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Total Synthesis of (−)-Oridonin: An Interrupted Nazarov Approach

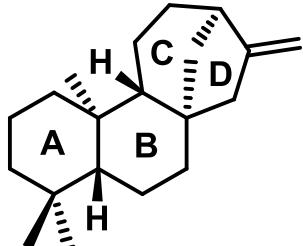
Lingran Kong,^{†,§} Fan Su,^{†,§} Hang Yu,[†] Zhe Jiang,[†] Yandong Lu,[†] and Tuoping Luo^{*,†,‡,§,||D}

[†]Key Laboratory of Bioorganic Chemistry and Molecular Engineering, Ministry of Education and Beijing National Laboratory for Molecular Science, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

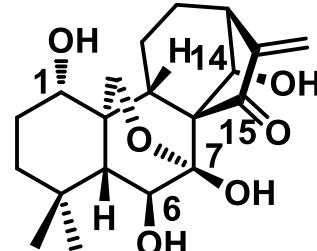
[‡]Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing 100871, China

 Supporting Information

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ent-kaurene (1)



(-)Oridonin (2)

- As a matter of fact, it is the major active ingredient of *Rabdosia rubescens*, an over-the-counter anti-inflammatory herbal medicine commonly available in China.
- Furthermore, recent researches have also piqued interest in the potential of **2** in the area of neuroprotection and neurodegenerative diseases.
- In terms of the mechanism-ofaction studies, a number of target proteins have been identified to react with the α -methylene cyclopentanone unit of **2**.
- Although semisynthesis of oridonin has been achieved and significant progress has been made in the chemical synthesis of ent-kaurenoids with high oxidation level, oridonin (**2**) still presents a daunting task for total synthesis, inviting the development of new and effective synthetic strategies given its unique structural features.

