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🔒 | RESEARCH ARTICLE | ORGANIC CHEMISTRY



Palladium-catalyzed cross-coupling of alcohols with olefins by positional tuning of a counteranion

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SCIENCE • 5 Sep 2024 • Vol 385, Issue 6713 • pp. 1067-1076 • DOI: [10.1126/science.ado8027](https://doi.org/10.1126/science.ado8027)

↓ 10,939 💬 3



Wenqian Miao
2025/01/18

Biography



M. Christina White

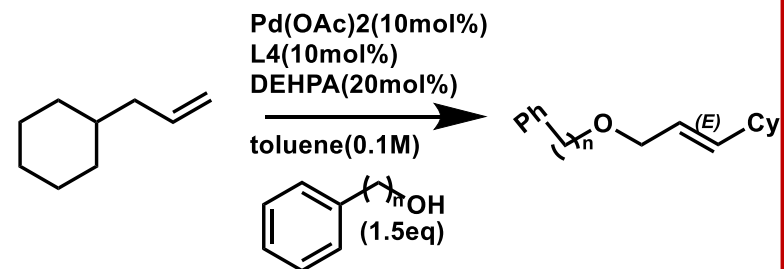
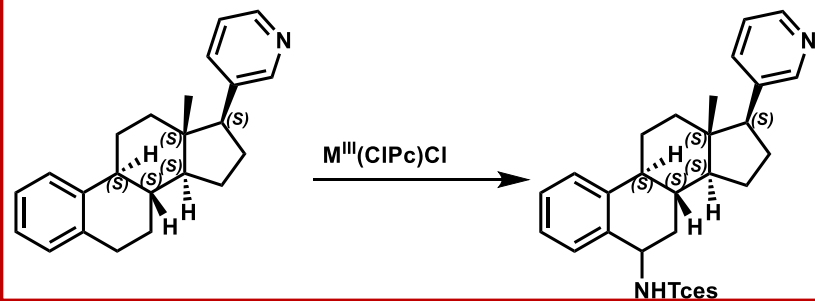
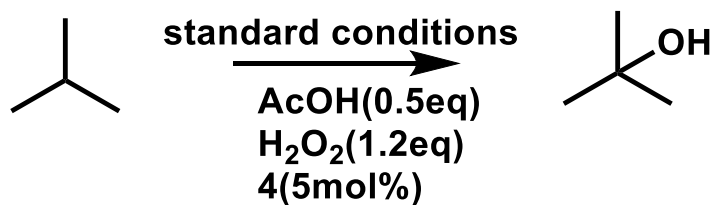
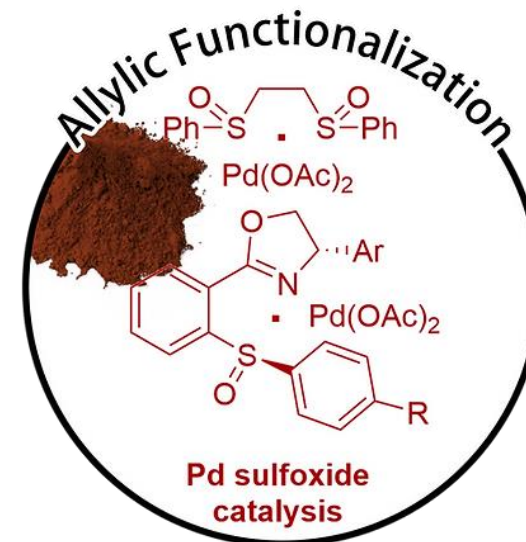
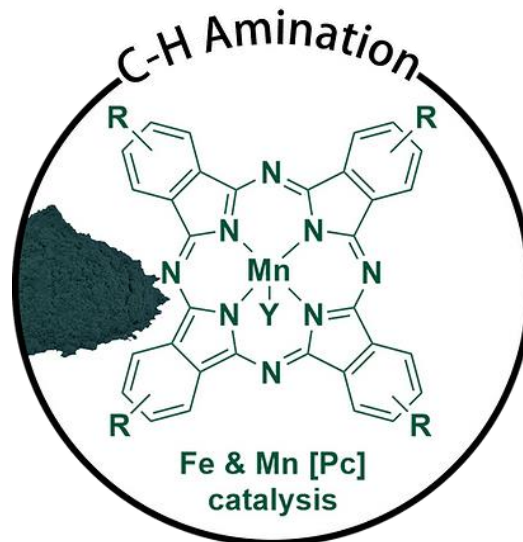
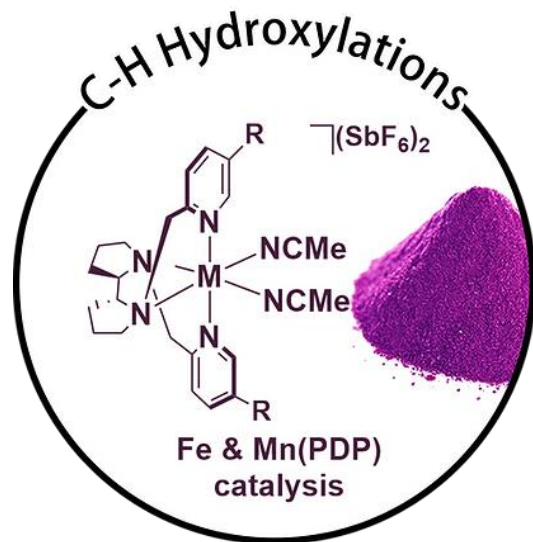
1992 She received her B.A. with highest honors in Biochemistry from Smith College




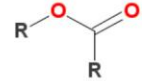





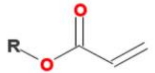
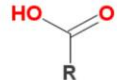

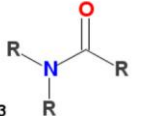
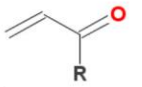
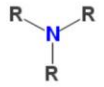

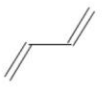
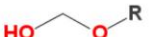
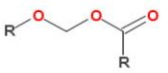
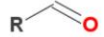
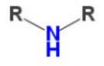
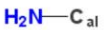


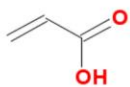


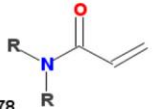

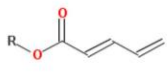




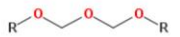
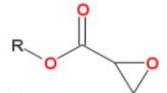
1998 She received her Ph.D. from Johns Hopkins University

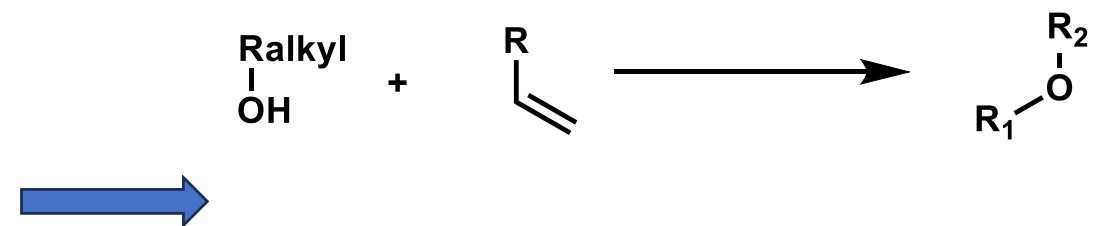
1999-2002 After a postdoctoral fellowship at Harvard University, she joined the faculty there in 2002

2005 She joined the faculty at the University of Illinois at Urbana-Champaign (UIUC)

Research



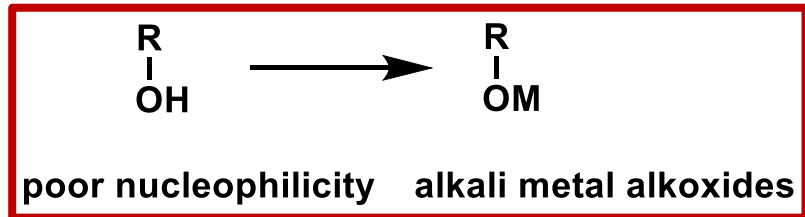
 61.07	 39.85	 35.24	 28.65	 28.43	 22.55
 15.86	 14.17	 13.60	 11.86	 10.58	 7.44
 6.73	 5.98	 5.66	 3.63	 2.97	 2.51
 2.47	 2.43	 2.23	 1.85	 1.84	 1.45
 1.30	 0.97	 0.91	 0.78	 0.61	 0.56
 0.56	 0.55	 0.55	 0.53	 0.49	 0.44



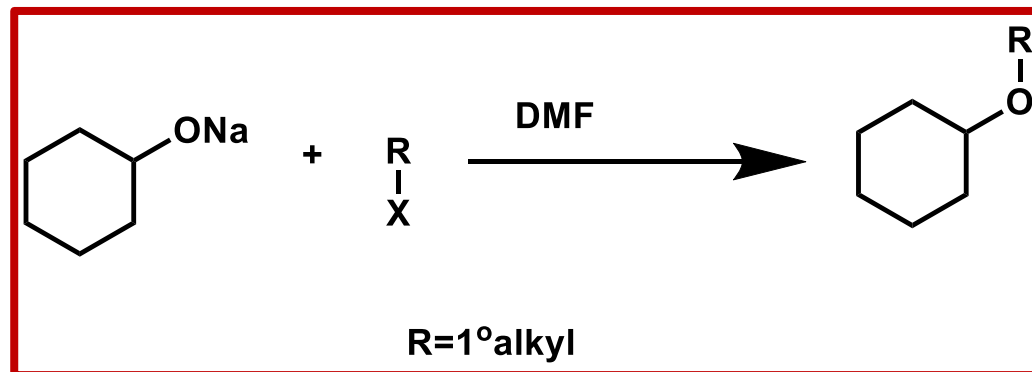
- ✓ Abundant feedstock
- ✓ Various structure
- ✓ Commercially available

Most frequent functional groups found in natural products. The number indicates percentage of molecules having this group.

