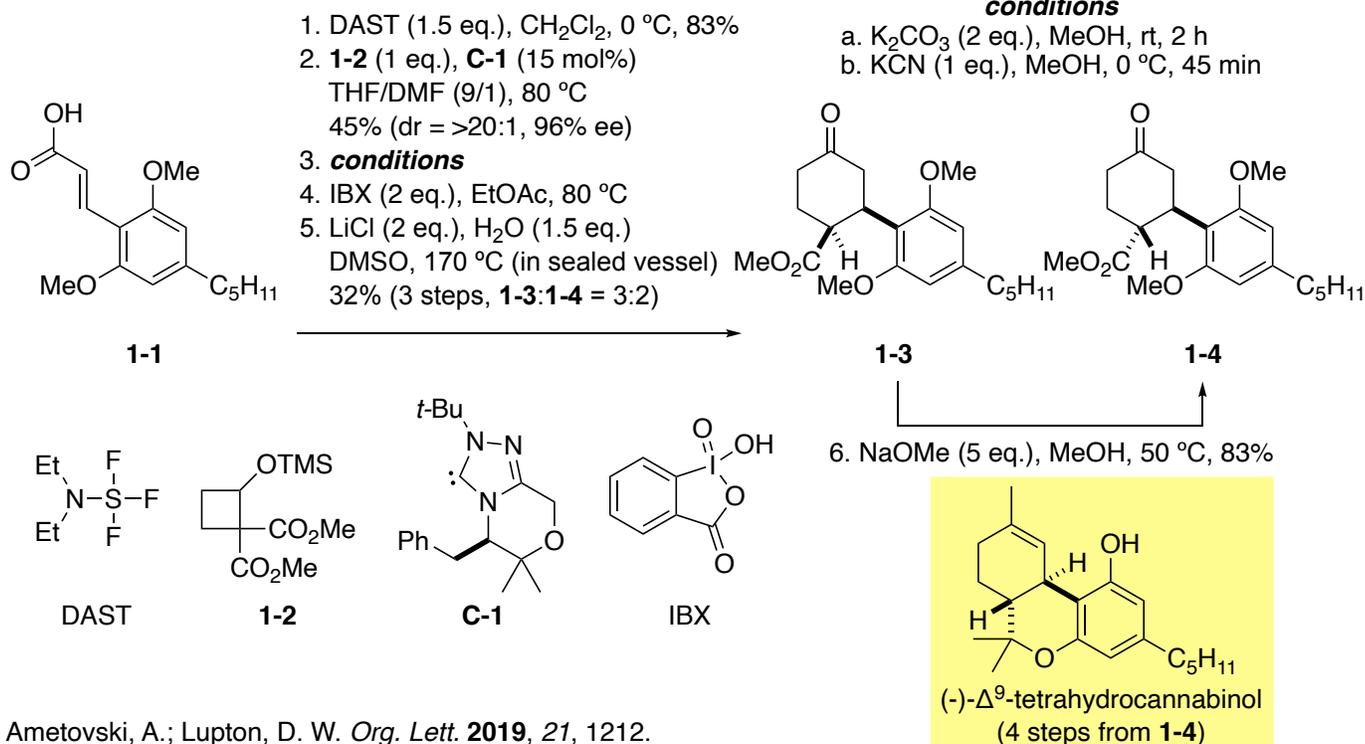


Problem Session (3) -Answer-

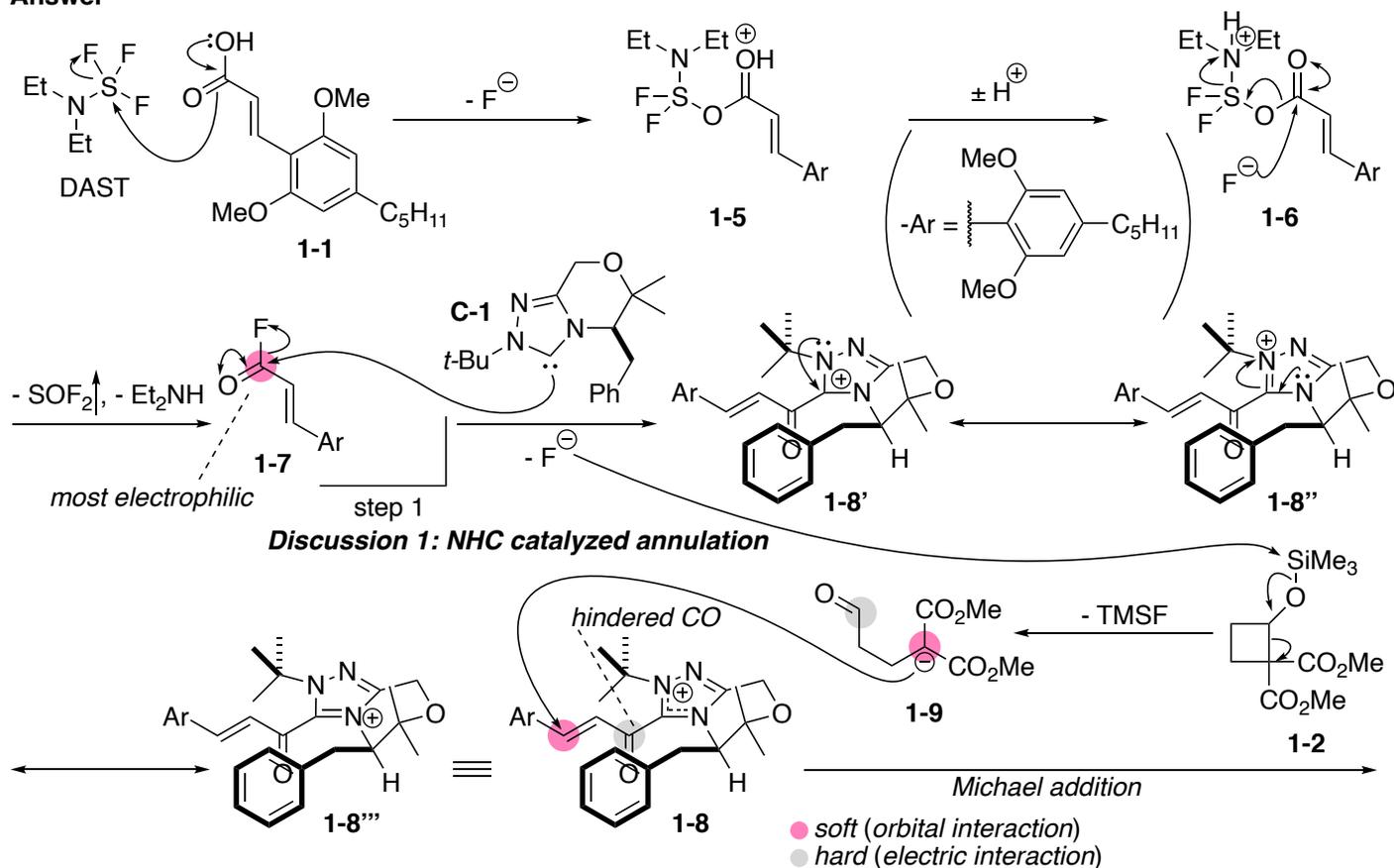
2021.7.24. Yuto Hikone

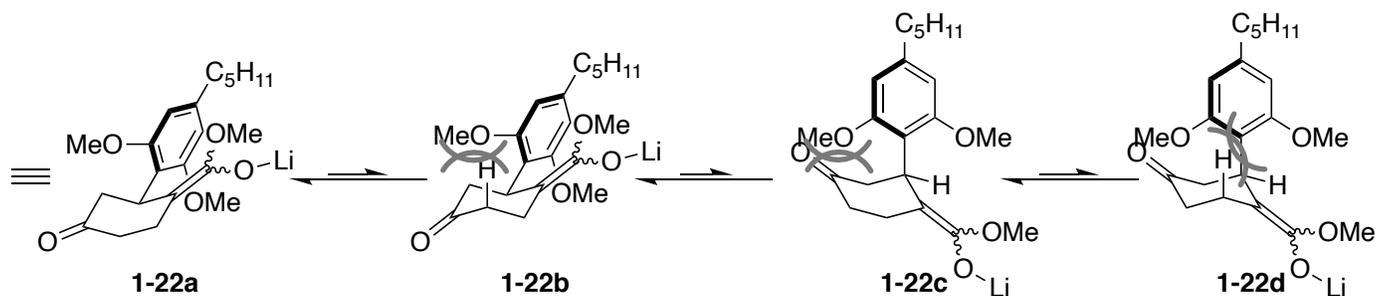
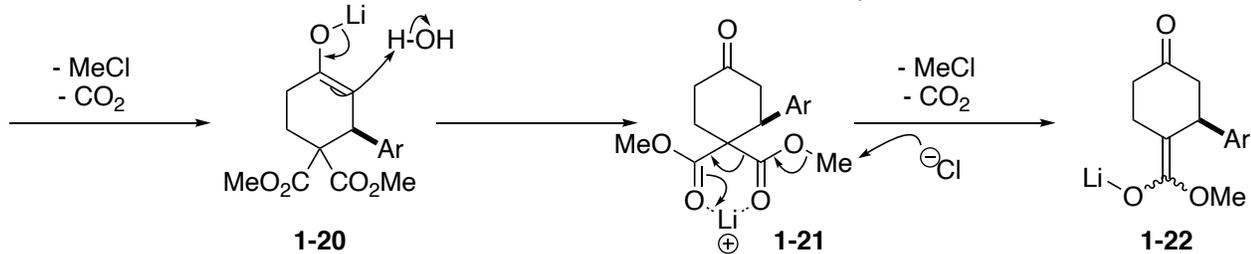
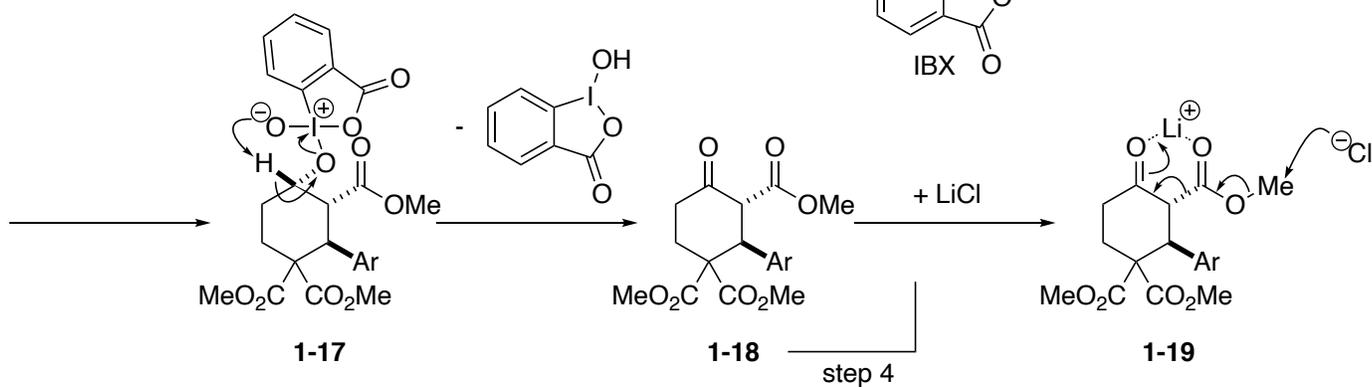
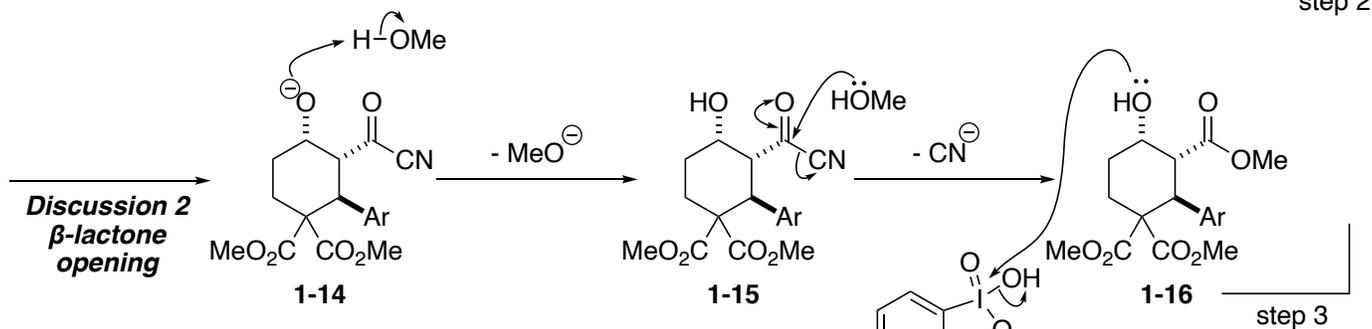
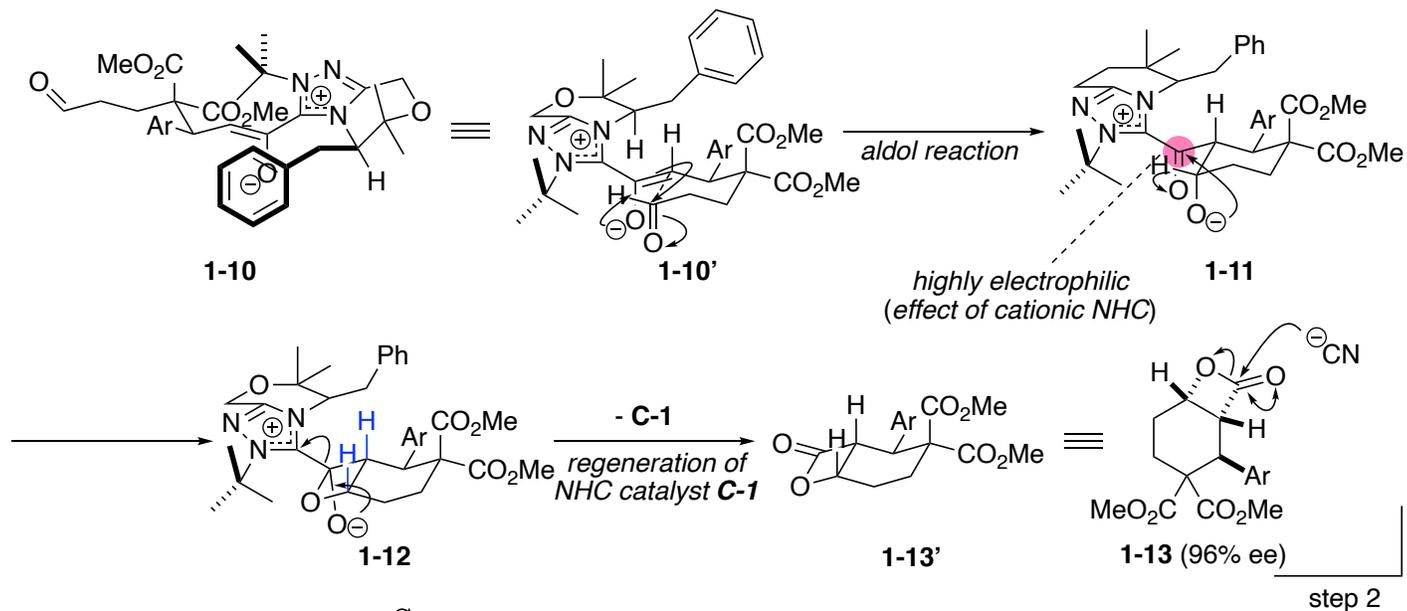
Topic: NHC (N-Heterocyclic Carbene) catalyst in total synthesis

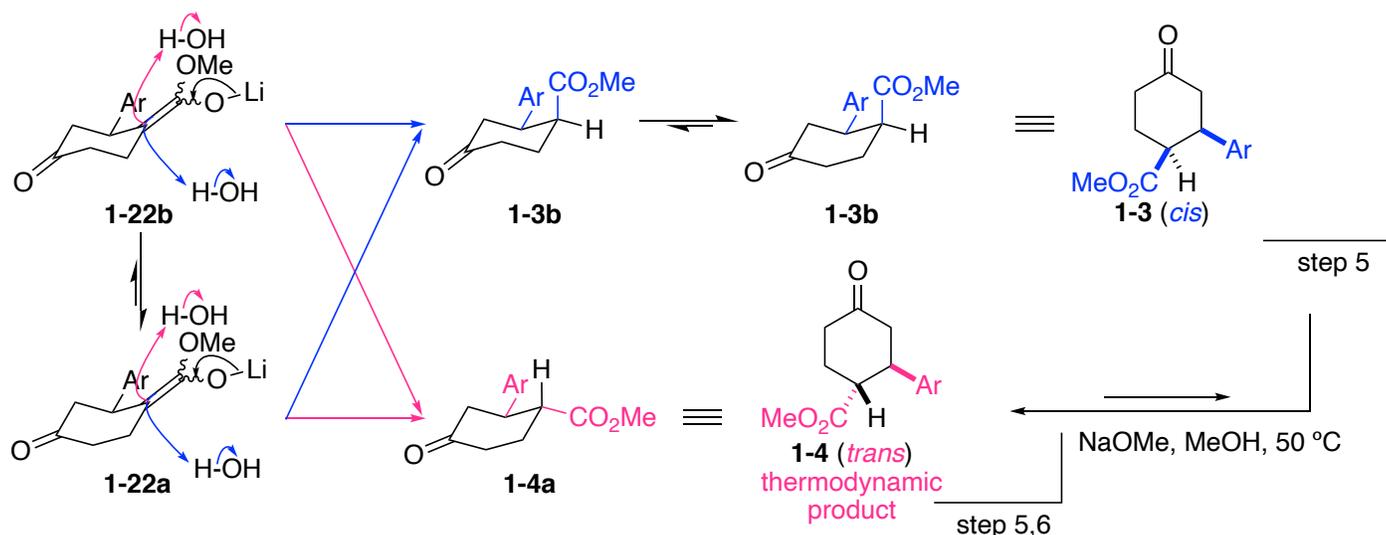
