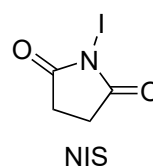
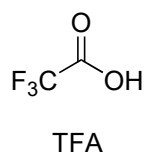
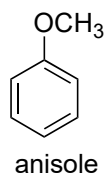
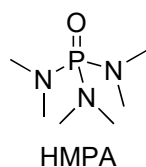
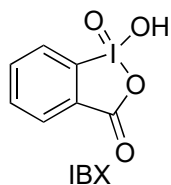
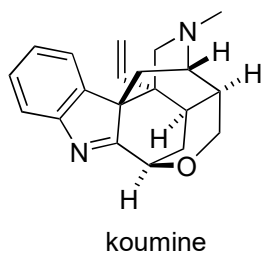
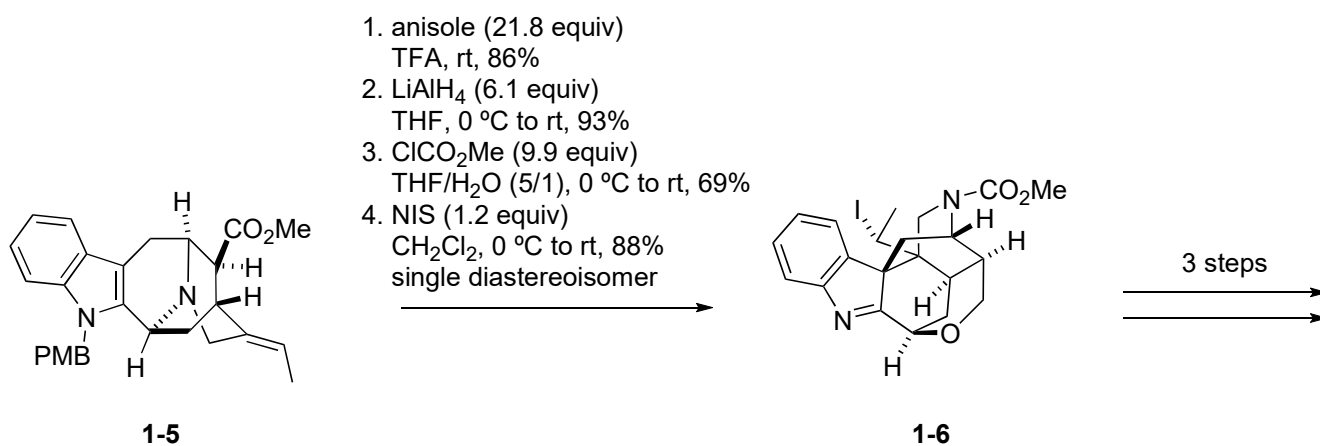
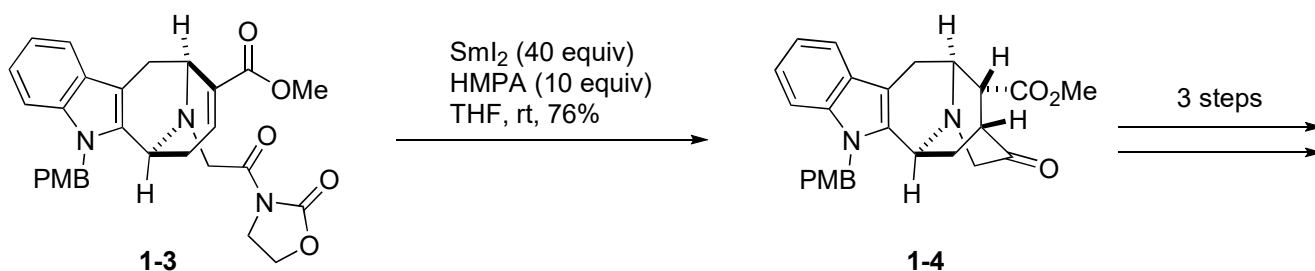
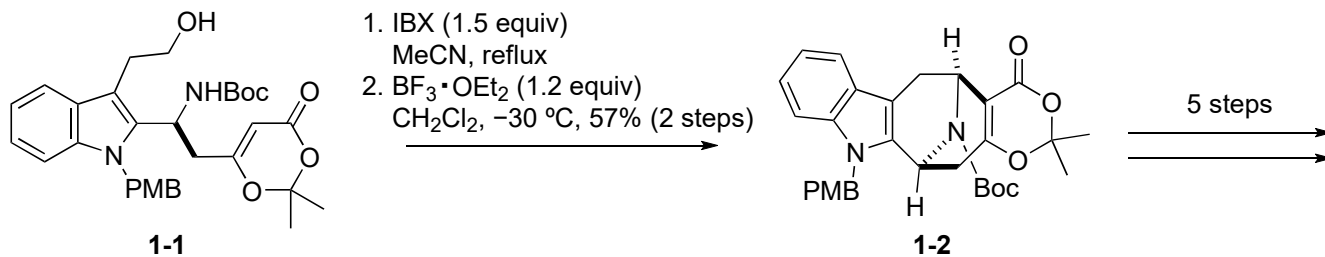


Problem Session (1)

2023.12.25 Yutaro Yamada

Please explain each reaction mechanism.