Williamson ether synthesis



Williamson ether synthesis



1、 the basicity of ROM

2、 SN2

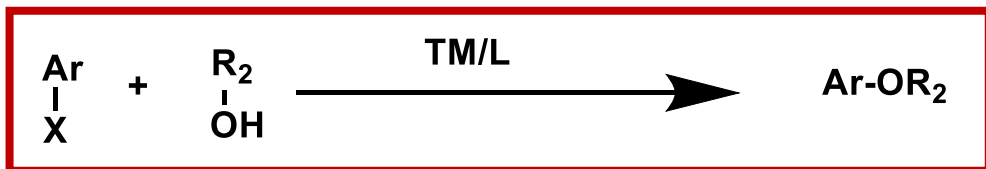
! Undesirable E2 eliminations

! Poorly suited to furnishing ethers in sterically hindered

! Racemization

! Poor control of site selectivity in polyol settings

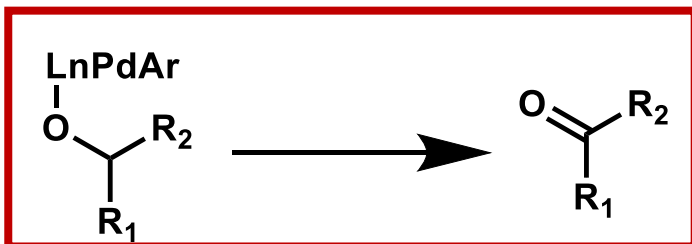
Transition metal-mediated crosscoupling



1、Forming C-O bond by reductive elimination is challenging

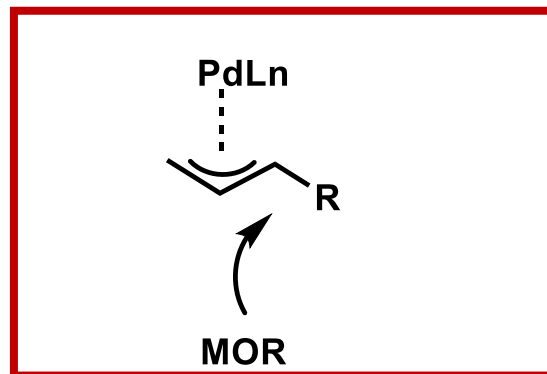


2、 β -hydride elimination byproducts



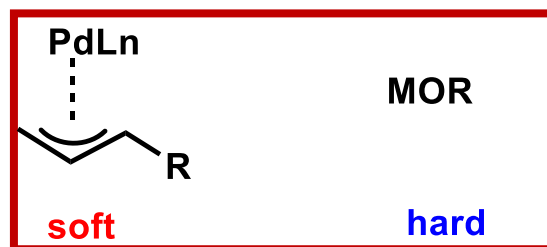
J. Am. Chem. Soc. 121, 3224–3225 (1999)
Org. Lett. 22, 5369–5374 (2020).

Allylic C–H functionalization



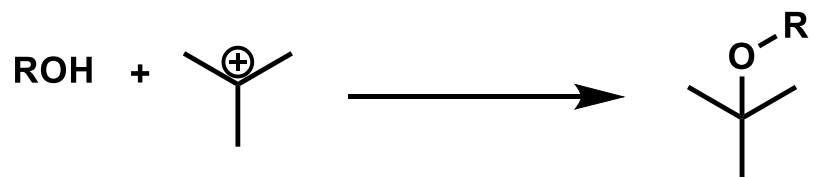
1、Undesirable E2 eliminations

2、mismatch between hard alkali metal alkoxide the relatively soft p-allyl transition metal electrophile

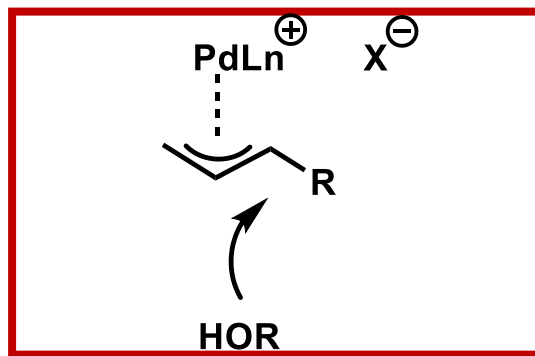
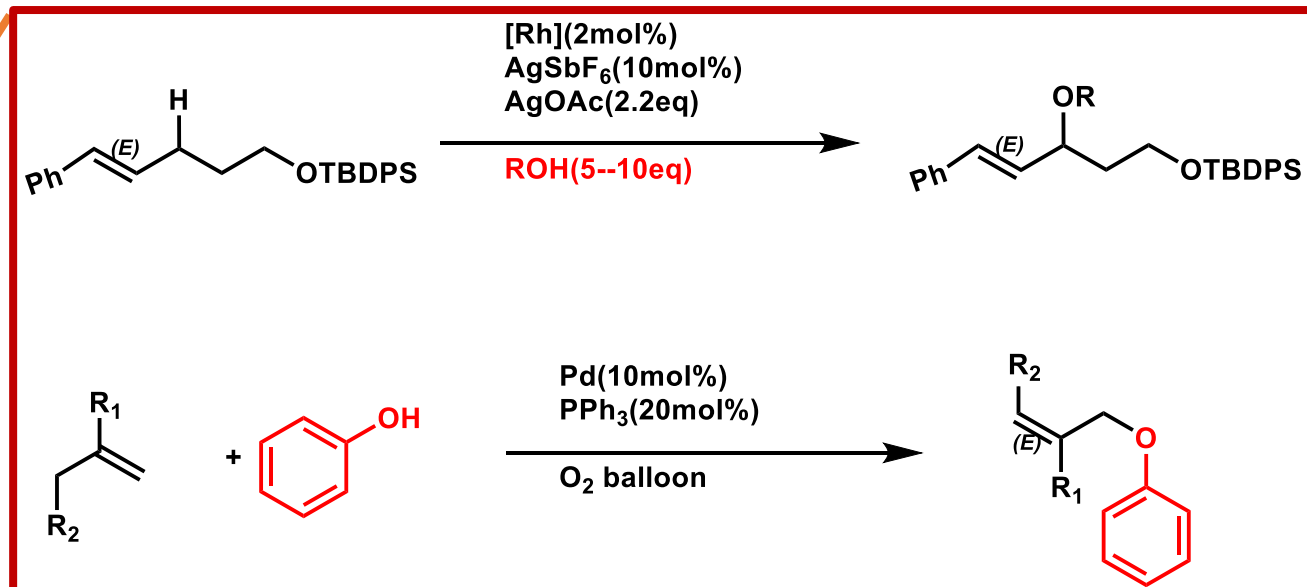


J. Am. Chem. Soc. 124, 7882–7883 (2002).
J. Org. Chem. 50, 3558–3566 (1985).

SN1



Reductive etherification

Cationic π -allyl-metalCationic π -allyl-metal

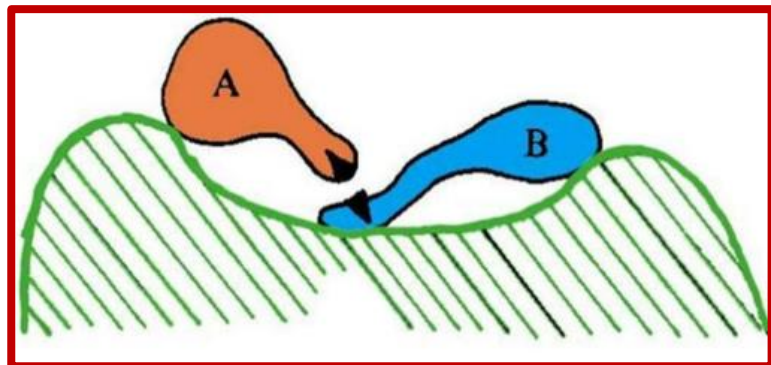
- Superstoichiometric quantities of the alcohol are needed
- Limited to simple styrenyl products

J. Org. Chem. 82, 10912–10919 (2017).

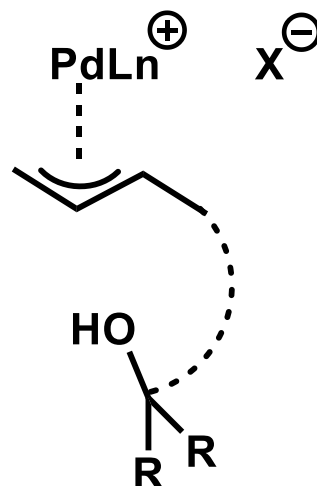
Angew. Chem. Int. Ed. 57, 14911–14915 (2018).

