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COMMUNICATION

Enantioselective Total Synthesis of (–)-Limaspermidine and (–)-Kopsinine by a Nitroaryl Transfer Cascade Strategy

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Dedicated to Prof. Dr. Henk Hiemstra on the occasion of his 70th birthday

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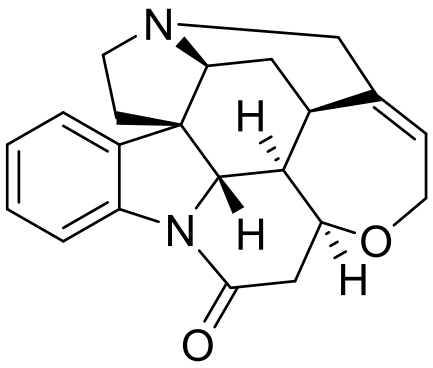
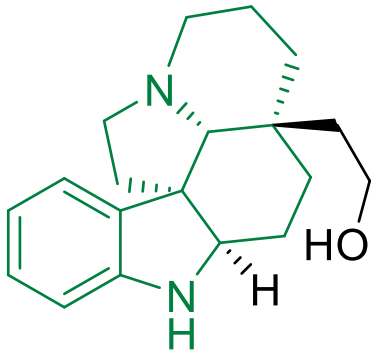
Supporting information for this article is given via a link at the end of the document.

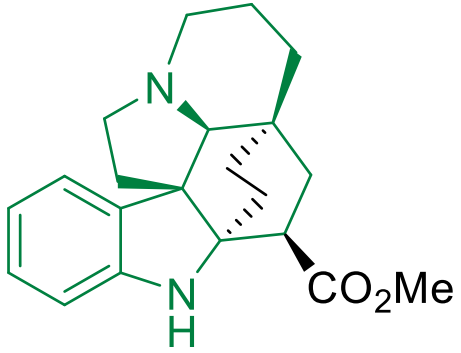
Background



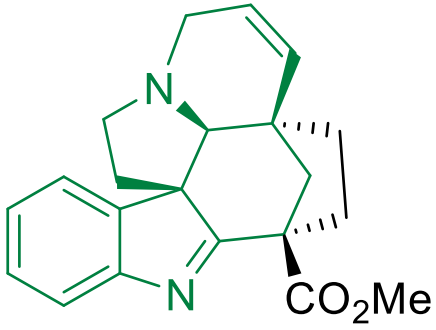
(-)-strychnine (**1**)



(+)-limaspermidine (**2**)

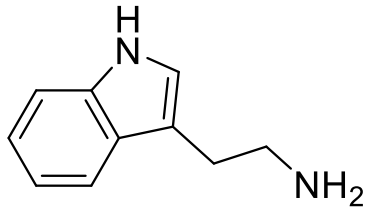


(-)-kopsinine (**3**)

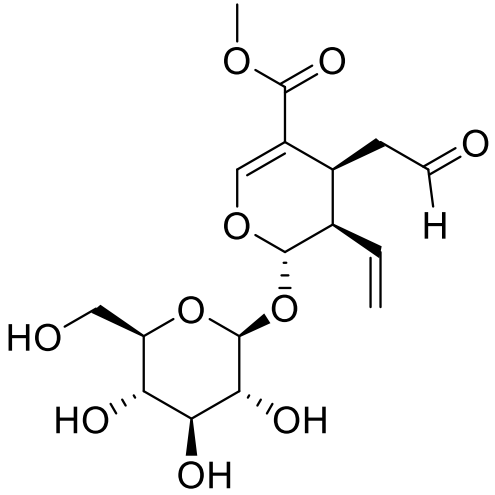


(-)-kopsifoline D (**4**)

