

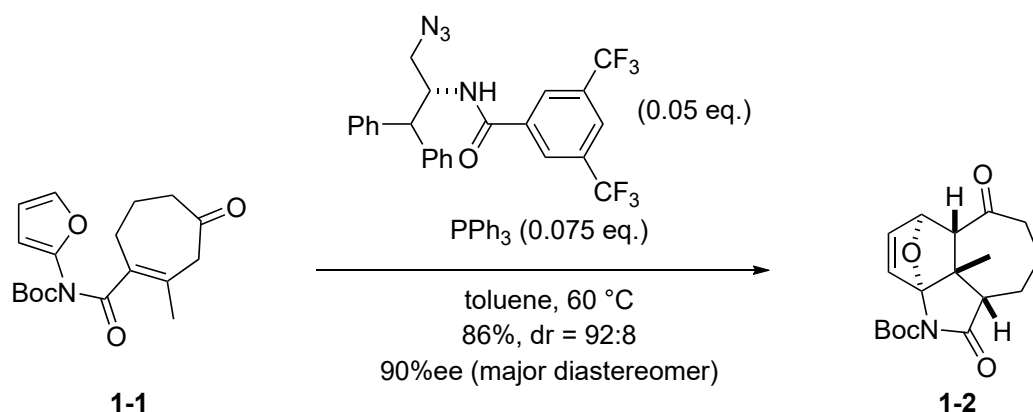
Problem Session (3)

2017. 12. 16 Kotaro Tokumoto

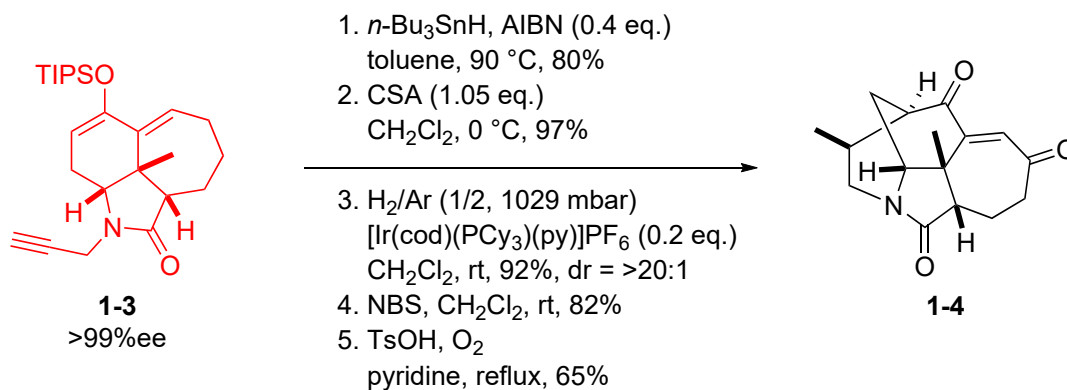
Please provide reasonable reaction mechanisms.

1

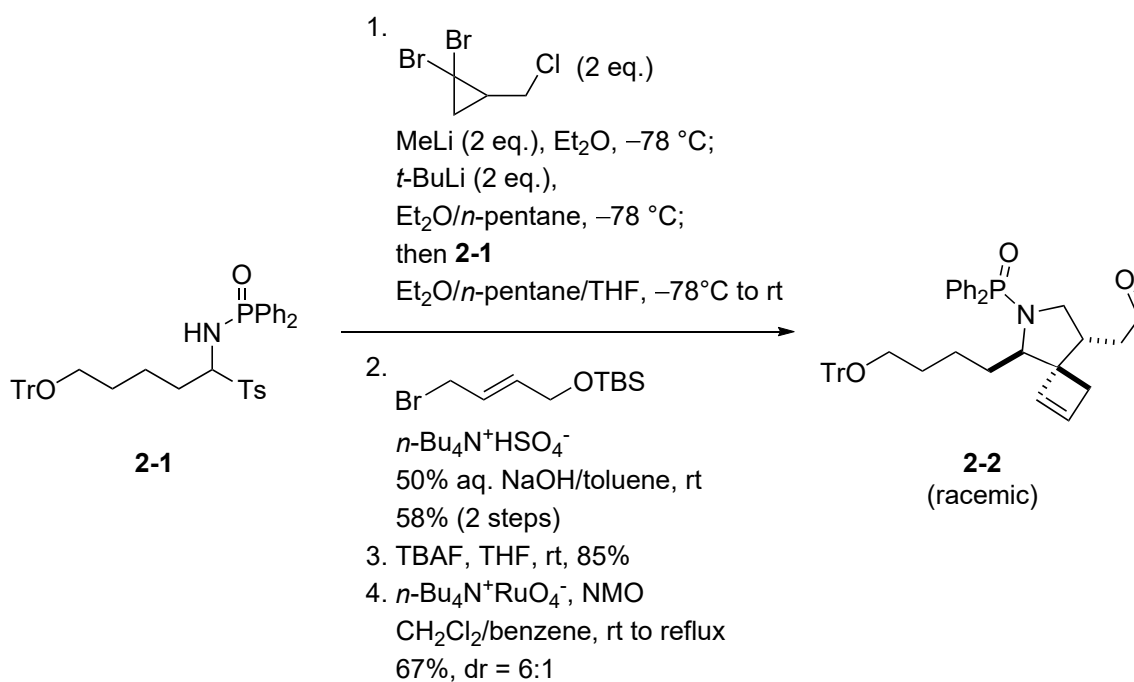
(1)



(2)



2



Problem Session (3) - Answer -

Synthetic Study of *Daphniphyllum* Alkaloids

2017. 12. 16 Kotaro Tokumoto

1 Total Synthesis of (-)-Himalensine A by Prof. D. J. Dixon group

• isolation

from Nepalese *Daphniphyllum himalense*

Zhang, H.; Shyaula, S. L.; Li, J.-Y.; Li, J.; Yue, J.-M. *Org. Lett.* **2016**, *18*, 1202.

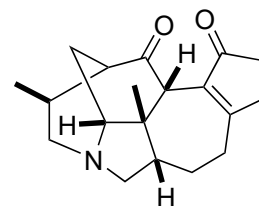
• bioactivity

not reported

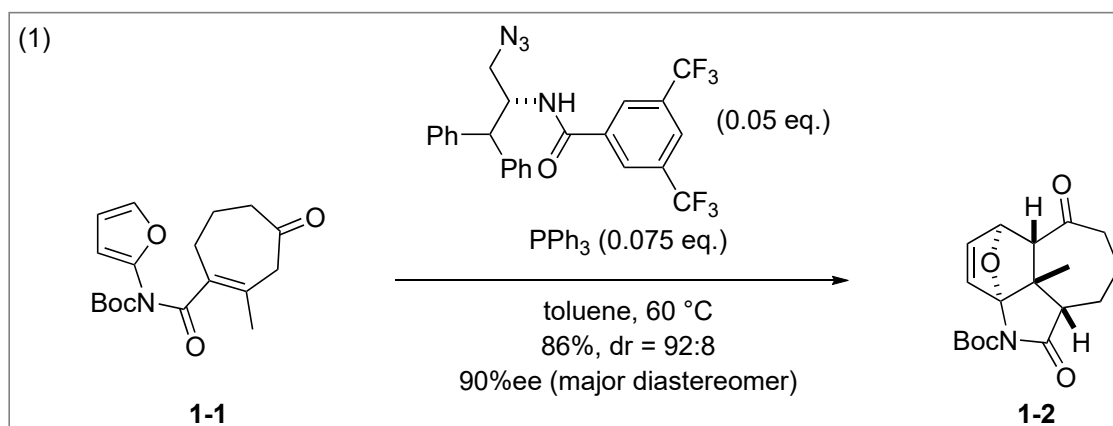
• total synthesis

Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J.

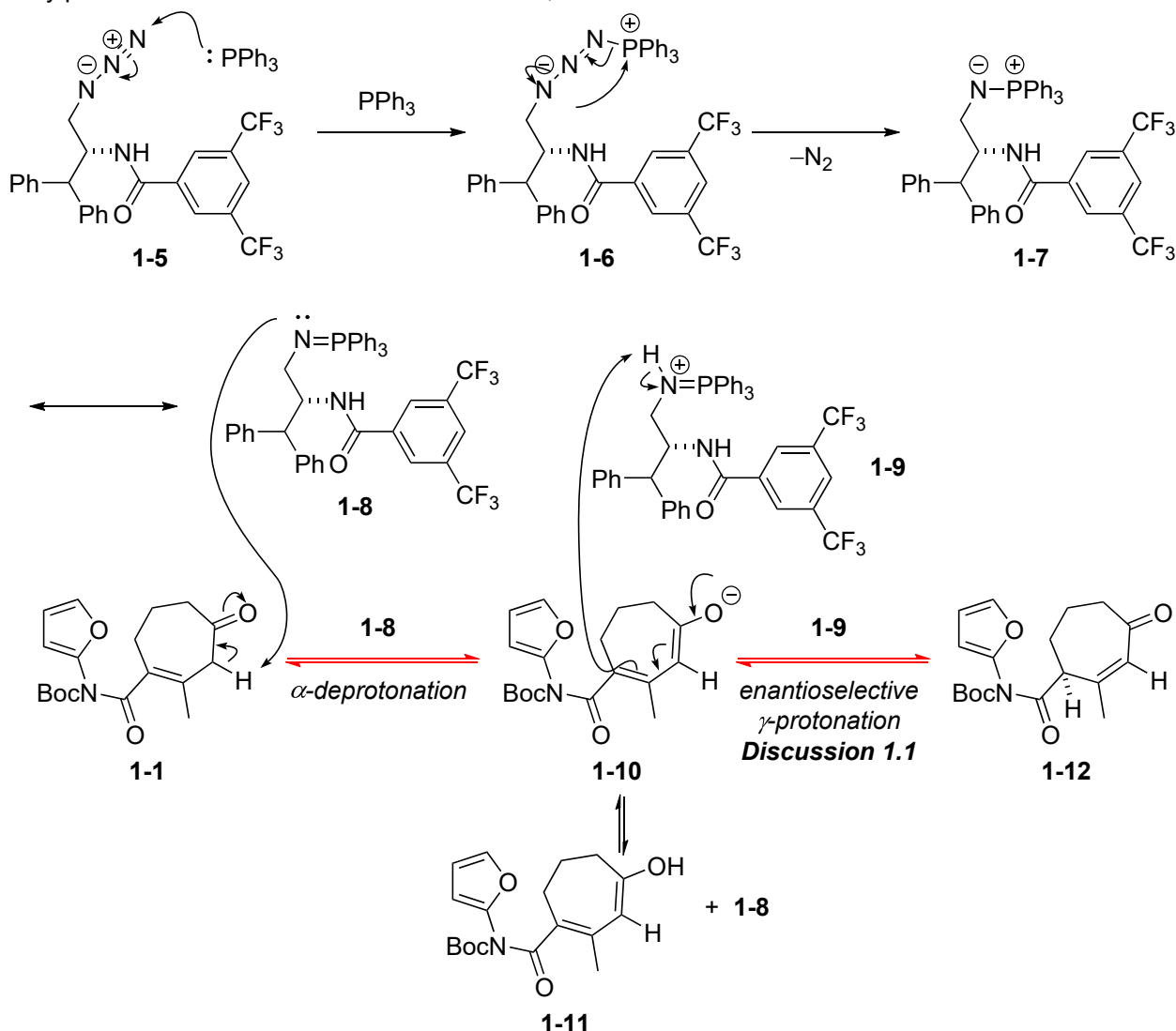
J. Am. Chem. Soc. doi: 10.1021/jacs.7b10956 (**problem 1**)

