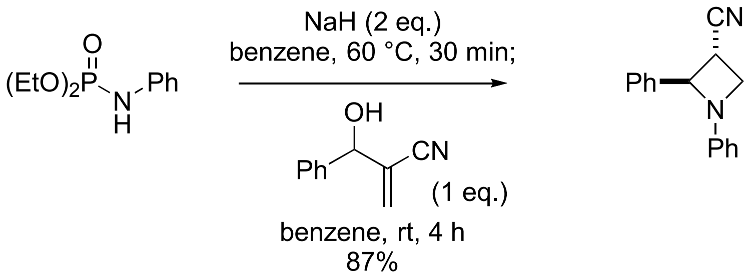
Problem Session

2015. 4. 18. Yamashita Tomoya

Please provide a reasonable reaction mechanism.

1)



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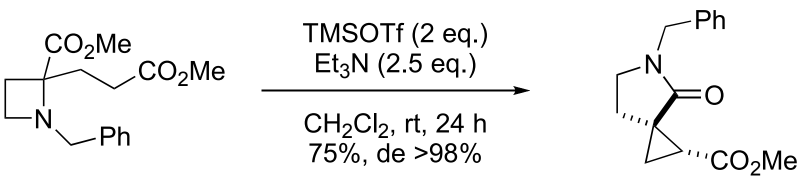

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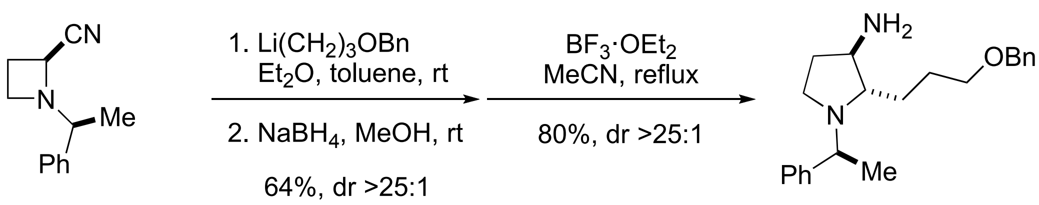
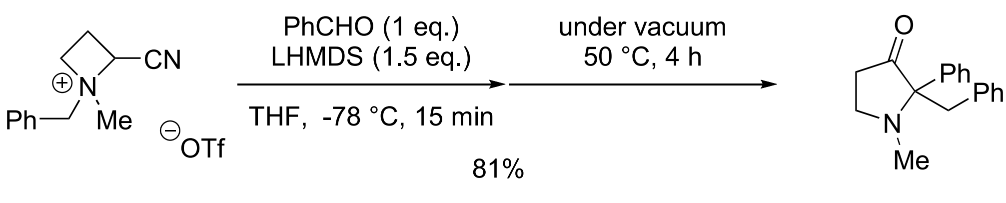


Fowden, L. *Biochem. J.* **1956**, *64*, 323.

4)



Problem Session Answer

2015. 4. 18. Yamashita Tomoya

Azetidine

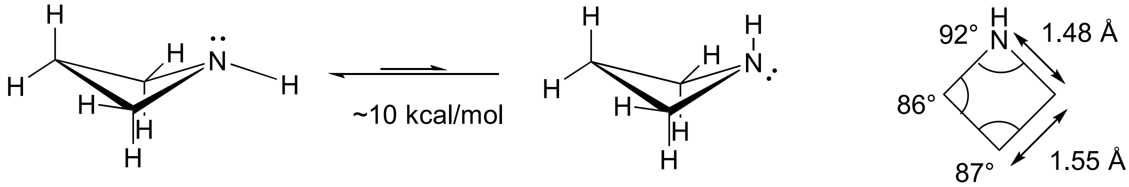
Introduction

(1) Azetidine = 4-membered saturated nitrogen heterocycles

	aziridine	azetidine	pyrrolidine	piperidine
pK_{aH}	7.98	11.29	11.31	11.22
ring strain (kcal/mol)	27.3	25.2	5.8	0

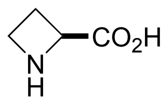
The chemistry of azetidines is *much less developed* compared to aziridines, pyrrolidines, or piperidines.
ring closure of azaheterocycles 5 > 3 > 6 > 7 ~ 4

conformation of azetidine

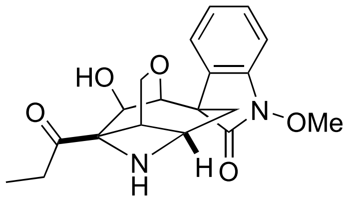


puckered square

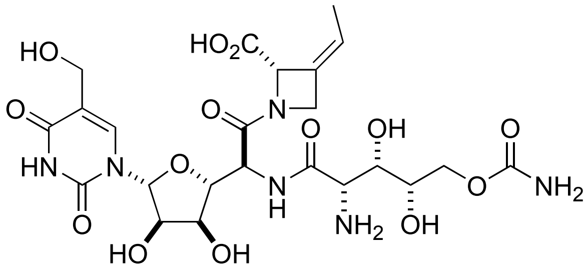
(2) Azetidine containing natural product