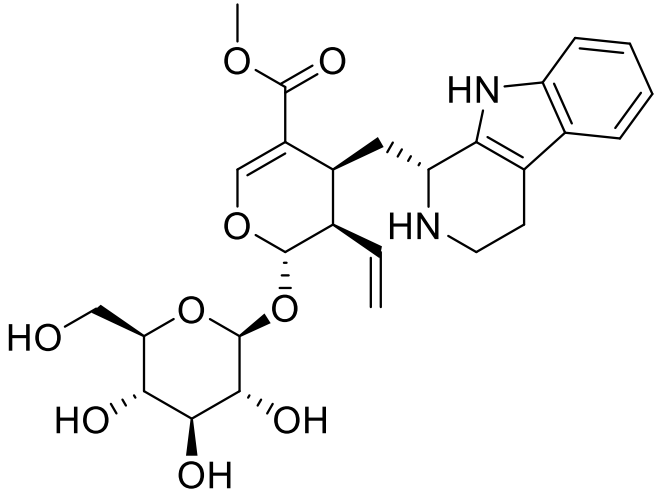
Background



Tryptamine

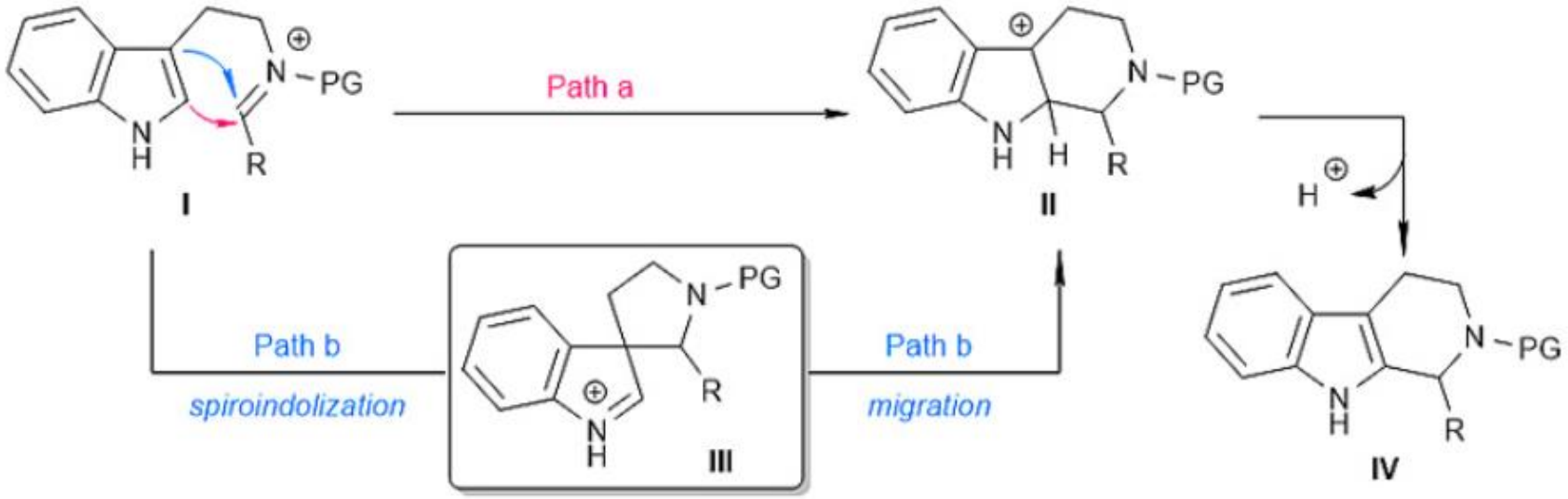


Secologanin

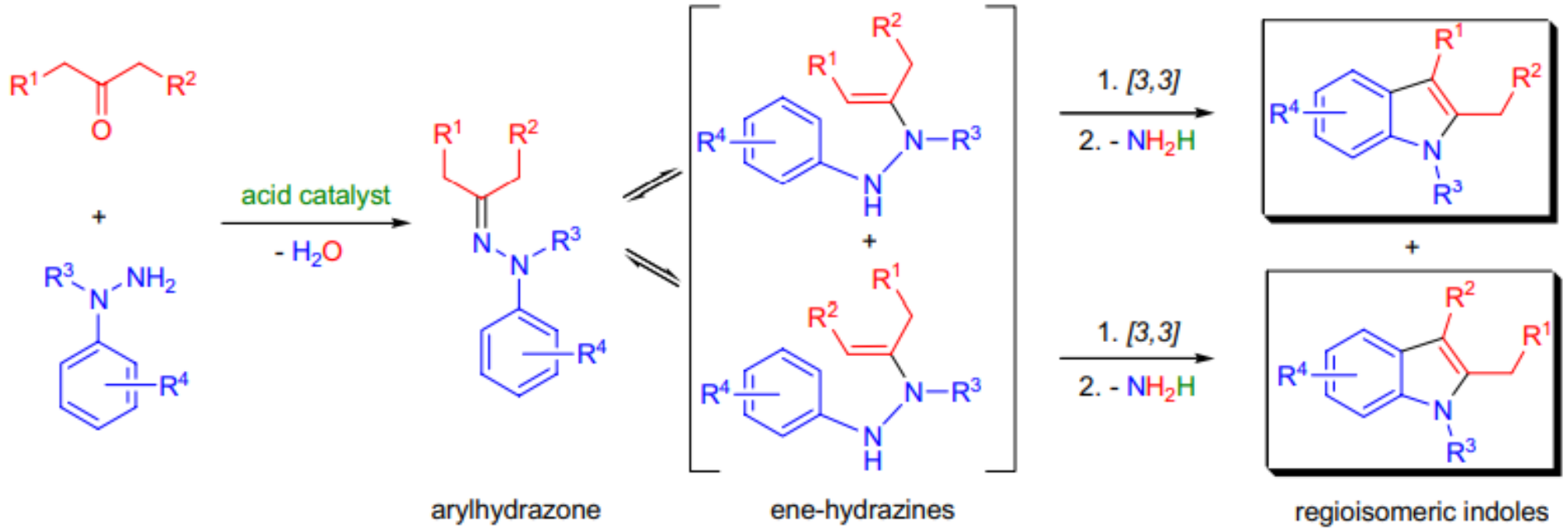


Strictosidine

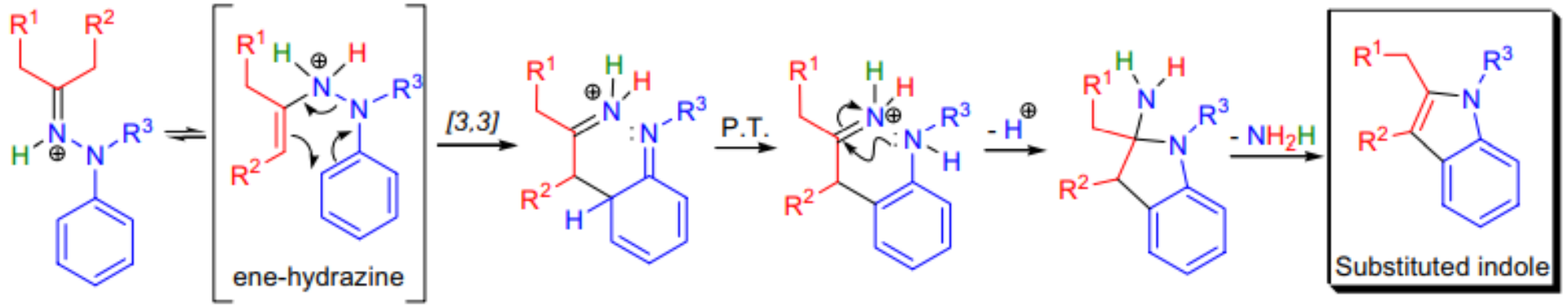
Pictet-Spengler reaction mechanism



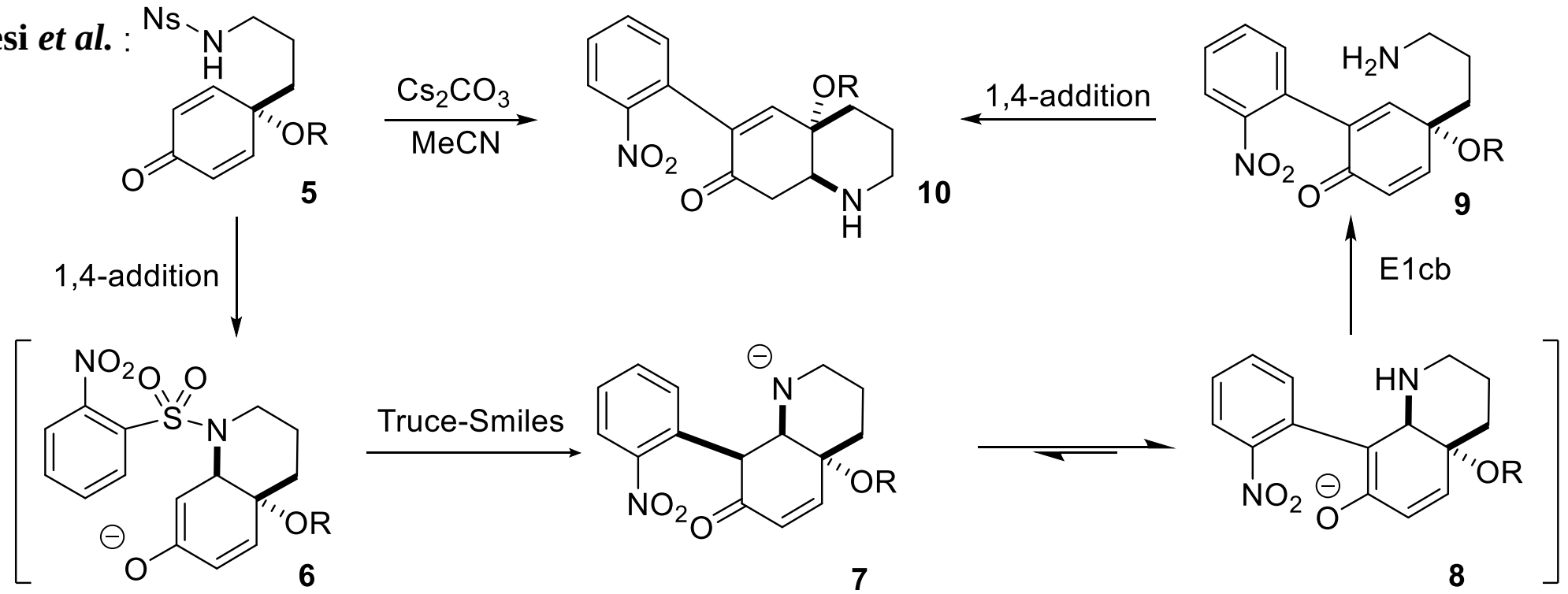
Fischer Indole Synthesis



Mechanism



a) Canesi *et al.* :