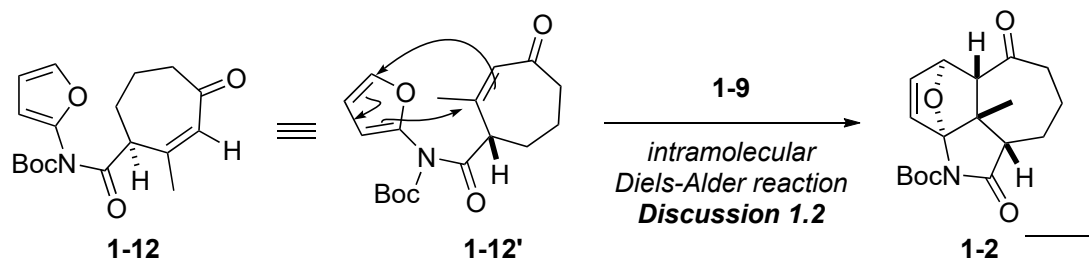


(-)-himalensine A
calyciphylline A-type family



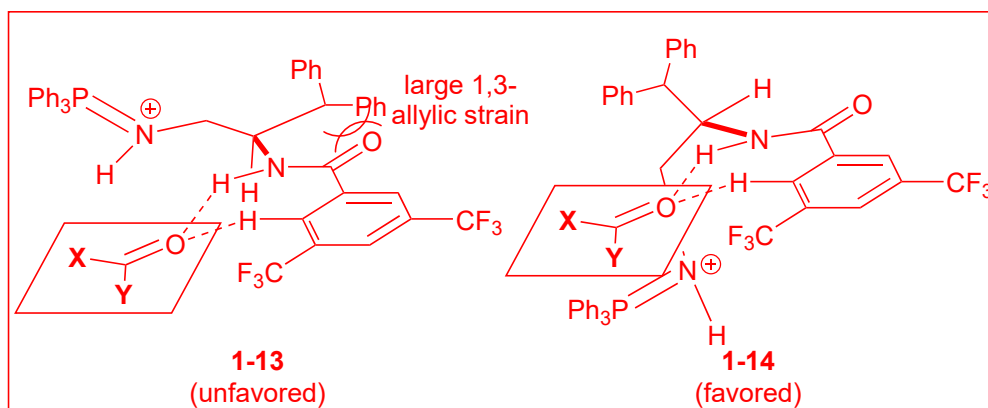
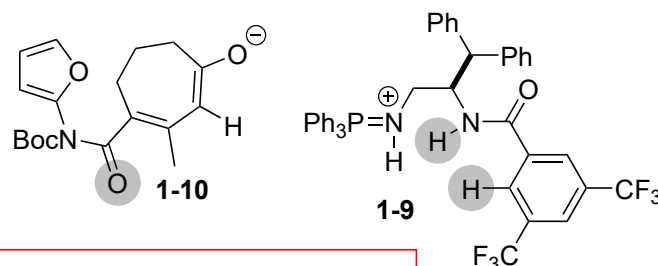
key points: enantioselective olefin isomerization, diastereoselective intramolecular Diels-Alder reaction



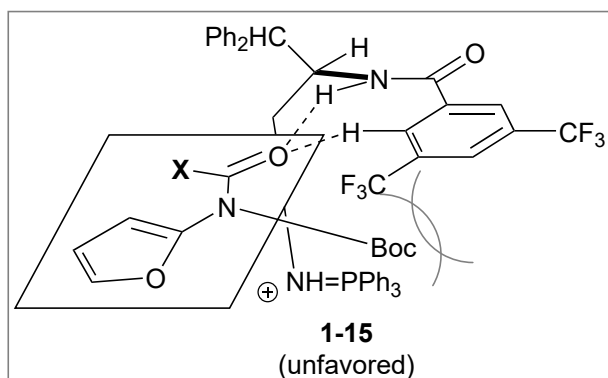


Discussion 1.1. enantioselectivity for γ -protonation

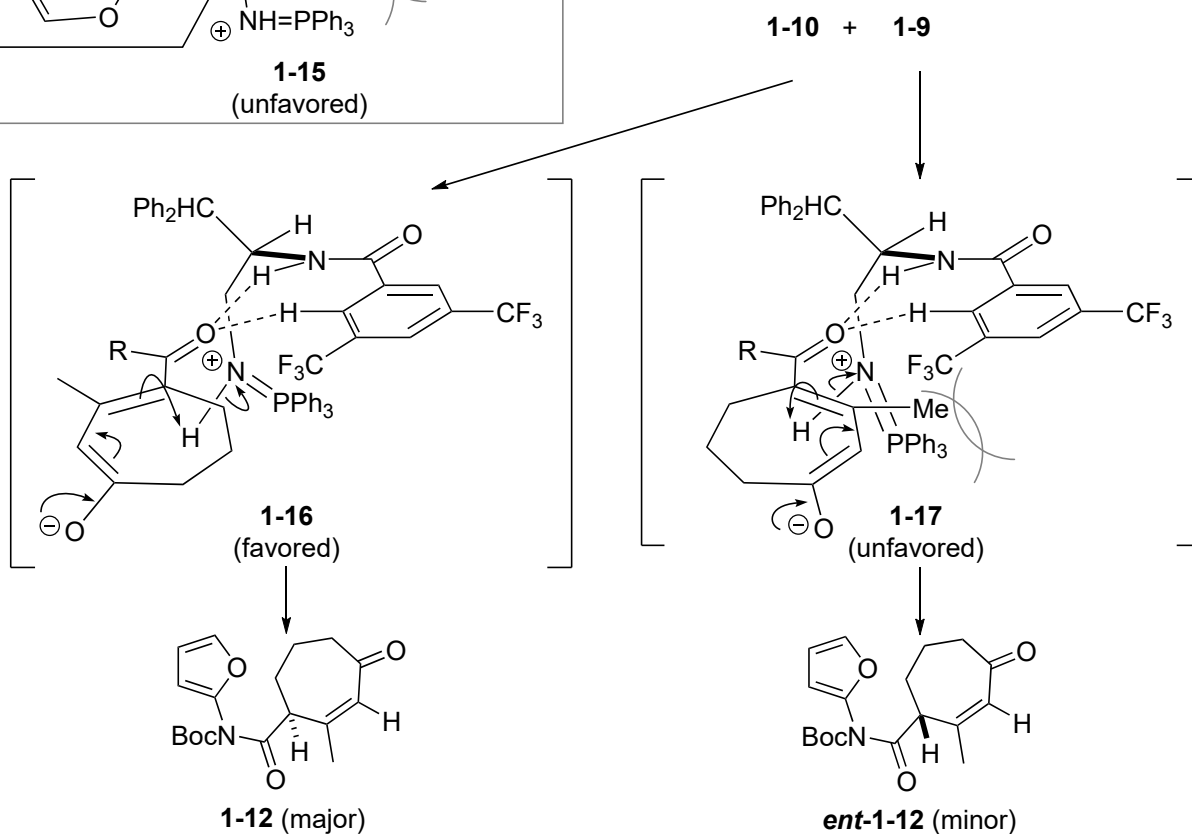
The catalyst **1-9** engages the amide carbonyl of the substrate with a dual hydrogen bonding interaction from both amide N-H and aryl C-H bonds.



The protonated moiety of **1-9** would approach the substrate with a conformation of **1-14** to minimize the 1,3-allylic strain.