Hypothesis: Increasing the rate of the bimolecular C(sp³)-O bond formation step would be the fundamental challenge and key-----proximity and orientation

Enzymes

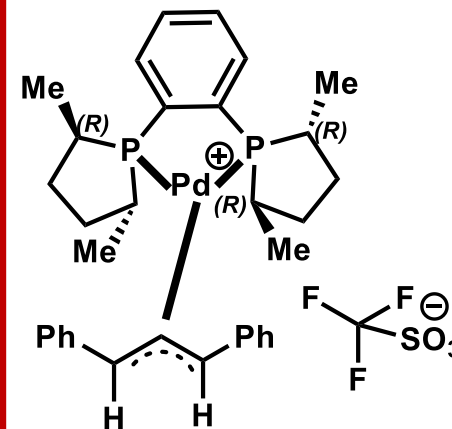


Substrate-enforced proximity

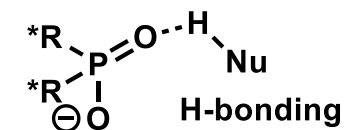


Ligand environment

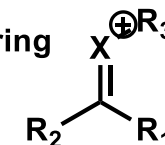
counterion orientation



proximity

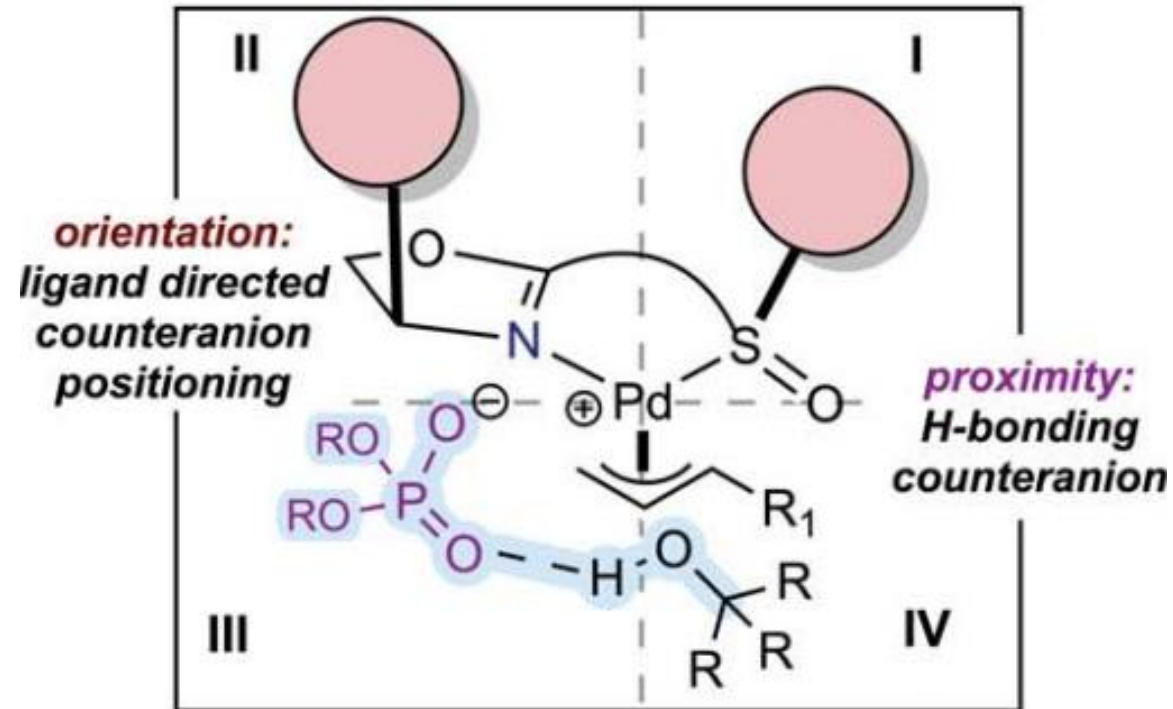


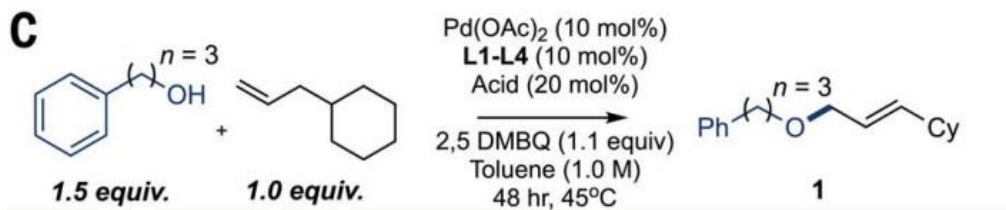
ion-pairing



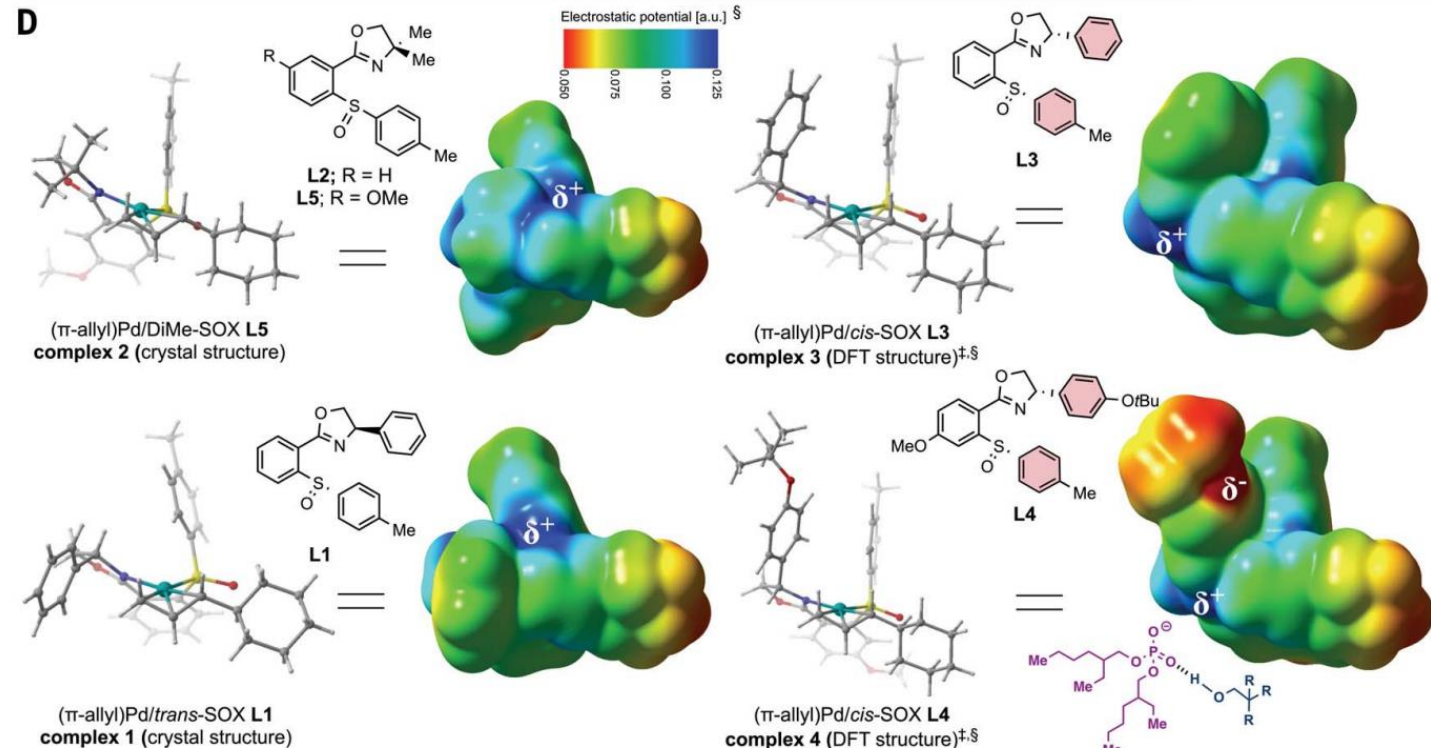
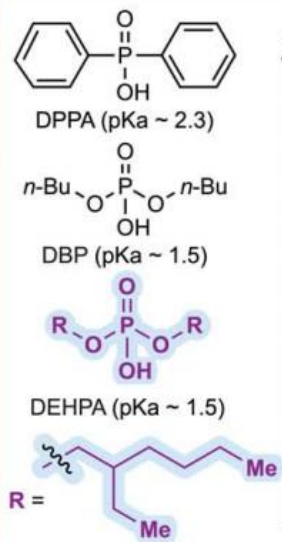
Hypothesis: Increasing the rate of the bimolecular C(sp³)-O bond formation step would be the fundamental challenge and key