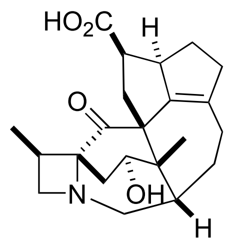
L-Aze



gelsemoxonine



polyoxin A

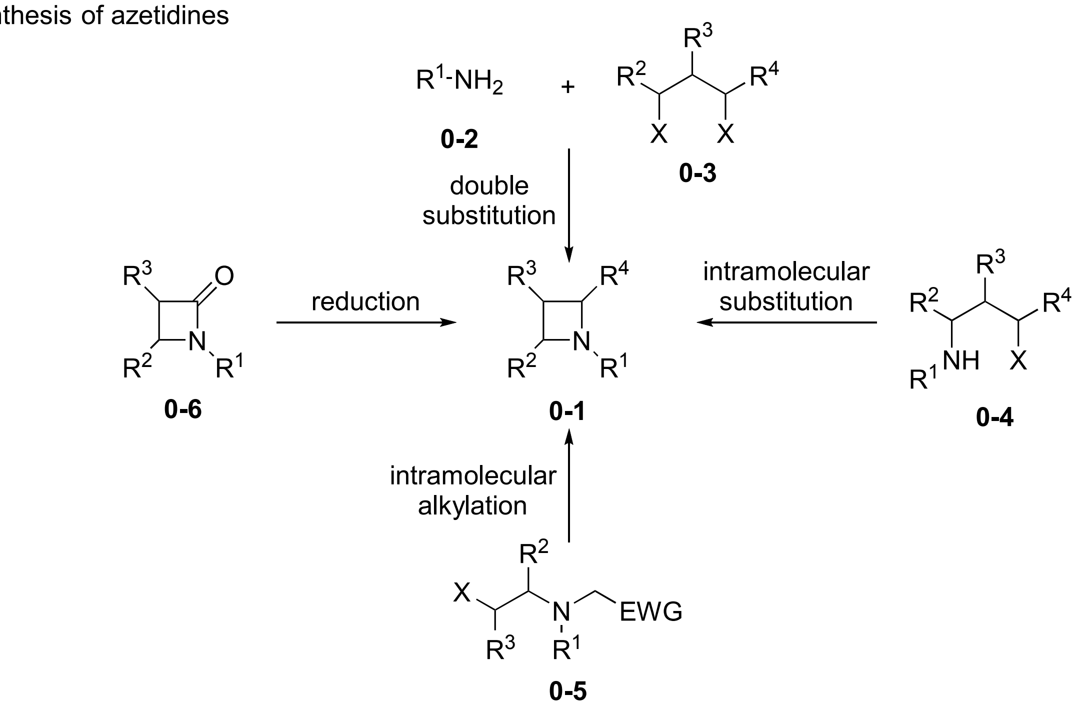


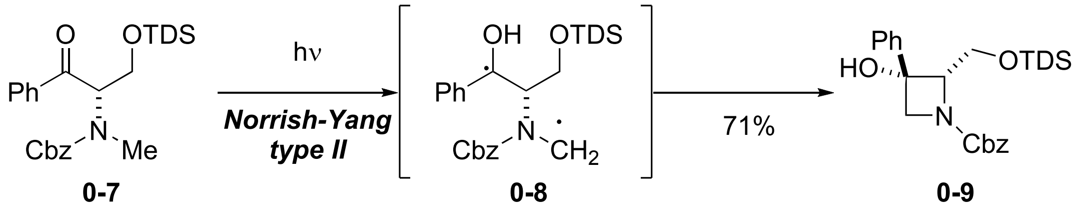
calydaphninone

For reviews, see:
1) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
2) Bott, T. M.; West, F. G. *Heterocycles* **2012**, *84*, 223.
3) Couty, F.; Drouillat, B.; Evano, G.; David, O. *Eur. J. Org. Chem.* **2013**, 2045.
4) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

For more on 4-membered heterocycles, see PS121006 by Dr. Murai K.