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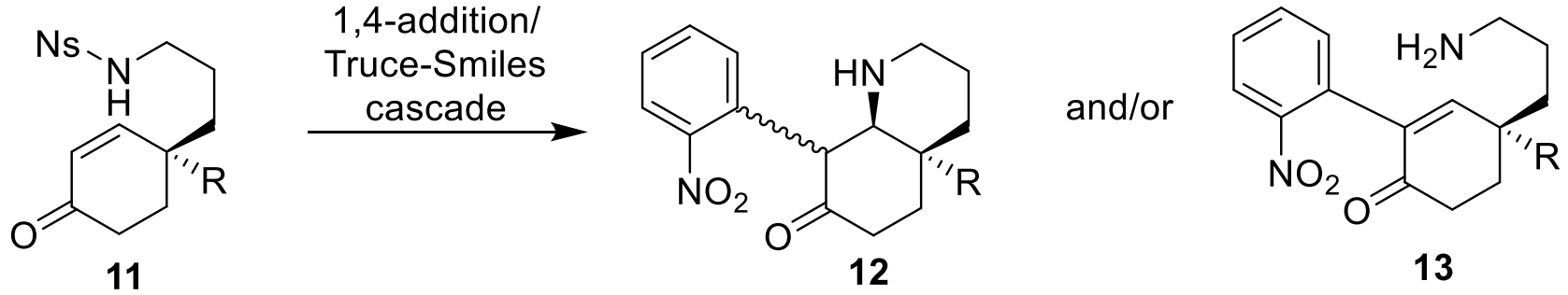
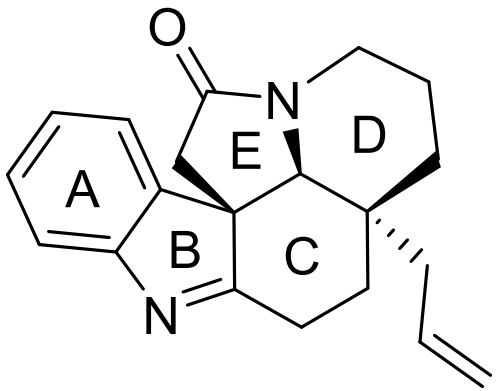


Retrosynthetic Analysis



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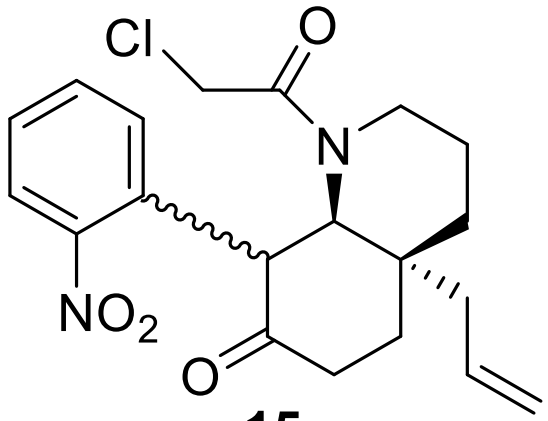
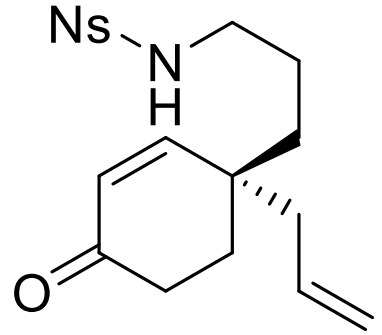
reductive cyclization



15

1,4-addition/ Truce-Smiles E1cb



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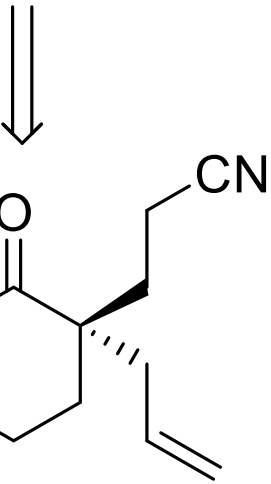
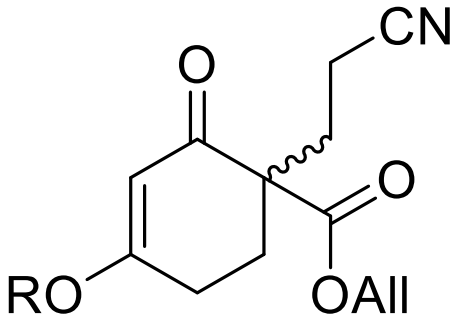


17

decarboxylative allylation



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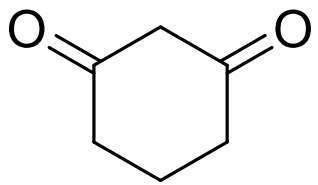
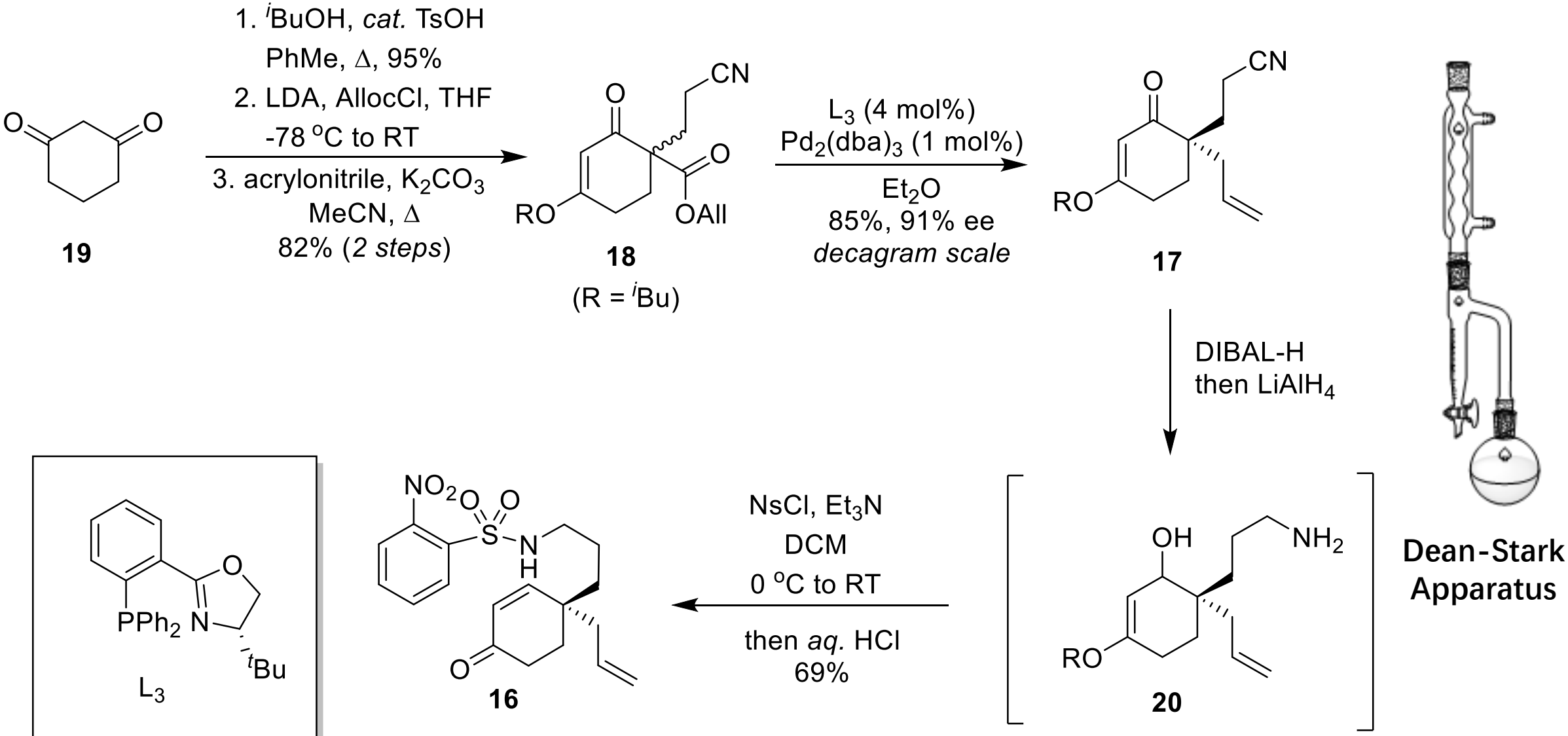
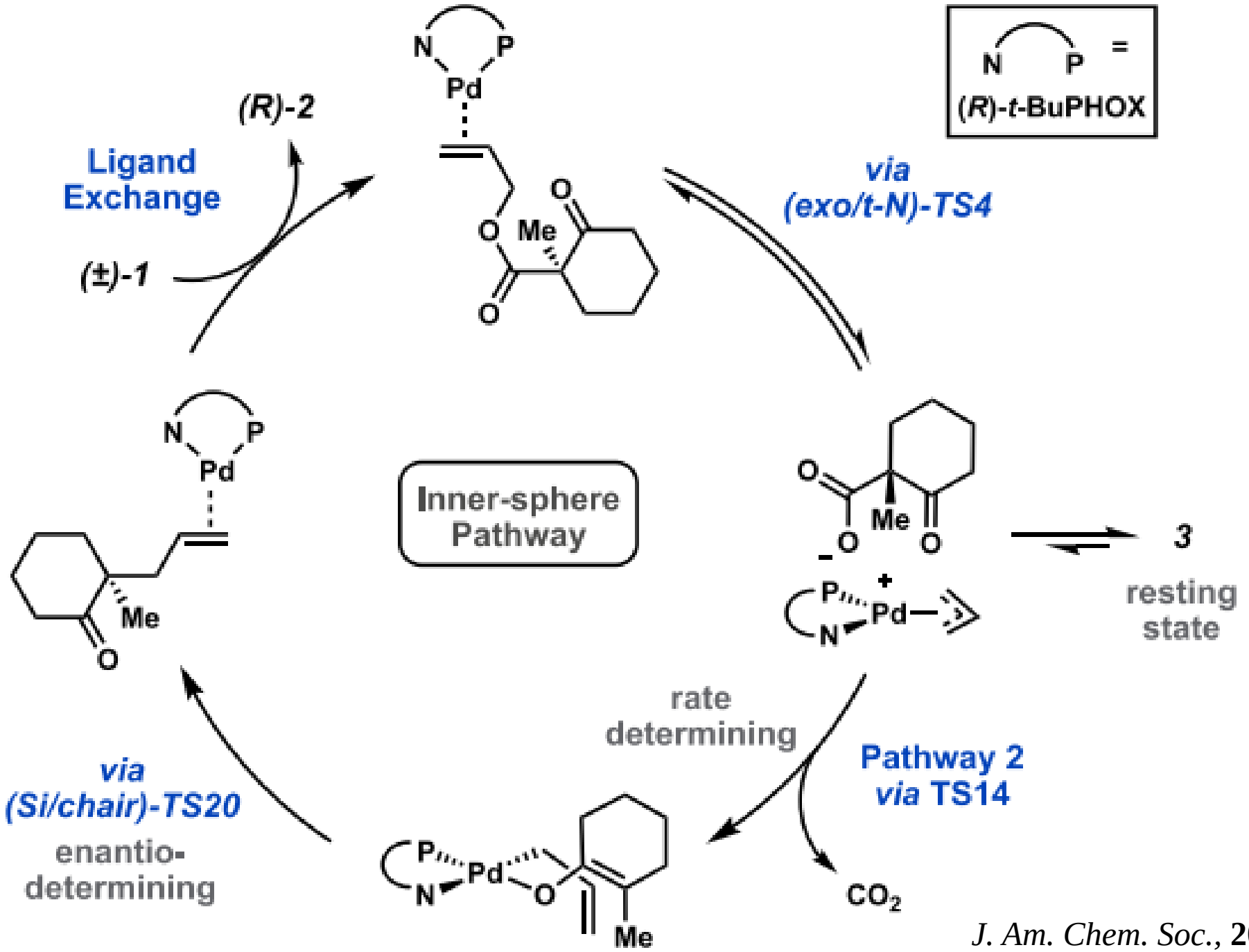