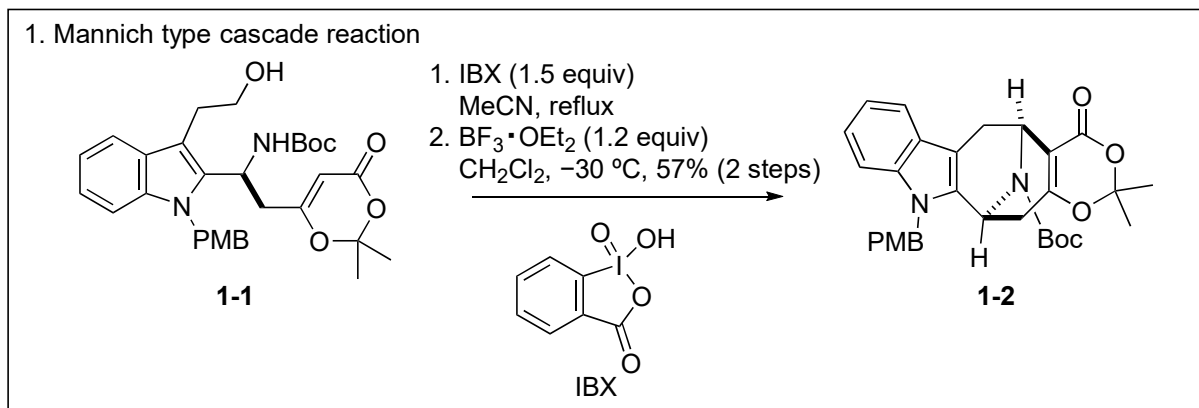


Problem Session (1) -Answer-

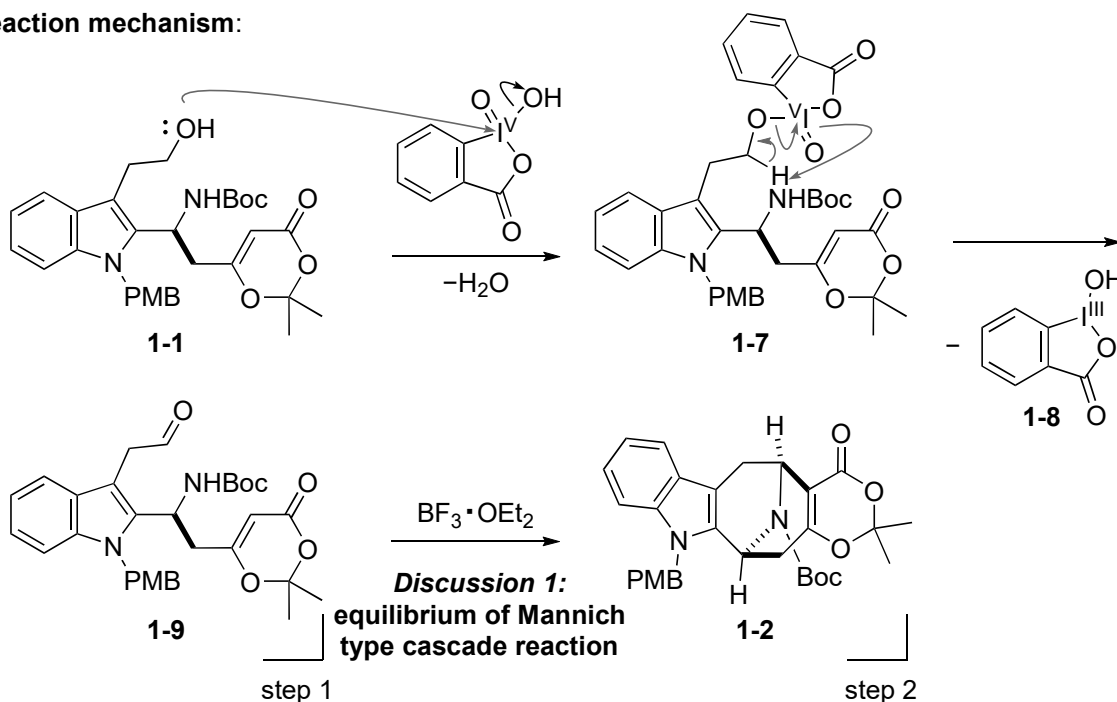
2023.12.25 Yutaro Yamada

topic: Total synthesis of koumine

main paper: Chen, W.; Ma, Y.; He, W.; Wu, Y.; Huang, Y.; Zhang, Y.; Tian, H.; Wei, K.; Yang, X.; Zhang, H., *Nat. Commun.* **2022**, 13, 908.