(3) Synthesis of azetidines

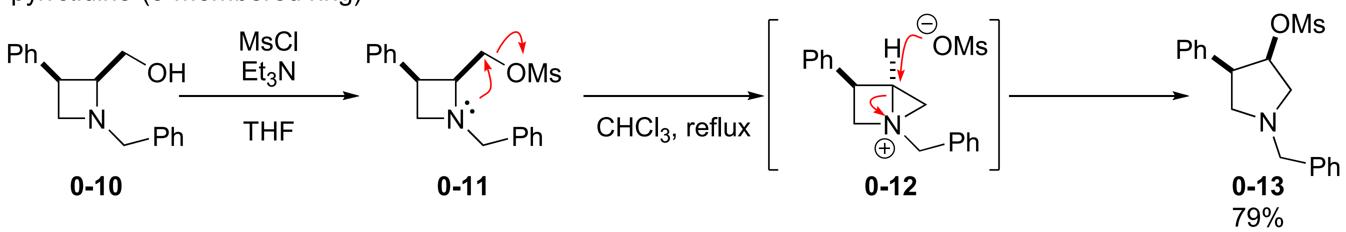




TDS = thexyldimethylsilyl

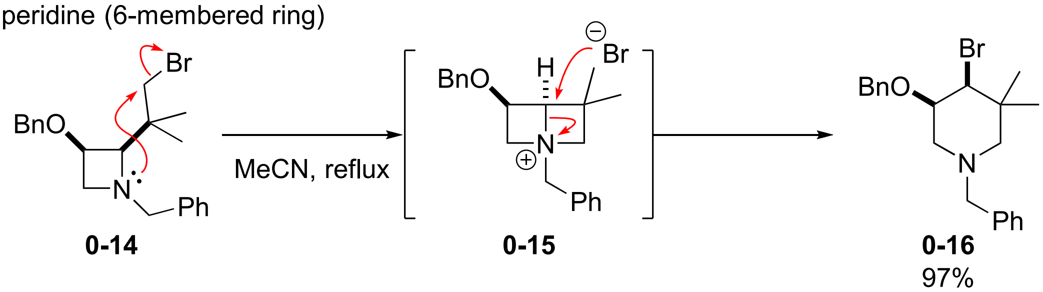
(4) Reaction of azetidine -ring expansion-

pyrrolidine (5-membered ring)



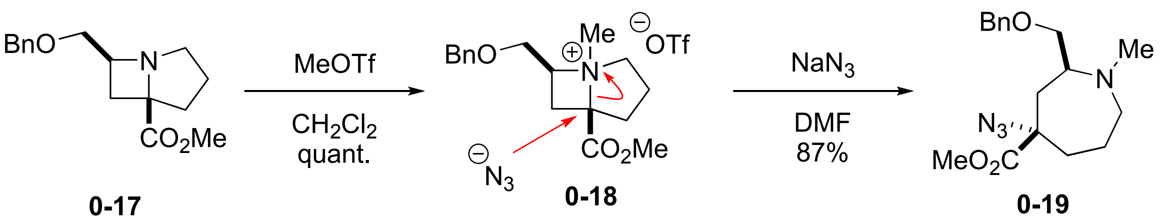
Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, 3286.

piperidine (6-membered ring)



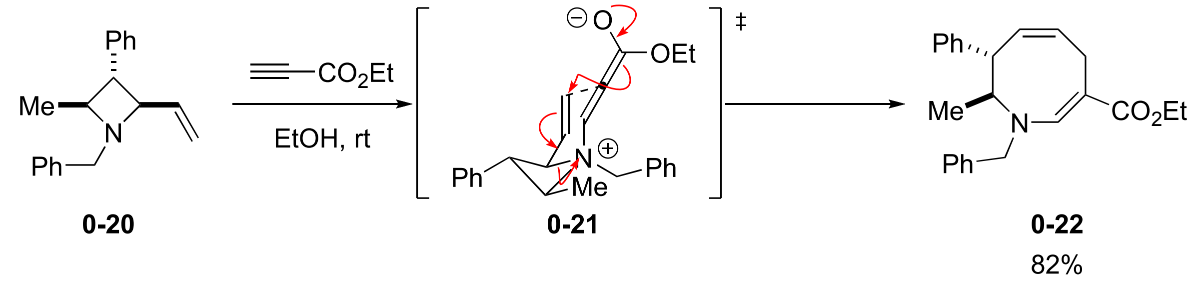
van Brabandt, W.; van Landeghem, R.; de Kimpe, N. *Org. Lett.* **2006**, *8*, 1105.

azepane (7-membered ring)