This work:

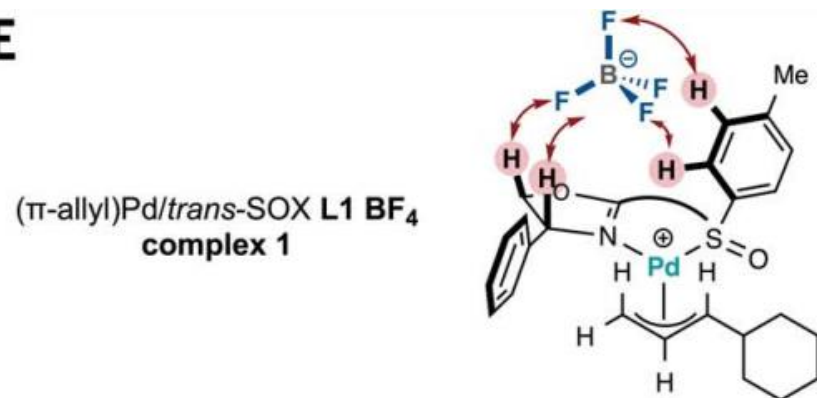




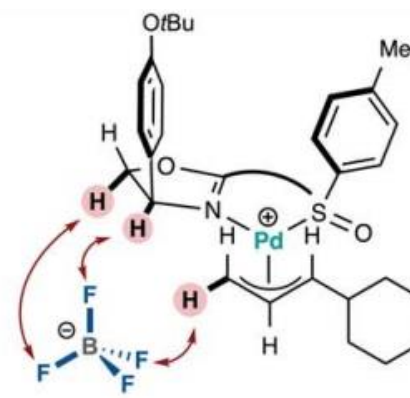
entry	variation	L:B*	% yield
1	<i>trans</i> -SOX L1 , no additive	-	< 5
2	<i>trans</i> -SOX L1 , DPPA	20:1	22
3	DiMe-SOX L2 , DPPA	11:1	30
4	<i>cis</i> -SOX L3 , DPPA	41:1	43
5	<i>cis</i> -SOX L4 , DPPA	50:1	64
6	<i>cis</i> -SOX L4 , DBP	38:1	66
7	<i>cis</i> -SOX L4 , DEHPA	43:1	72
8	<i>trans</i> -SOX L1 , DEHPA	15:1	30
9	DiMe-SOX L2 , DEHPA	8:1	36
10	<i>cis</i> -SOX L4 , TFA	19:1	10
11	<i>trans</i> -SOX L1 , TFA	11:1	6
12	<i>cis</i> -SOX L4 , ---	-	< 5
13†	5% Pd(OAc) ₂ , <i>cis</i> -SOX L4 , DEHPA	47:1	71



E

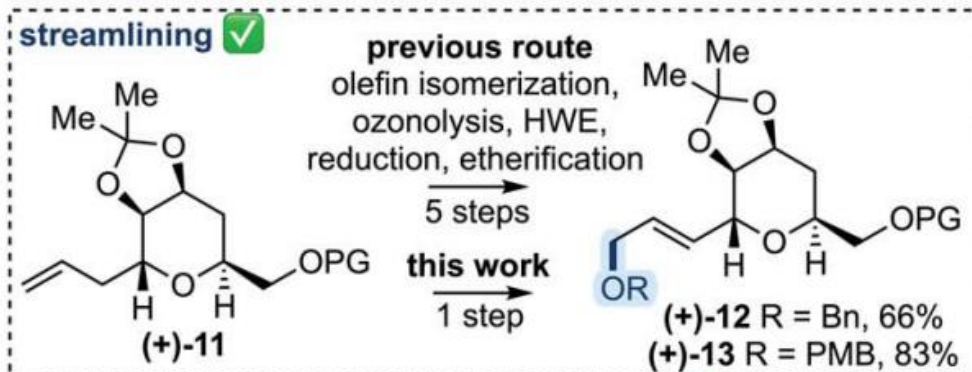
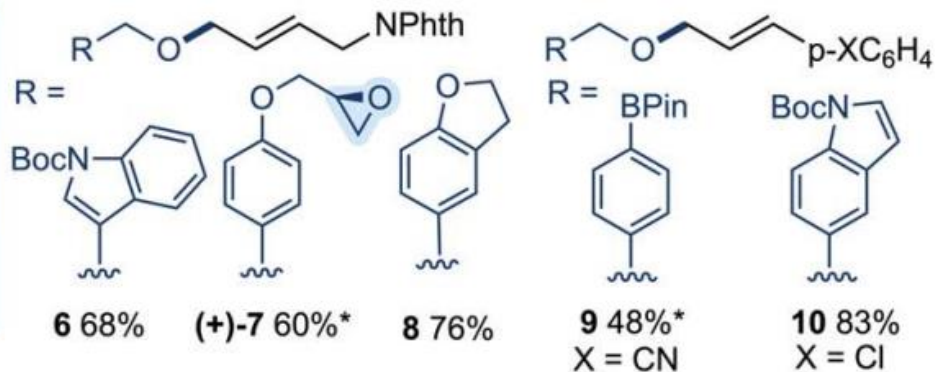
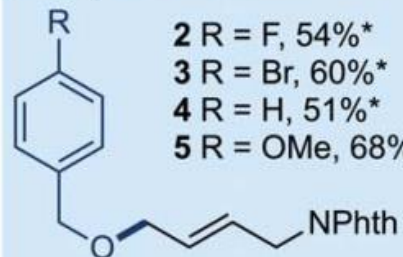


= major ¹⁹F — ¹H
HOESY contacts

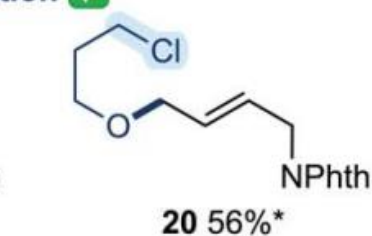
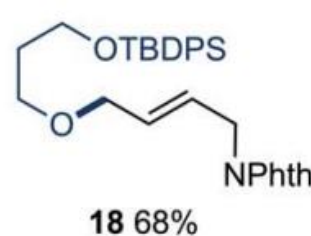
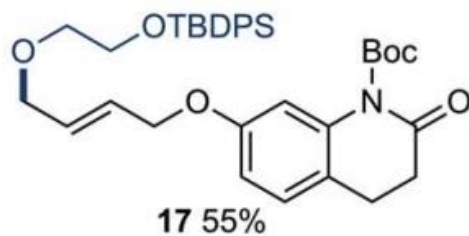
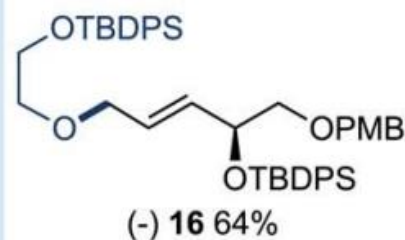
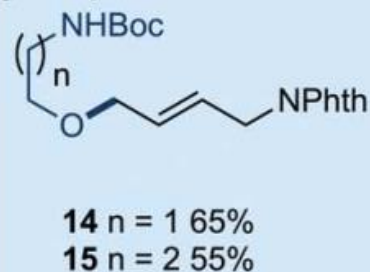