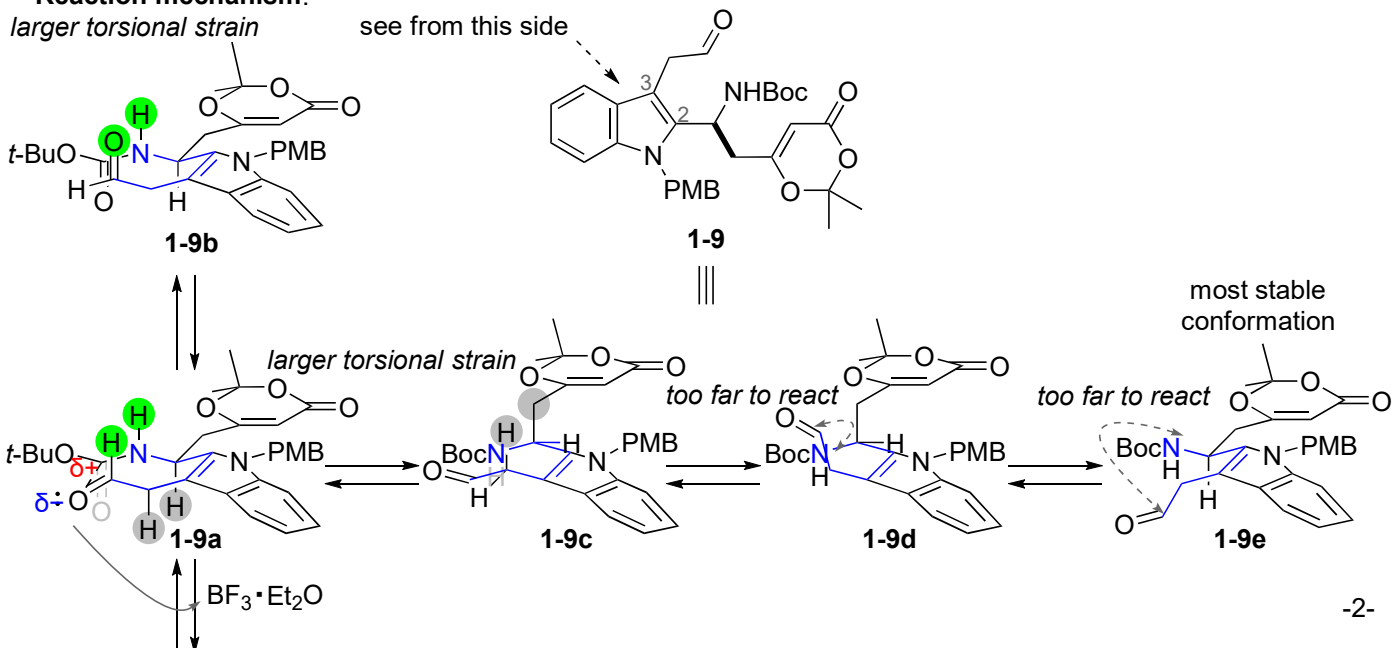


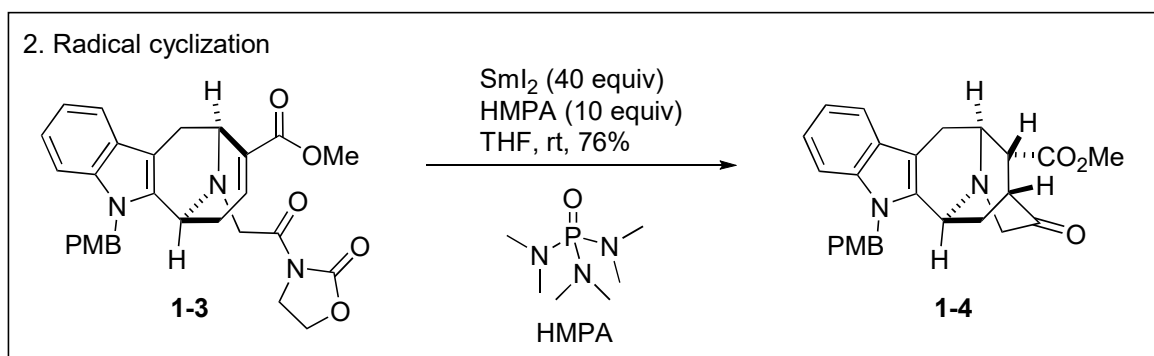
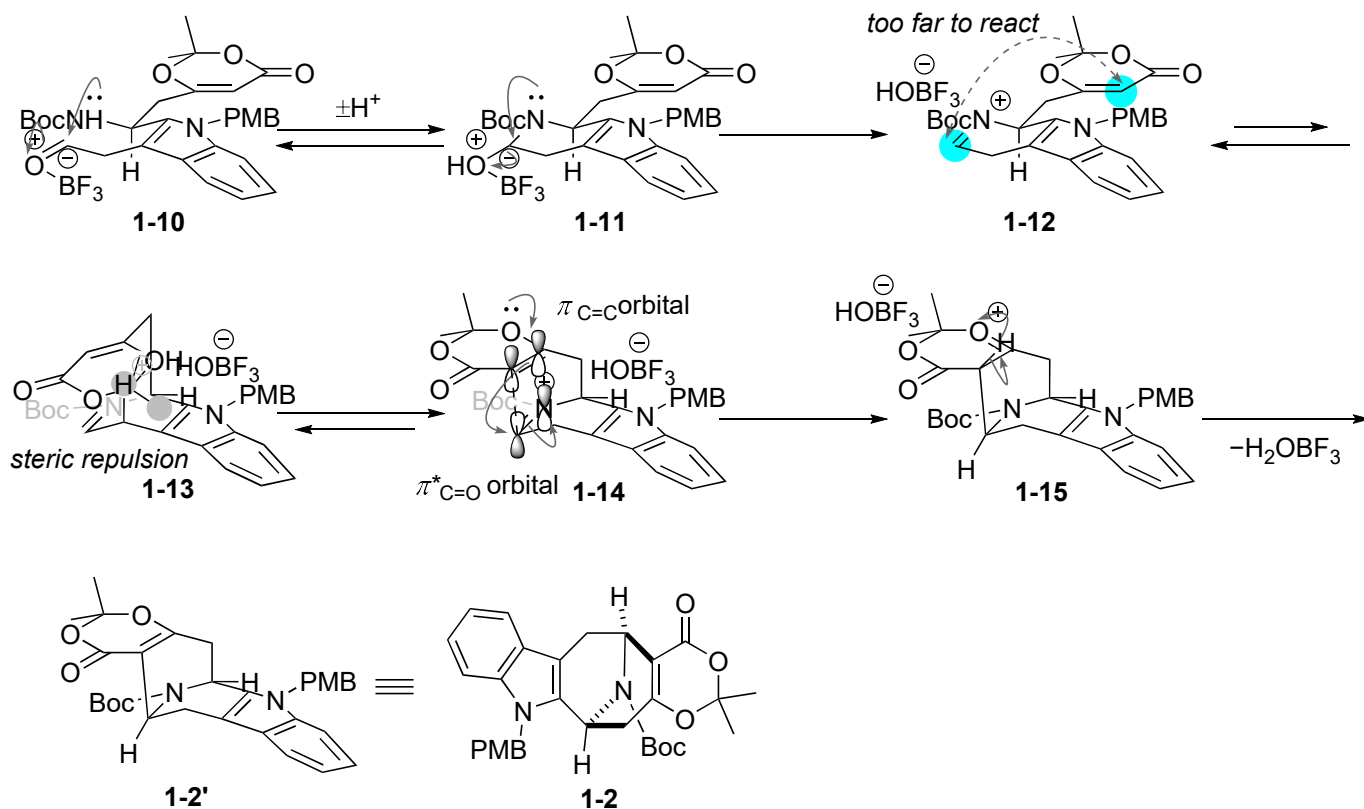
Reaction mechanism:



Discussion 1: equilibrium of Mannich type cascade reaction

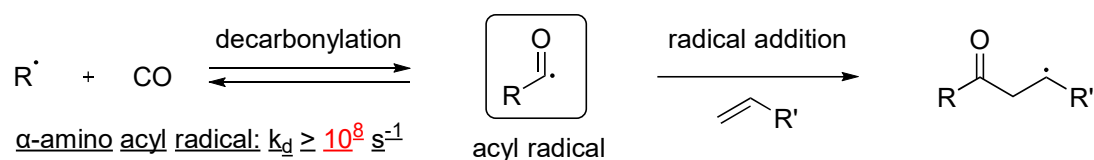
Reaction mechanism:





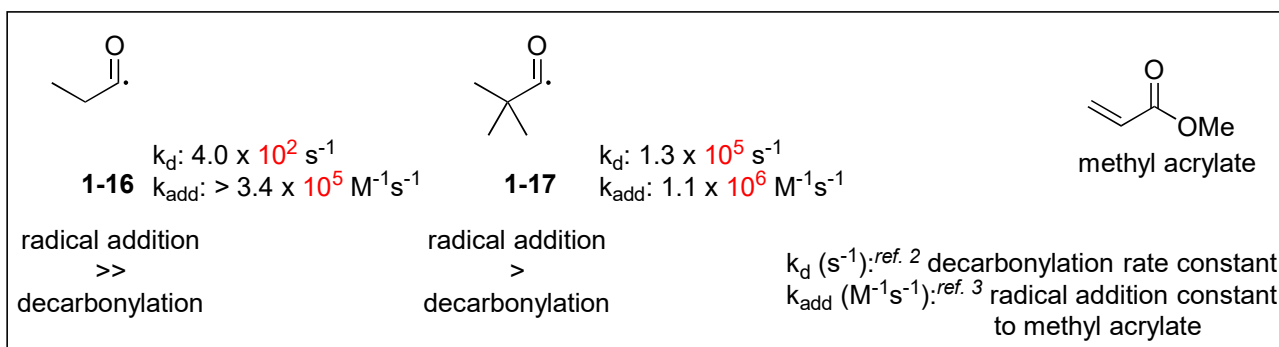
Discussion 2: Sml₂ mediated coupling

1. Sml₂ mediated coupling reaction developed by Skrydstrup group ^{ref 1}
- 1-1: Back ground of acyl radical

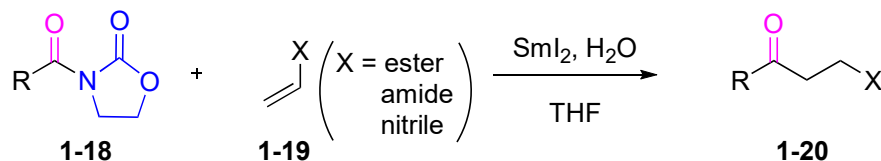


The addition of acyl radicals to olefins is known as one of the C-C bond formation reactions. However, acyl radicals have a potential for decarbonylation in addition to radical addition reactions. The reaction rate of the decarbonylation process depends on the structure of the acyl radical.

As illustrated in the box below, when the acyl radical undergoes decarbonylation and generated radical is primary radical, the reaction rate constant for the decarbonylation reaction is small due to the instability of the generated radical. Conversely, if the resulting radical is tertiary radical, the rate constant for this reaction becomes considerably larger.