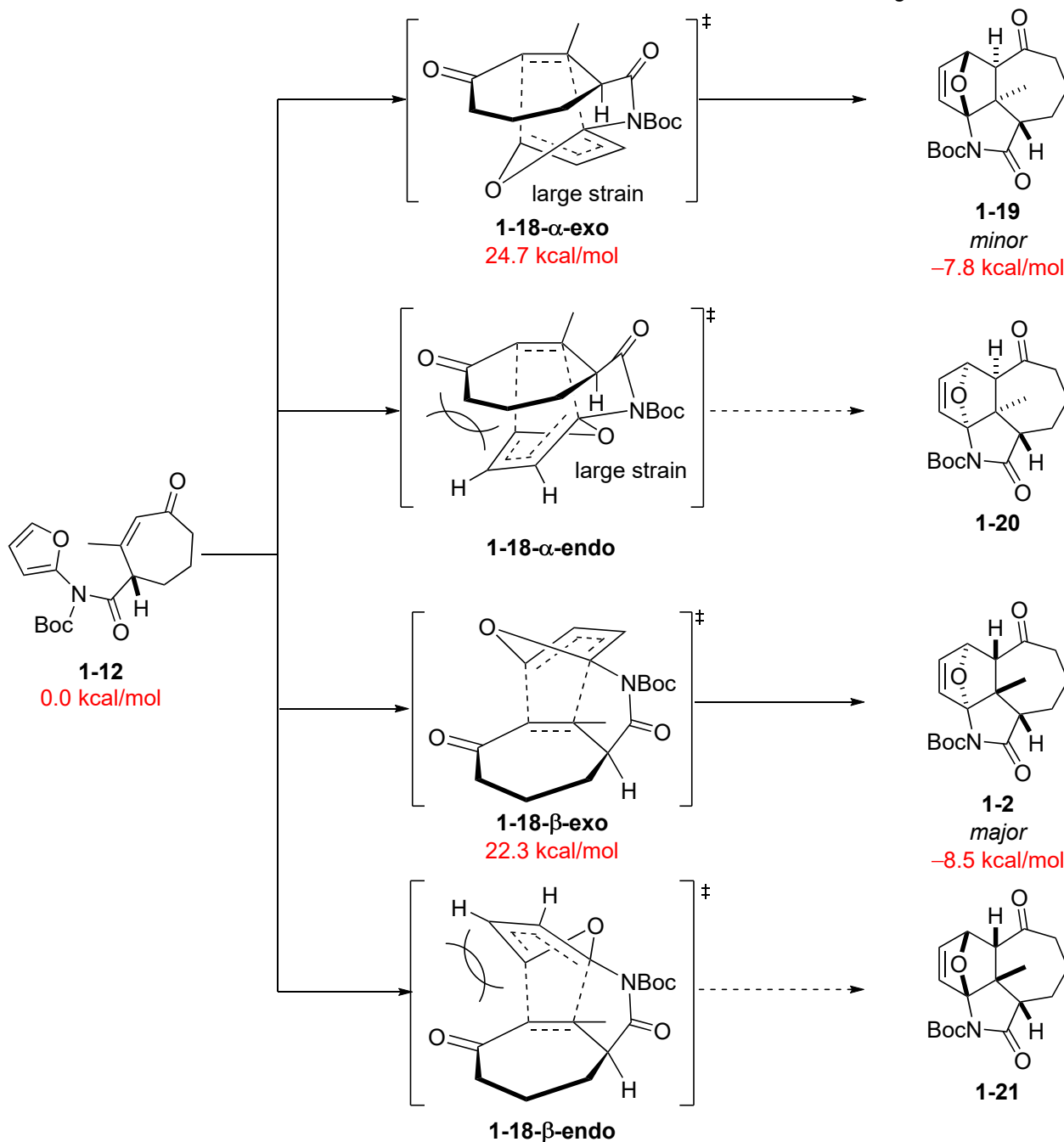


X should be the fran-containing moiety of **1-10** because if **Y** is the fran-containing moiety, large steric effect between Boc group and aryl group exists.



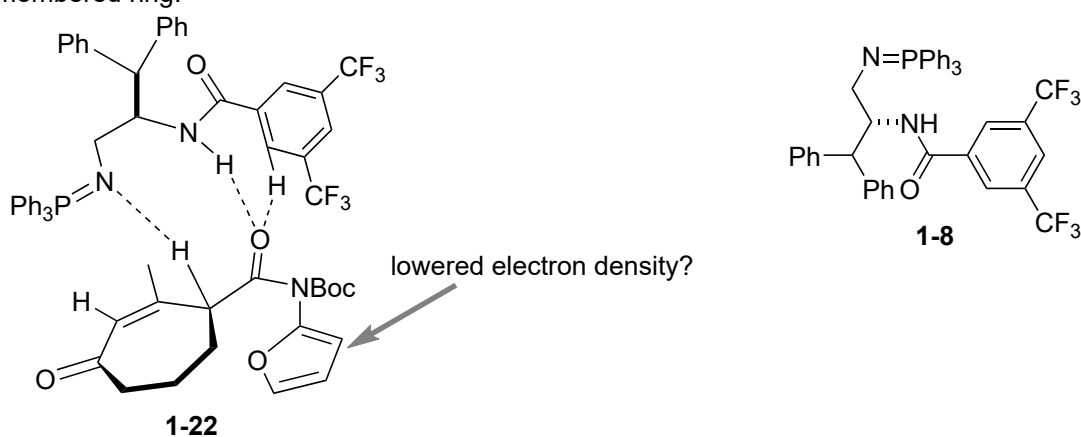
Discussion 1.2. face-and exo/endo selectivity in DA

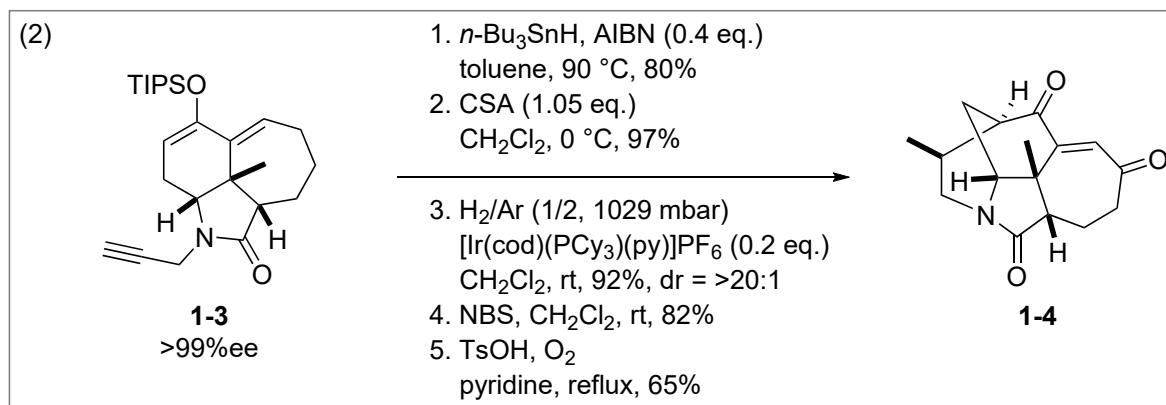
Endo addition is disfavored due to the steric effect between furan C-H and 7-membered ring.



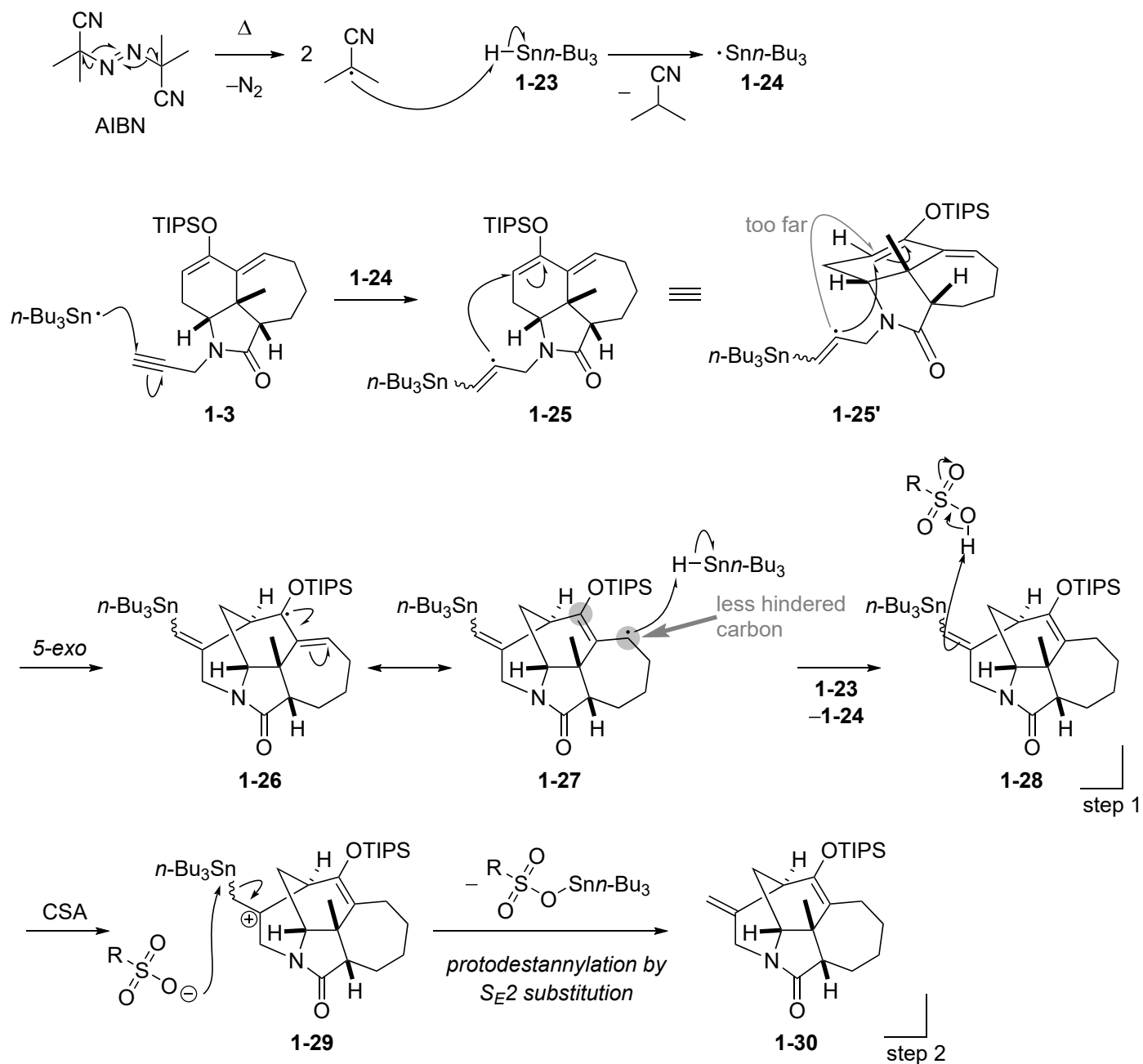
According to the authors' DFT calculation, **1-2** and **1-19** are ca. 8 kcal/mol more stable than **1-12**, presumably due to the large strain of 7-membered ring of **1-12**. Therefore, the DA would be irreversible.