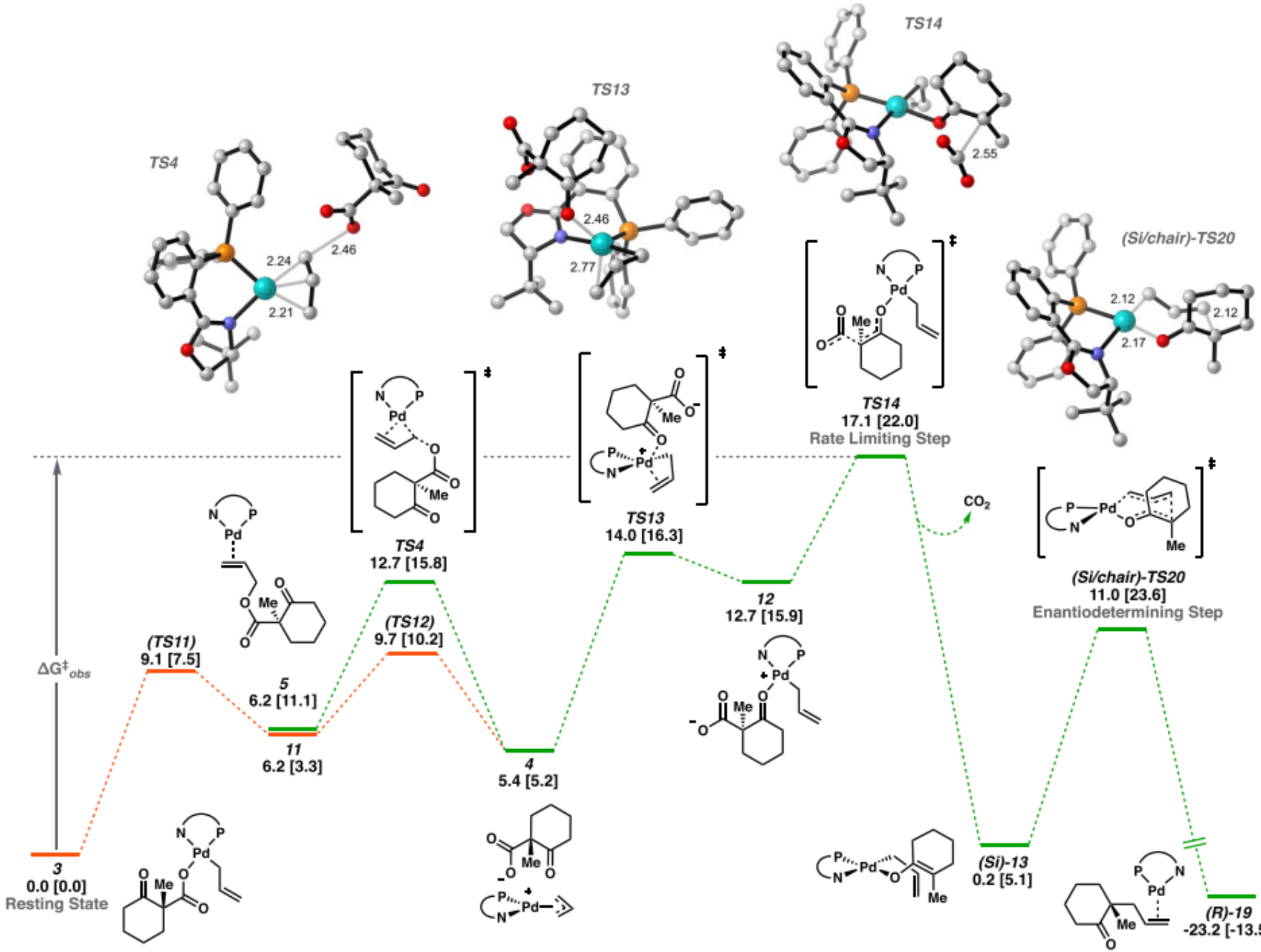
19

Synthesis Strategy





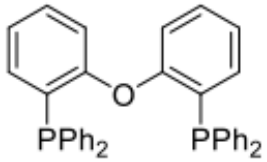
J. Am. Chem. Soc., **2020**, *142*, 13917.



