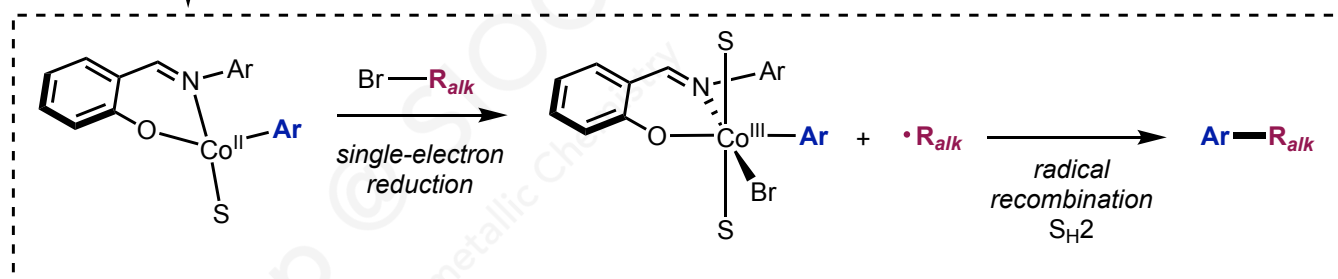


没有生成低价钴物种

EPR、NMR、氧化性探针

略过量的碱没有抑制作用

对比实验



L,X-配体不易解离且对高价态钴有利

缺乏证据：

芳基钴物种

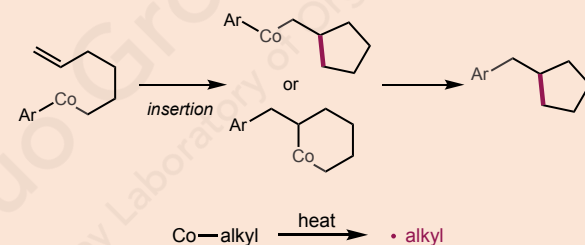
烷基溴与钴的作用

三价钴中间体

当量实验、原位表征/分离鉴定

自由基由单电子还原产生

自由基钟实验



与理论计算结合进一步验证

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