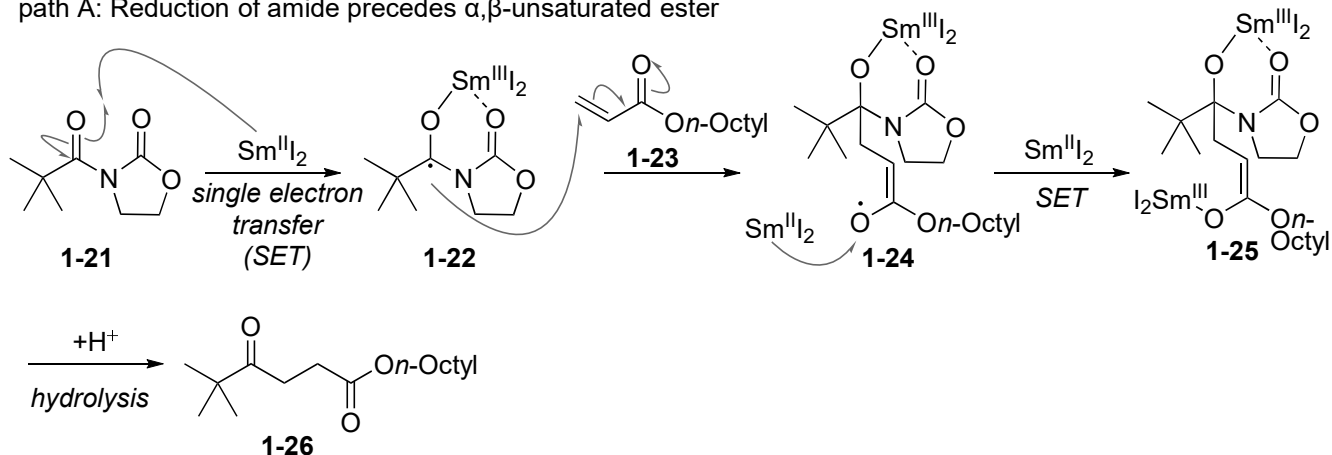
1-2: Reaction design



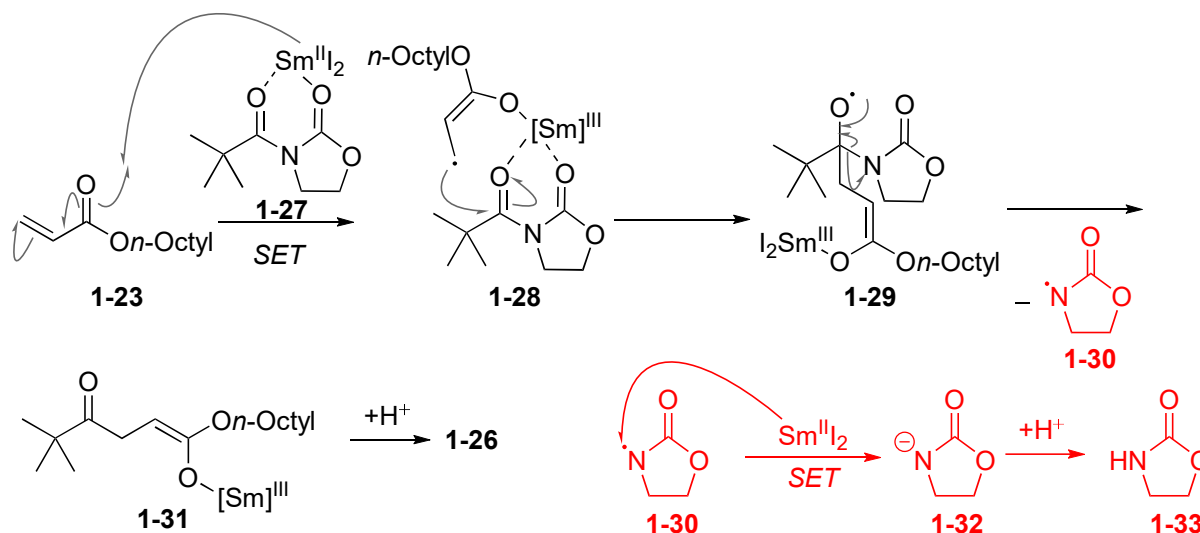
- It has been reported that imides can be readily reduced using $\text{Sm}^{\text{II}}\text{I}_2$.^{ref. 4}
- Regioselective reduction of the *N*-acyl carbonyl group was anticipated due to its lower $\pi^*_{\text{C=O}}$ orbital in comparison to the same $\pi^*_{\text{C=O}}$ orbital of oxazolidinone.
- > Coupling products retained the carbonyl group.

2: Possible reaction mechanism

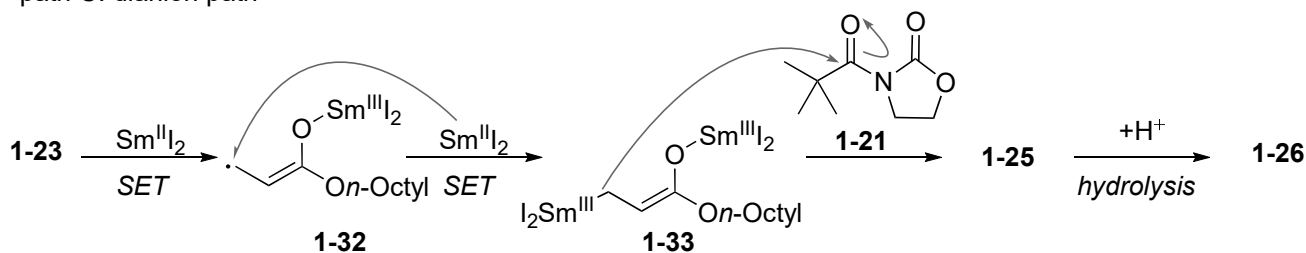
path A: Reduction of amide precedes α,β -unsaturated ester



path B: Reduction of α,β -unsaturated ester precedes amide



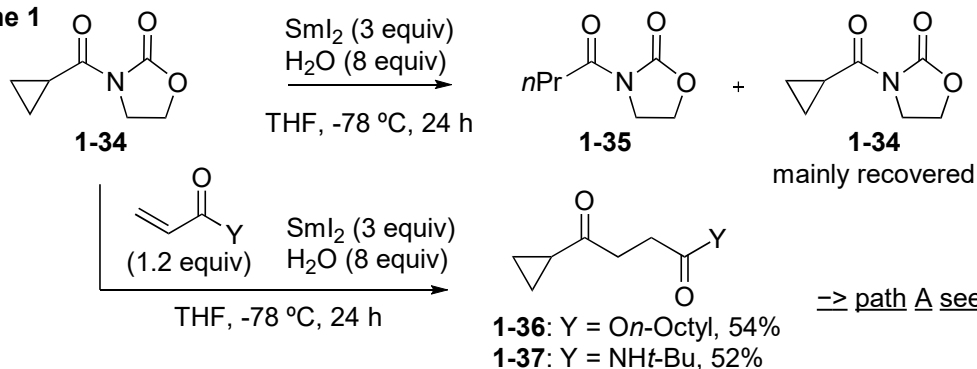
path C: dianion path



3: Mechanistic studies

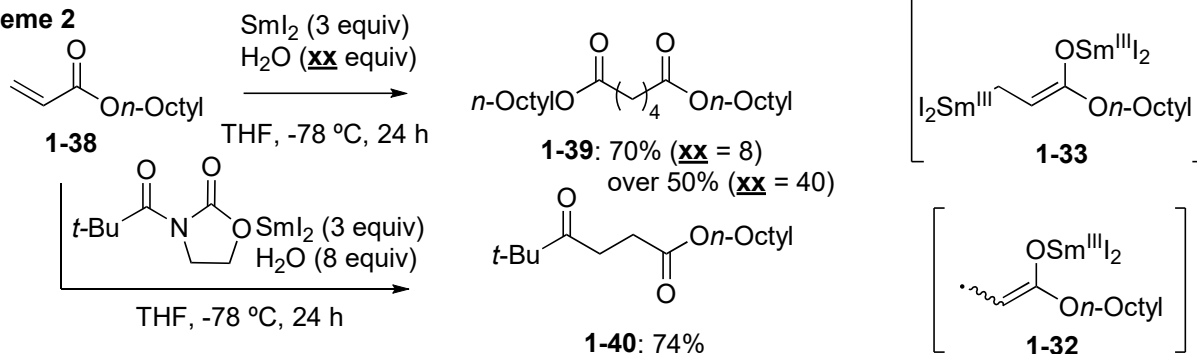
3-1: Coupling reaction toward cyclopropyl derivative 1-32