1. As for step 3, choose the best basic conditions (the conditions are shown above right).
As for step 6, just provide a reason for complete conversion of **1-3** to **1-4**.



Answer



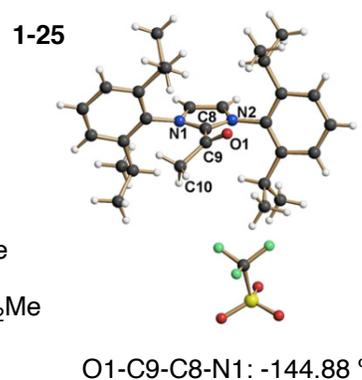
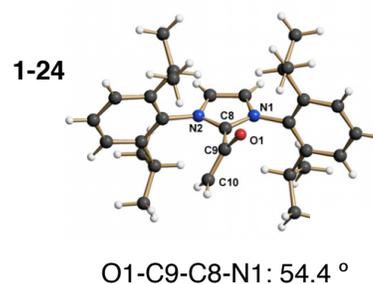
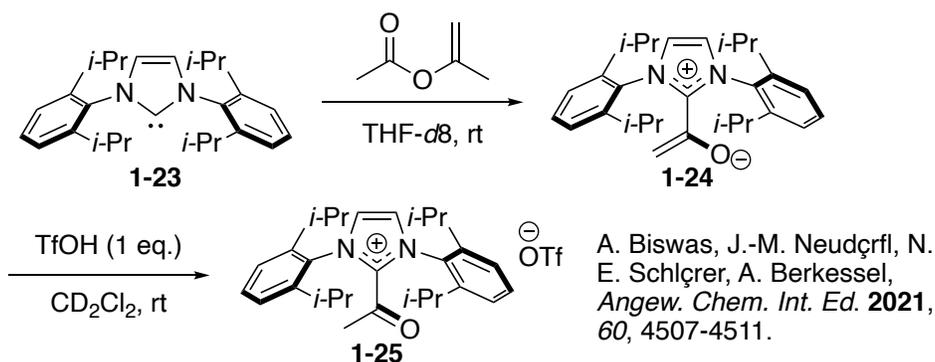




While methylester in **1-3** is axial-oriented, there's no substitutions axial-oriented in **1-4**. Therefore, epimerization occurred toward thermodynamic product **1-4**.