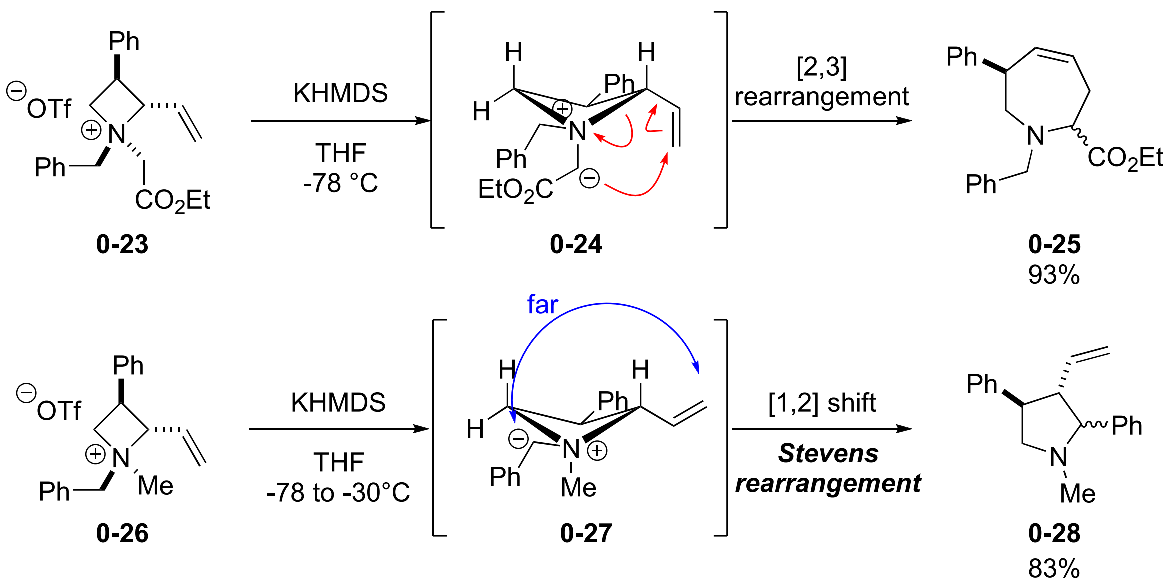
Sivaprakasam, M.; Couty, F.; David, O.; Marrot, J.; Sridhar, R.; Srinivas, B.; Ramama, R. *Eur. J. Org. Chem.* **2007**, 5734.

azocane (8-membered ring)



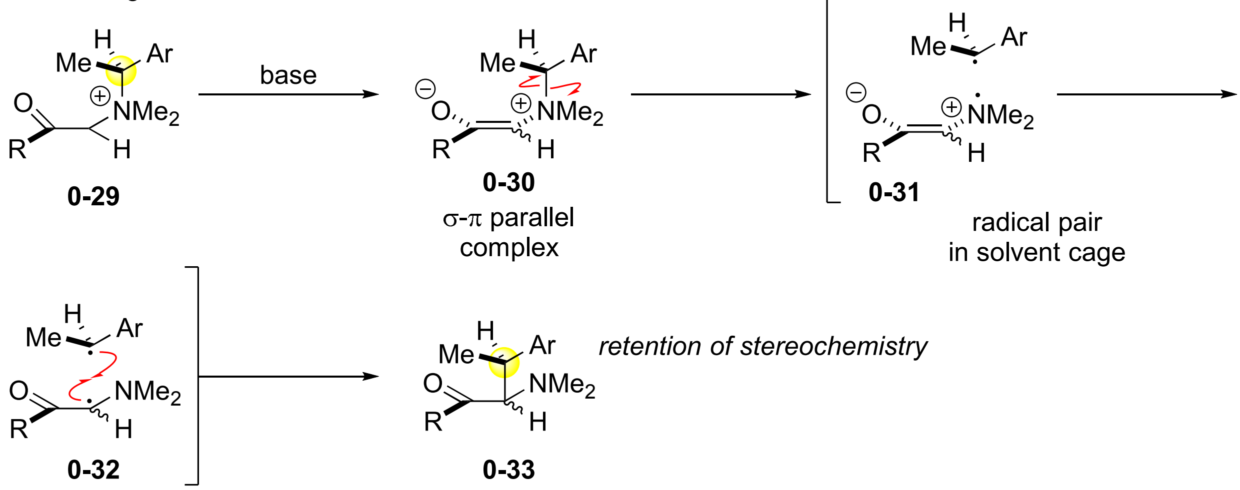
Drouillat, B.; Couty, F.; Razafimahaléo, V. *Synlett* **2009**, *19*, 3182.