Scheme 1

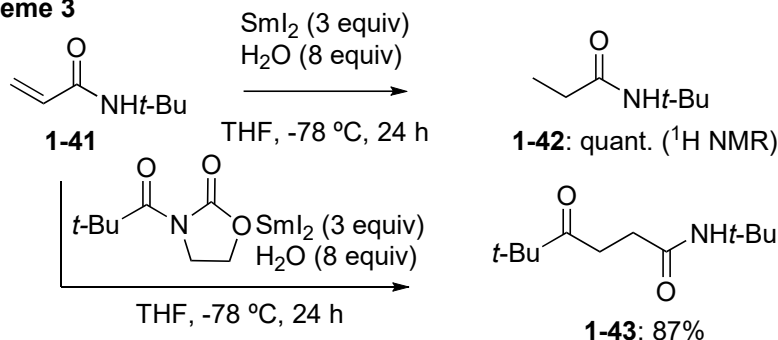


3-2: Investigation of whether it is a radical reaction or a polar reaction.

Scheme 2

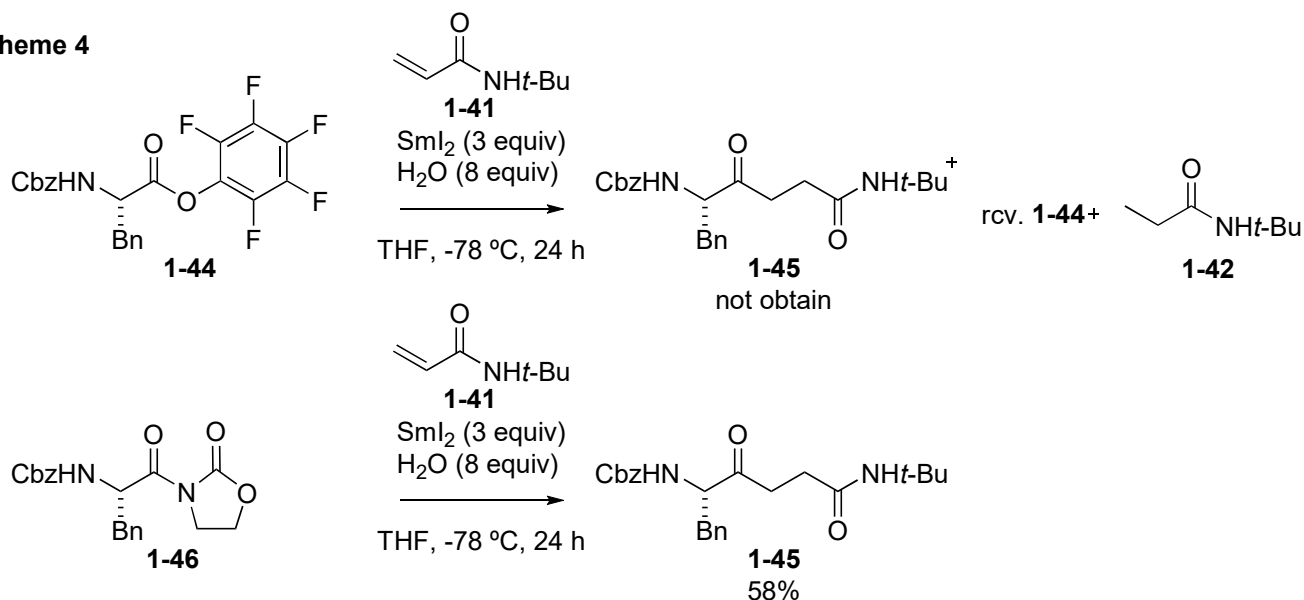


Scheme 3



Organosamarium species (Sm^{III}) are classified as hard Lewis acids, and 1,2-addition is favored over 1,4-addition. Therefore, dimer 1-39 was generated by radical addition to 1-38 of formed organosamarium species, rather than conjugate addition. Moreover, the fact that increasing the amount of water did not significantly decrease the yield supports the mechanism of radical addition.

Scheme 4

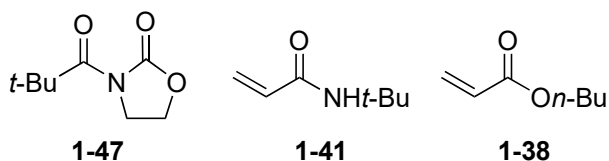


In the coupling reaction using pentafluorophenyl ester (**1-43**) which has better leaving group compared to oxazolidinone, **1-45** was not obtained and starting material was recovered.

Judging from the results, path B is more favorable.

4: Reaction rate constant

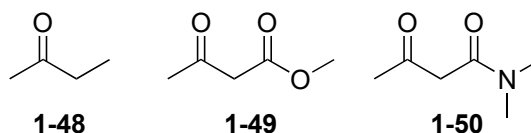
substrate	rate constant (s^{-1})
1-47	$< 1.90 \times 10^{-3}$
1-40	3.80×10^{-3}
1-37	8.10×10^{-3}



The reduction rate of α,β -unsaturated carbonyl compounds is faster than oxazolidinone.

5: Chelation effect (reduction rate constant)

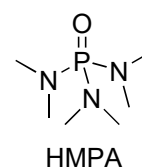
substrate	rate constant ($\text{M}^{-1}\text{s}^{-1}$)
1-48	7×10^{-4}
1-49	2.2×10^{-1}
1-50	7.5×10^2



A comparison of the reduction using SmI_2 with **1-48**, **1-49**, and **1-50** was conducted to investigate the effect of coordination and chelation on reaction rate. The fact that **1-49** and **1-50** have higher rate constant suggests that chelation enhances the reaction rate in reduction using SmI_2 .