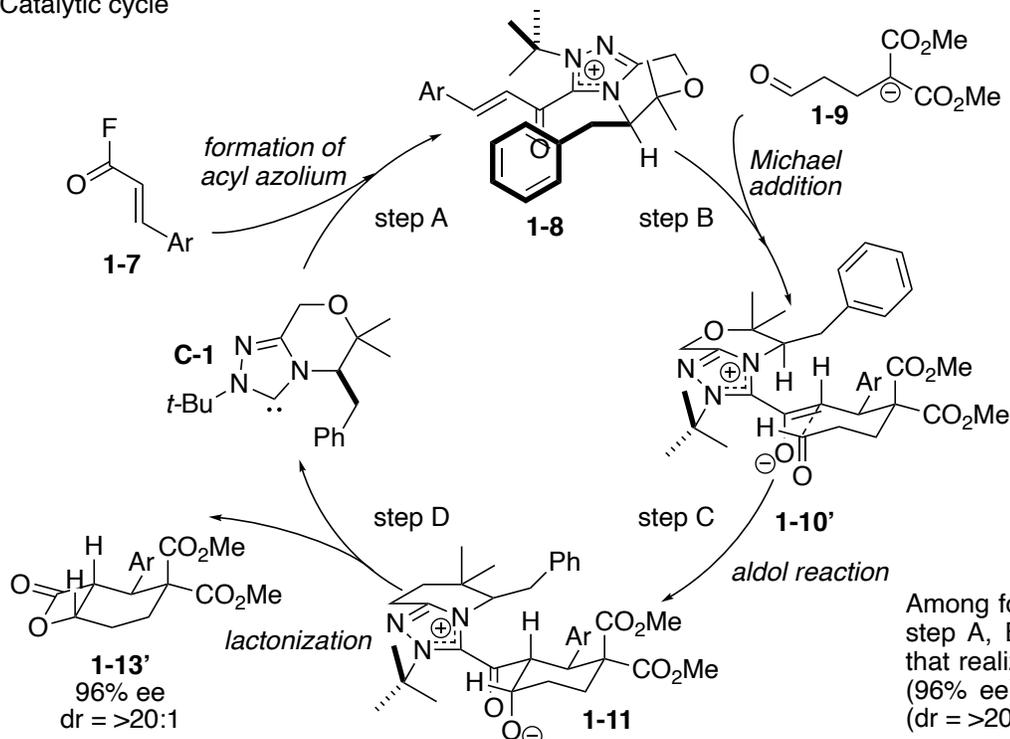
Discussion 1: NHC catalyzed annulation

1-1. X-ray structure of azolium enolate and acyl azolium triflate



1-2. Enantio/diastereoselective formation of cyclohexyl β -lactone

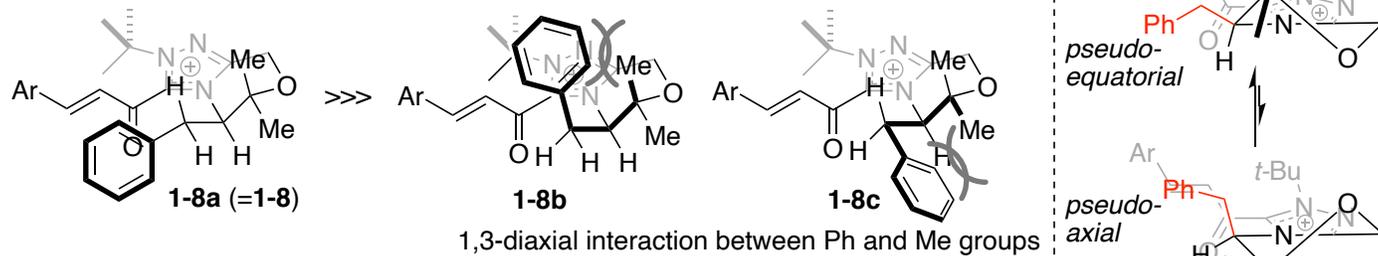
• Catalytic cycle



step A: formation of acyl azolium

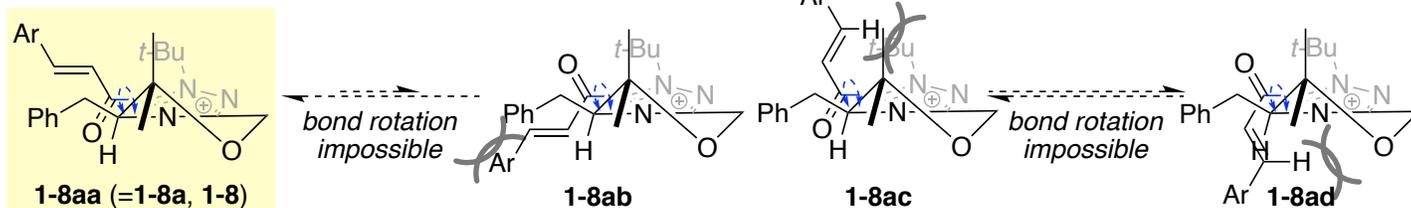
Conformation of acyl azolium **1-8**

(i) NHC side



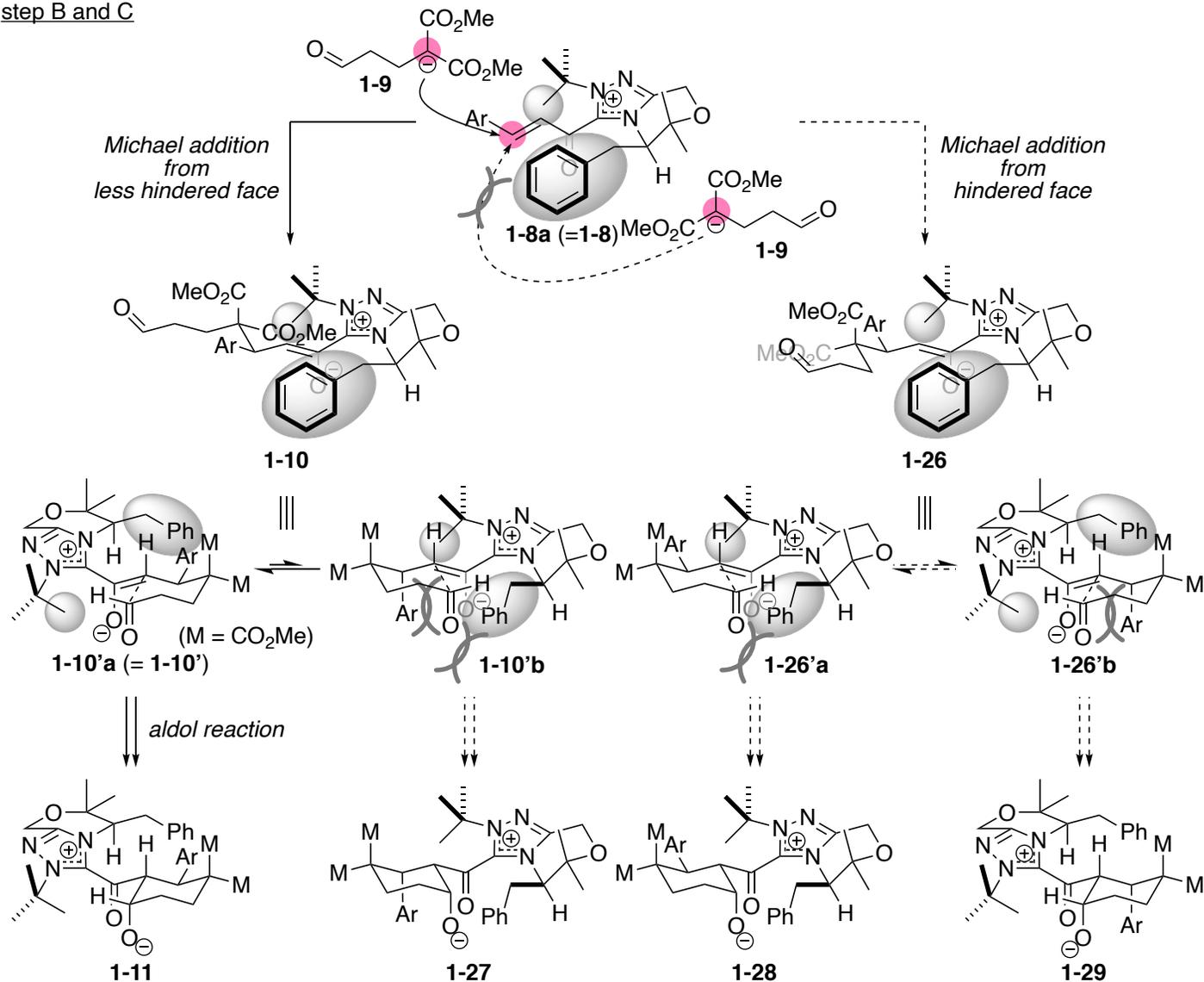
(ii) Enone side

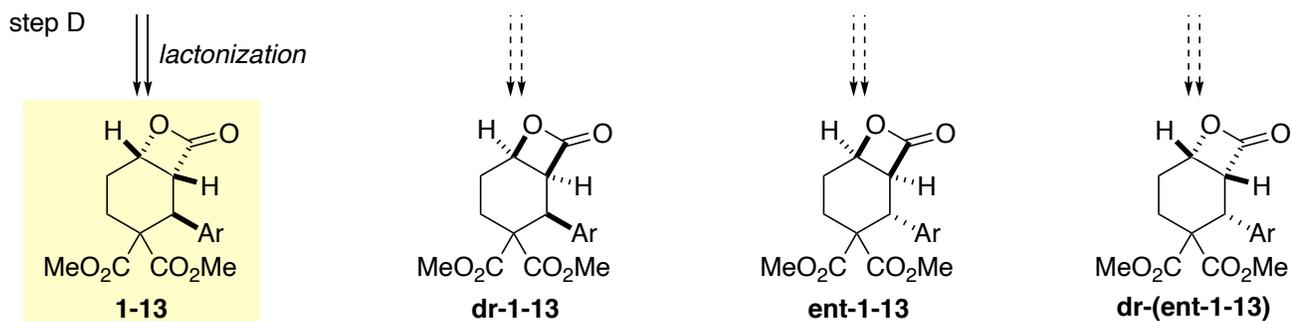
E-enone



Considering above factor (i) and (ii), **1-8a** is the dominant product at the step A.