The Gibbs energy of the DA is higher by 6.5 kcal/mol when complexed to catalyst **1-8** than the reaction in its absence. It seems that **1-8** is responsible for the enantioselective [1,3]-prototropic shift, which is then followed by the uncatalyzed DA. I think that the hydrogen bonds between **1-8** and **1-12** lower the electron density of the furan ring which is conjugated to the carbonyl. Furthermore, there seems to be steric effects when furan approaches to the 7-membered ring.

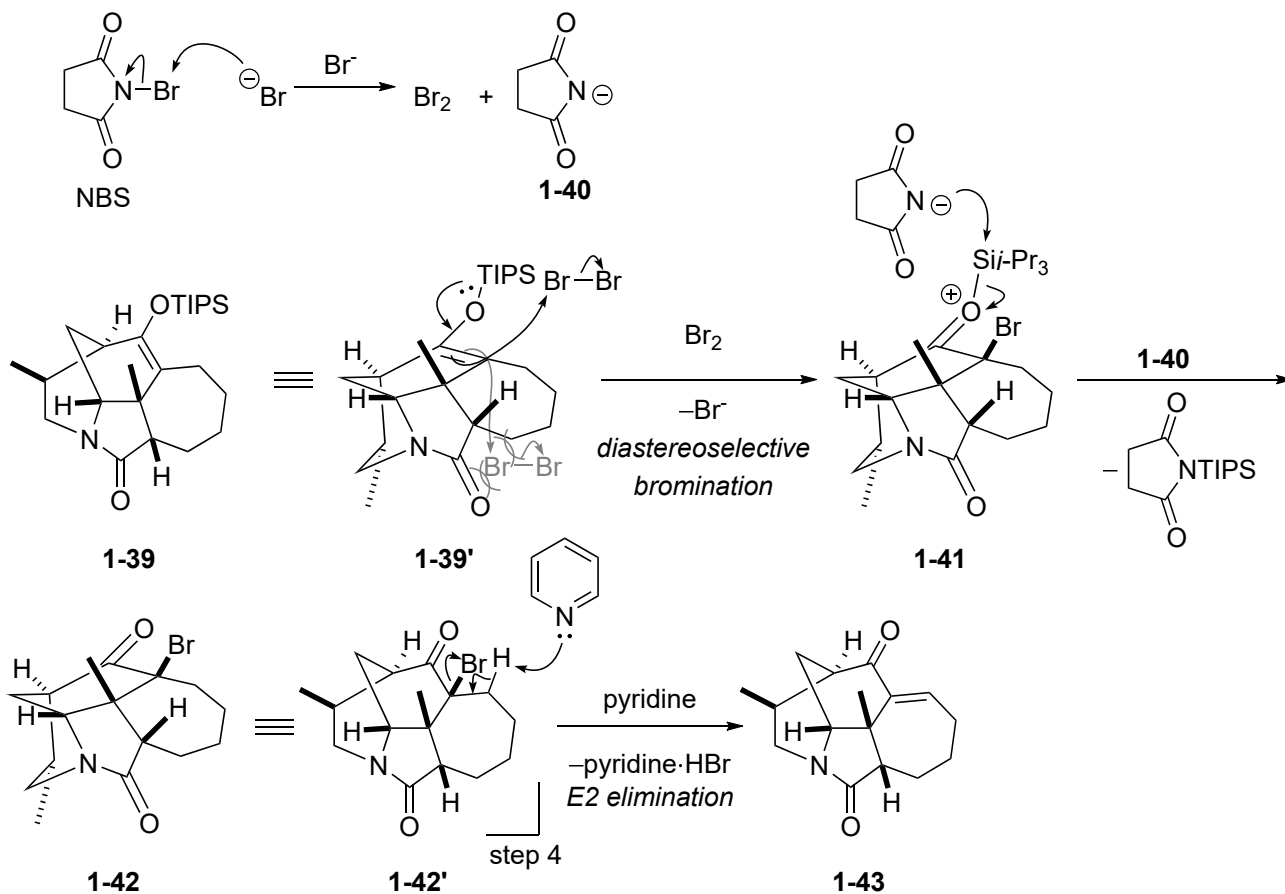
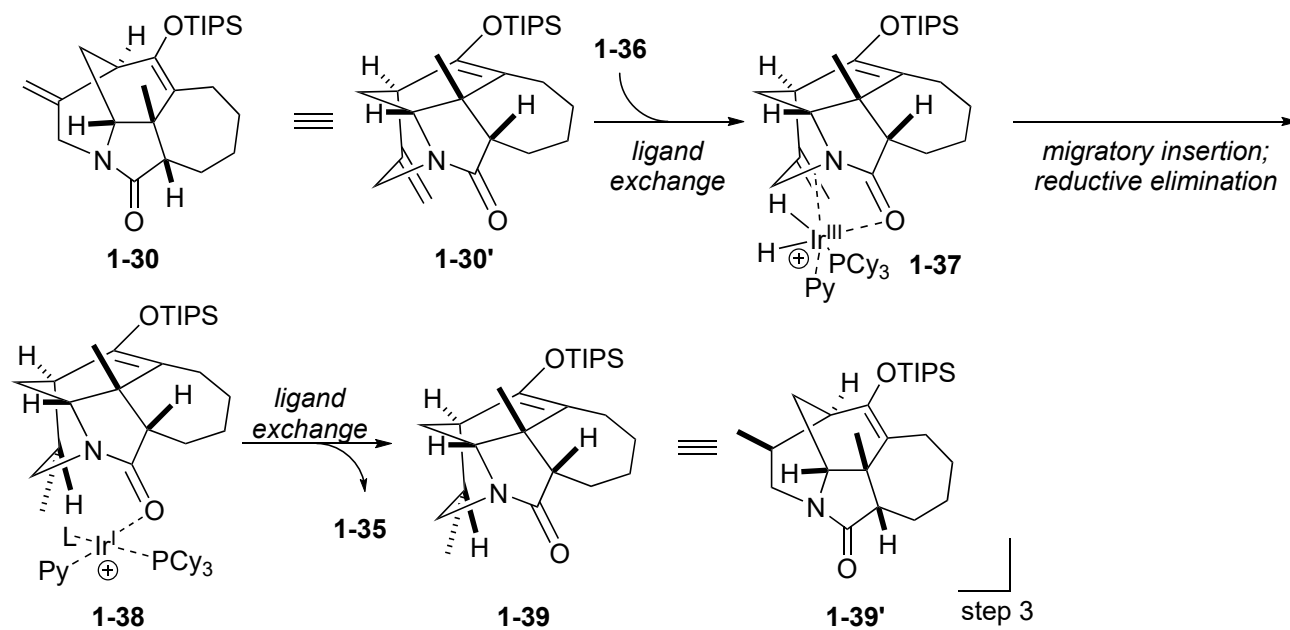
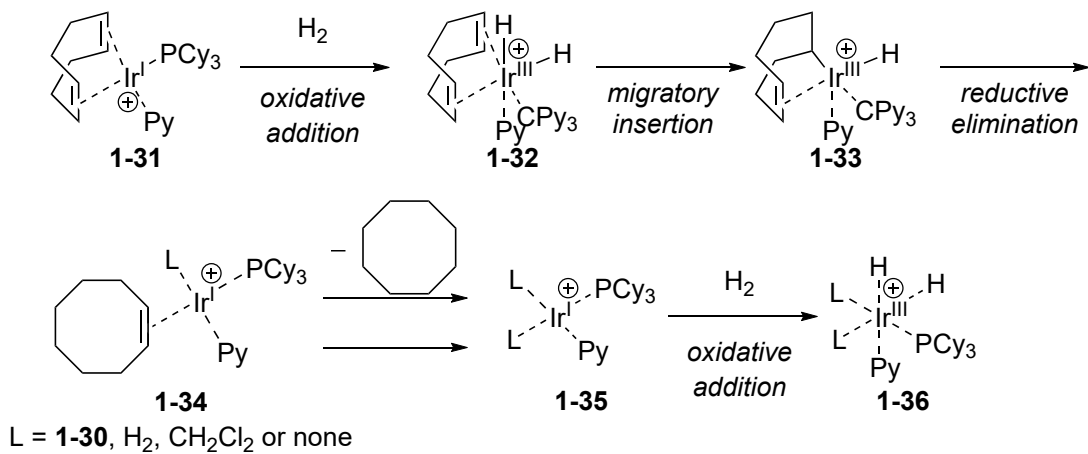


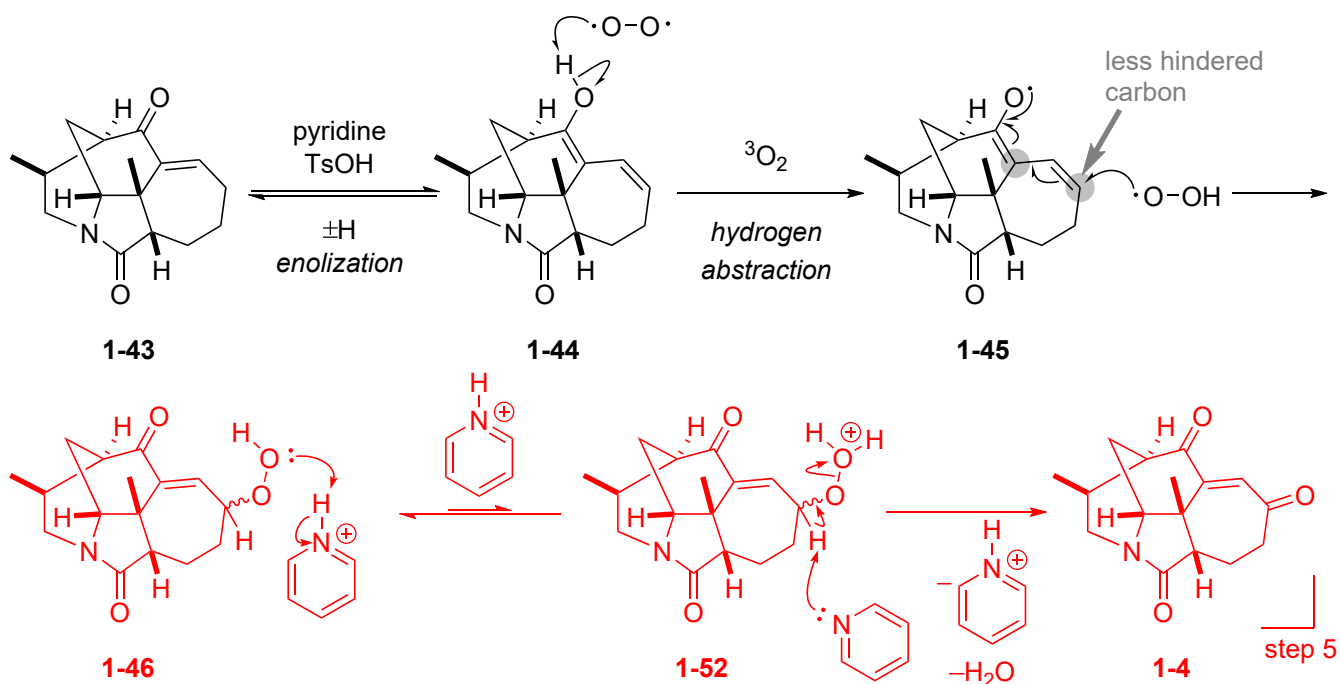


key points: radical cyclization, enantioselective olefin reduction, γ -oxidation of enone