[2,3] rearrangement versus [1,2] shift

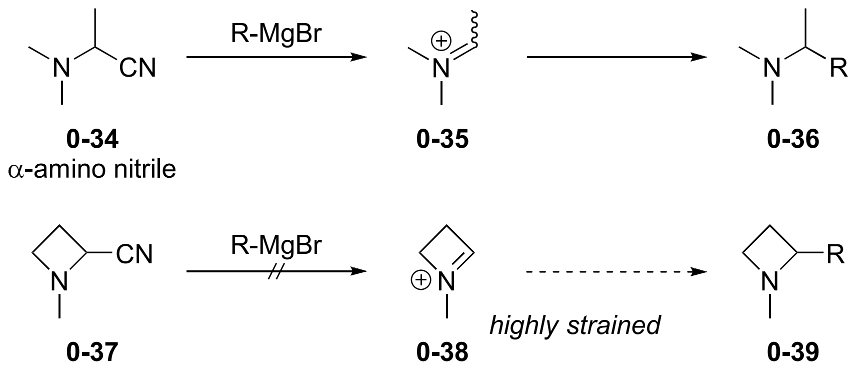


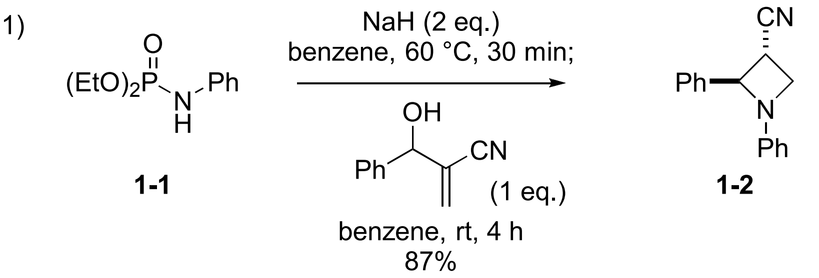
Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214.

Stevens rearrangement



Bruylants reaction

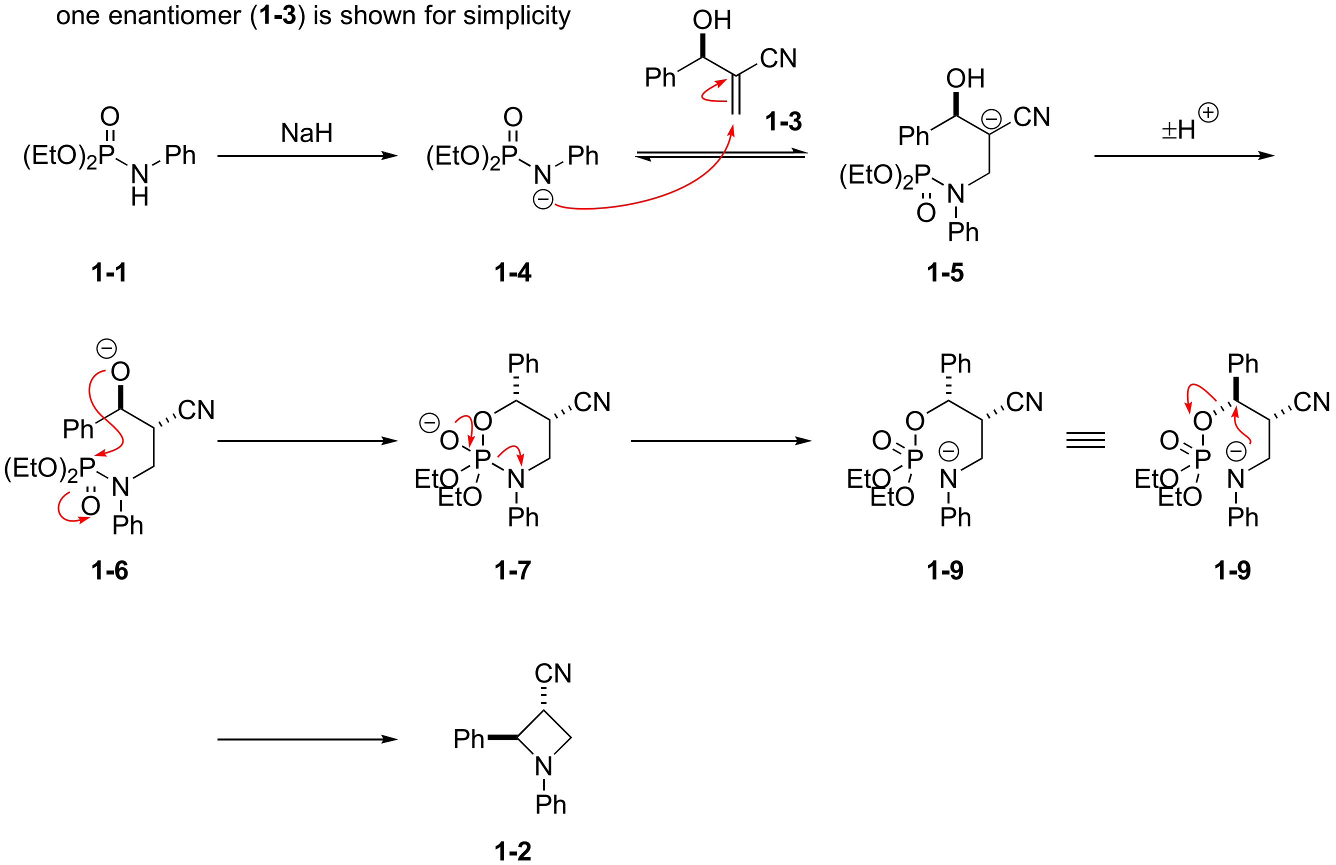




Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 5652.