Substrate scope: primary (1°) alcohol

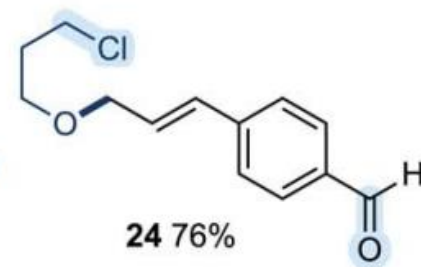
benzylic alcohols



lynchpin alcohols



pitolisant synthesis

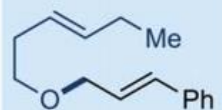


phenol tolerance

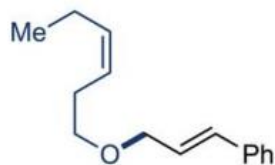


Substrate scope: primary (1°) alcohol

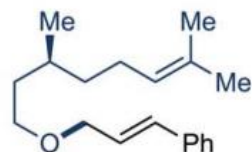
olefin tolerance



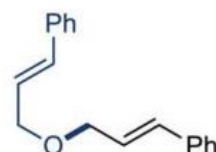
27 60%



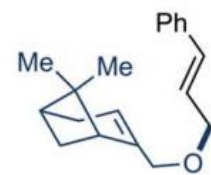
28 70%



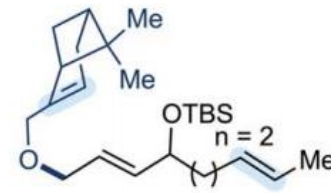
(-)-29 61%*



30 81%*

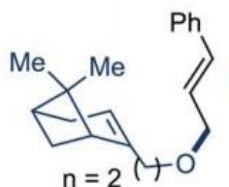


(-)-31 79%*

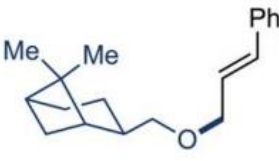


(±)-32 45%

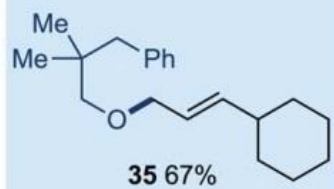
steric hindrance



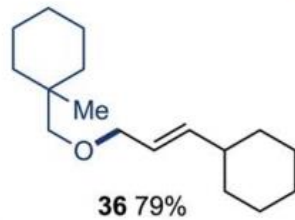
(-)-33 74%*



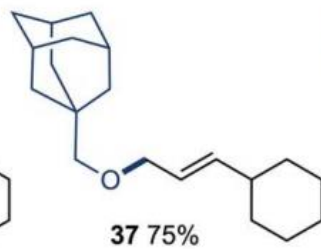
(-)-34 88%*‡



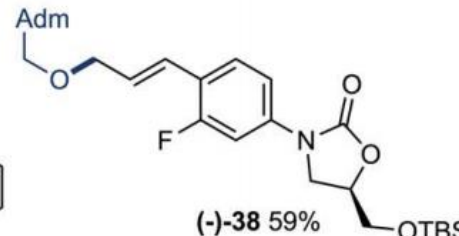
35 67%



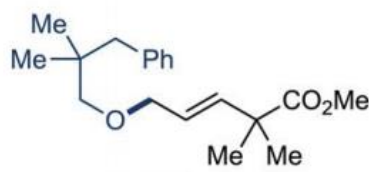
36 79%



37 75%

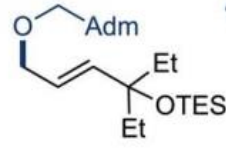


(-)-38 59%

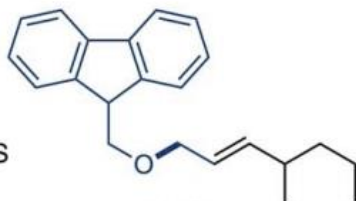


39 83%

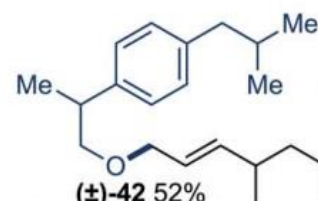
no epimerization ✓



40 57%



41 63%



(±)-42 52%

ibuprofen derivative

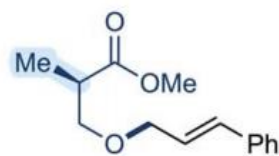


naproxen derivatives

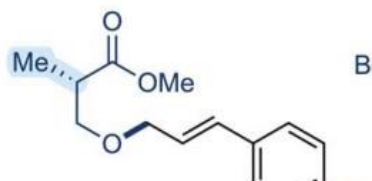
(+)-43 R = 71%*

(-)-44 R = 74%*

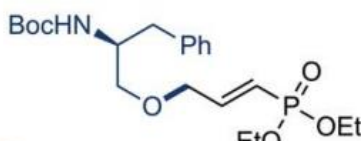
(-)-45 R = 73%*



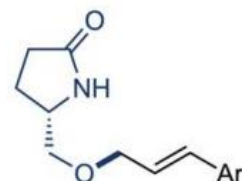
(-)-46 62%



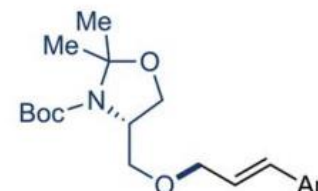
(+)-47 R = H, 59%



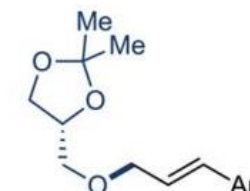
(-)-49 62%†



(+)-50 63%†

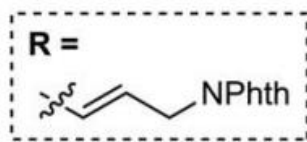
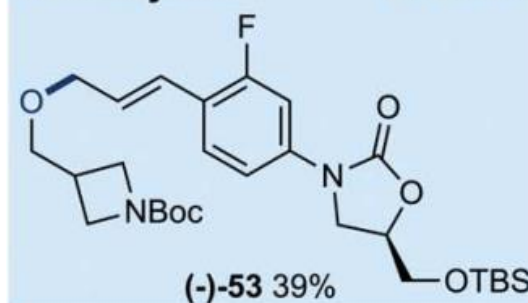


(+)-51 69%

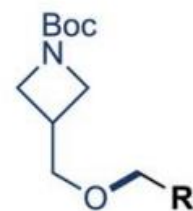


(-)-52 61%*

heterocycles #7 O-Het



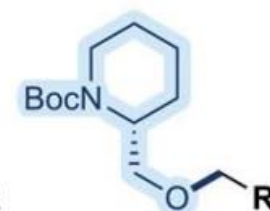
#20 O-Het



#9 O-Het



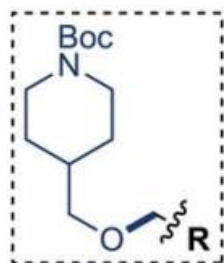
#1 N-Het



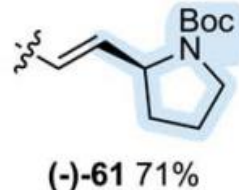
#3 O-Het



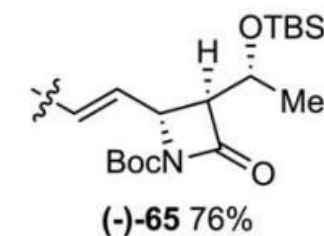
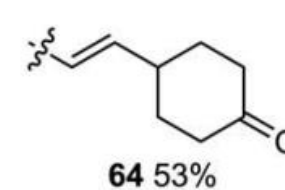
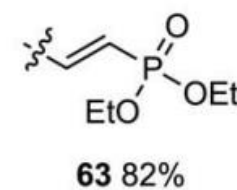
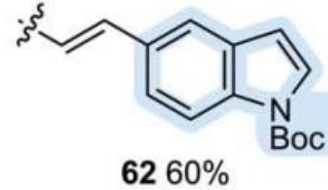
#3 N-Het



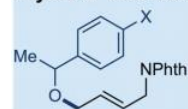
#5 N-Het



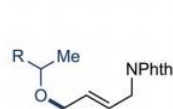
#9 N-Het



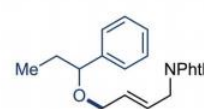
acyclic 2° alcohols



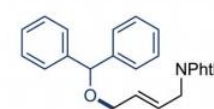
(±)-66 X = H, 69%*
 (-)-67 X = H, 67%* (100% es)
 (+)-68 X = H, 59%* (100% es)
 (±)-69 X = OMe, 64%*
 (±)-70 X = CF₃, 52%*



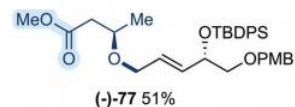
(±)-71 R = Cy, 76%*
 (±)-72 R = Me, 58%*
 (±)-73 R = n-Pr, 71%*
 (±)-74 R = Bn, 59%*