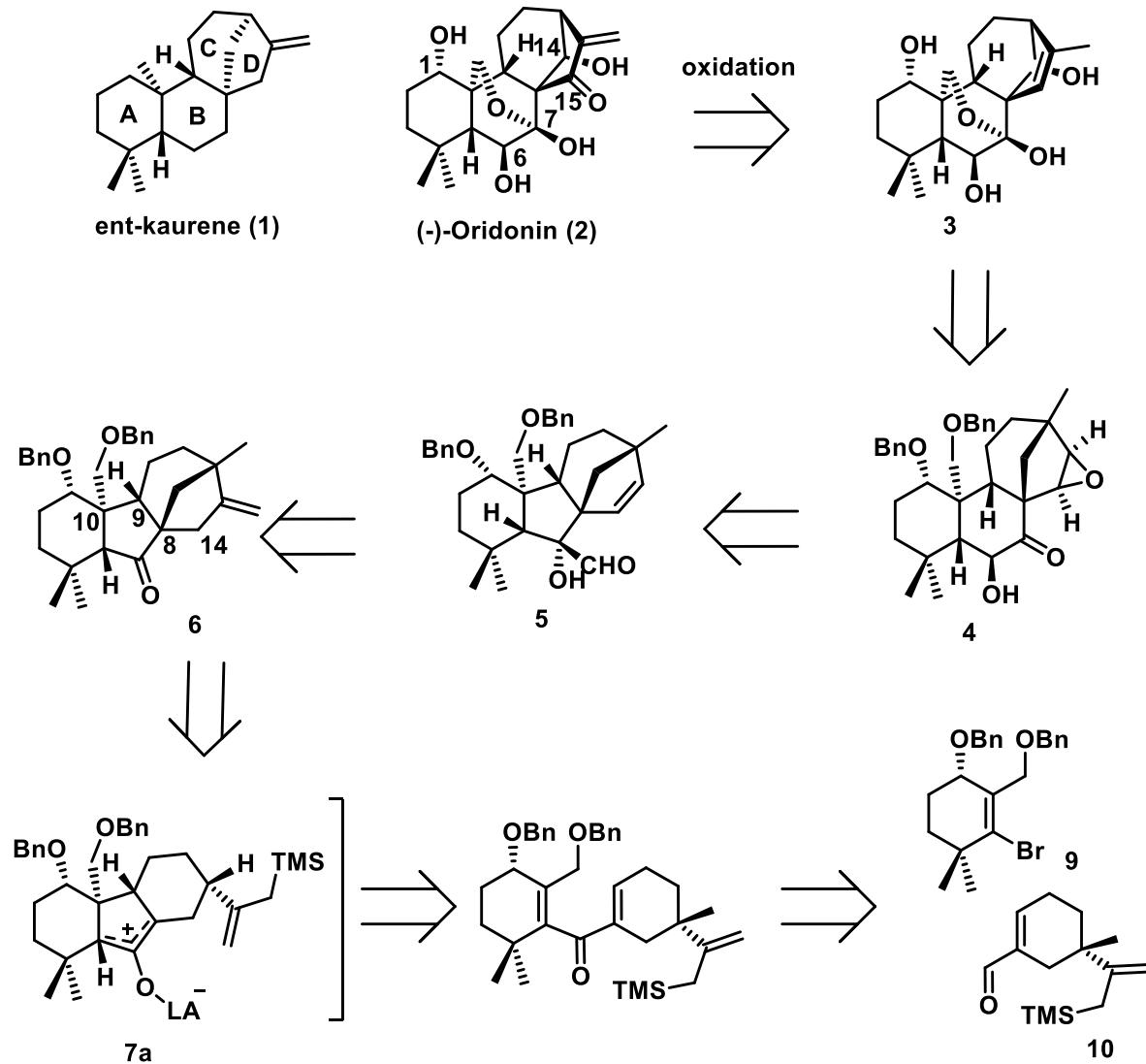
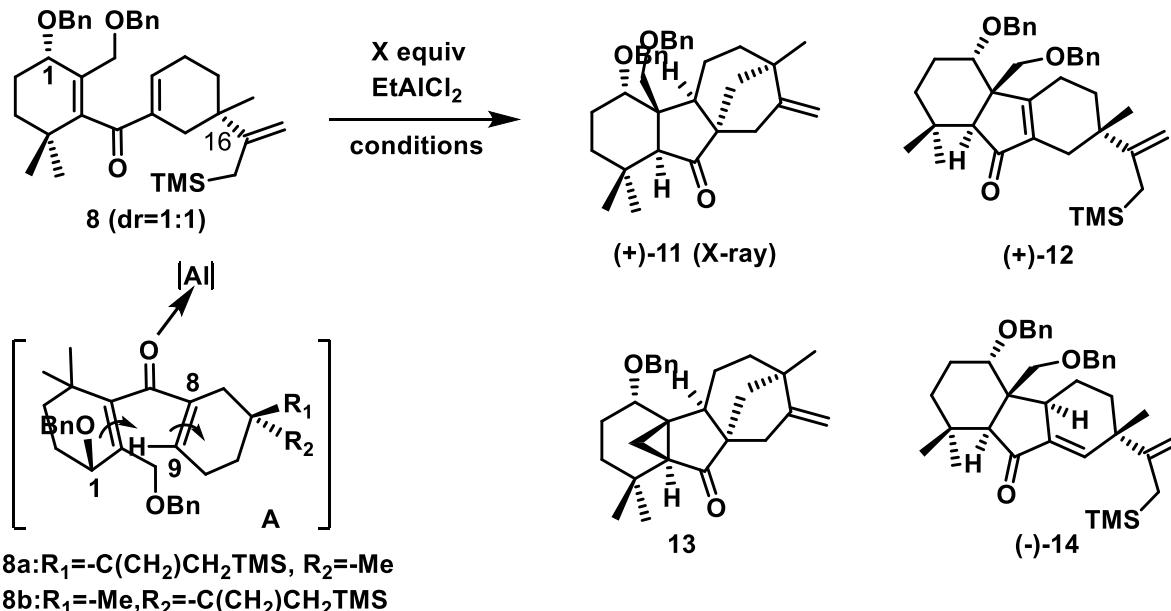
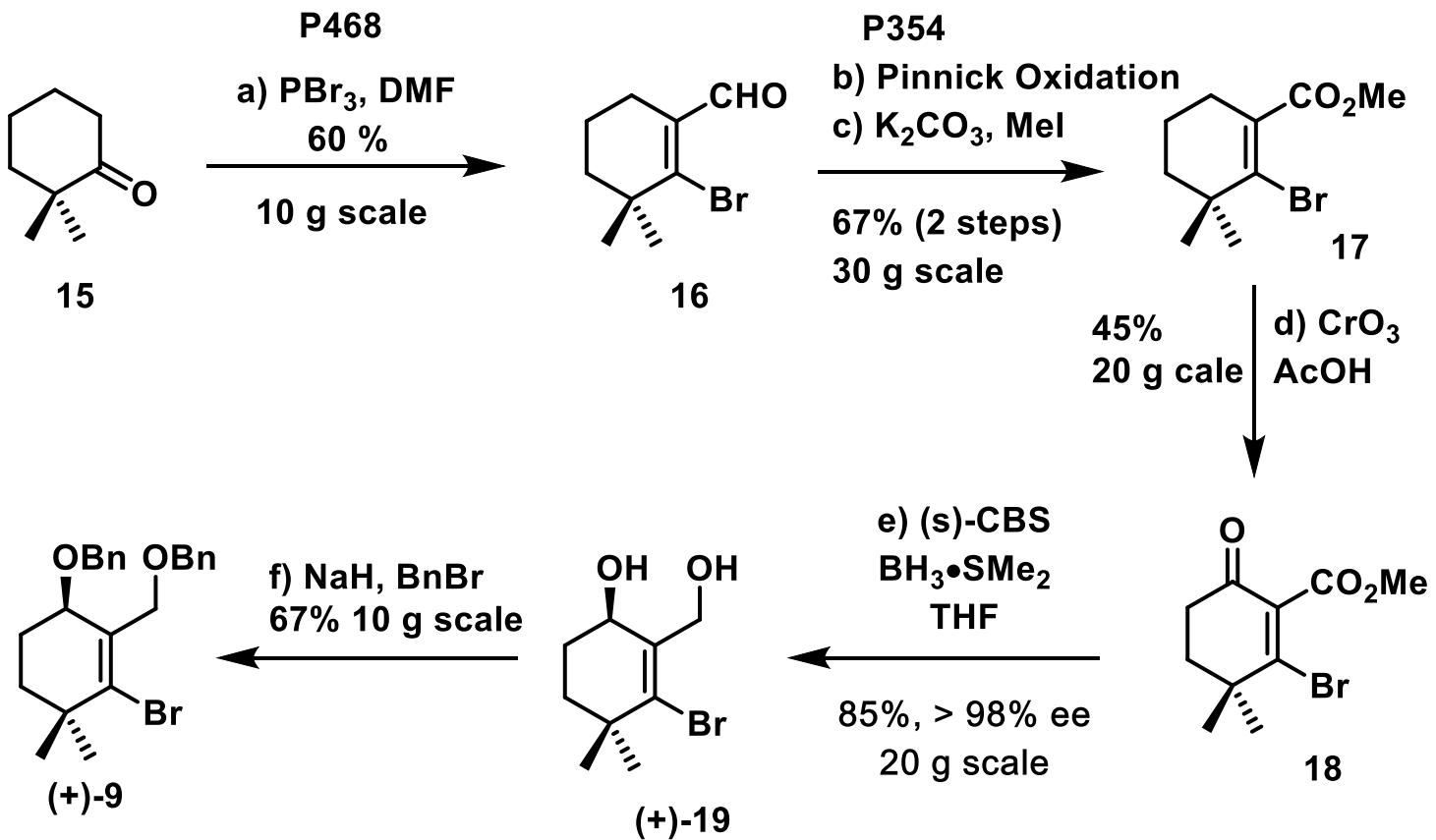