For detailed mechanistic study of protodestannylation of vinyltrialkyltins, see:
Cochran, J. C.; Bayer, S. C.; Bilbo, J. T.; Brown, M. S.; Colen, L. B.; Gaspirini, F. J.;
Goldsmith, D. W.; Jamin, M. D.; Kenneth, A. N. *Organometallics*, **1982**, *1*, 586.

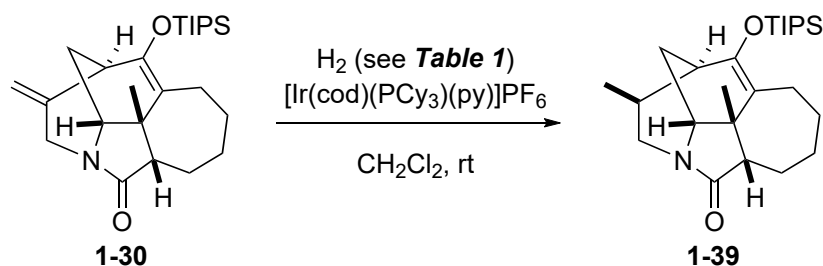




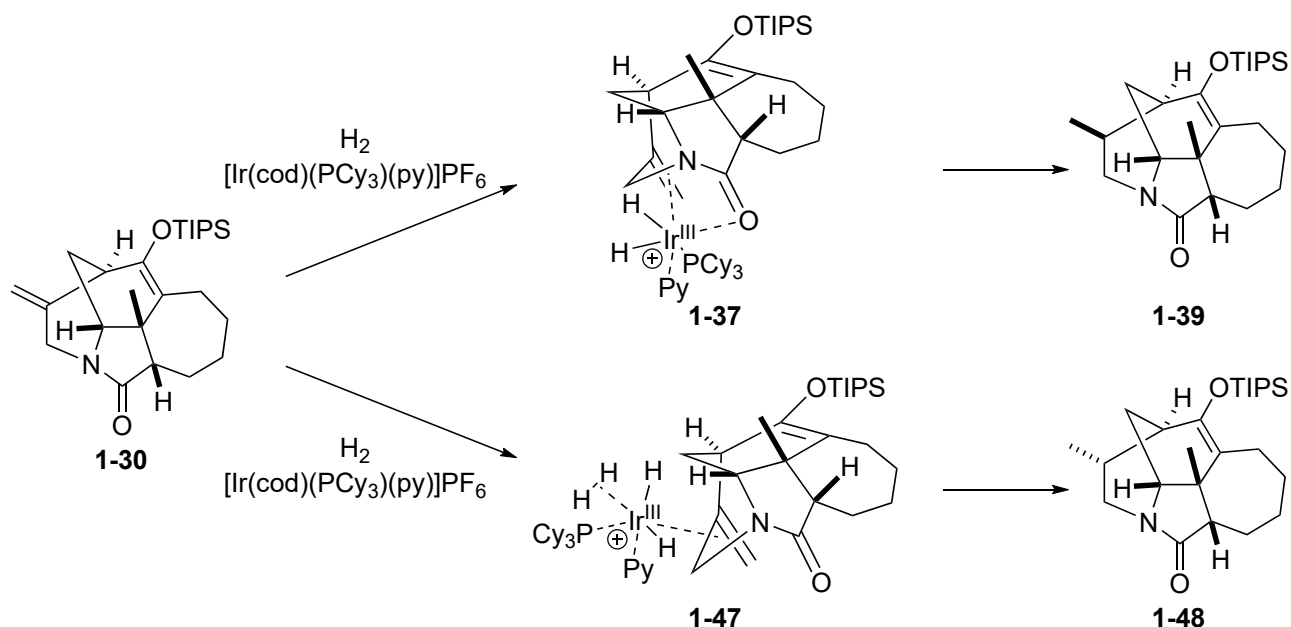
Discussion 1.3. effect of partial pressure of hydrogen in Ir-catalyzed orefin hydrogenation

Table 1. Effect of partial pressure of H₂ for dr.

pressure / mbar	dr
1086	2.2:1
1055	2.8:1
1029	3.4:1
1029 (50% Ar)	6.8:1
1029 (66% Ar)	>20:1

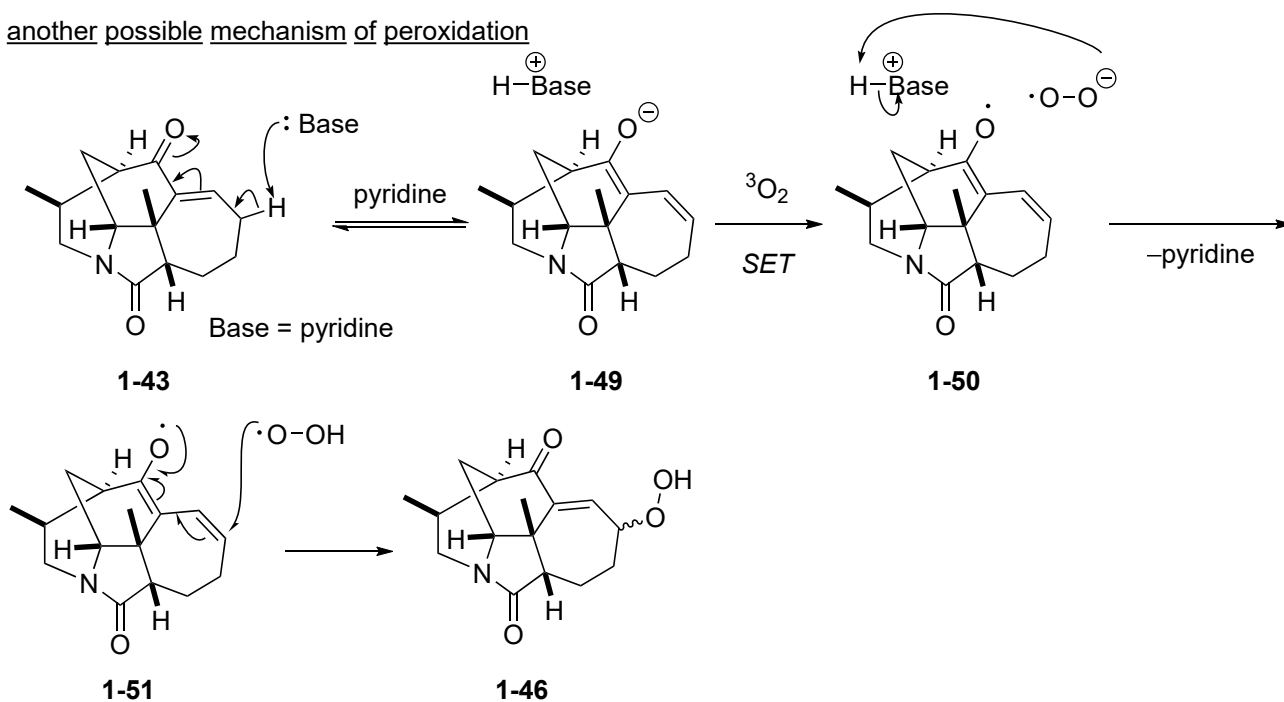


When partial pressure of H₂ is too high, coordination of H₂ to the catalyst in preference to the lactam carbonyl seems to occur.

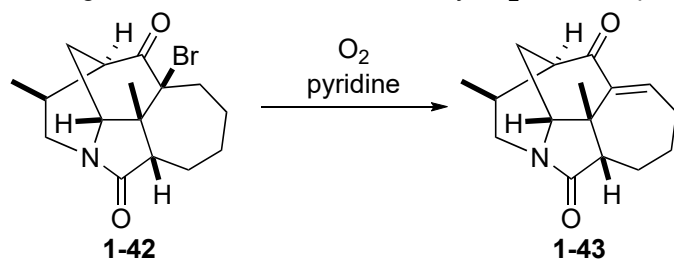


Discussion 1.4. unusual γ -oxidation of enone

• another possible mechanism of peroxidation

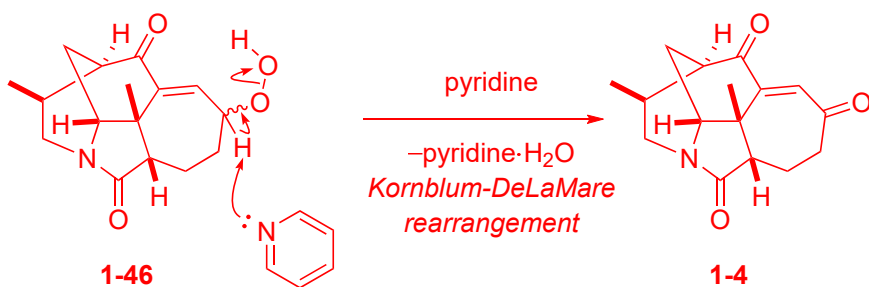


According to the authors, the oxidation by $^3\text{O}_2$ does not proceed smoothly without Bronsted acid.