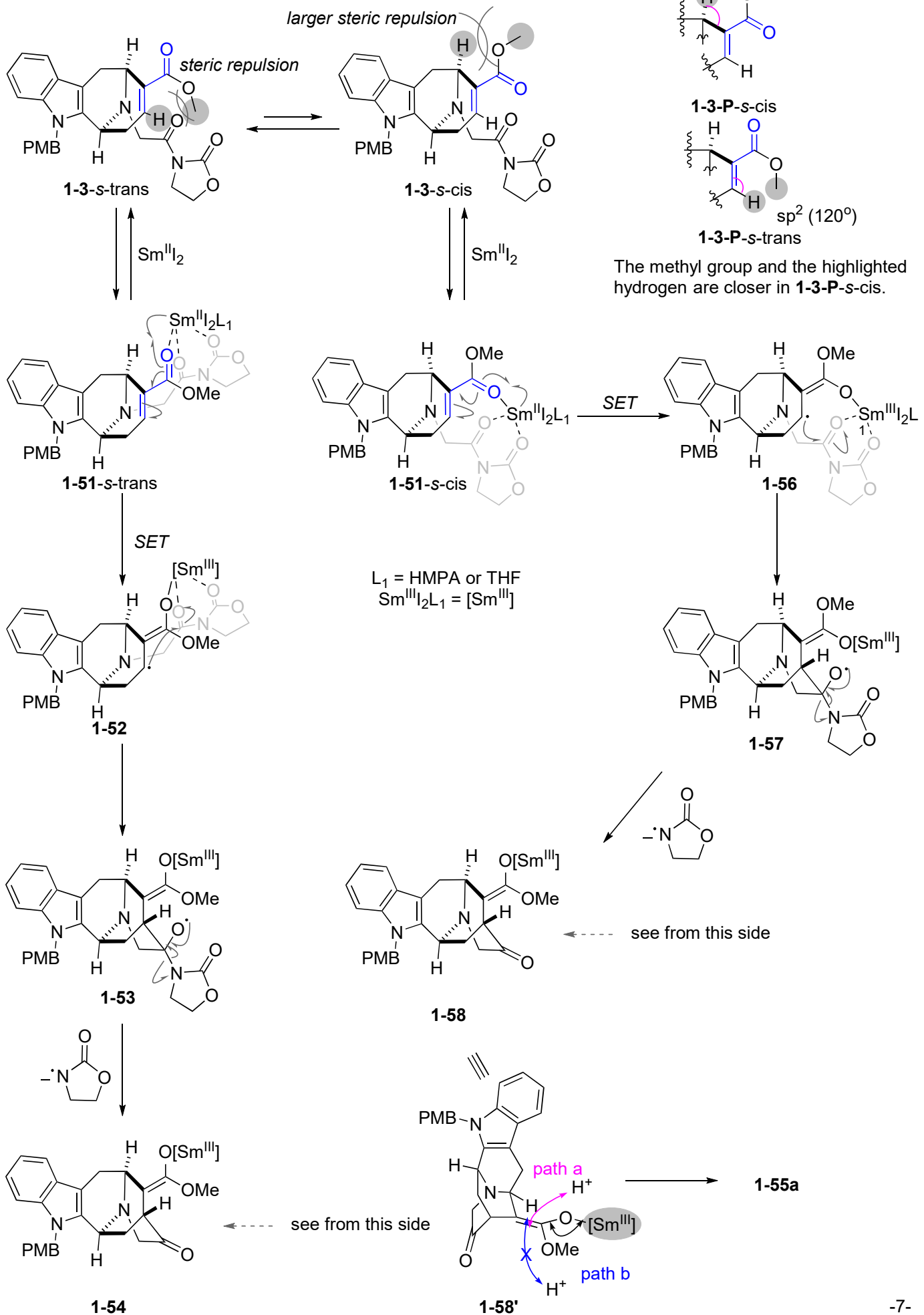
6: Redox potential of $\text{Sm}^{\text{II}}\text{I}_2$

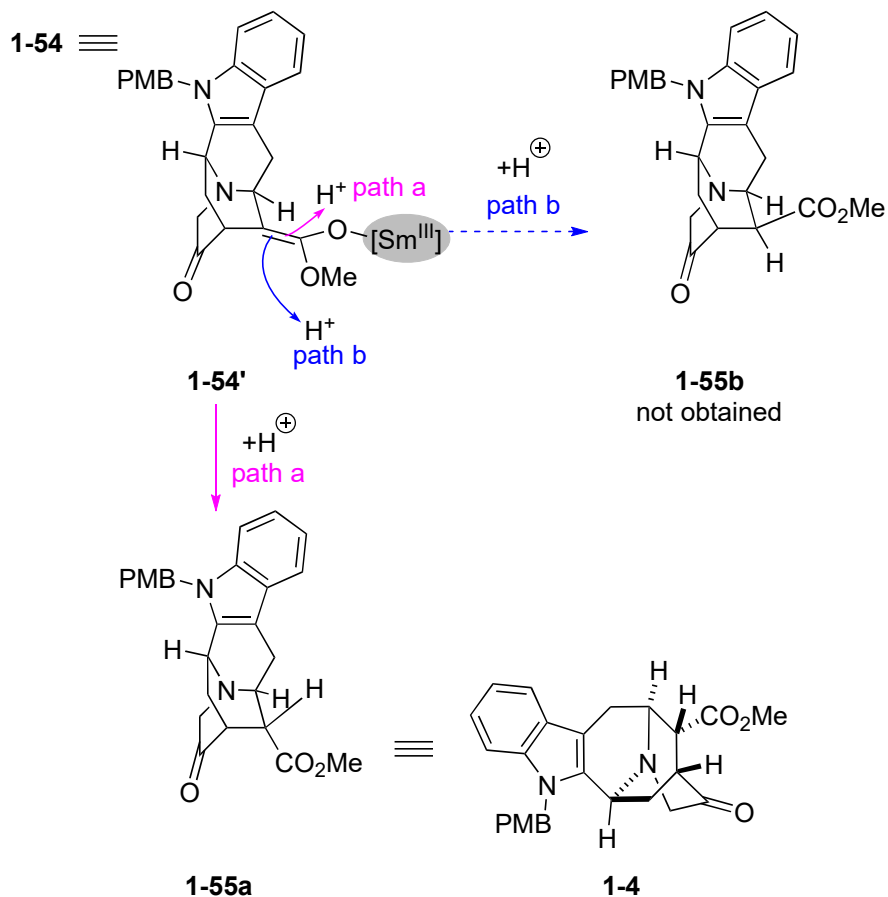
entry	reductant	solvent	$E_{1/2}$ [V] (vs. SCE)
1	$\text{Sm}^{\text{II}}\text{I}_2$	THF	-0.98
2	$\text{Sm}^{\text{II}}\text{I}_2(\text{H}_2\text{O})_n$	THF	-1.3
3	$\text{Sm}^{\text{II}}\text{I}_2(\text{HMPA})_4$	THF	-1.75



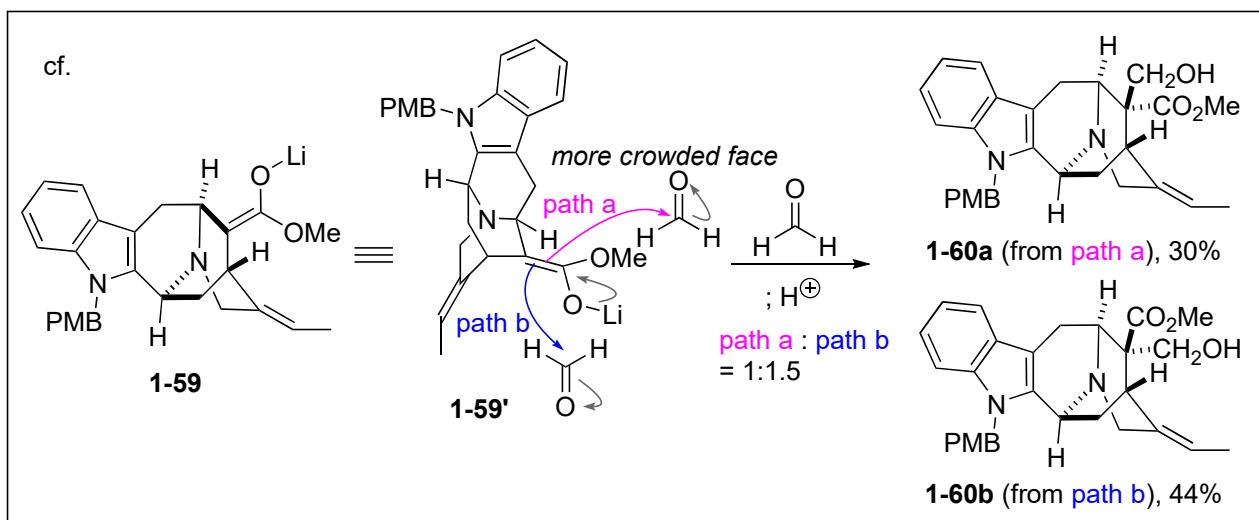
The change in the chemical species coordinating to SmI_2 alters the redox potential, that is, the reduction potential of SmI_2 .