Figure 1. (-)-Oridonin (**2**) and its retrosynthetic analysis.



entry	X	conditions	yield (%) ^a			
			11	12	13	14
1	0.3	DCM, 40 °C, 2 h ^b	24	13	0	0
2	2	THF, 40 °C, 24 h ^{b,c}	0	0	0	0
3	0.35	MeCN, 40 °C, 8 h ^b	15	27	0	0
4	0.3	DCM, 40 °C, 1 h ^d	23	nd	0	0
5	0.35	MeCN, 40 °C, 8 h ^d	20	43	10	0
6	1.5	DCM/THF = 20:1, 40 °C, 24 h ^d	32	0	0	20
7	1.5	DCM/THF = 20:1, 40 °C, 24 h ^e	35	0	0	21

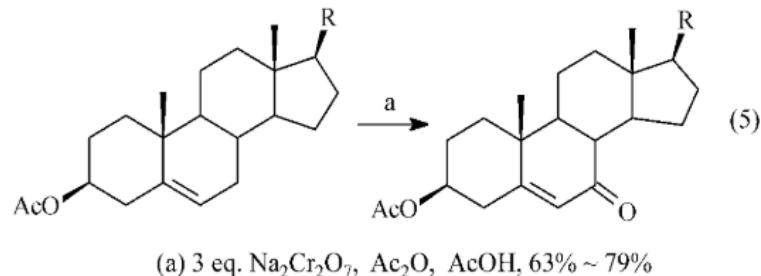
^aIsolated yield after flash chromatography. ^b[8] = 0.05 M (0.04 mmol). ^cSubstrate 8 was recovered. ^d[8] = 0.05 M (0.4 mmol). ^e[8] = 0.1 M (2 g scale).



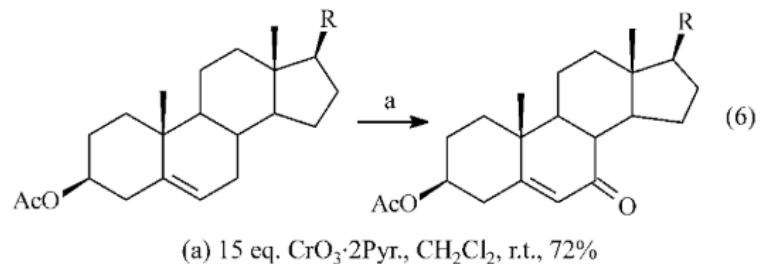
Reagents and conditions: (a) PBr_3 , DMF, CHCl_3 , 0 to 70°C , 60%; (b) NaHPO_4 , H_2O_2 , NaClO_2 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0 to 30°C ; (c) K_2CO_3 , CH_3I , DMF, rt, 67% (2 steps); (d) CrO_3 , AcOH , Ac_2O , DCM, rt, 45%, 67% brsm; (e) (S)-oxazaborolidine (0.60 equiv), $\text{BH}_3 \bullet \text{SMe}_3$ (1.6 equiv), THF, 0°C , then 18, -40°C , 85%; (f) NaH , BnBr , THF, 30°C , 67%;

1.2 铬盐为氧化剂的烯丙位氧化

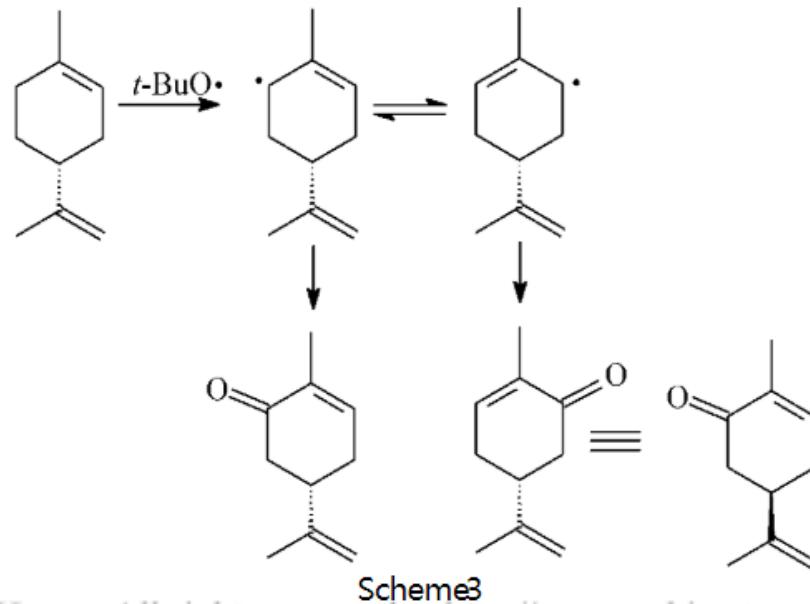
含金属铬离子的化合物作为烯丙位氧化剂是比较常见的。早期应用的是重铬酸钠(Eq. 5)^[13, 14]，因为重铬酸钠的氧化性过强，且反应需要醋酸，这使得其应用范围收到很大影响。