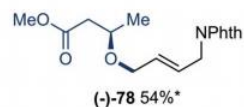
(±)-75 60%*



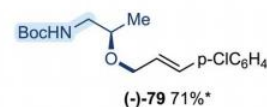
76 39%*



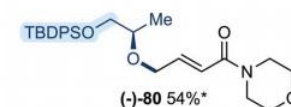
(-)-77 51%



(-)-78 54%*

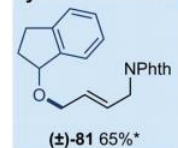


(-)-79 71%*



(-)-80 54%*

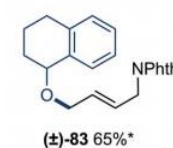
cyclic 2° alcohols



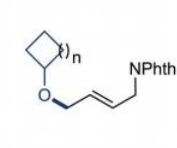
(±)-81 65%*



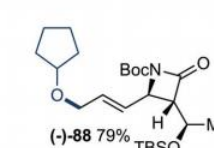
(±)-82 61%*



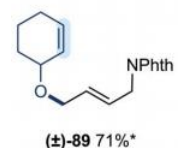
(±)-83 65%*



84 n = 1, 76%*
 85 n = 2, 75%*
 86 n = 3, 75%*
 87 n = 4, 74%*



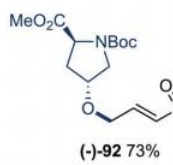
(-)-88 79%*



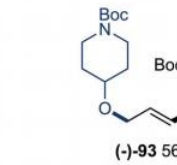
(±)-89 71%*



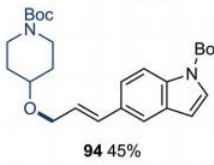
(±)-90 n = 1, 54%*
 91 n = 2, 61%*



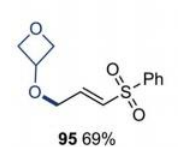
(-)-92 73%



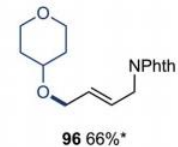
(-)-93 56%



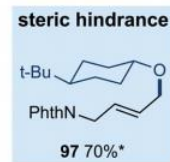
94 45%



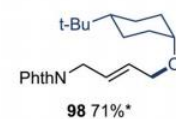
95 69%



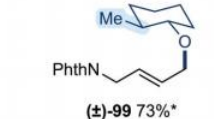
96 66%*



97 70%*

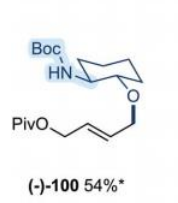


98 71%*

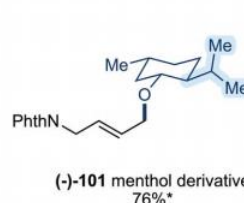


(±)-99 73%*

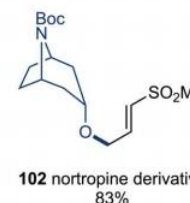
steric hindrance



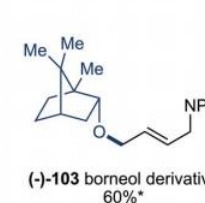
(-)-100 54%*



(-)-101 menthol derivative
76%*



102 nortropine derivative
83%

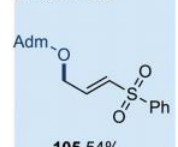


(-)-103 borneol derivative
60%*

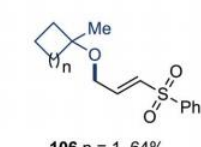


(+)-104 fenchol derivative
51%

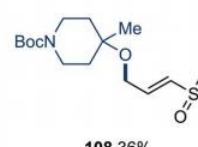
3° alcohols



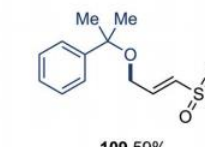
105 54%



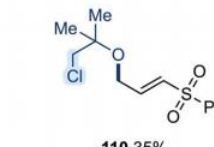
106 n = 1, 64%
 107 n = 3, 57%



108 36%



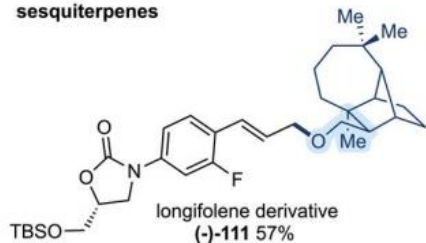
109 59%



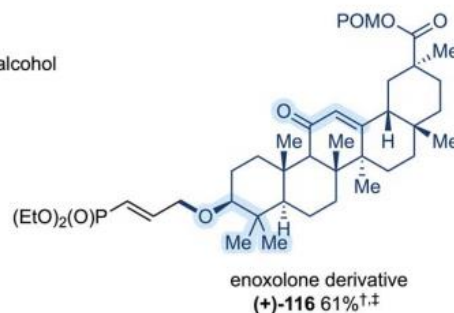
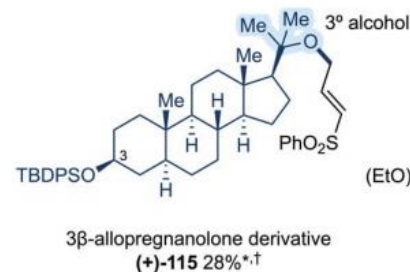
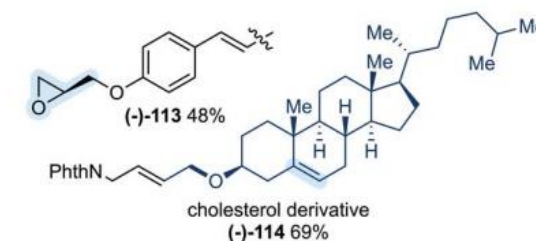
110 35%

A alcohol natural products

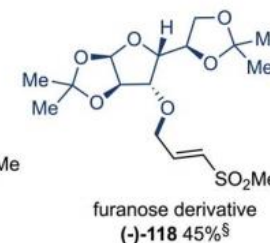
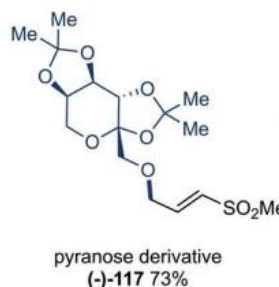
sesquiterpenes



steroids

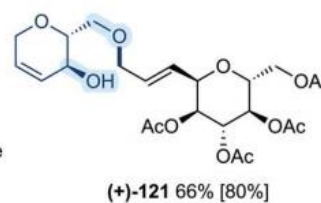
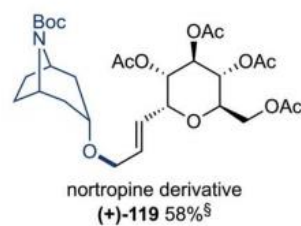


sugars

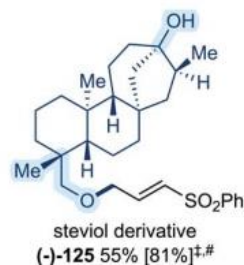
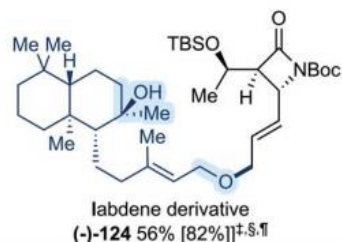
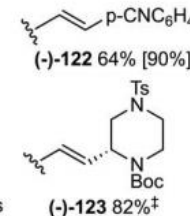
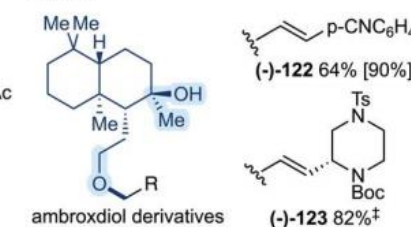


B polyols site-selectivity ✓

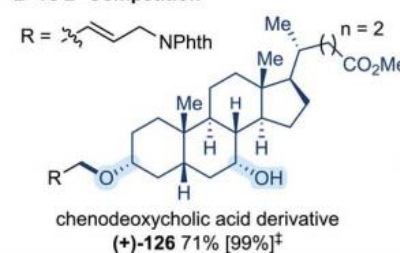
1° vs 2°: yield [alcohol mass balance]