Reaction mechanism:

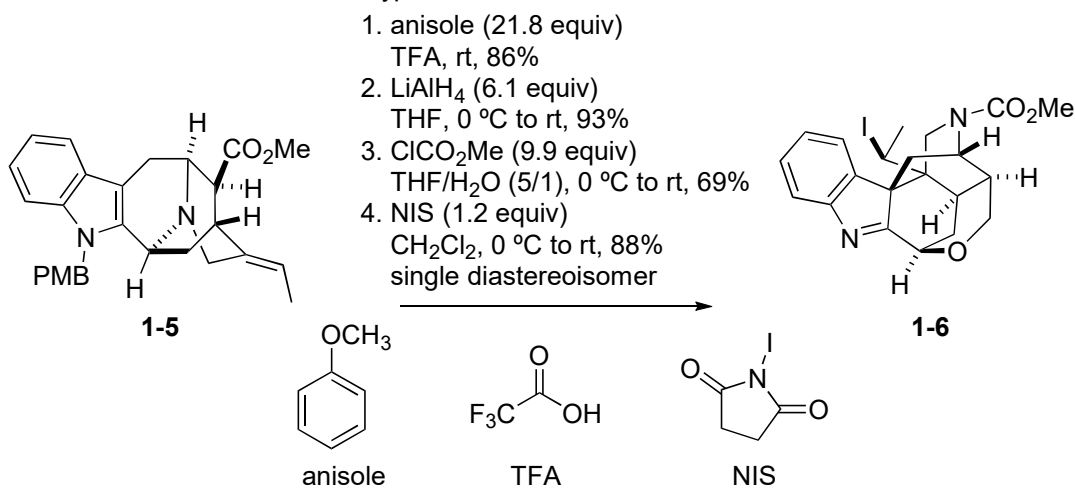




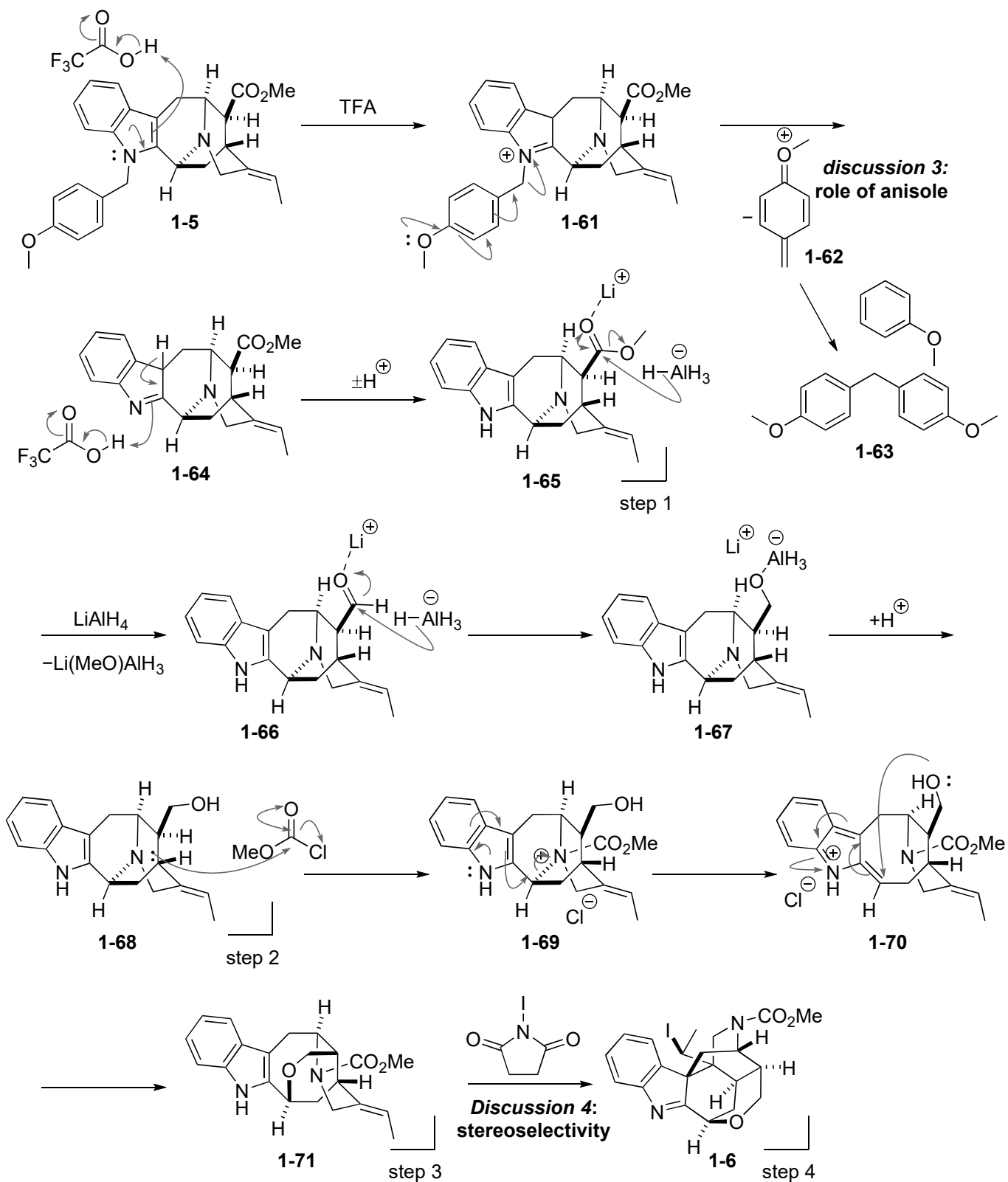
The highlighted Sm^{III} becomes a significantly large chemical species, including ligands. Therefore, these ligands are directed towards the sterically available space below the molecule. Protonation is observed to occur in a manner that avoids the large Sm^{III} species.



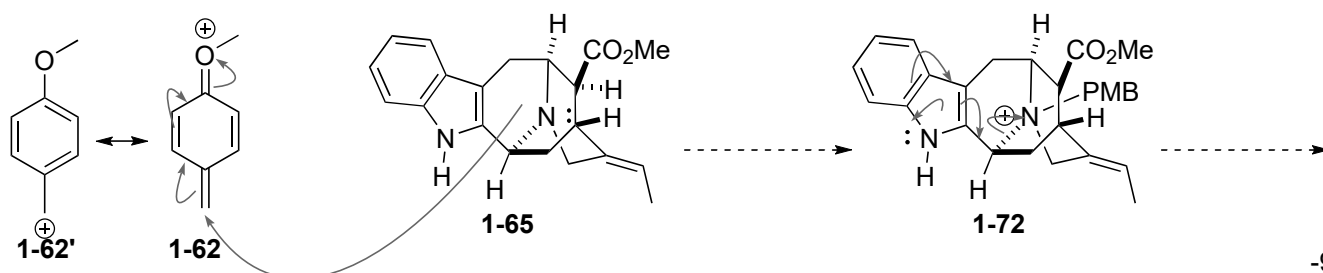
3. Construction of the koumine-type alkaloid skeleton.