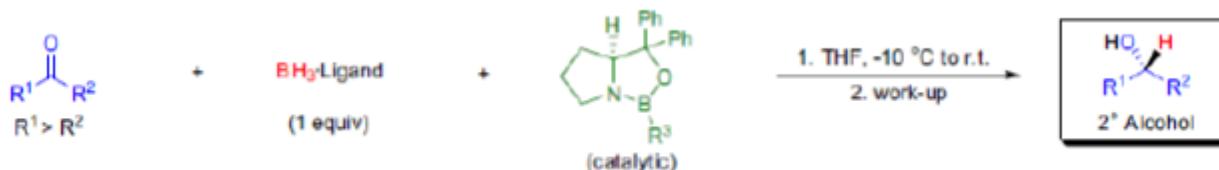


Collins 试剂($\text{CrO}_3 \cdot 2\text{Pyr}$)是较温和的常用试剂之一(Eq. 6)^[15]。

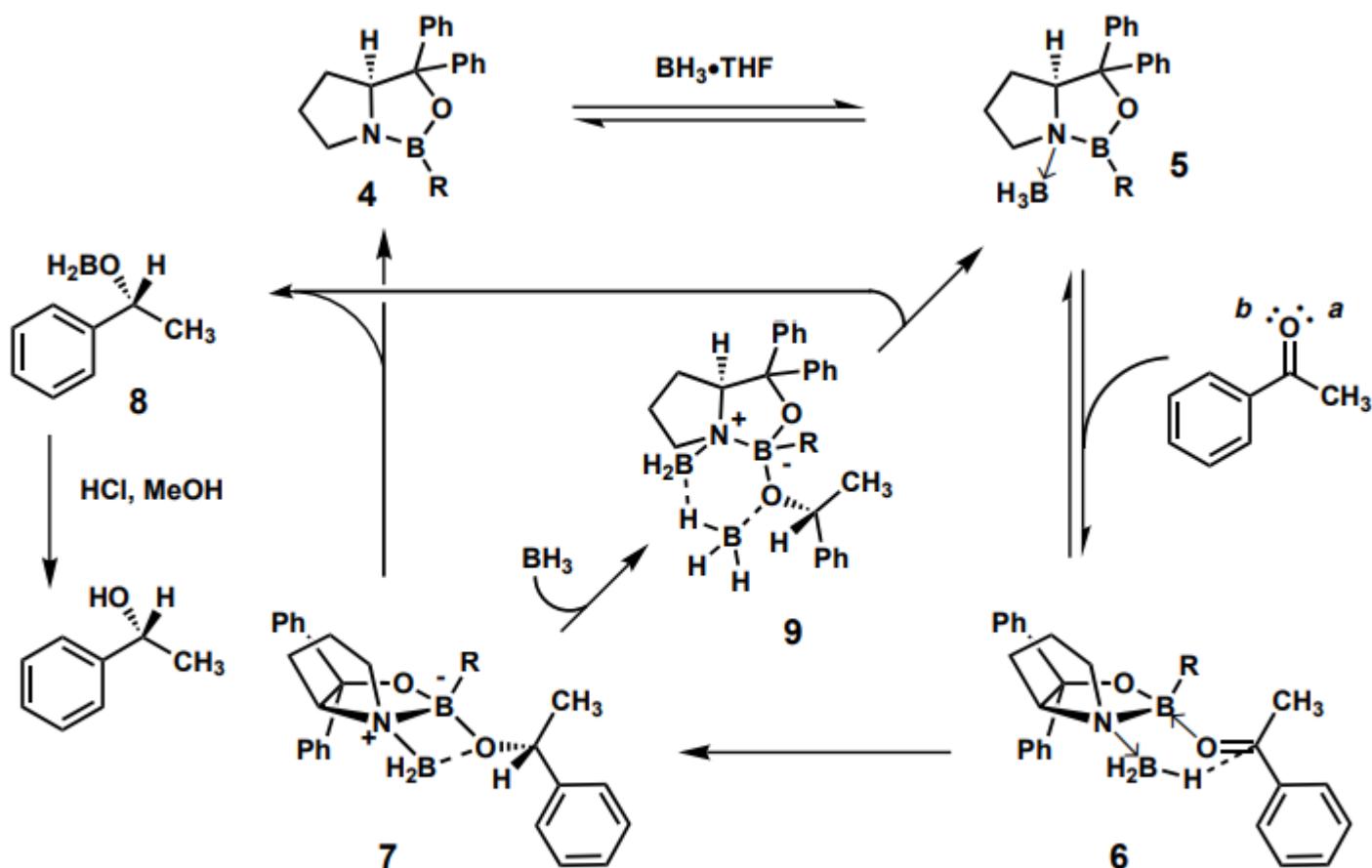


在如下的反应中，烯丙位的氧化是在有硅胶载体存在下进行(表 5)^[21]。载体是含 0.018 mmol/g 的 CrO_3 和 ZrO_2 的硅胶吸附物，反应中用 0.007~0.02 eq. CrO_3 和 2 eq. TBHP。这个氧化反应表现出一定的区域选择性：烯丙位只有为仲碳时才被氧化；处于环系内的优先于非环系的烯丙位碳。产物的消旋是由 Scheme 3 所示的反应的自由基机理决定的。