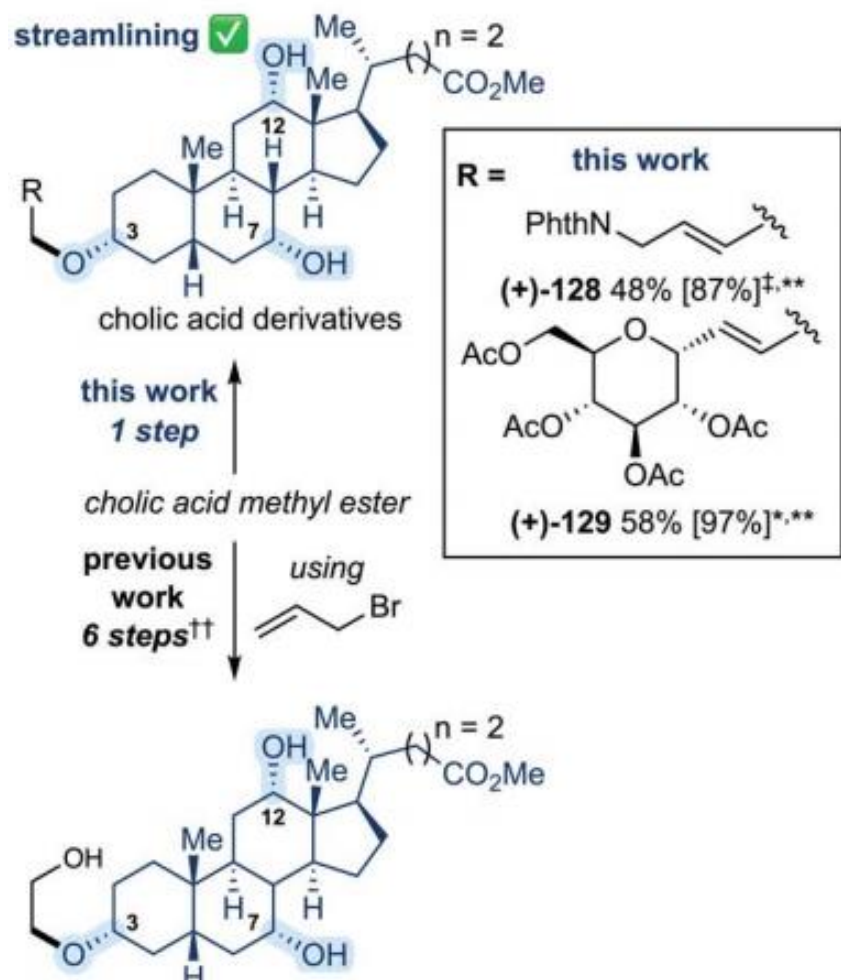


1° vs 3°

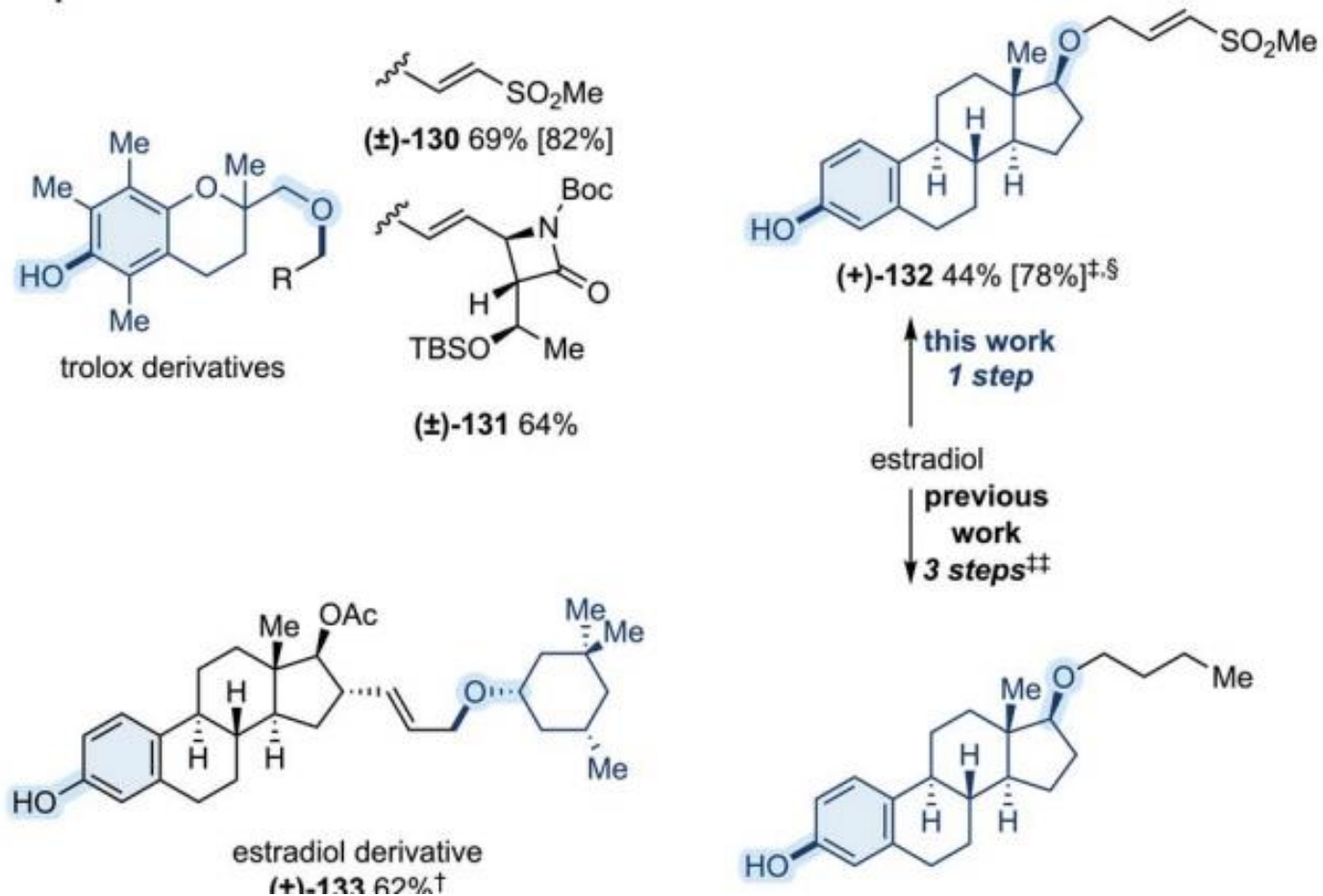


2° vs 2° Competition

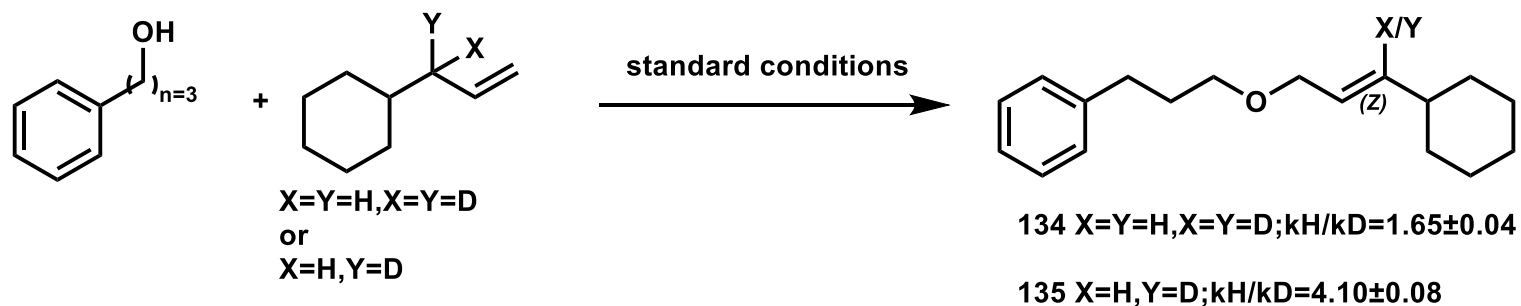




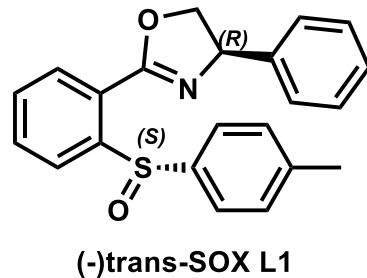
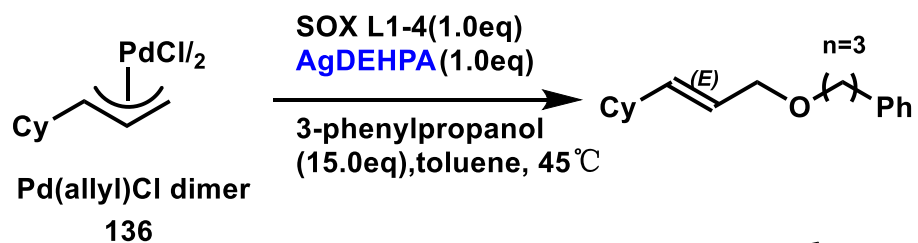
C phenols