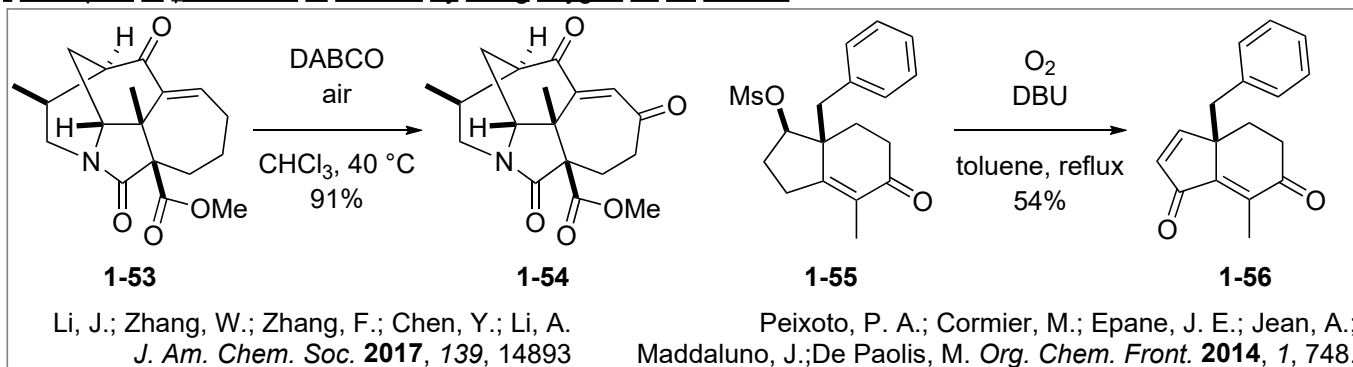


It seems that Bronsted acid catalyzes enolization of enone **1-42**, and that hydrogen abstraction pathway is favored.

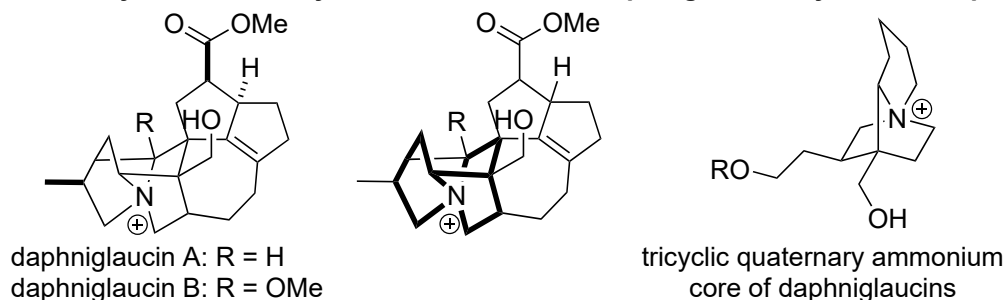
• another possible mechanism of transformation of hydroperoxide **1-46** to dienone **1-4**



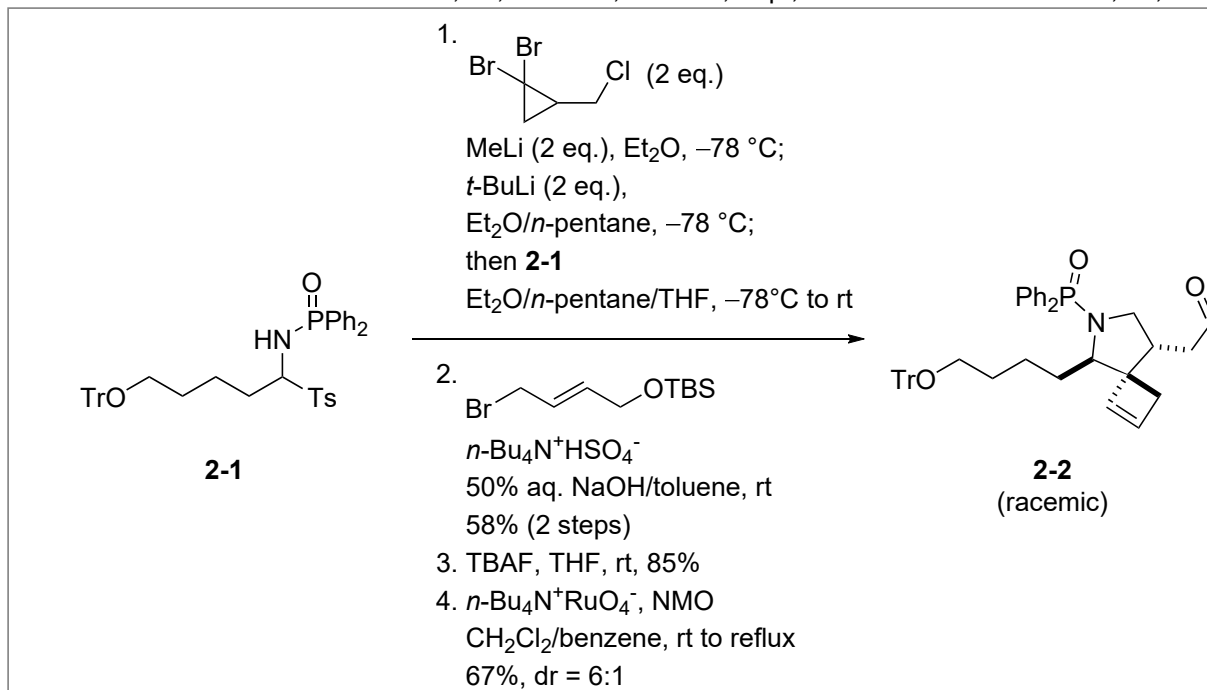
• examples of γ -oxidation of enones by using oxygen as an oxidant



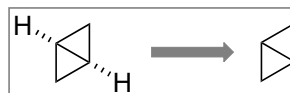
2 Synthesis of the Tricyclic Quaternary Ammonium Core of Daphniglaucins by Prof. P. Wipf group



Ueda, M.; Walczak, M. A. A.; Wipf, P. *Tetrahedron Lett.* **2008**, *49*, 5986.



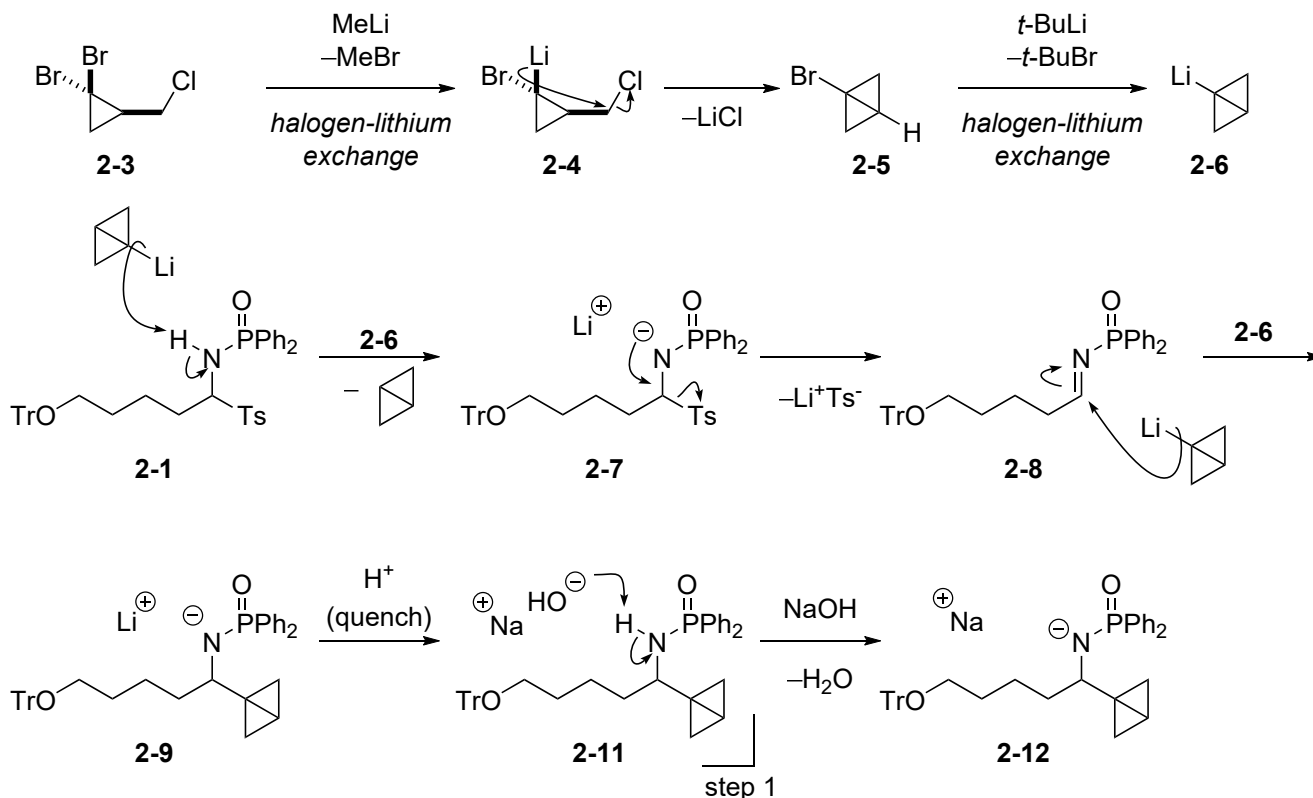
key points: bicyclobutane addition, formal ene reaction