step B and C





Discussion 2: β -lactone opening

Strong-base conditions: NaOMe

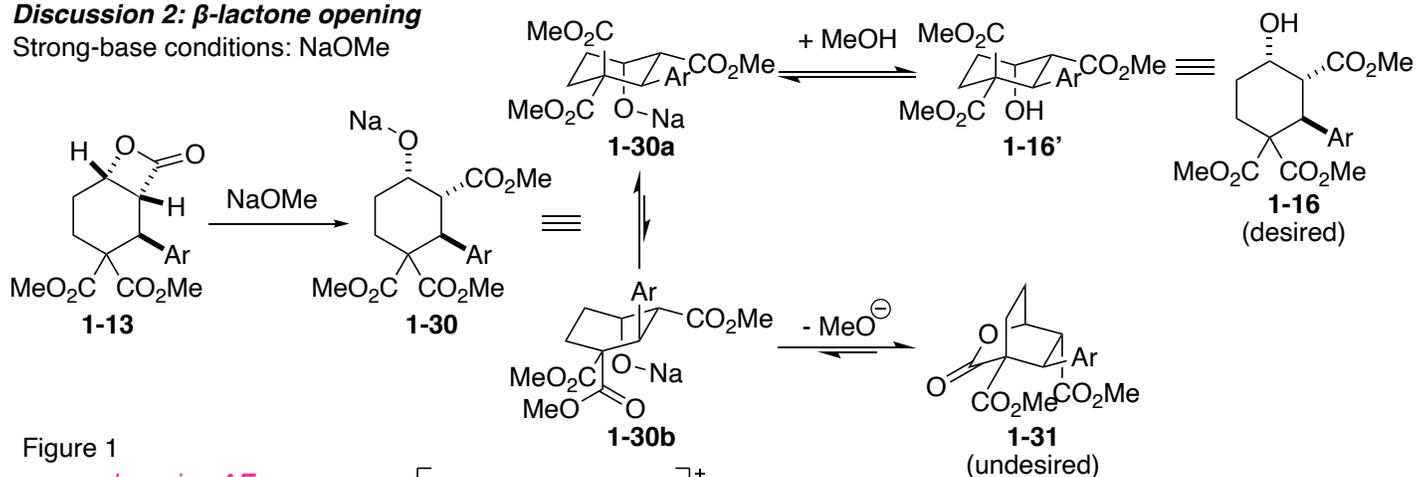


Figure 1

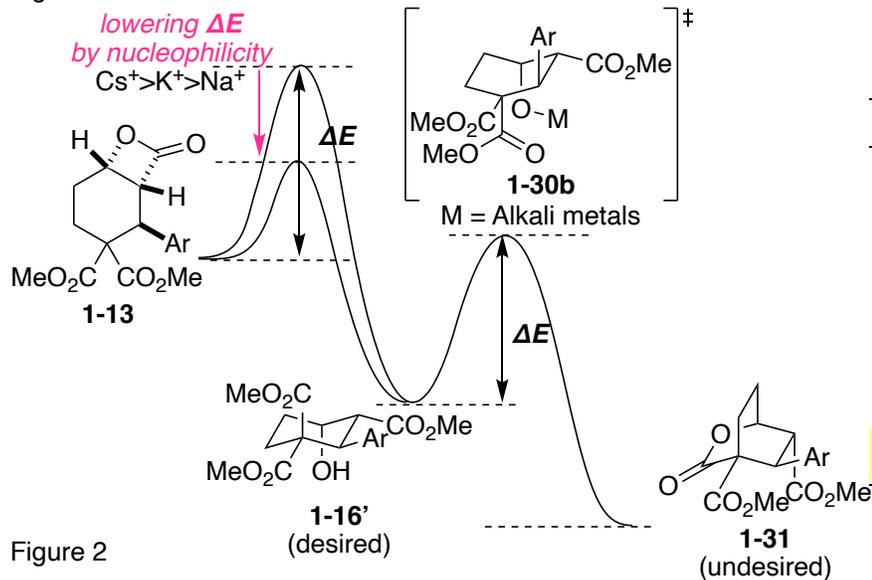
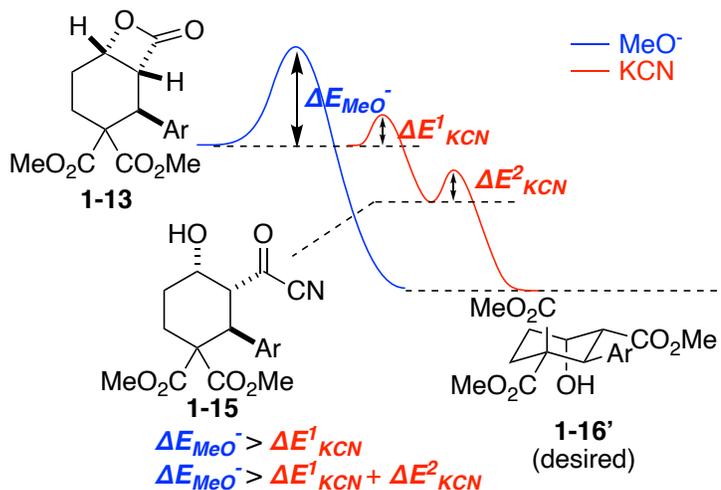


Figure 2



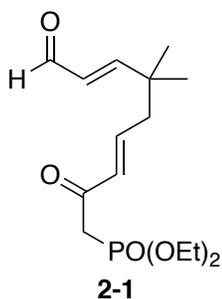
Screening of inorganic base-mediated β -lactone opening (in MeOH)

entry	conditions	1-16 : 1-31
1	NaOMe, rt, 2 h	1 : 9 (1-31 : 91%)
2	NaOMe, rt, 0.5 h	1 : 2
3	K ₂ CO ₃ , rt, 1 h	1 : 1
4	Cs ₂ CO ₃ , rt, 1 h	1.5 : 1
5	Cs ₂ CO ₃ , 0 °C, 1.5 h	2 : 1
6	KCN, 0 °C, 0.75 h	3 : 1

In strong-basic conditions (entry 1-5), increase in the nucleophilicity of methoxide ($Cs^+ > K^+ > Na^+$) lead to the increase of the ratio of 1-16/1-31. It is suggested that activation energy ΔE from 1-13 to 1-16' gets lower as the nucleophilicity of methoxide against β -lactone increases ($Cs^+ > K^+ > Na^+$), leading to the facile formation of 1-16' (Figure 1). In this case, nucleophilicity doesn't have an effect against ΔE from 1-16' to 1-31.

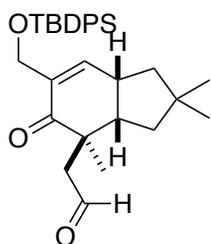
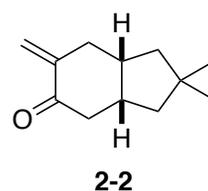
Due to the high nucleophilicity of CN^- , activation energy ΔE^1_{KCN} and total $\Delta E^1_{KCN} + \Delta E^2_{KCN}$ from 1-13 to 1-16' are smaller than ΔE_{MeO^-} , leading to the improvement of the ratio of 1-16/1-31 (Figure 2).

2.

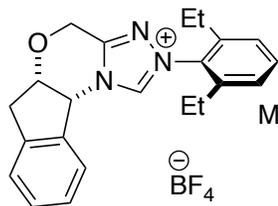
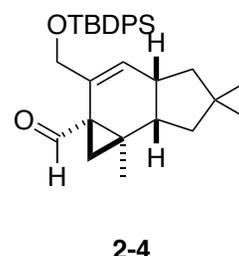


1. **C-2** (5 mol%), *i*-Pr₂NEt (0.9 eq.)
CH₂Cl₂, 40 °C
76% (dr = >20:1, 98% ee)
2. LiAlH(O*t*-Bu)₃ (2.7 eq.)
THF/CH₂Cl₂ (1/10), 0 °C, 84%
3. H₂ (balloon), Pd/C (0.2 eq.)
hexane/EtOAc (1/1), 23 °C
4. (CH₂O)_n (5 eq.), H₂O (2 drops)
Ba(OH)₂ (1.05 eq.), THF, 23 °C*

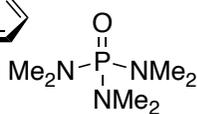
* Yield was determined at the next step as a three-step yield.



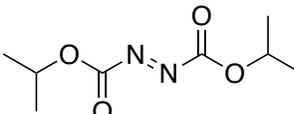
5. VCl₃·(THF)₃ (2 eq.), Zn (12 eq.)
HMPA (5 eq.), CH₂Cl₂, 85%
6. DIAD (3 eq.), PPh₃ (3 eq.)
4-nitrobenzoic acid (3 eq.)
THF, 0 °C to ambient temperature
61%