J. Am. Chem. Soc., **2020**, *142*, 13917.

Reaction Optimization

Entry[a]	Cat	Ligand	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
1	$Pd_2(dba)_3$	**L1**	THF	65	77	-
2	$Pd_2(dba)_3$	**L2**	THF	65	93	68
3	$Pd_2(dba)_3$	**L3**	THF	65	92	81
4	$Pd_2(dba)_3$	**L4**	THF	65	94	81
5	$Pd_2(dba)_3$	**L5**	THF	65	92	-53
6	$Pd_2(dba)_3$	**L6**	THF	65	97	2
7	$Pd_2(dba)_3$	**L7**	THF	65	92	9
8	$Pd_2(dba)_3$	**L8**	THF	65	81	4



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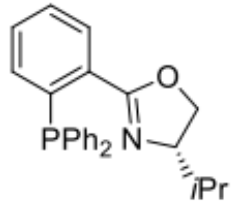

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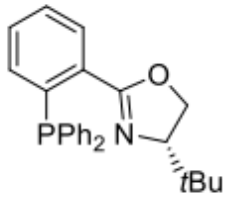

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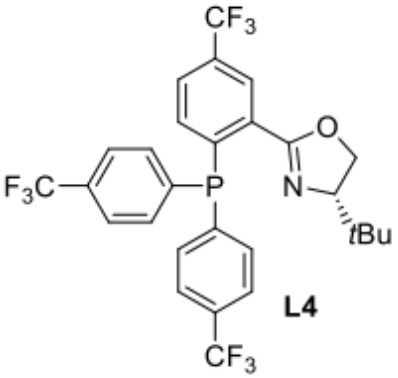

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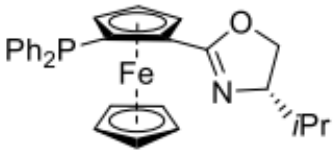

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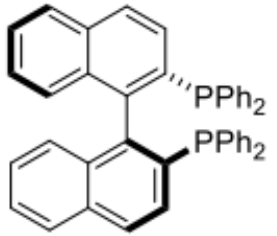

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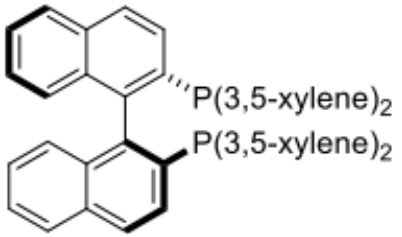

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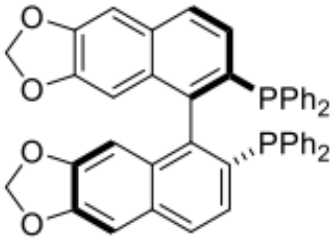
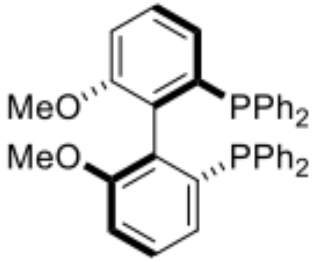


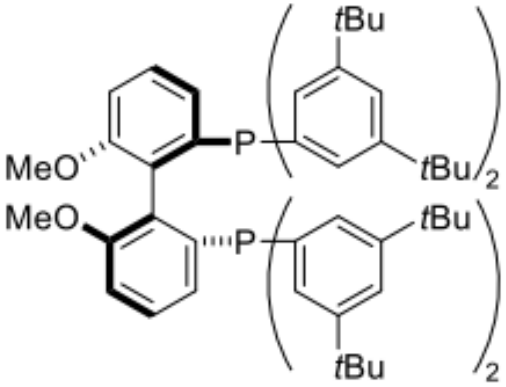
L8

Reaction Optimization

Entry[a]	Cat	Ligand	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
9	$Pd_2(dba)_3$	**L9**	THF	65	98	1
10	$Pd_2(dba)_3$	**L10**	THF	65	85	-6
11	$Pd_2(dba)_3$	**L11**	THF	65	80	1
12	$Pd_2(dba)_3$	**L12**	THF	65	90	1
13	$Pd_2(dba)_3$	**L13**	THF	65	69	-5
14	$Pd_2(dba)_3$	**L14**	THF	65	77	0



L9



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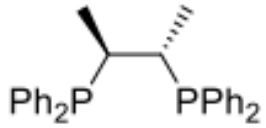

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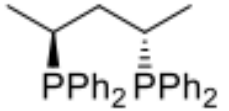

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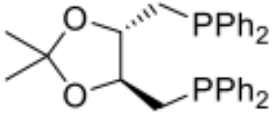
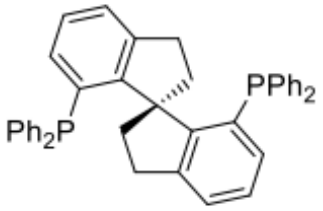


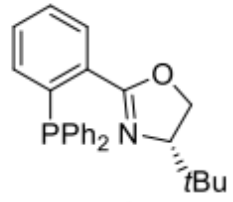
L13



L14

Reaction Optimization

Entry[a]	Cat	Ligand	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
15	$Pd_2(dba)_3$	**L15**	THF	65	97	-10
16	$Pd_2(dba)_3$	**L16**	THF	65	no conv.[d]	-
17	$Pd_2(dba)_3$	**L17**	THF	65	no conv.[d]	-
18	$Pd_2(dba)_3$	**L18**	THF	65	no conv.[d]	-
19	$Pd_2(dba)_3$	**L3**	toluene	RT	35	87
20	$Pd_2(dba)_3$	**L4**	toluene	RT	40	90



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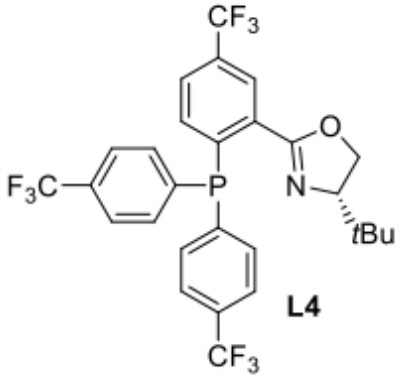

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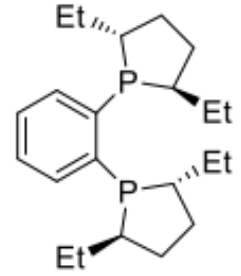

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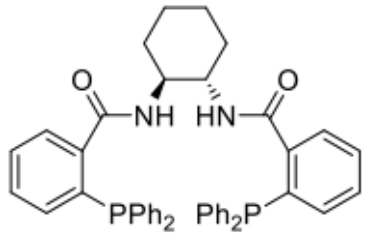

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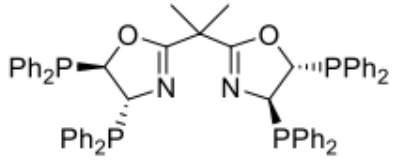

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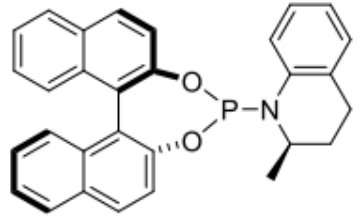
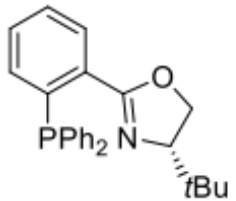


L18

Reaction Optimization

Entry[a]	Cat	Ligand	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
21	$Pd_2(dba)_3$	**L3**	toluene	65	97	83
22	$Pd_2(dba)_3$	**L4**	toluene	65	46	89
23	$Pd_2(dba)_3$	**L3**	1,4-dioxane	RT	no conv.[d]	
24	$Pd_2(dba)_3$	**L4**	1,4-dioxane	RT	36	90
25	$Pd_2(dba)_3$	**L3**	1,4-dioxane	80	66	80
26	$Pd_2(dba)_3$	**L4**	1,4-dioxane	80	no conv.[d]	
27	$Pd_2(dba)_3$	**L3**	diethyl ether	RT	84	91
28	$Pd_2(dba)_3$	**L4**	diethyl ether	RT	86	90
29[e]	$Pd_2(dba)_3$	**L3**	diethyl ether	RT	96	91