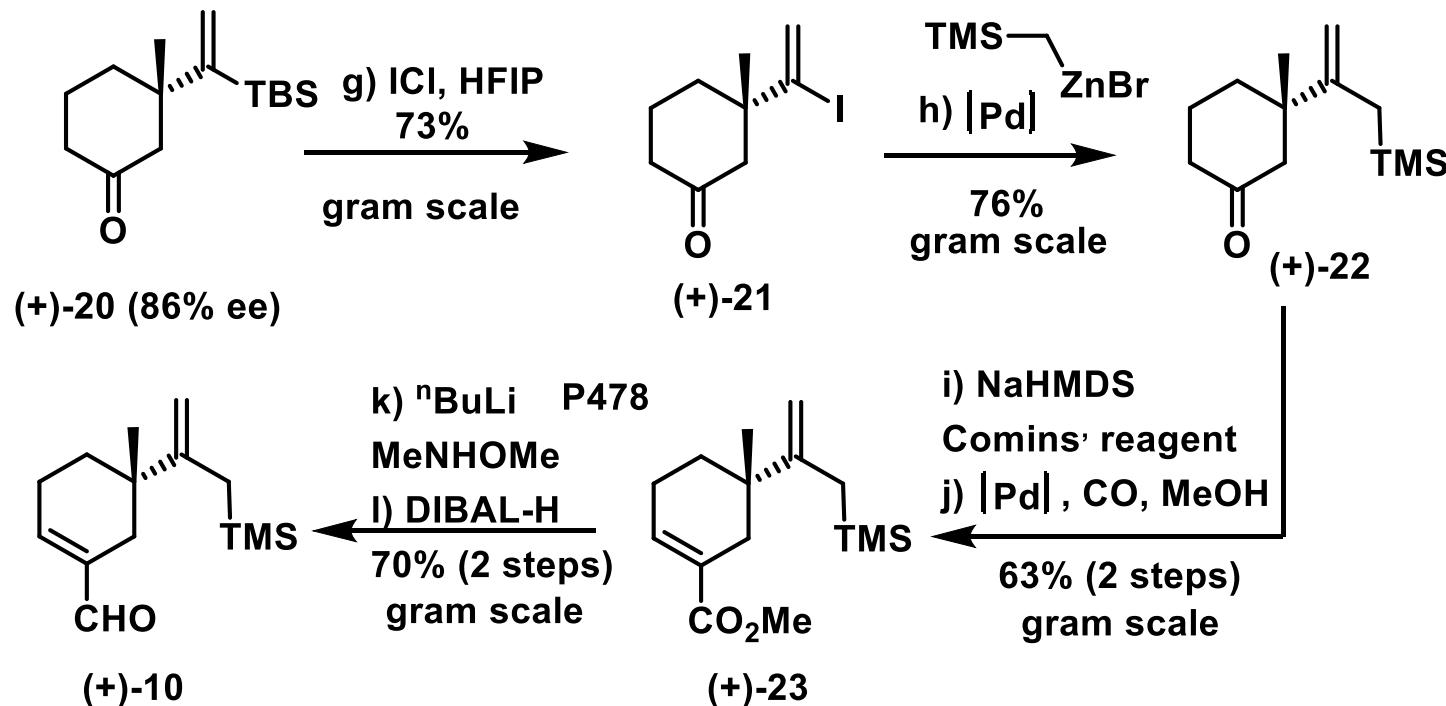




$\text{R}^{1,2}$ = alkyl, aryl; Ligand: THF, Me_2S , 1,4-thioxane, diethylaniline; R^3 = H, alkyl

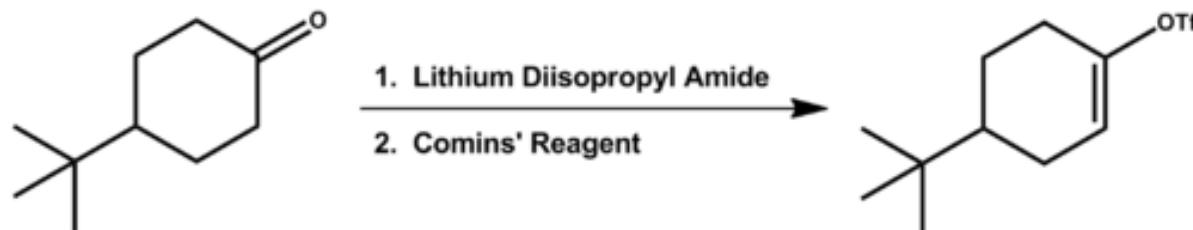


Scheme 5. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines **4**.