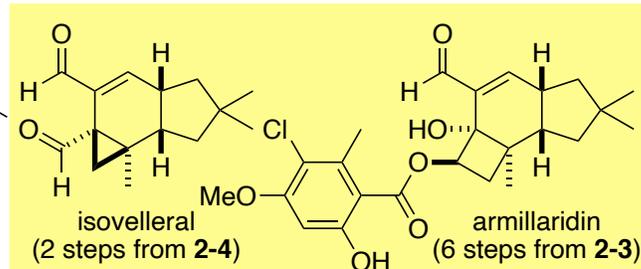
C-2



HMPA

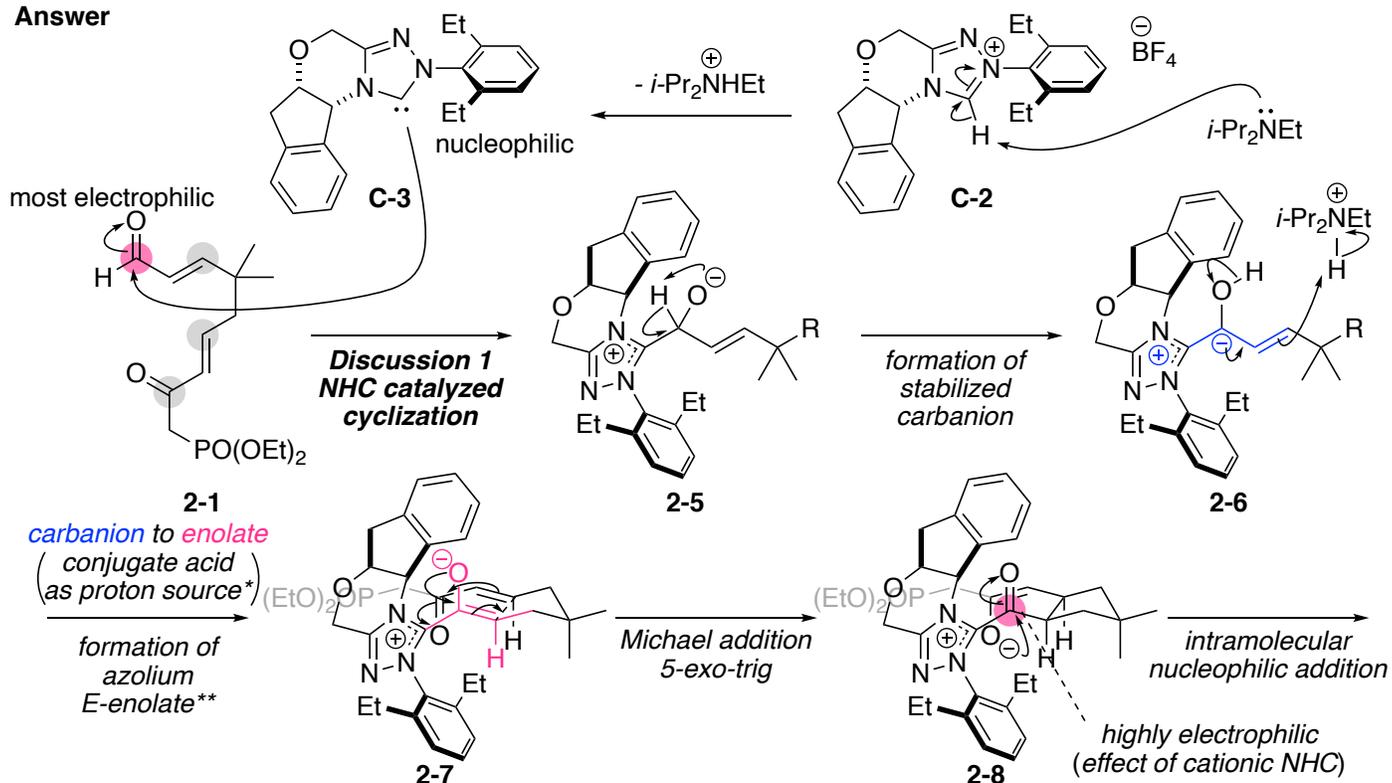


DIAD



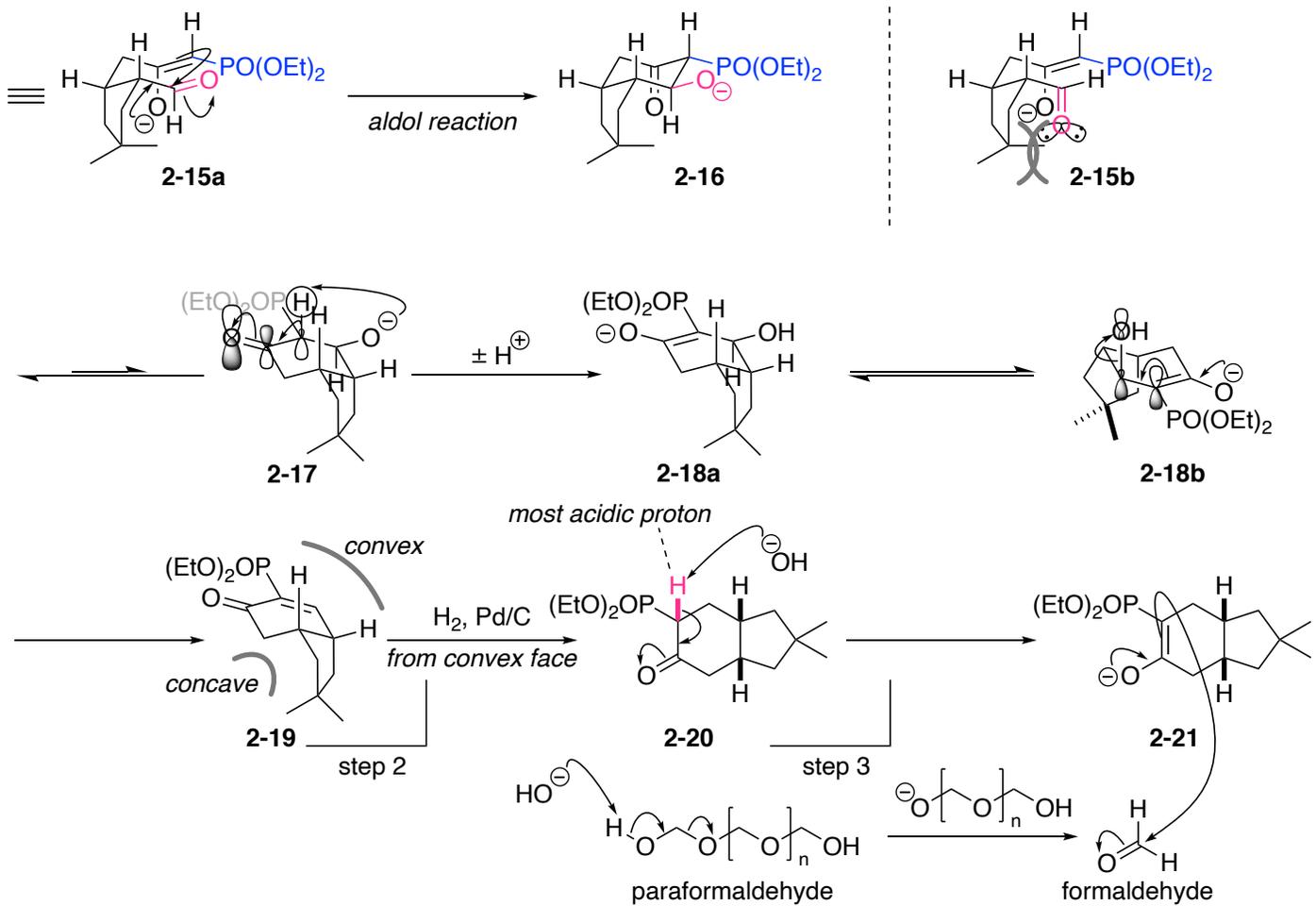
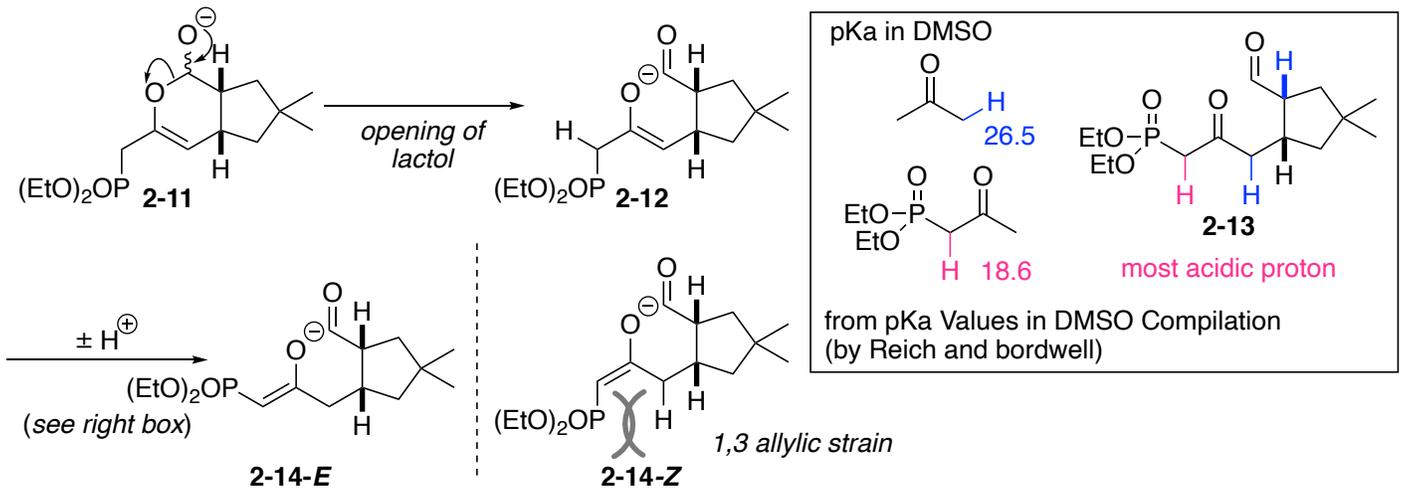
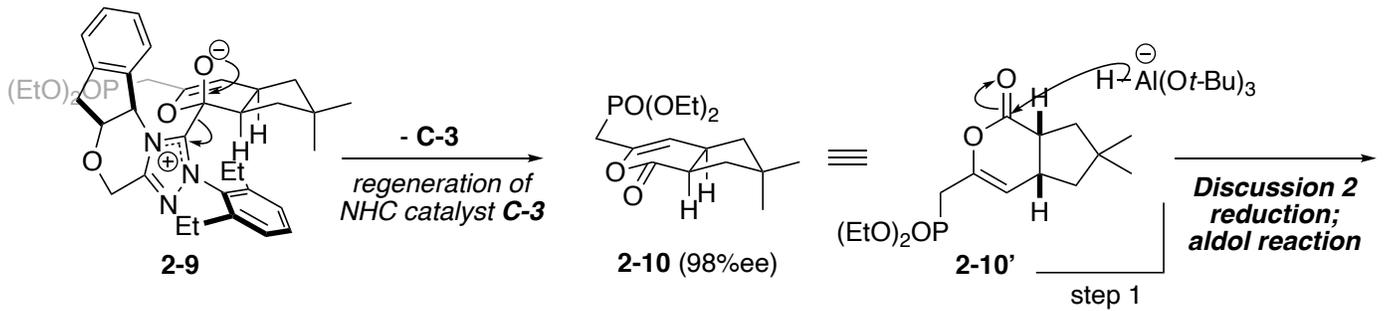
Hovey, M. T.; Cohen, D. T.; Walden, D. M.; Cheong, P. H. Y.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 9864–9867.