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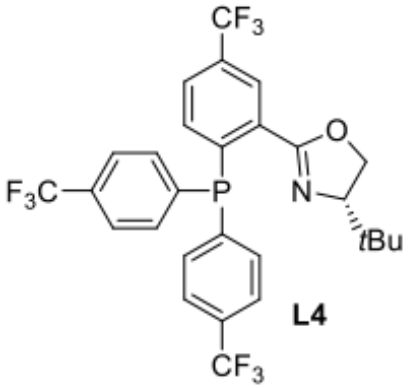
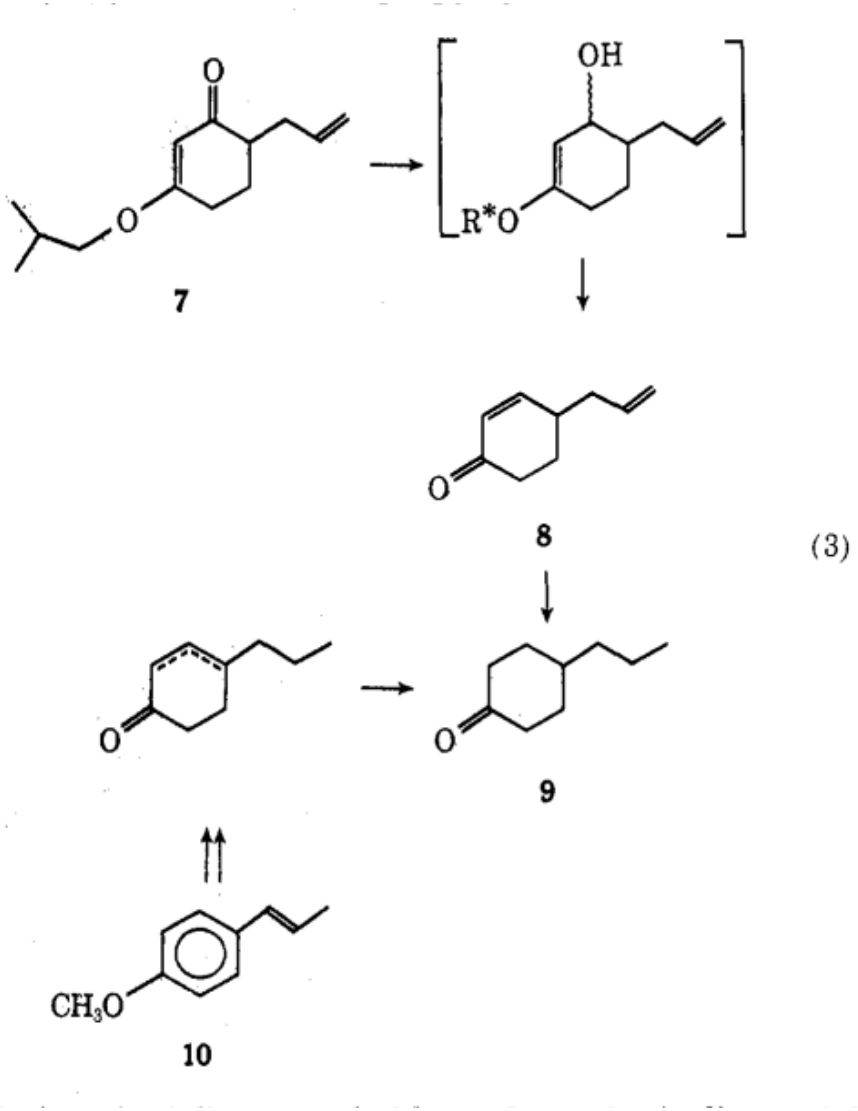


L4

Stork-Danheiser Reaction



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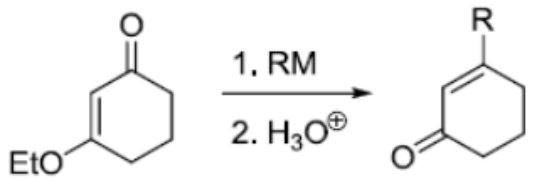
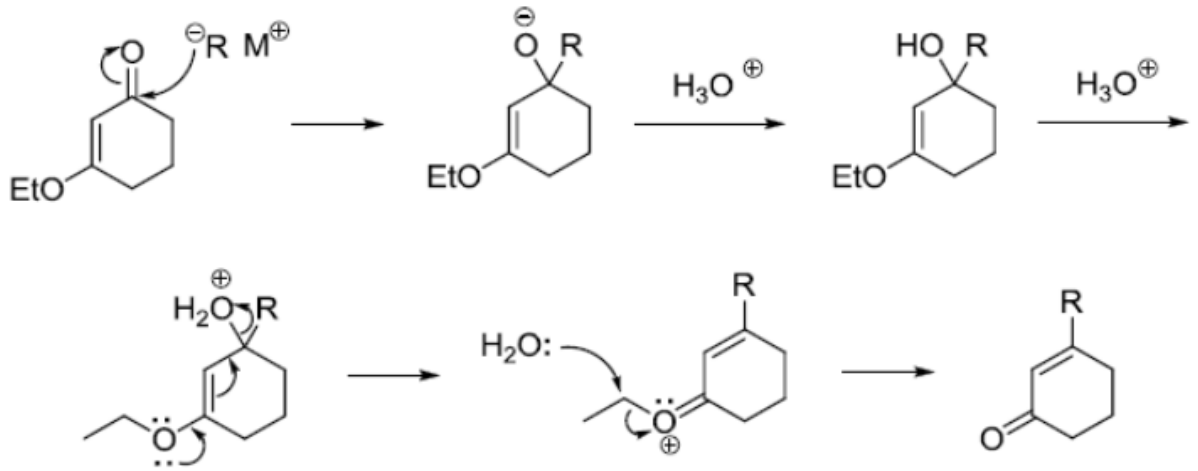
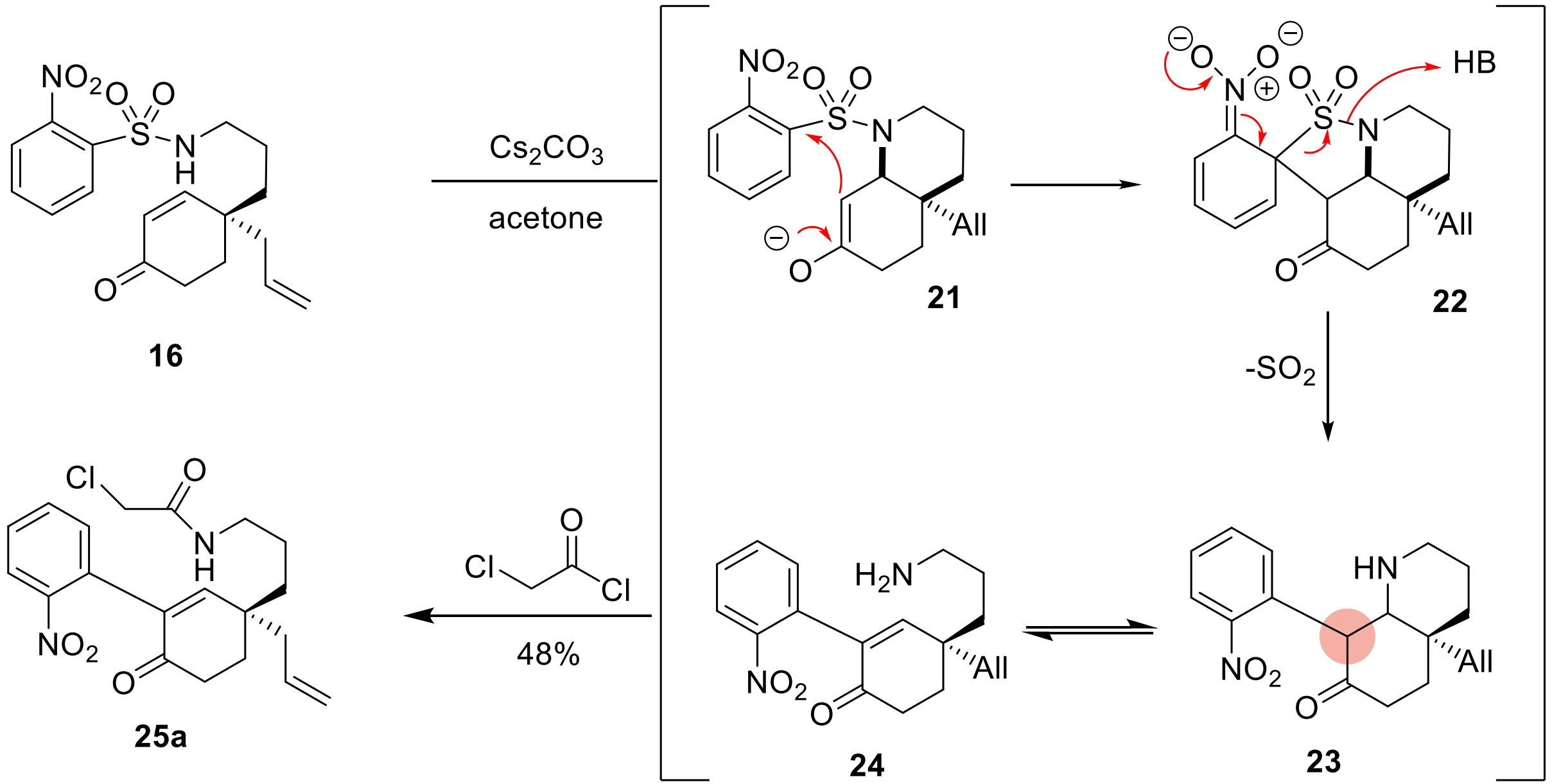