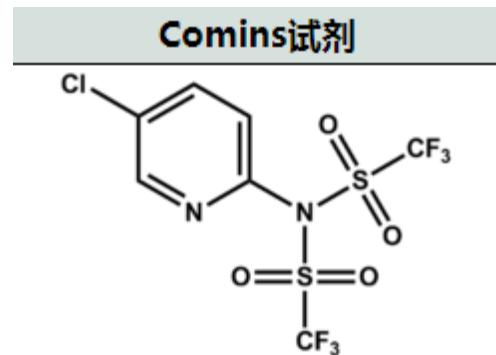


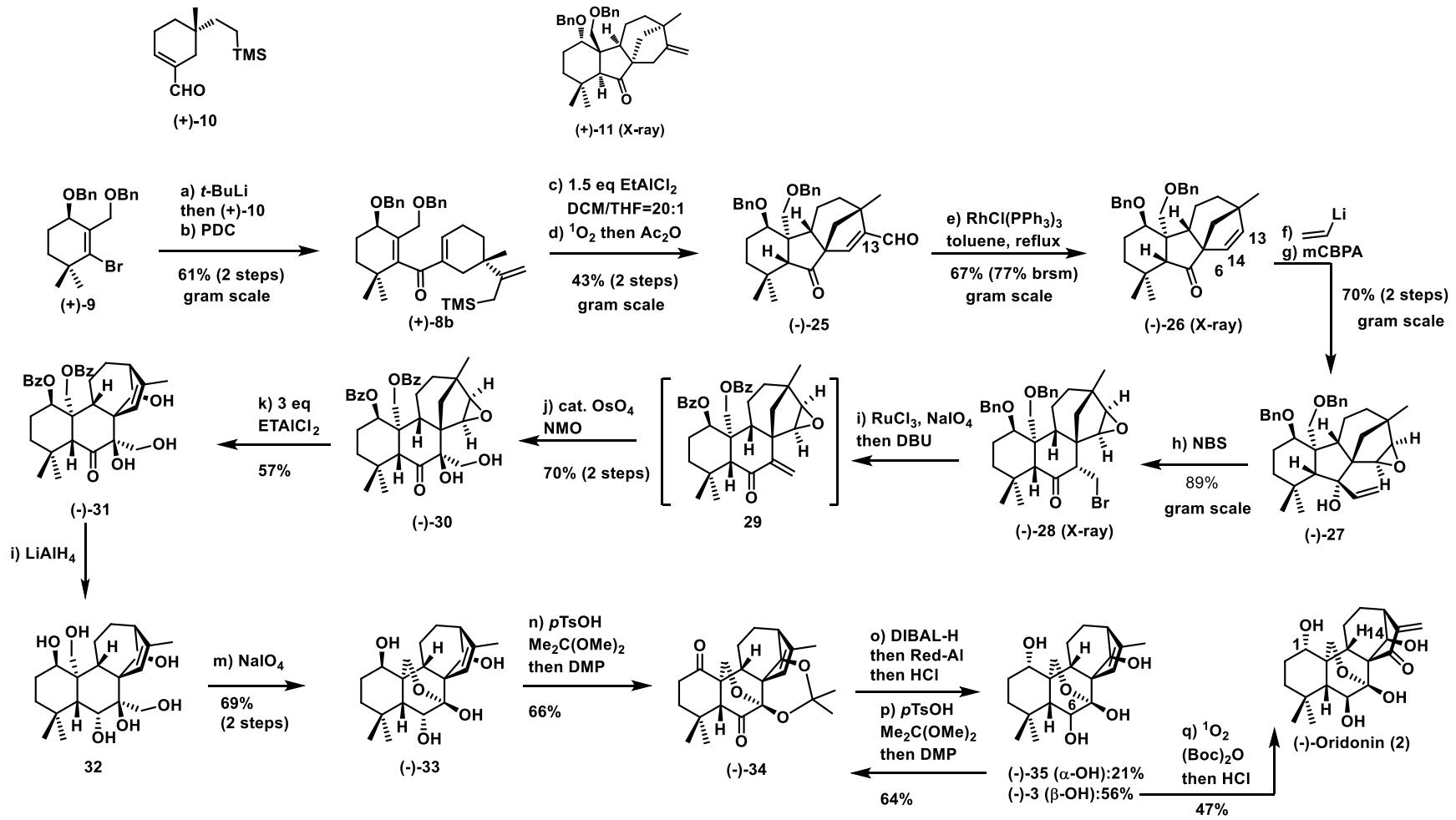
(g) ICl, diglyme, HFIP, 40 °C, 73%; (h) $\text{Pd}(\text{MeCN})_2\text{C}_2$ (0.1 equiv), $\text{TMSCH}_2\text{ZnBr}$, DMF, 45 °C, 76%; (i) NaHMDS, diglyme, then Comins' reagent, *t*-BuOMe, -78 °C; (j) $\text{Pd}(\text{OAc})_2$ (0.12 equiv), PPh_3 (0.24 equiv), CO, Et_3N , DMF/MeOH, 45 °C, 63% (2 steps); (k) $\text{CH}_3\text{NHOCH}_3 \cdot \text{HCl}$, *n*-BuLi, THF, -78 °C; (l) DIBAL-H, THF, -78 °C, 70% (2 steps).

Comins试剂是一种三氟甲磺酰化合物，可用于从相应的酮烯醇式合成三氟甲磺酸酯。^[1]



它最早由Daniel Comins于1992年报道。^[2] 三氟甲磺酸乙烯酯对于铃木反应来说是很有用的底物。^[3]