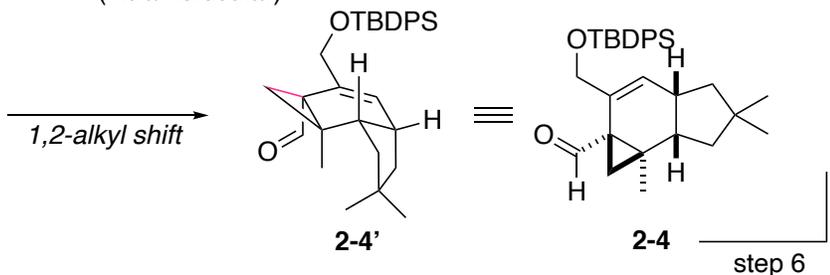
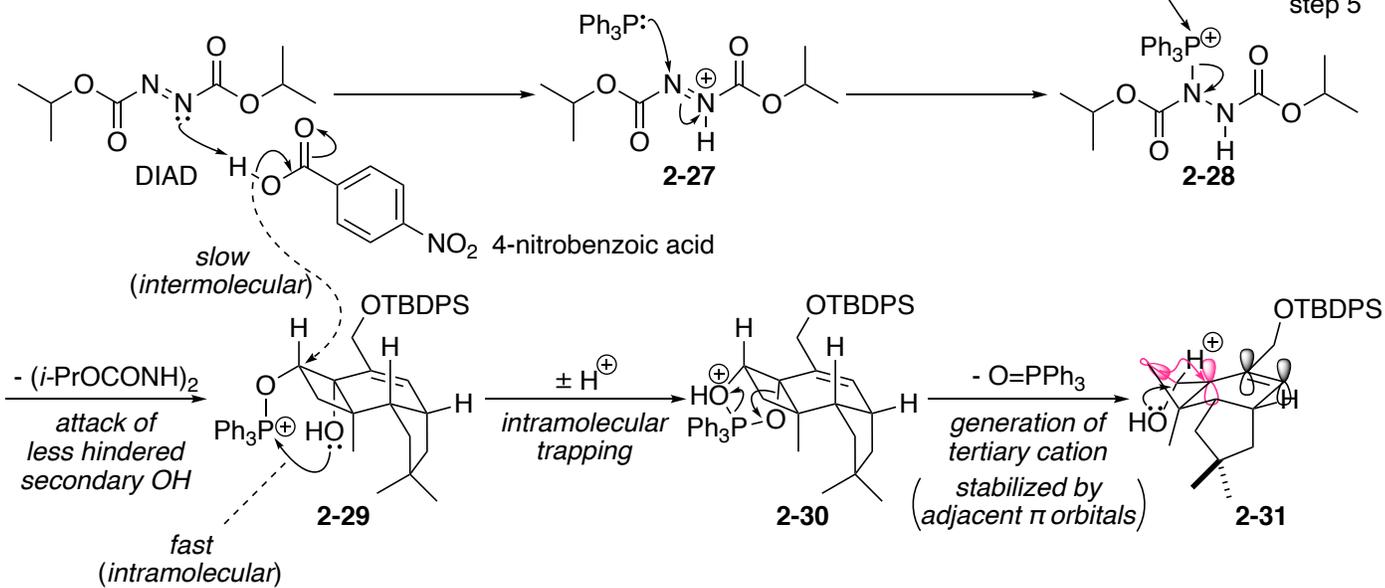
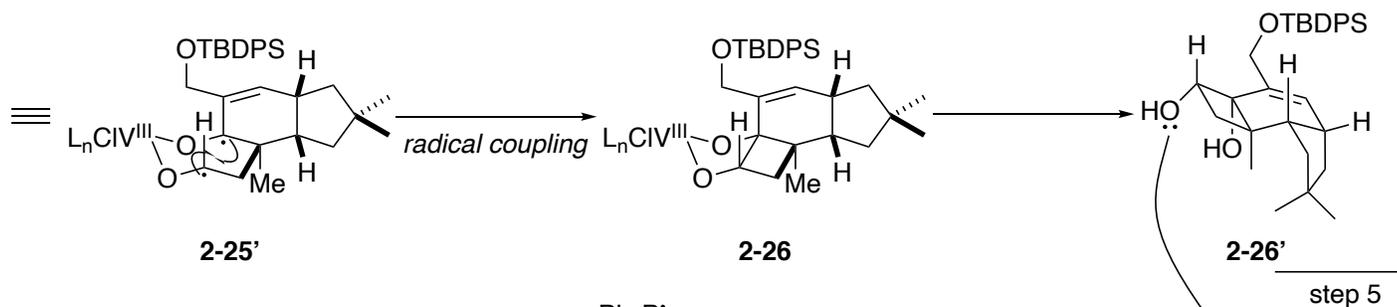
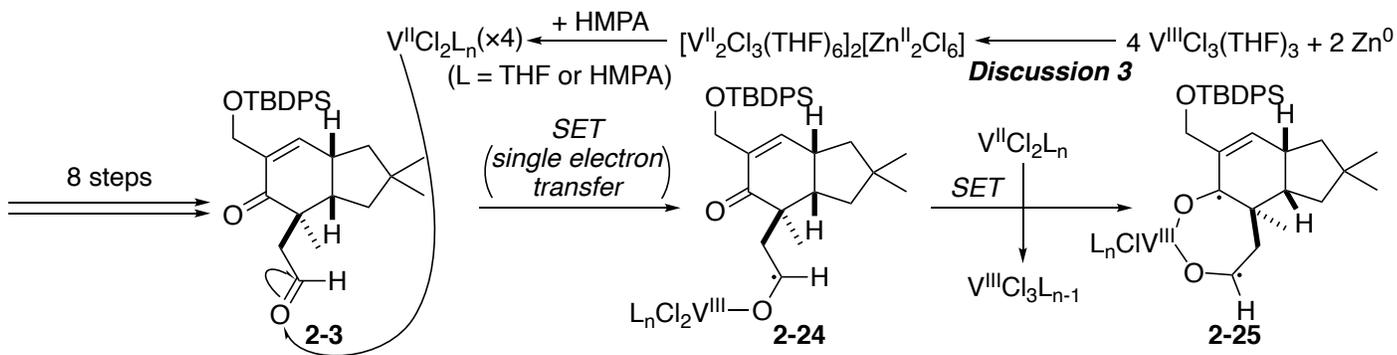
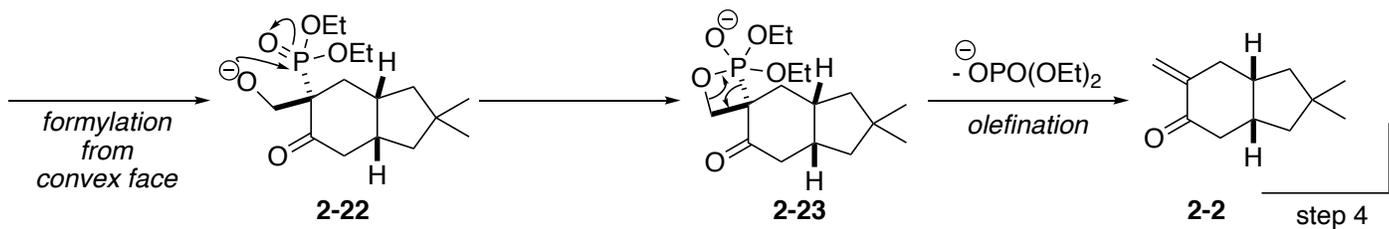
Answer



*Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. *Nature chemistry* **2015**, *7*, 842-847.

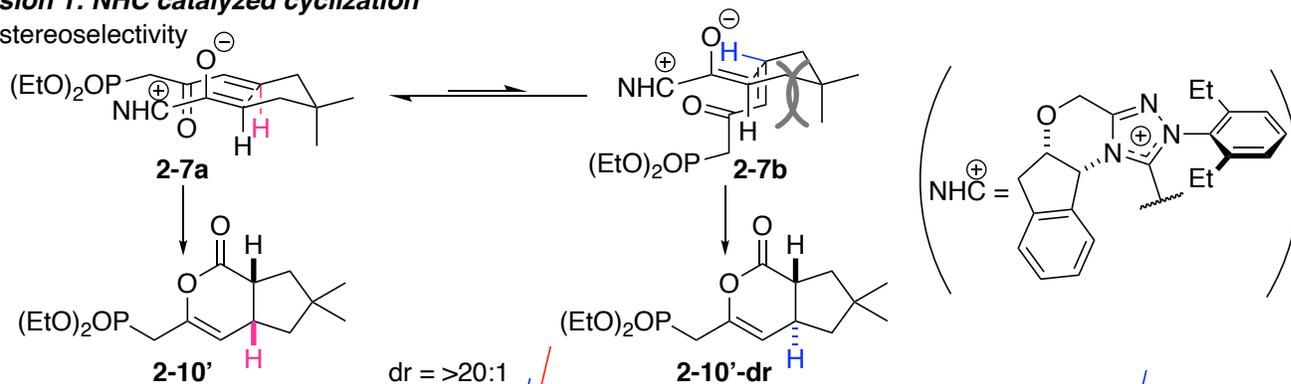
** Z-enolate cannot be generated considering the 1,3-allylic strain.





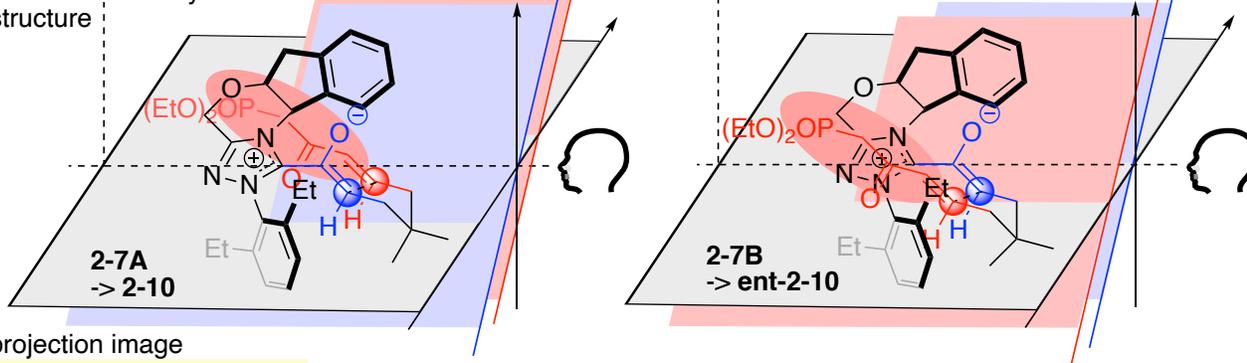
Discussion 1: NHC catalyzed cyclization

1-1. diastereoselectivity

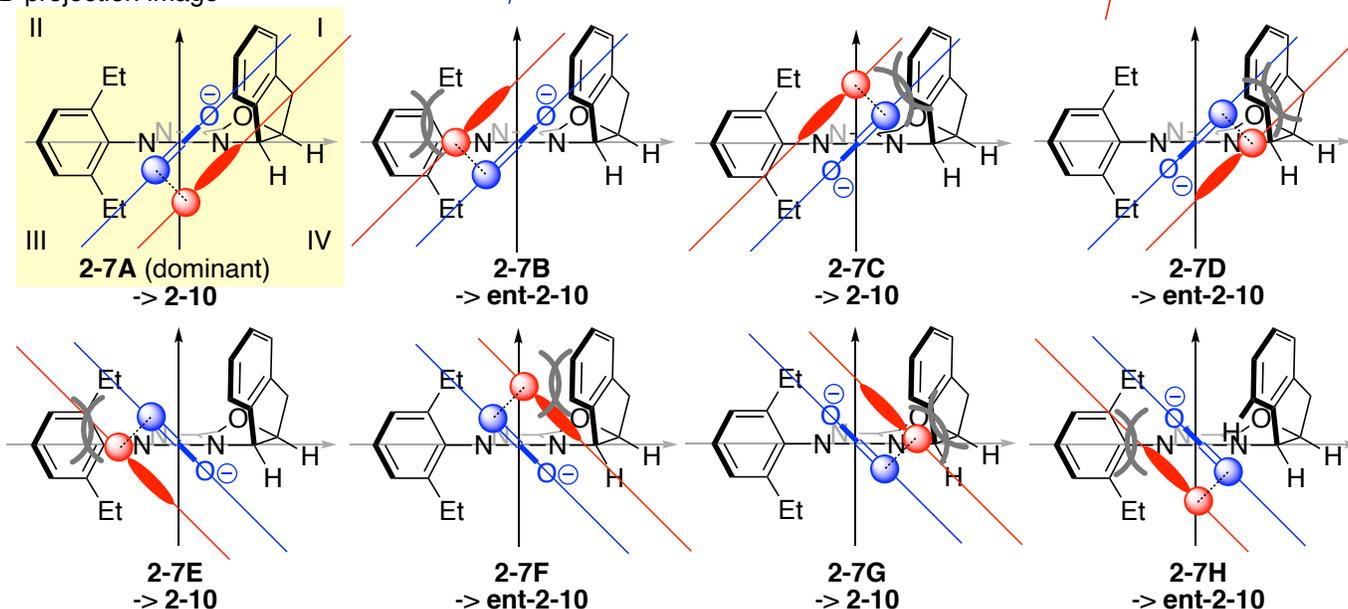


1-2. enantioselectivity

3D structure



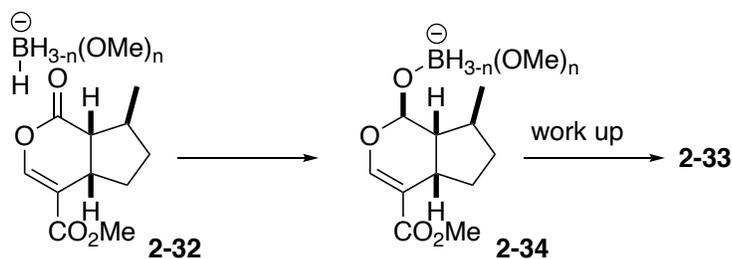
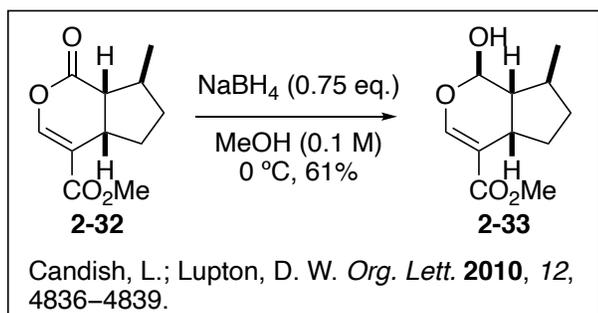
2D projection image



While first quadrant is fully occupied, fourth quadrant is unoccupied (second and third quadrants are equally occupied). This leads to the twist of the plane on which enolate and enone are placed (blue and red) against the one on which the catalyst is located (gray). Among eight projections, **2-7A** is the sterically least demanding one.