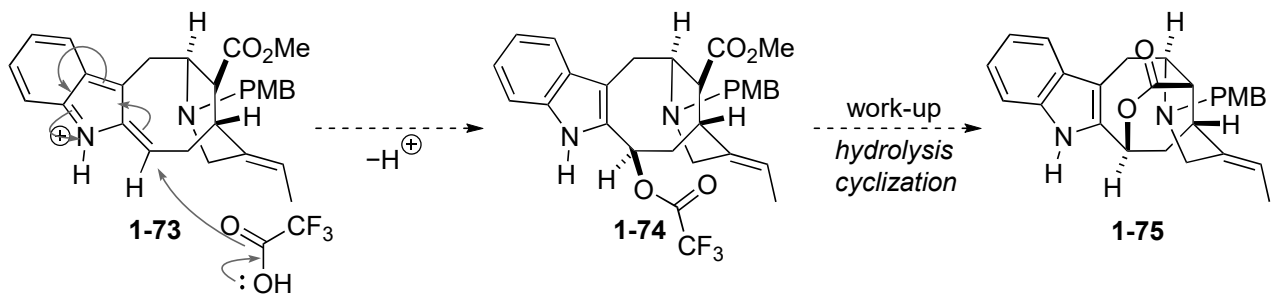


Reaction mechanism:

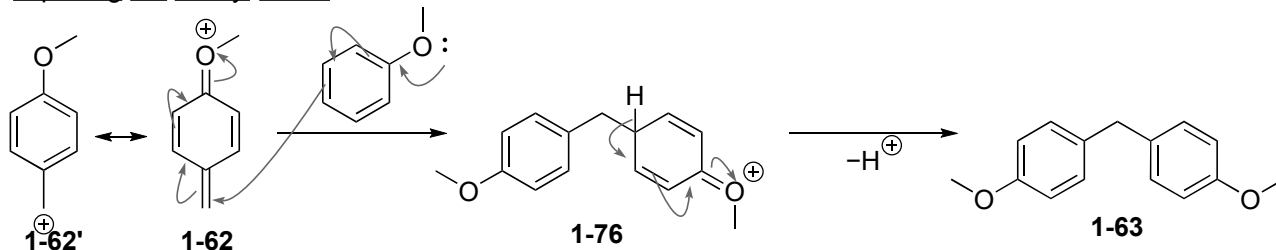


Discussion 3: role of anisole *ref. 5*
proposed side reaction



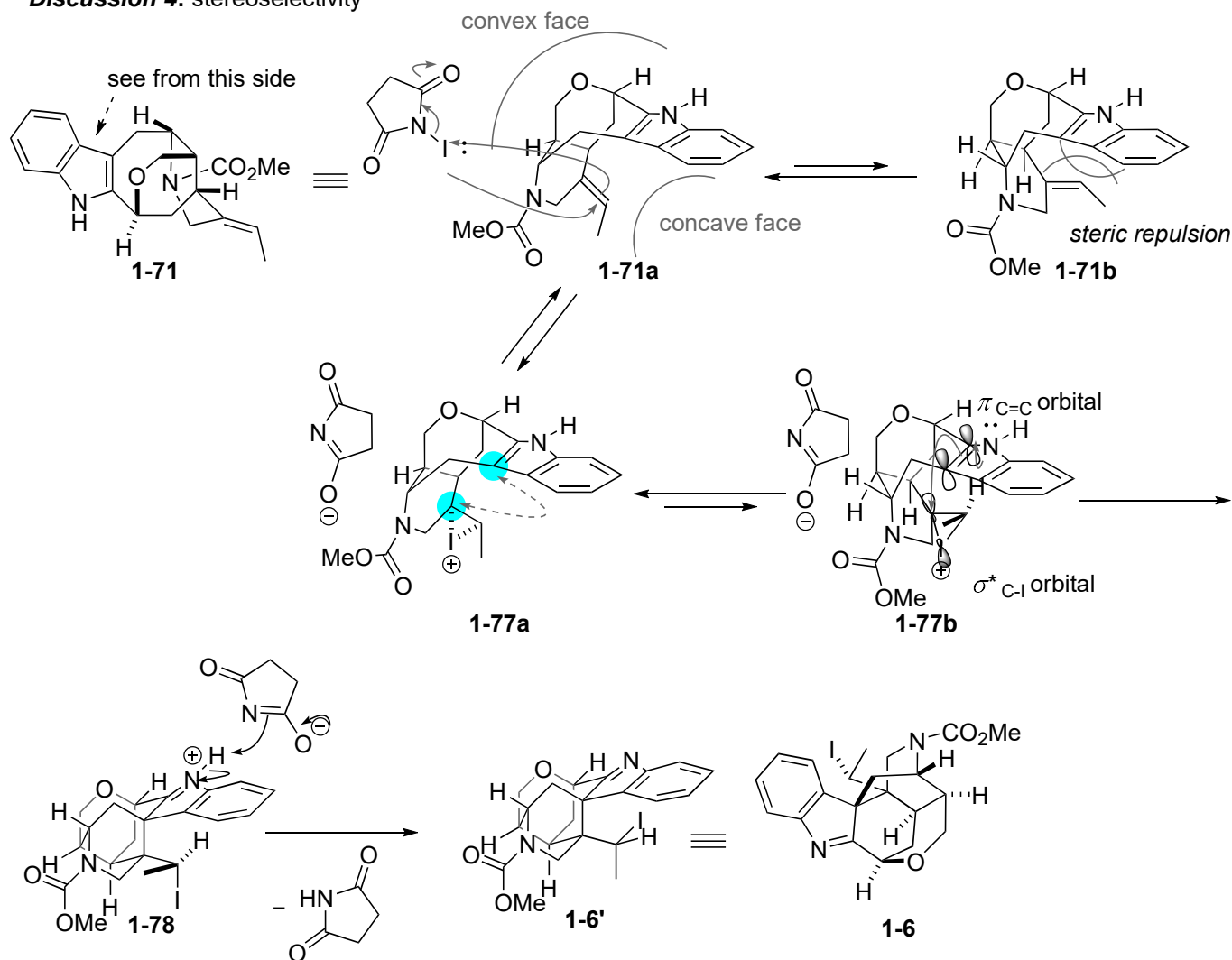


capturing the benzyl cation



Benzyl cation generated from the deprotection of *p*-methoxybenzyl (PMB) is expected to undergo a side reaction. For example, tertiary amine of **1-5** or **1-65** can attack the cation and be *p*-methoxybenzylated. Addition of 21.8 equivalents of anisole can suppress this side reaction by trapping the generated benzyl cation.

Discussion 4: stereoselectivity



reference

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- Kern, N.; Dombay, T.; Blanc, A.; Weibel, J.; Pale, P., *J. Org. Chem.* **2012**, *77*, 9227.