β烷氧基烯酮和有机金属化合物（格氏试剂或有机锂）反应接着进行酸处理得到另一种烯酮的反应，新生成的烯酮的羰基的位置是原料中烯醇醚的烯碳的位置。

反应机理



J. Org. Chem., **1973**, *38*, 1775.


16
Cs2CO3
acetone
21
22
HB
-SO2
23
24
48%
25a

Reaction Optimization

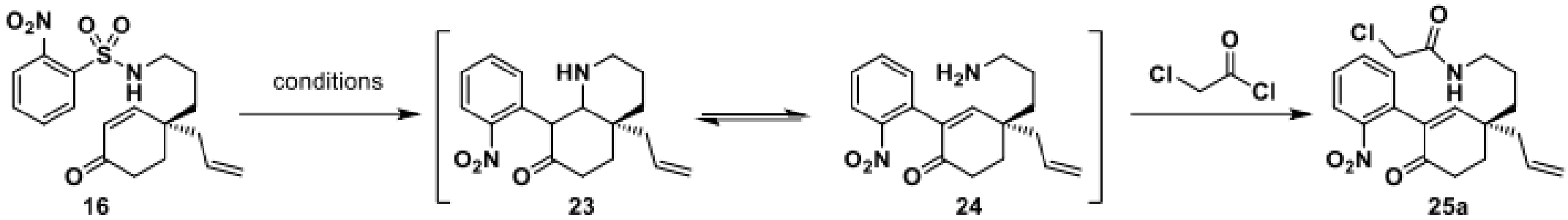


Table S2. List of conditions tested.

Entry	Solvent	Cs_2CO_3 (eq.)	Temperature (° C)	Time (h)	Electrophile (eq)[a]	Conversion of **16**	Yield of **25a** [b]
1	acetonitrile	3	60	18	No	Full	Mixture[c]
2	DMSO	3	60	18	No	Full	Mixture [c]
3	DMSO	**2**	60	18	No	Full	Mixture [c]
4	DMSO	**1**	60	18	No	Full	Mixture [c]
5	DMF	3	60	18	No	Full	Mixture [c]
6	acetone	2	56	18	No	Full	Mixture [c,d]
7	THF	2	60	18	No	Slow	Mixture [c]

Reaction Optimization

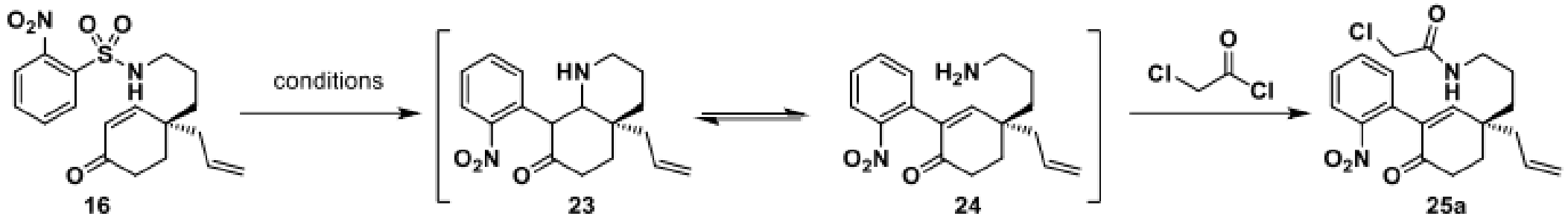
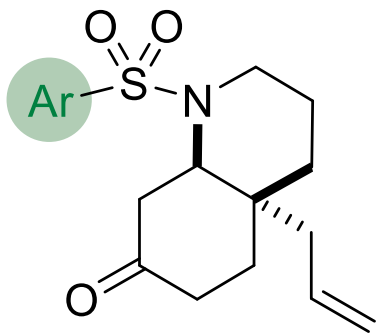


Table S2. List of conditions tested.

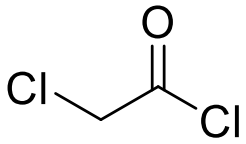
Entry	Solvent	Cs_2CO_3 (eq.)	Temperature (° C)	Time (h)	Electrophile (eq)[a]	Conversion of **16**	Yield of **25a** [b]
8	chloroform	2	60	18	No	No	0%
9	DMSO	2	100	18	No	Full	Mixture [c]
10	DMSO	2	60	18	yes	Full	0%
11	acetonitrile	2	60	18	yes	Full	17%
12	DMF	2	60	18	yes	Full	17%
13	**acetone**	**2**	**56**	**18**	**yes**	**Full**	**50% (48%[d])**
14	acetone	2	100[f]	3	yes	Full	29%

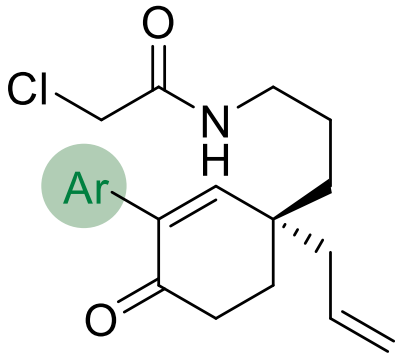


26a-h

Cs_2CO_3
acetone, reflux

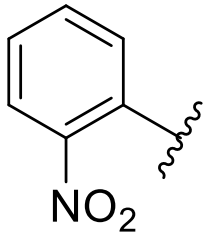
then



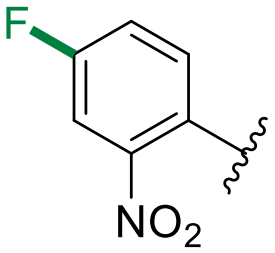


25a-h

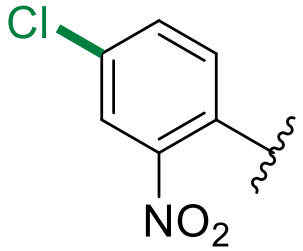
Ar =



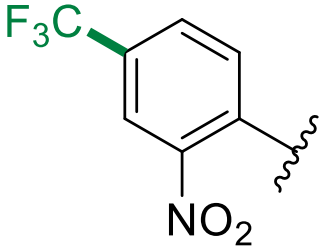
25a
48% (18 h)