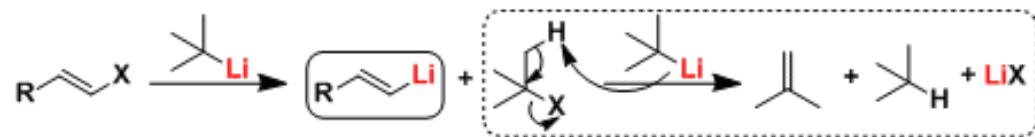


^a Reagents and conditions: (a) $t\text{-BuLi}$, Et_2O , -78°C , then (+)-10; (b) PDC, DMF, 0 $^\circ\text{C}$ to rt, 61% (2 steps); (c) EtAlCl_2 , DCM/THF = 20:1, 40 $^\circ\text{C}$; (d) TPP, O_2 , CDCl_3 , rt, then Ac_2O , pyridine, DMAP, rt, 43% (2 steps); (e) $\text{RhCl}(\text{PPh}_3)_3$, toluene, reflux, 67%, 77% brsm; (f) vinyl bromide, $t\text{-BuLi}$, -78°C , then (-)-26, 0 $^\circ\text{C}$; (g) $m\text{CPBA}$, NaHCO_3 , DCM, 0 $^\circ\text{C}$, 70% (2 steps); (h) NBS, DCM, rt, 89%; (i) $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 , $\text{CH}_3\text{CN}/\text{CCl}_4$, 0.2 M buffer, rt, then DBU; (j) OsO_4 , NMO, acetone/ H_2O , 40 $^\circ\text{C}$, 70% (2 steps); (k) EtAlCl_2 , toluene, 0 $^\circ\text{C}$ to rt, 57%; (l) LiAlH_4 , Et_2O , rt; (m) NaIO_4 , THF/buffer, 10 $^\circ\text{C}$ to rt, 69% (2 steps); (n) $p\text{TsOH}$, 2,2-dimethoxypropane, acetone, rt, then NaHCO_3 , DMP, DCM, 0 $^\circ\text{C}$ to rt, 66%; (o) DIBAL-H, DCM/ether, -100°C to rt, then Red-Al, rt, then $\text{HCl}(\text{aq})$ 35, 21%; 3, 56%; (p) $p\text{TsOH}$, 2,2-dimethoxypropane, acetone, rt, then NaHCO_3 , DMP, DCM, 0 $^\circ\text{C}$ to rt, 64%; (q) TPP, O_2 , CDCl_3 , rt, then $(\text{Boc})_2\text{O}$, pyridine, DMAP, DCM, 0 $^\circ\text{C}$, then $\text{HCl}(\text{aq})$, dioxane, 47%. PDC, pyridinium dichromate; TPP, 5,10,15,20-tetraphenylporphyrin; $m\text{CPBA}$, m -chloroperoxybenzoic acid; NBS, N -bromosuccinimide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMP, Dess–Martin periodinane; NMO, 4-methylmorpholine N -oxide.

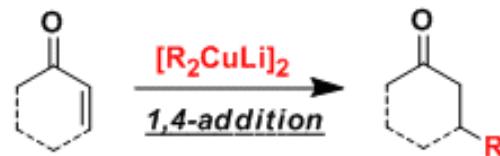
◦ 反应机理

锂-卤素交换反应是依照单电子移动(SET)机理或者是卤素位的亲核加成-消除机理进行的。

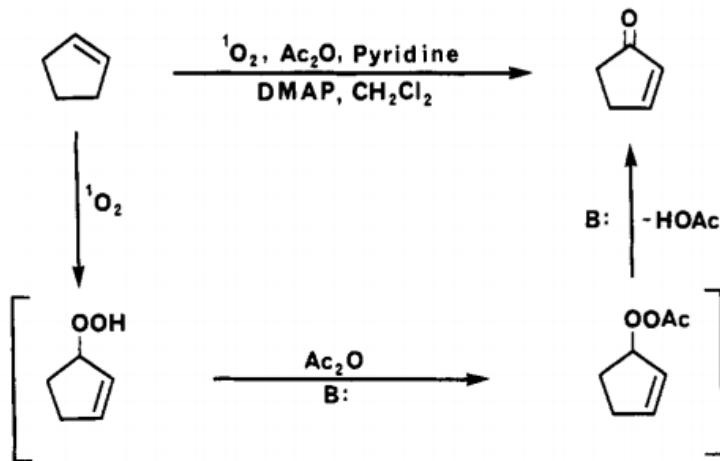
(参考：*J. Organomet. Chem.* 1988, 352, 1.) 使用t-BuLi进行锂-卤素交换反应的时候，相对于卤代底物，二当量的锂试剂是必须的。(为了使得金属锂交换后生成的t-丁基卤化物与另一当量的t-BuLi反应消耗)



※另外，作为亲核试剂使用的时候，可以转化成銅锂配合物(R_2CuLi)、该试剂的碱性被有效抑制，而其亲核性不变，可以一哦那个与亲核加成或取代反应。锂试剂比较hard，与 α,β 不饱和羧基化合物进行反应的时候、1,2-加成往往优于1,4-加成。而形成銅锂配合物后，该试剂可以用于1,4-选择性加成反应。