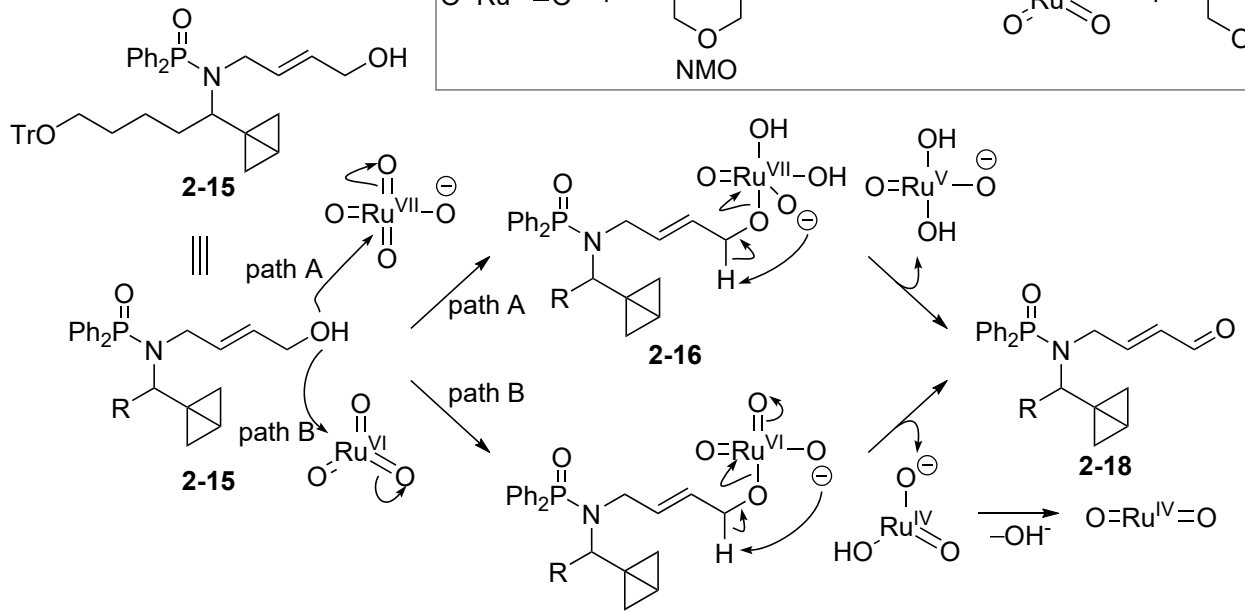
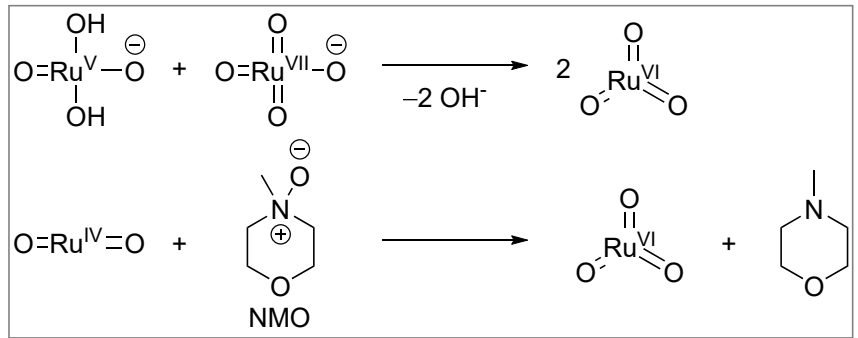
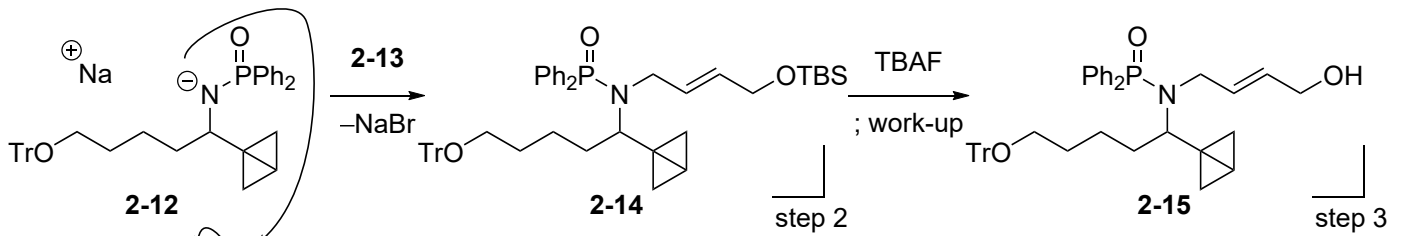


In the answer to the problem 2...

[a] All bold and dashed bonds represent relative stereochemistry.

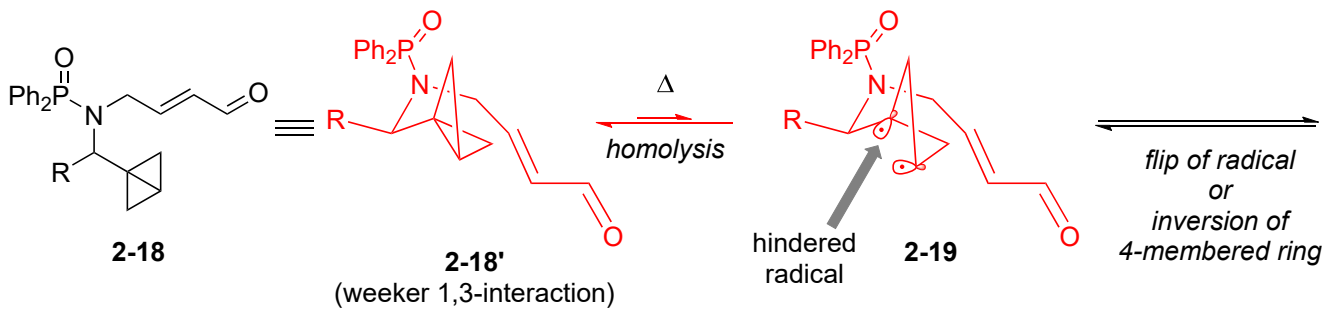
[b] All bicyclo[1.1.0]butane skeletons are *cis* isomers.