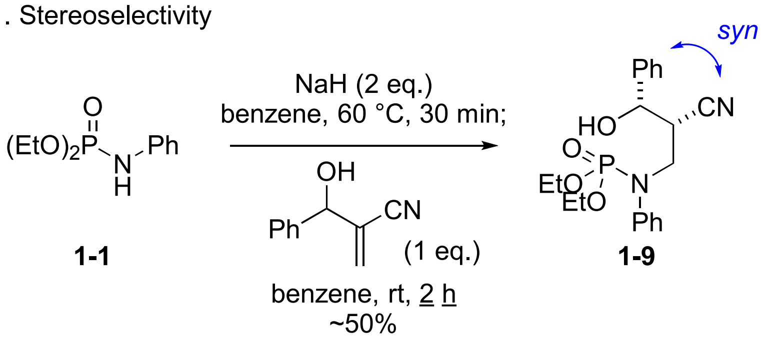
Proposed mechanism:

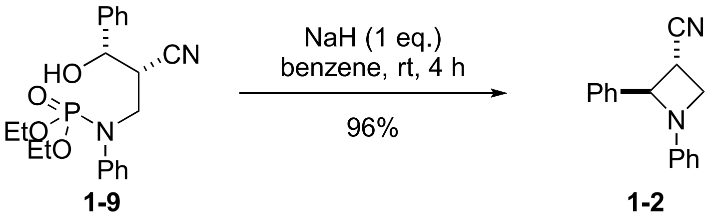
one enantiomer (**1-3**) is shown for simplicity



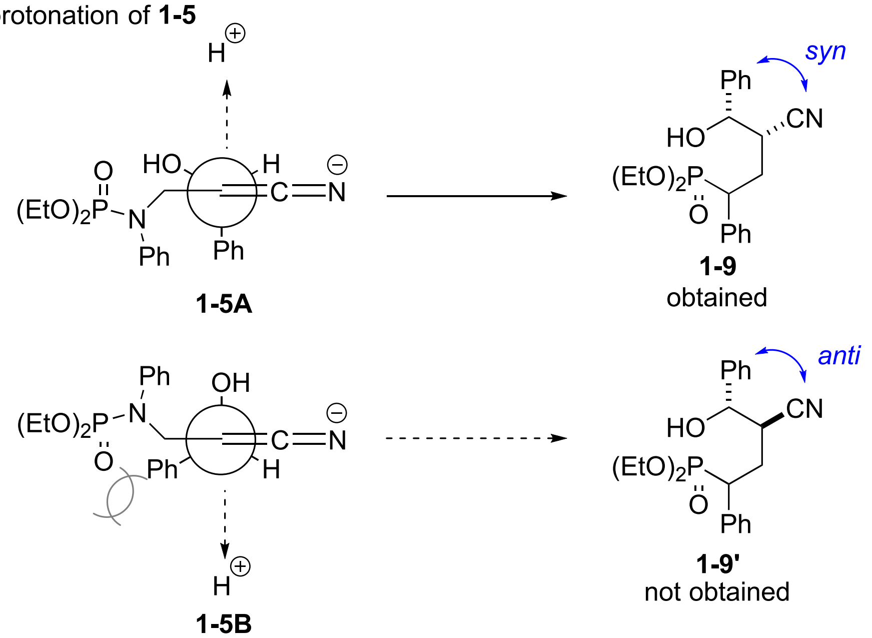
Discussion:

1. Stereoselectivity

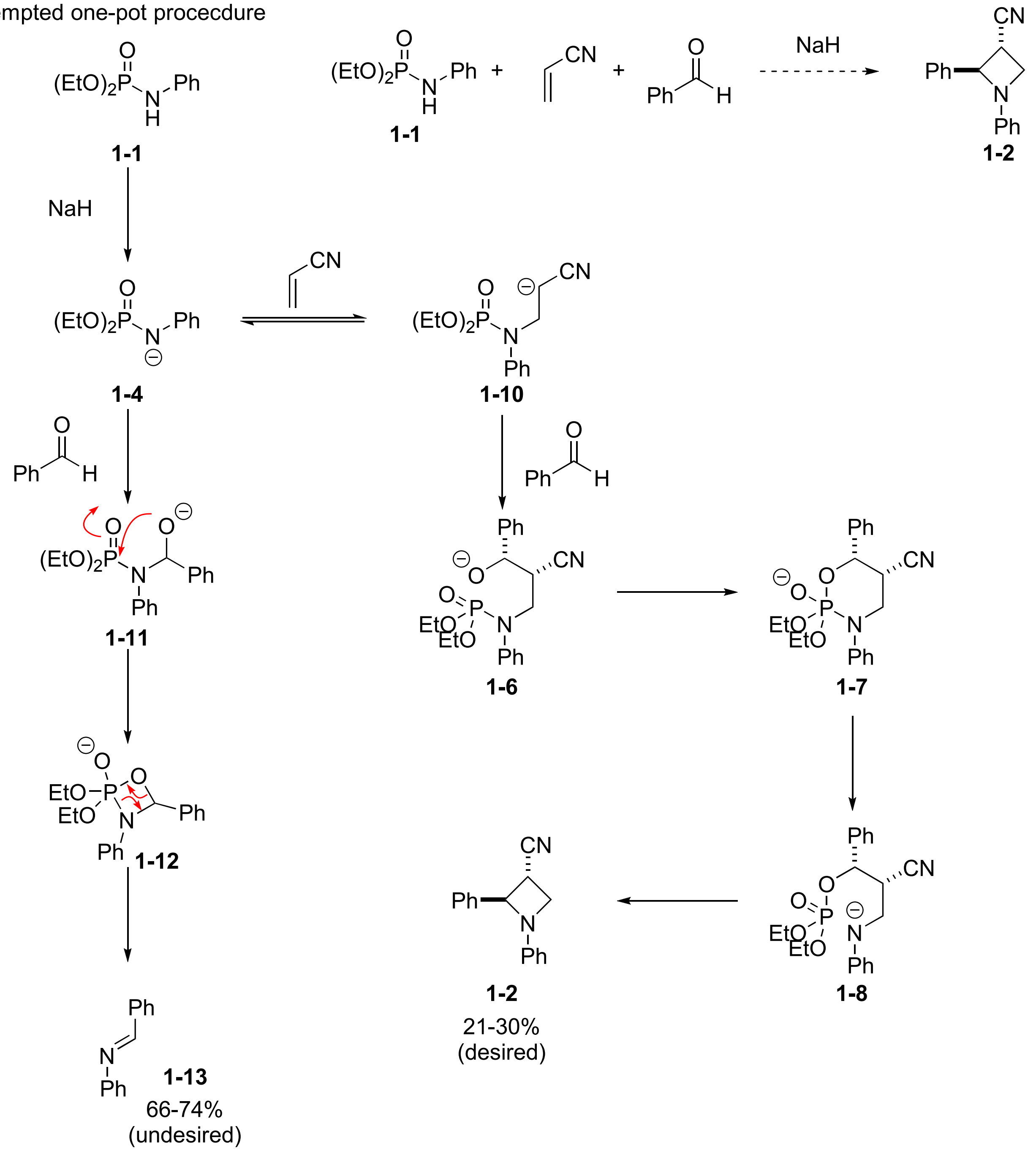




protonation of **1-5**



2. Attempted one-pot procecdure



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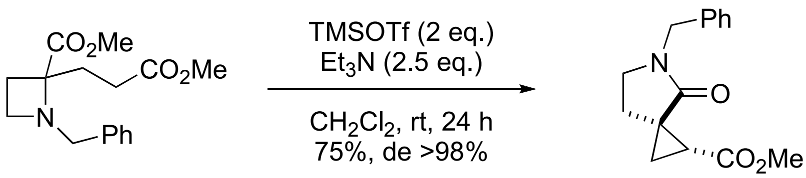
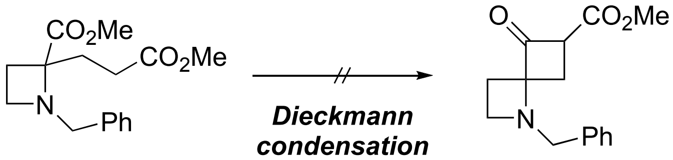


2-1 **2-2**

Nocquet, P.-A.; Hazelard, D.; Compain, P. *Eur. J. Org. Chem.* **2011**, 6619.