1、 Intra- and intermolecular KIE

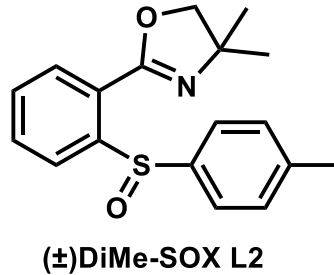


2、 The impact of ligand geometry on rate



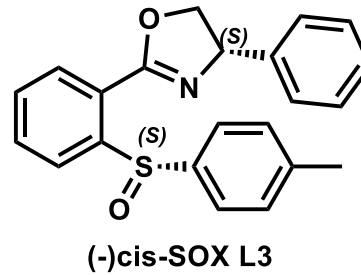
stoich. k_{rel}= 1.0

catalytic. k_{rel}= 1.0



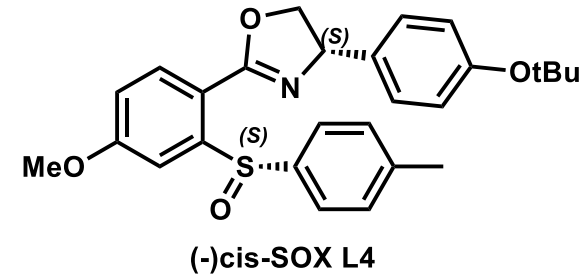
0.9

1.2



2.5

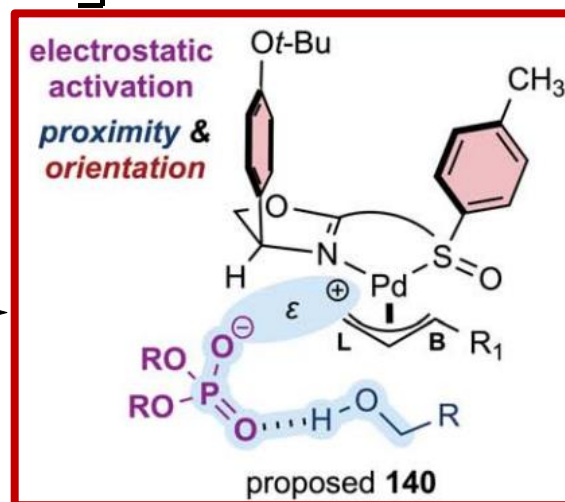
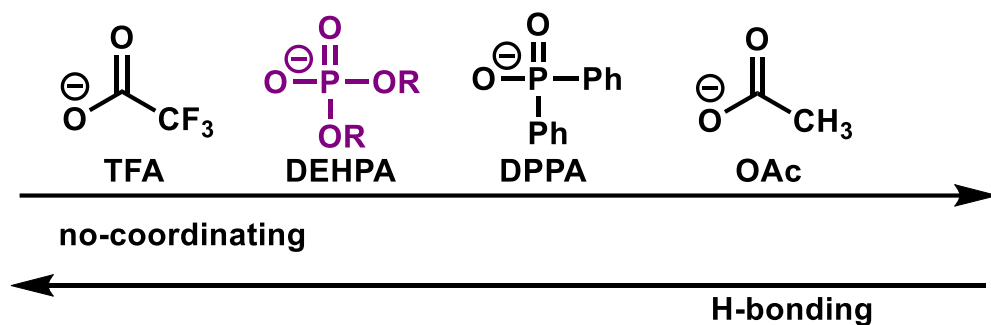
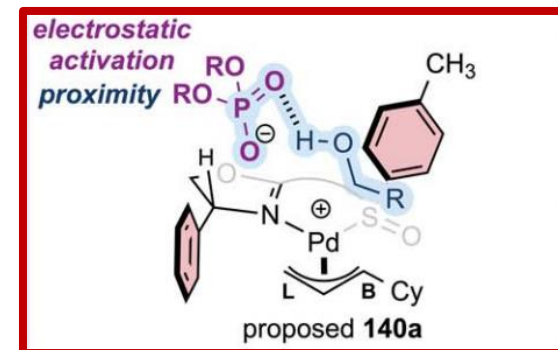
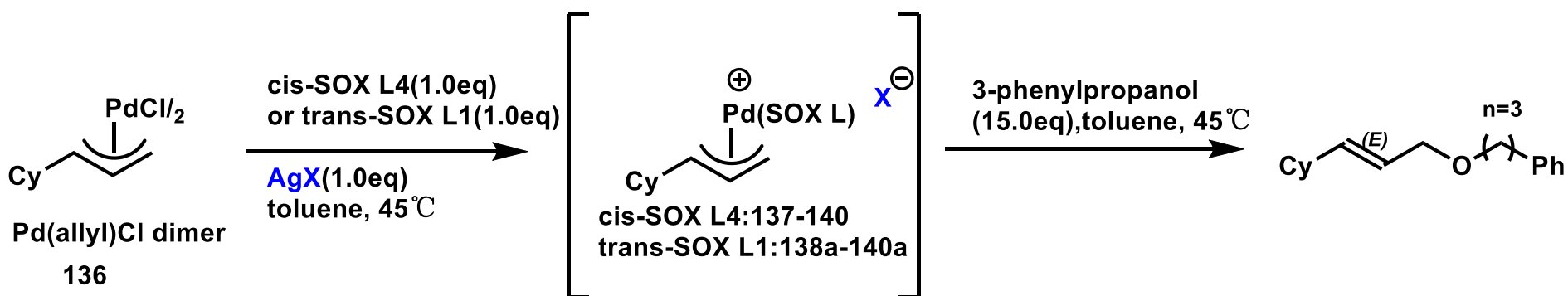
2.8



4.7

4.2

3、The effect of the counter anion on the rate

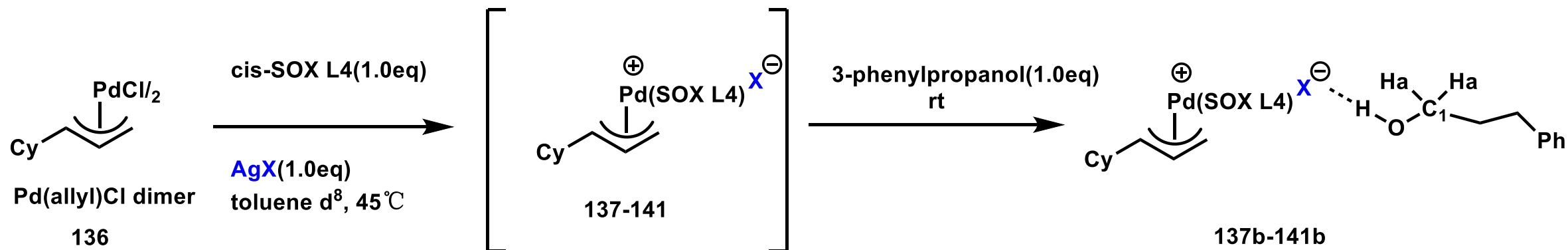


*Intermolecular**

complex	ligand	counterion (X)	k_{rel}
137	(-) cis-SOX L4	OAc	1.0
138a	(-) trans-SOX L1	TFA	2.7
139a	(-) trans-SOX L1	DPPA	2.9
140a	(-) trans-SOX L1	DEHPA	7.3
138	(-) cis-SOX L4	TFA	11.1
139	(-) cis-SOX L4	DPPA	16.6
140	(-) cis-SOX L4	DEHPA	33.9

proximity
proximity & orientation

4、H-bonding between the counter anion and the alcohol nucleophile



¹³C-¹H coupling as a measure of H-bonding

	¹ J _{C1-Ha} [†]	Δ ¹ J _{C1-Ha} [†]
free alcohol	140.19 Hz (141.23 Hz)	0 Hz (0 Hz)
137b OAc	139.71 Hz (140.96 Hz)	-0.48 Hz (-0.27 Hz)
138b TFA	140.18 Hz (141.24 Hz)	-0.01 Hz (+0.01 Hz)
139b DPPA	139.60 Hz (140.80 Hz)	-0.59 Hz (-0.43 Hz)
140b DEHPA	139.20 Hz (140.75 Hz)	-0.99 Hz (-0.48 Hz)
141b BF ₄	140.24 Hz (141.30 Hz)	+0.05 Hz (+ 0.07 Hz)

effect of solvent polarity with 140 & 140b

solvent	ε [‡]	β [‡]	k _{rel}	Δ ¹ J _{C1-Ha} [§]
DCM	8.93	0.10	1.0	-0.63 Hz
CHCl ₃	4.89	0.10	1.1	-0.48 Hz
toluene	2.38	0.11	3.9	-0.99 Hz
benzene	2.27	0.10	2.5	-0.88 Hz
dioxane	2.21	0.37	0.7	-0.13 Hz

Thank you for your attention