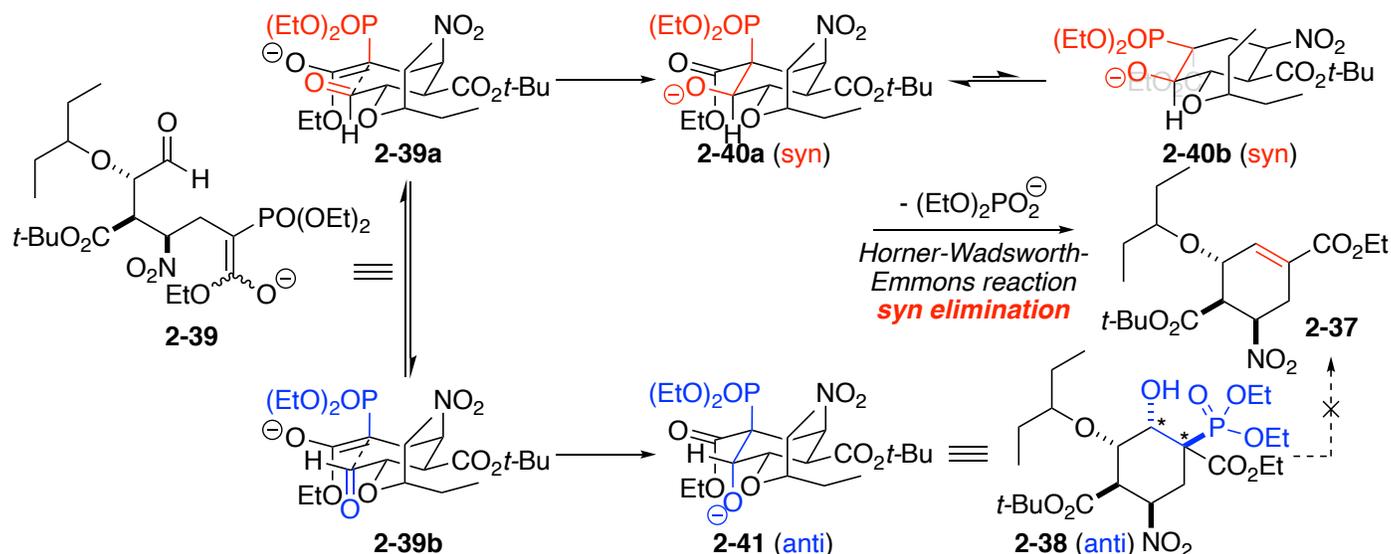
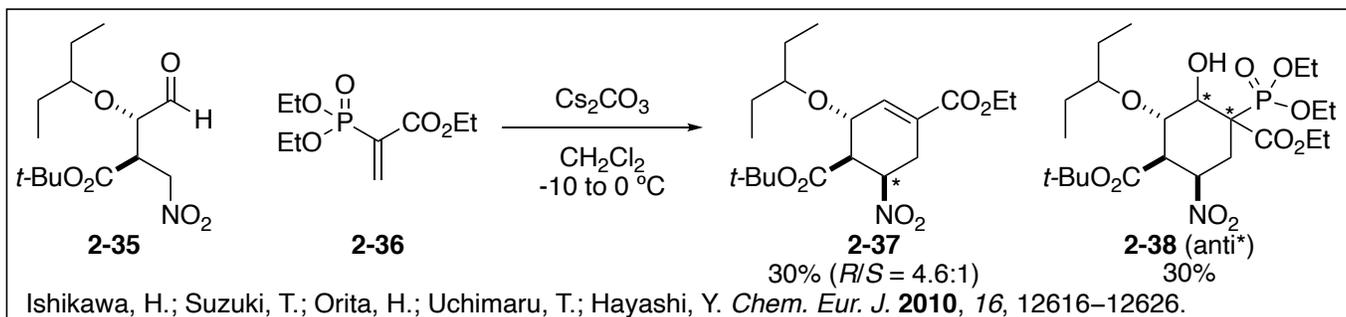
Discussion 2: reduction; aldol reaction

2-1. reduction of dihydropyranone



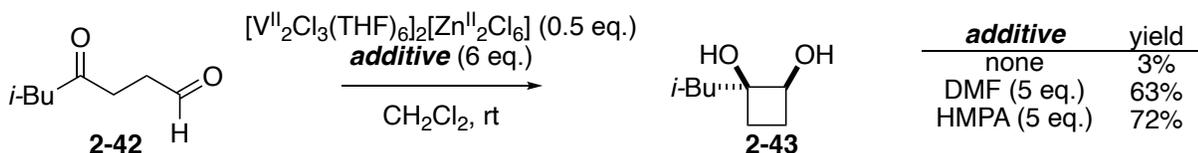
- NaBH_4 (small reductant)
-> Formation of O-B bond suppressed the lactol opening.
- $\text{LiAlH}(\text{O}t\text{-Bu})_3$ (bulky reductant)
-> Bulky *tert*-butyl groups prevented coordination of oxygen atom to aluminum, leading to the lactol opening.

2-2. aldol reaction

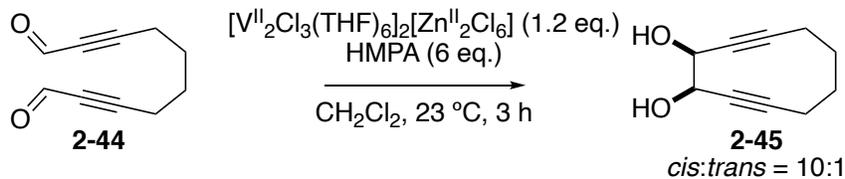


Discussion 3. vanadium mediated pinacol coupling

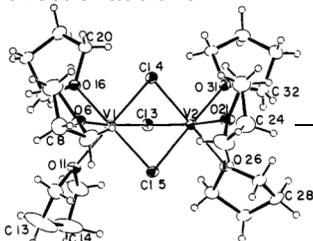
1. Effect of additive (Raw, A. S.; Pedersen, S. F. *J. Org. Chem.* **1991**, *56*, 830.)



2. Diastereoselectivity (Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859–5860.)



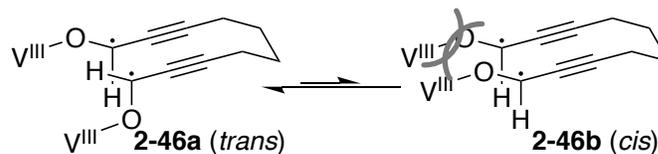
1. effect of additive



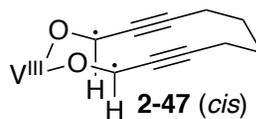
* Bouma, R. J.; Teuben, J. H.; Beukema, W. R.; Bansemer, R. L.; Huffman, J. C.; Caulton, K. G. *Inorg. Chem.* **1984**, *23*, 2715.

2. diastereoselectivity

non-chelation model



chelation model

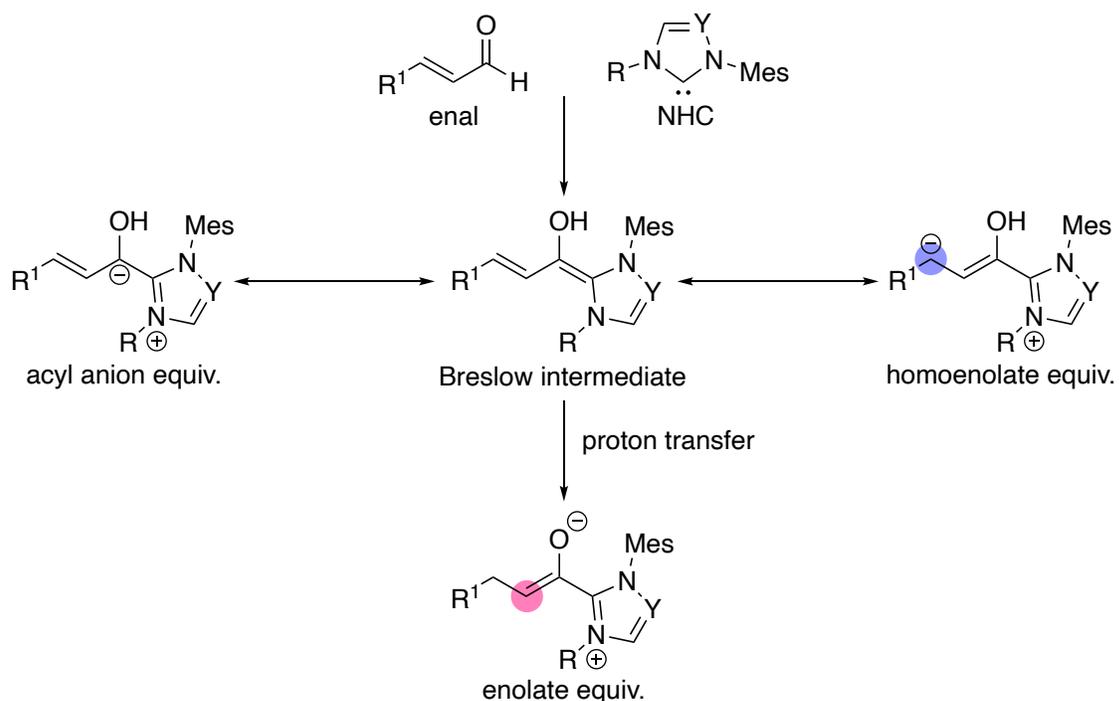


Diastereoselectivity of coupling adduct could be explained by chelation model.