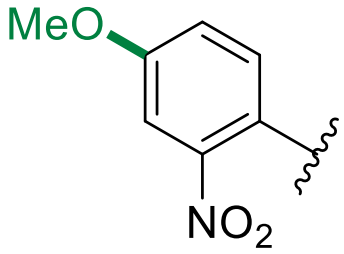
25b
50% (3 h)



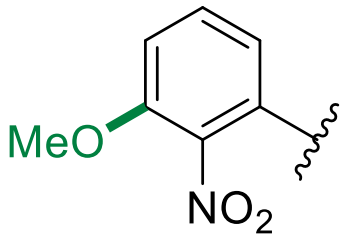
25c
60% (3 h)



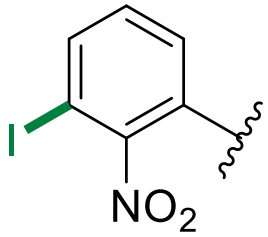
25d
21% (2 h)



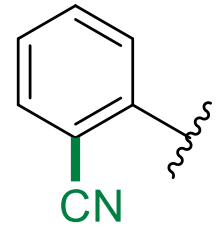
25e
44% (72 h)



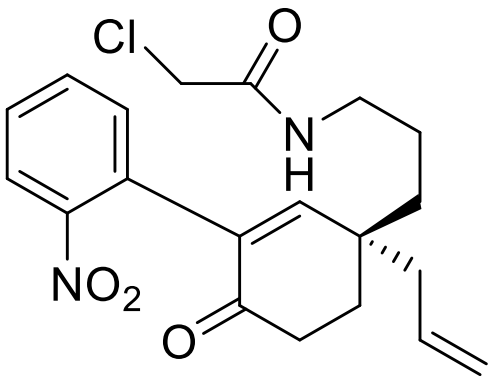
25f
no conv.



25g
0%

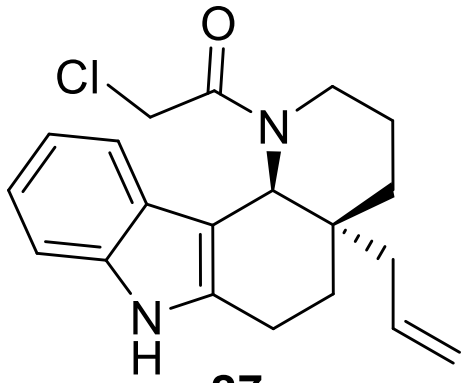


25h
no conv.



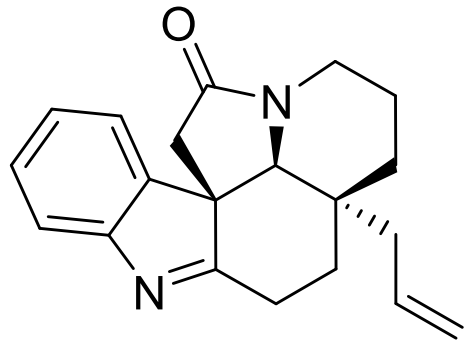
25a

Fe, AcOH
80 °C, 62%



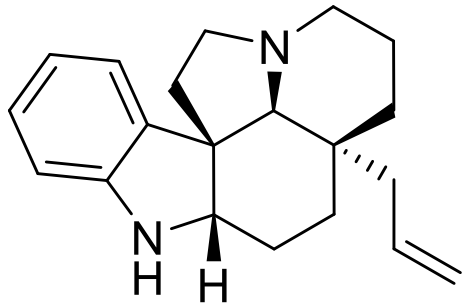
27

NaI, acetone
then AgOTf
81%



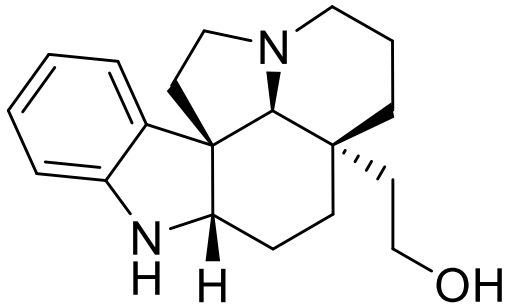
14

$LiAlH_4$, THF
99%
(*89% from 27*)

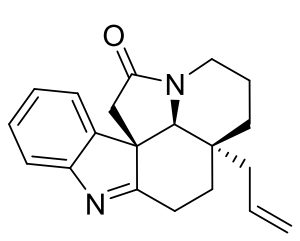


28

HCl, MeOH
then O_3, MeOH/DCM
then $NaBH_4$, 59%

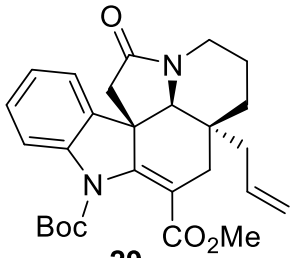


(-)-limaspermidine (*ent-**2***)



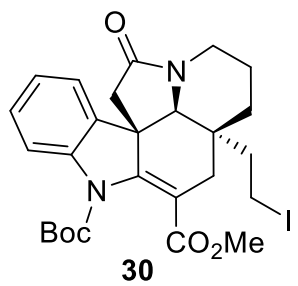
14

1. LDA, then $NCCO_2Me$
   THF, -78 °C, 37% (*52% brsm*)
2. Boc_2O, DMAP, DMF, quant.



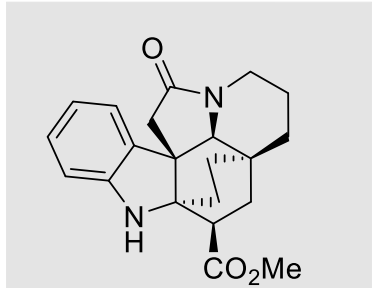
29

1. O_3, MeOH/DCM, -78 °C
   then $NaBH_4$, -78 °C to RT, 97%
2. I_2, PPh_3, Im., DCM, 85%



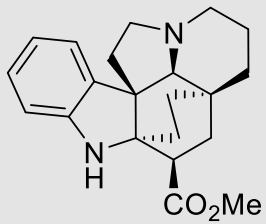
30

1. SmI_2, THF/HMPA
2. TFA/DCM
   91% (*2 steps*)

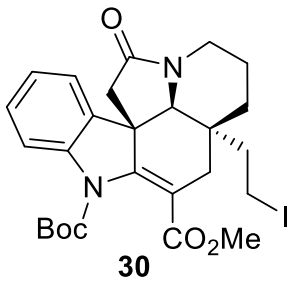


(-)-kopsiniliam (**31**)

1. Lawesson's reagent
   toluene, 90 °C, 85%
2. Raney Ni, EtOH, reflux, 50%

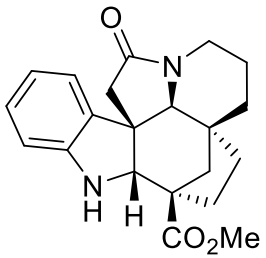


(-)-kopsinine (**3**)



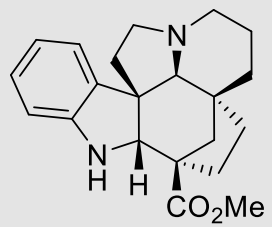
30

1. TFA/DCM, then
   i-Pr_2NEt, DCM, 59%
2. $NaBH_4$, MeOH, 27%



32

1. Lawesson's reagent
   toluene, 90 °C, 48%
2. Raney Ni, EtOH, Δ, 76%



33
(tetrahydrokopsifoline D)