Scheme I

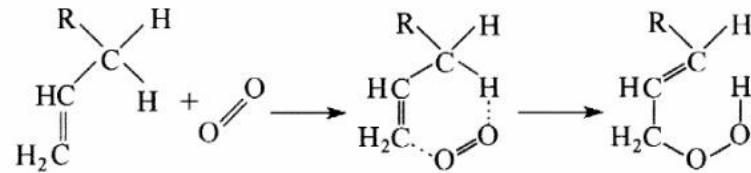


J. Org. Chem. **1983**, *48*, 4135-4137.

烷基取代的烯烃与 ${}^1\text{O}_2$ 反应生成氢过氧化物，同时双键移动到 α -位。

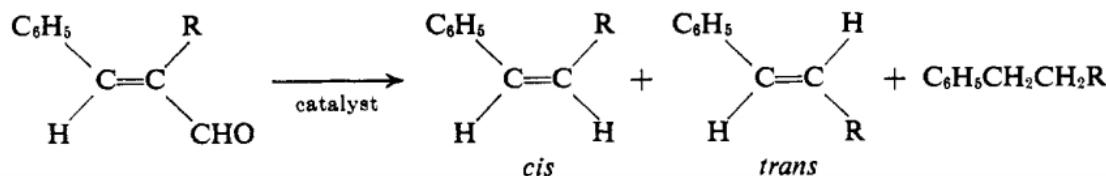


机理



反应中，单线态氧既与双键发生加成，又提取双键邻位取代基上的氢原子，生成氢过氧化物，同时导致双键移位。

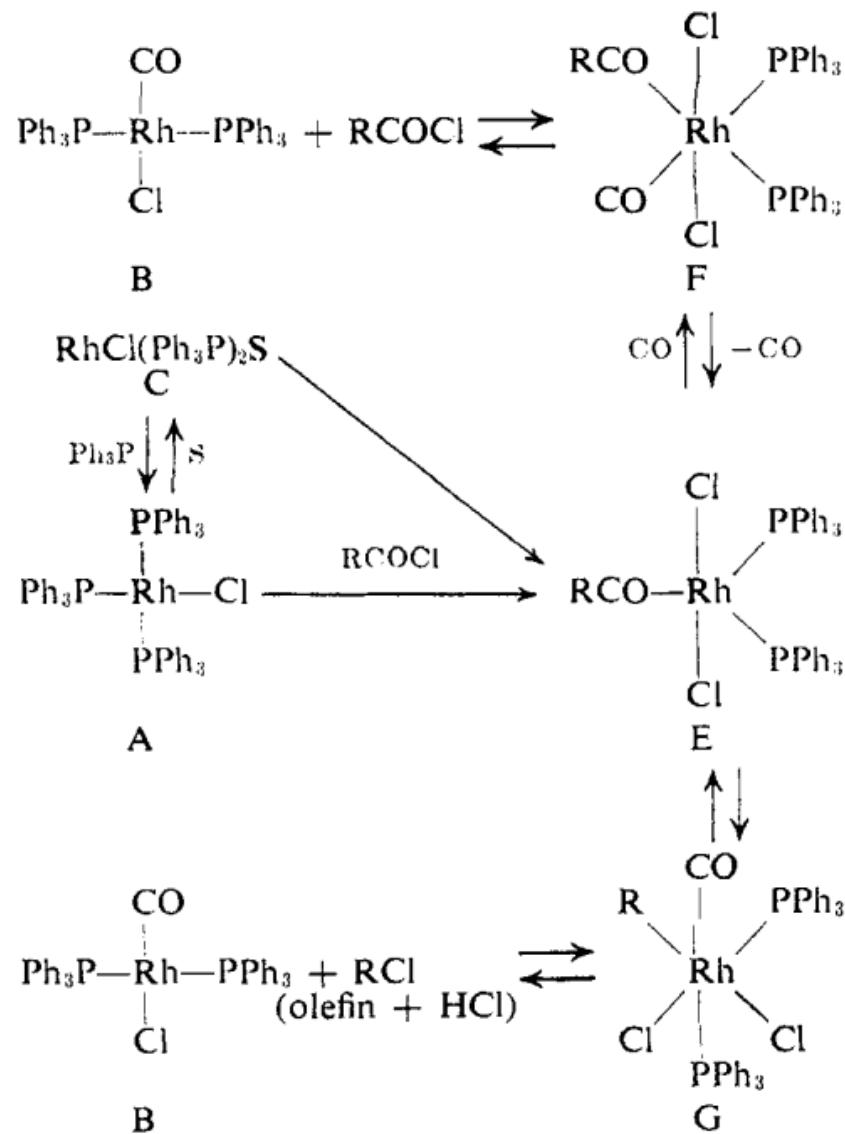
Table VI. Decarbonylation of Substituted Cinnamaldehydes



R	Amt, g	Catalyst	Amt, g	Reaction			Con- ver- sion, %	Yield, %	Product distribution, %		
				Temp, °C	Time, hr	cis			trans	A	
CH ₃	10	PdCl ₂	0.2	250–260	4.5	80	78 ^a	67	33	0	
CH ₃	10	RhCl(CO)(Ph ₃ P) ₂	0.1	250–260	7	67	77 ^a	88	12	0	
CH ₃	10	RhCl(CO)[(p-CH ₃ OC ₆ H ₄) ₃ P] ₂	0.25	250–260	4	87	87 ^a	90	10	0	
CH ₃ CH ₂	10	PdCl ₂	0.2	250–260	9	..	76 ^b	38.5	49.3	12.2	
CH ₃ CH ₂	10	RhCl(CO)(Ph ₃ P) ₂	0.3	250–260	3	91	87 ^a	80	20	Trace	

^a Yield based on the converted aldehydes. ^b Yield based on the charged aldehyde.

Scheme II



The decarbonylation of aldehydes can be explained in the same way. Instead of acyl halides, aldehydes undergo the oxidative addition and the whole process can be expressed by replacing the chlorine atom with hydrogen in the mechanism shown for acyl halides.

此类的保护基是比较强的保护基，一般不使用相对强的酸性条件的话是无法脱去的。在全合成的最终阶段的时候，这种难脱去的保护基经常会带来很多麻烦。

如果使用四氧化钌的话，可以氧化转化成甲基酯，或者苯基酯。然后用比较温和的碱性条件，可以进行选择性的脱保护。



•四氧化钌(RuO_4)是一种反磁性的、正四面体构型的钌化合物。正如理论预测的那样，它是对称的非极性分子，但很不稳定。现在的使用方法是使用催化量的四氧化钌，或者向乙腈、水和四氯化碳的溶剂中添加高碘酸钠（作用是氧化三氯化钌）使它循环再生，大大减少了四氧化钌的使用量。

因为四氧化钌很贵，所以往往使用催化量的前体和便宜的再氧化剂在体系中形成Ru(VIII)的方法。溶剂的话经常使用不与反应试剂反应的四氯化碳。另外，四氧化钌会与醚类溶剂剧烈反应。如果底物能跟氧化剂配位的话，氧化剂就会失活。但是可以利用添加配位性混合溶剂比如乙腈的方法来防止。综上所述、 $\text{RuCl}_3(\text{cat.})\text{-NaIO}_4/\text{CH}_3\text{CN-CCl}_4\text{-H}_2\text{O}$ 二相体系是用的最多的。

反应机理

首先溶解在有机相中的 RuO_4 不断地被消耗生成水溶性的 RuO_2 转移到水层中。再在水层中被再氧化剂氧化生成 RuO_4 回到有机相中。按照此种方法进行的催化氧化反应。