Problem Session (3) -Appendix-

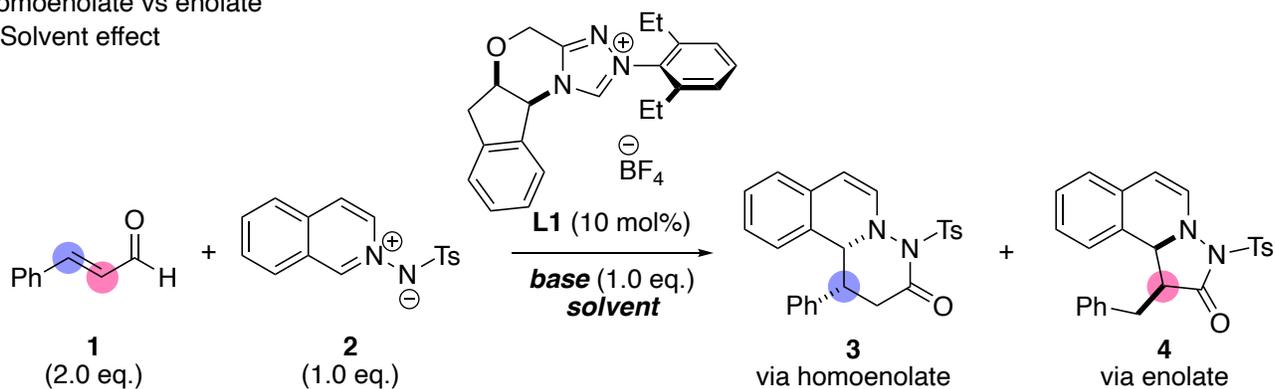
2021.7.24. Yuto Hikone

1. Course of the reaction between NHC catalyst and enal



2. Homo enolate vs enolate

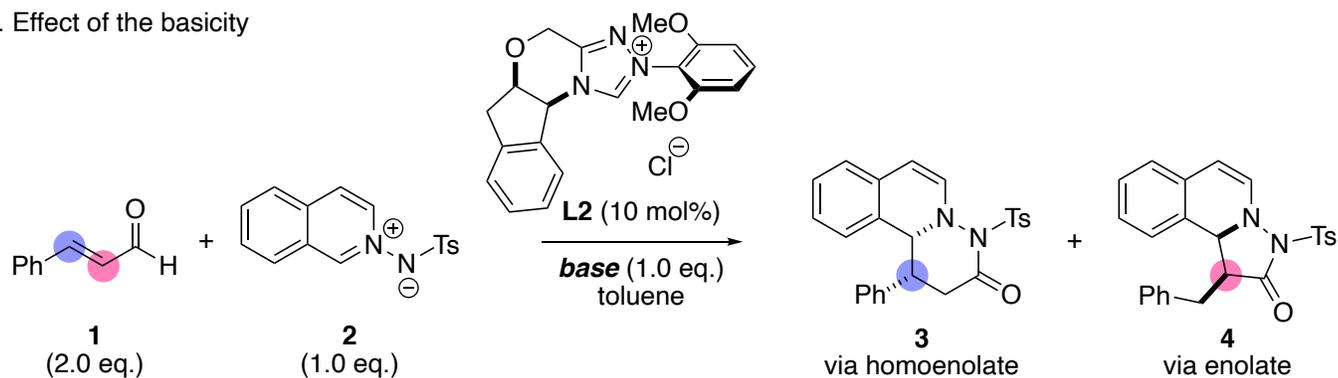
2-1. Solvent effect



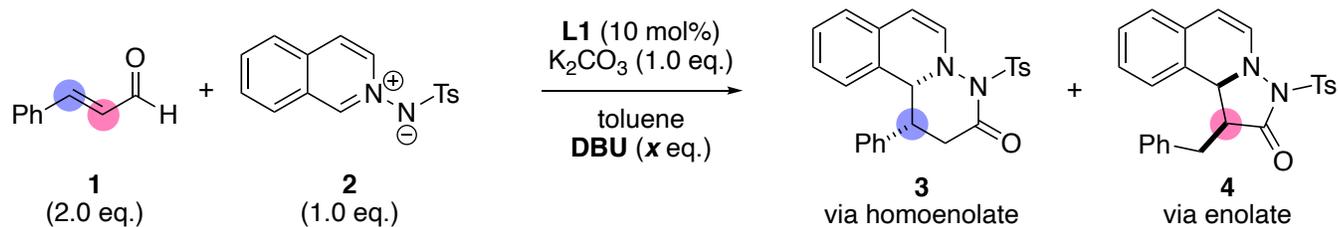
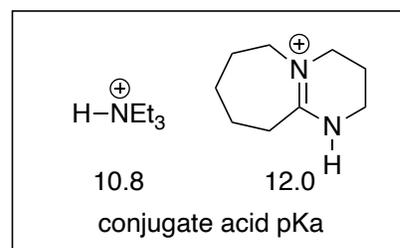
entry	base	solvent	3 : 4
1	DBU	THF	86%, 20:1
2	K ₂ CO ₃	THF	88%, 20:1
3	K ₂ CO ₃	CH ₂ Cl ₂	70%, 8:1
4	K ₂ CO ₃	toluene	37%, 1:7

Solvent has an great influence on the ratio of 3/4.

2-2. Effect of the basicity



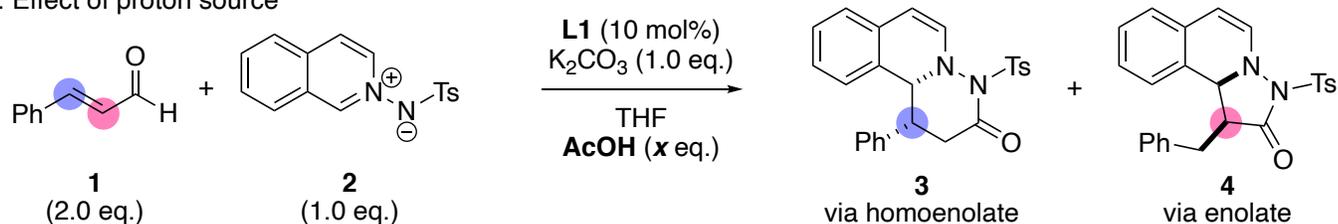
entry	base	3 : 4
1	DBU	15:1
2	Et ₃ N	1:3



entry	DBU (<i>x</i> eq.)	3 : 4	percentage of 3
1	0	1:7.1	12%
2	0.02	1:4.3	17%
3	0.05	1:1.8	36%
4	0.1	1:1.5	40%
5	0.2	1.6:1	62%
6	0.5	2.8:1	73%
7	1.0	7.2:1	88%

Homoemolate adduct **3** was more preferentially generated to enolate adduct **4** as the basicity increased.

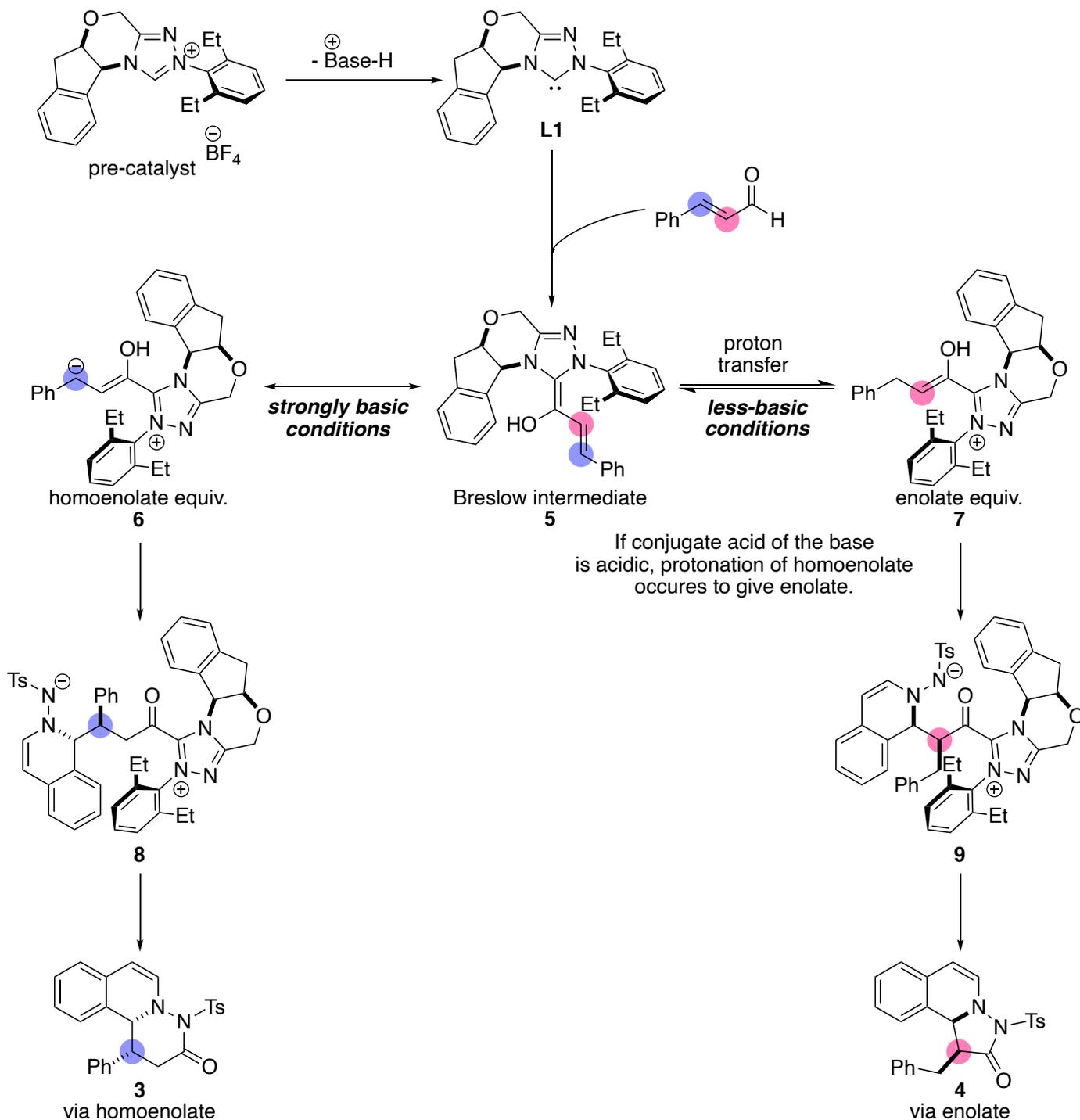
2-3. Effect of proton source



entry	AcOH (<i>x</i> eq.)	3 : 4	percentage of 3
1	0	20:1	95%
2	0.1	1:1.3	44%
3	0.2	1:1.4	41%
4	0.33	1:1.8	36%
5	0.66	1:2	33%
6	1	1:2.5	28%

Enolate adduct **4** was more preferentially generated to homoenolate adduct **3** as the acidity increased.

2-4. Proposed mechanism



Proton concentration has an important role in determining the course of the reaction.

If the proton concentration is high, protonation of the homoenolate equiv. **6** proceeds to afford enolate equiv. **7**.

3. X-ray structure of Breslow intermediate

X-ray structure of isolable-analogues of the Breslow intermediate are shown below.