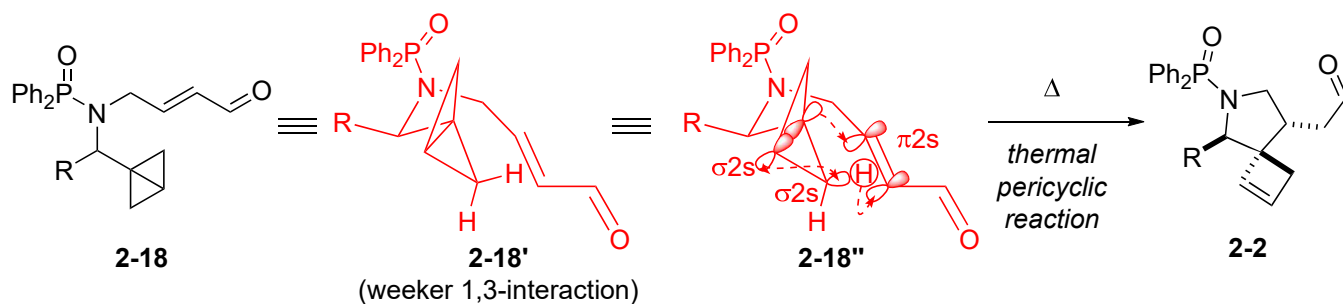


• possible reaction mechanisms for formal ene reaction **2-17**

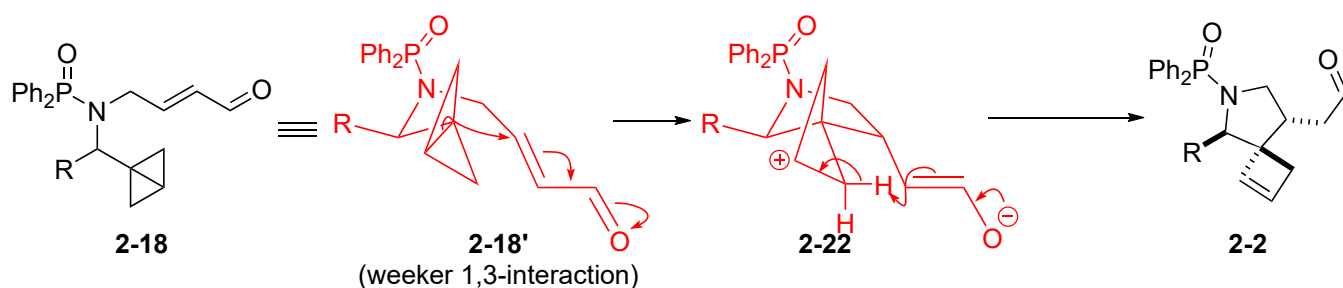
(a) radical path



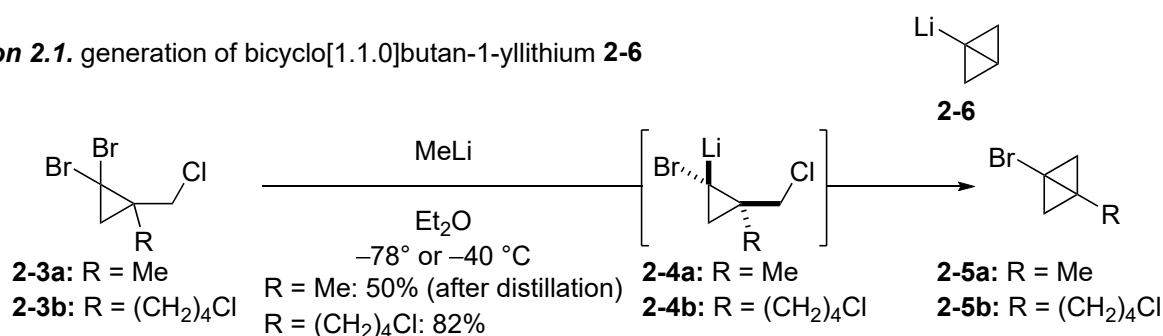
(b) concerted path



(c) zwitterionic path



Discussion 2.1. generation of bicyclo[1.1.0]butan-1-yllithium **2-6**

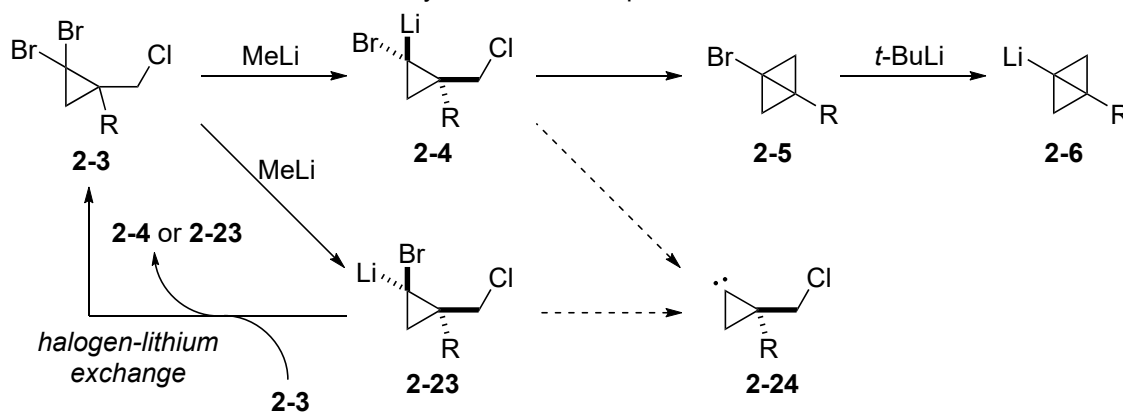


Nilsen, N. O.; Skattebol, L. *Tetrahedron Lett.* **1984**, 25, 2887.
Fuch, J.; Szeimies, G. *Chem. Ber.* **1992**, 125, 2517.

Halogen-lithium exchange could occur at both of bromine atom.

It seems that when another bromine atom is lithiated, the resultant organolithium participates in halogen-lithium exchange with unreacted **2-3**.

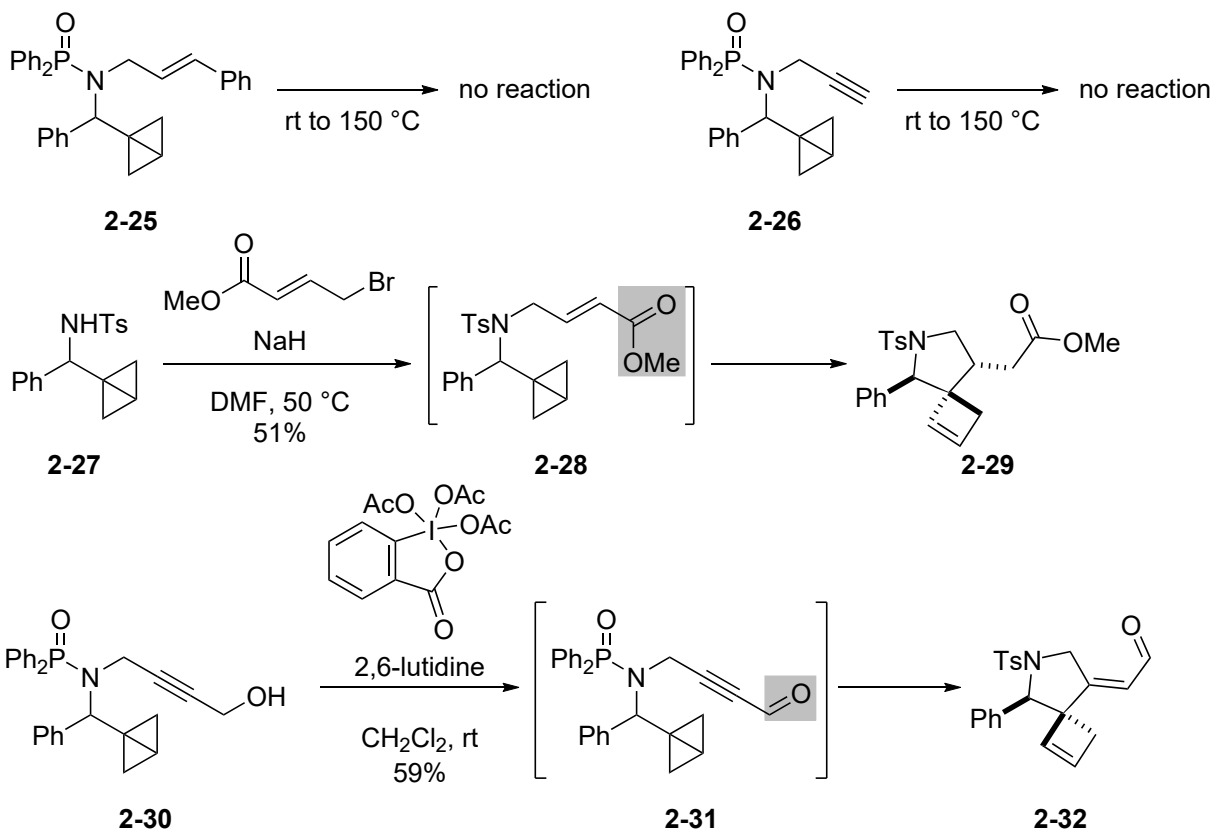
Generation of carbene **2-24** would be very slow at low temperature.



see: Seyferth, D.; Lambert Jr., R. L.; Massol, M. *J. Organomet. Chem.* **1975**, 88, 255.

Discussion 2.2. reaction mechanism of formal ene reaction

• the importance of carbonyl group

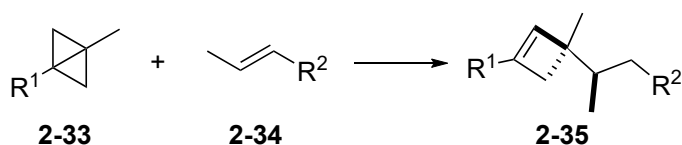


rationale for these results

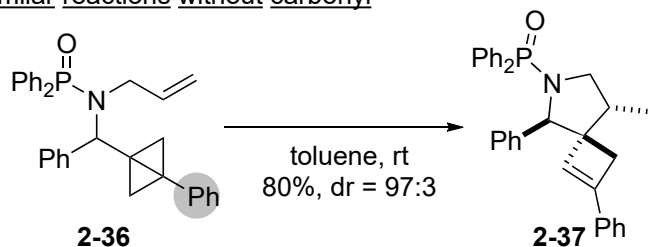
- radical path
Radical of **2-20** is nucleophilic, and reacts favorably with electron-deficient olefins.
- concerted path
carbonyl group lowers the gap between HOMO of bicyclobutane and LUMO of olefin.
This can accelerate the formal ene reaction.
- zwitterionic path
carbonyl group is needed for 1,4-addition.

Table 2. Frontier molecular orbital calculations of the HOMO-LUMO gap as a function of R¹ and R² with a HF/6-31G* basis set using MACSPARTAN 06.

	HOMO of R ¹ bicyclobutane / eV		LUMO of R ² bicyclobutane / eV	ΔE / eV
Ph	-7.95	H	5.25	13.20
H	-9.37	H	5.25	14.62
CHO	-9.73	H	5.25	14.98
H	-9.37	CHO	2.95	12.32



• similar reactions without carbonyl

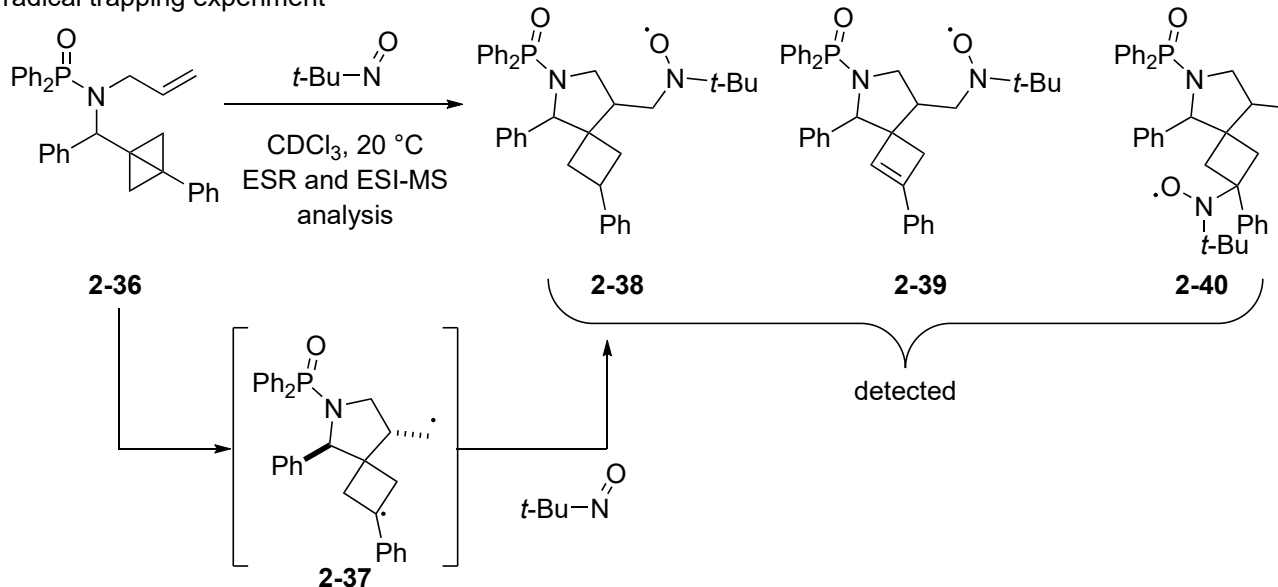


(a) Wipf, P.; Walczak, M. A. A. *Angew. Chem., Int. Ed.* **2006**, 45, 4172.

(b) Walczak, M. A. A.; Shin, B.-K.; Wipf, P.; Saxena, S. *Org. Biomol. Chem.* **2009**, 7, 2363.

(3-phenylbicyclo[1.1.0]butyl)methylamine derivatives react with unactivated olefins under milder conditions.

radical trapping experiment



-> formal ene reaction of (bicyclo[1.1.0]butylmethyl)amine derivatives seems to be radical reaction.