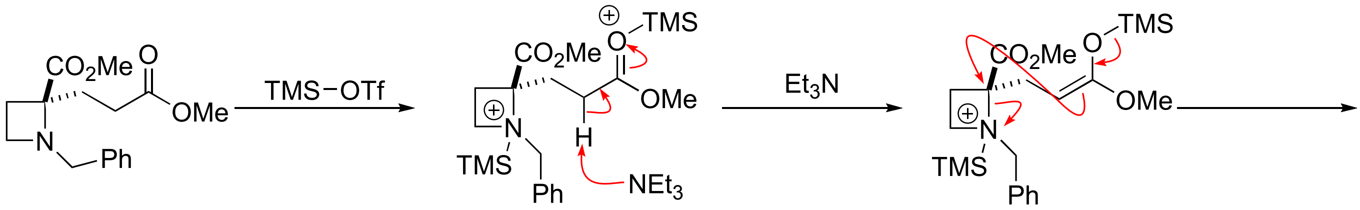
Attempted Dieckmann condensation



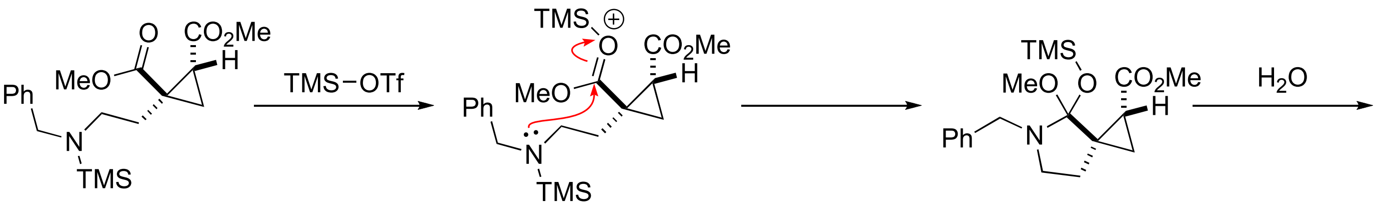
2-1 **2-3**

Proposed mechanism:

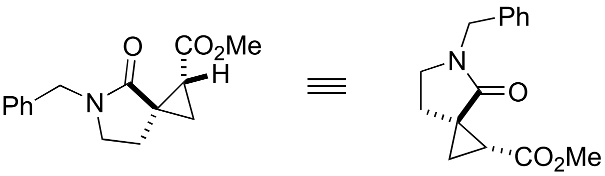
one enantiomer is shown



2-1 **2-4** **2-5**



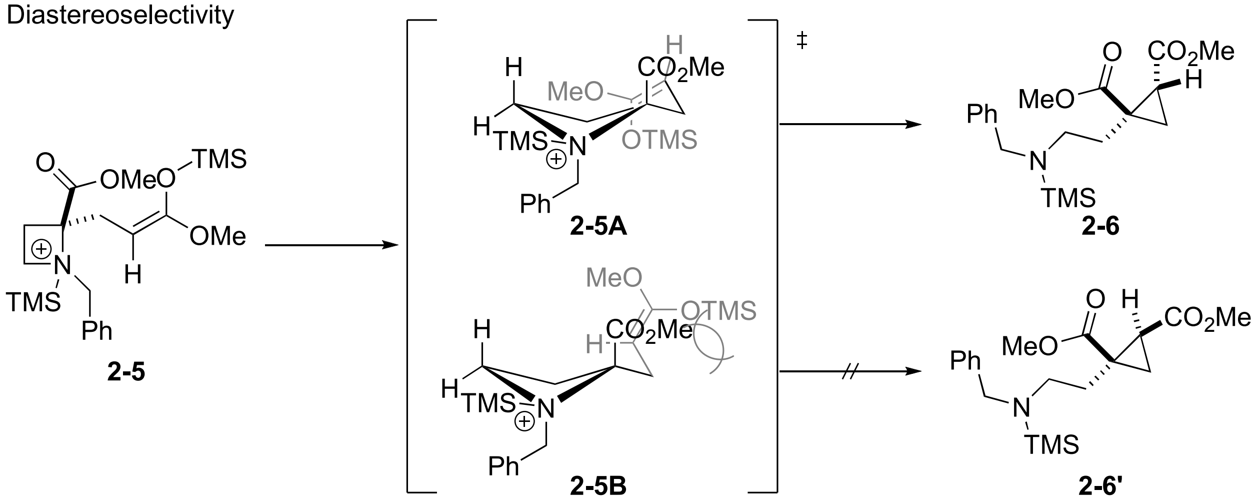
2-6 **2-7** **2-8**



2-2 **2-2**

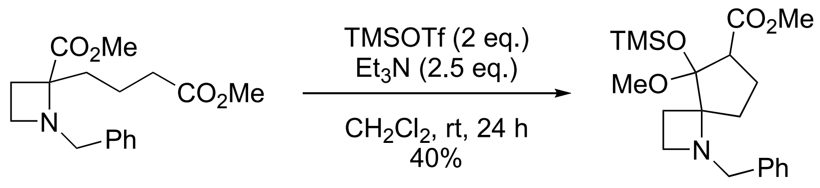
Discussion:

1. Diastereoselectivity



2-5 **2-6** **2-6'**

2. One carbon extension enables Dieckmann condensation



2-9 **2-10**

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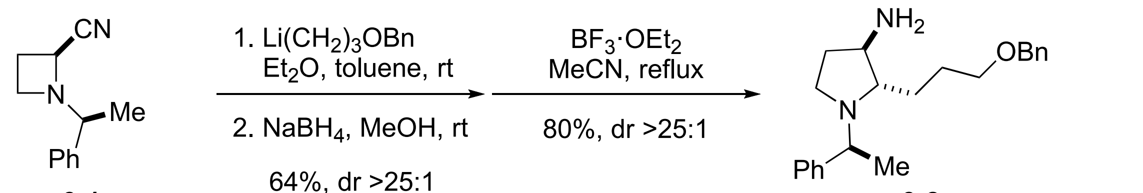
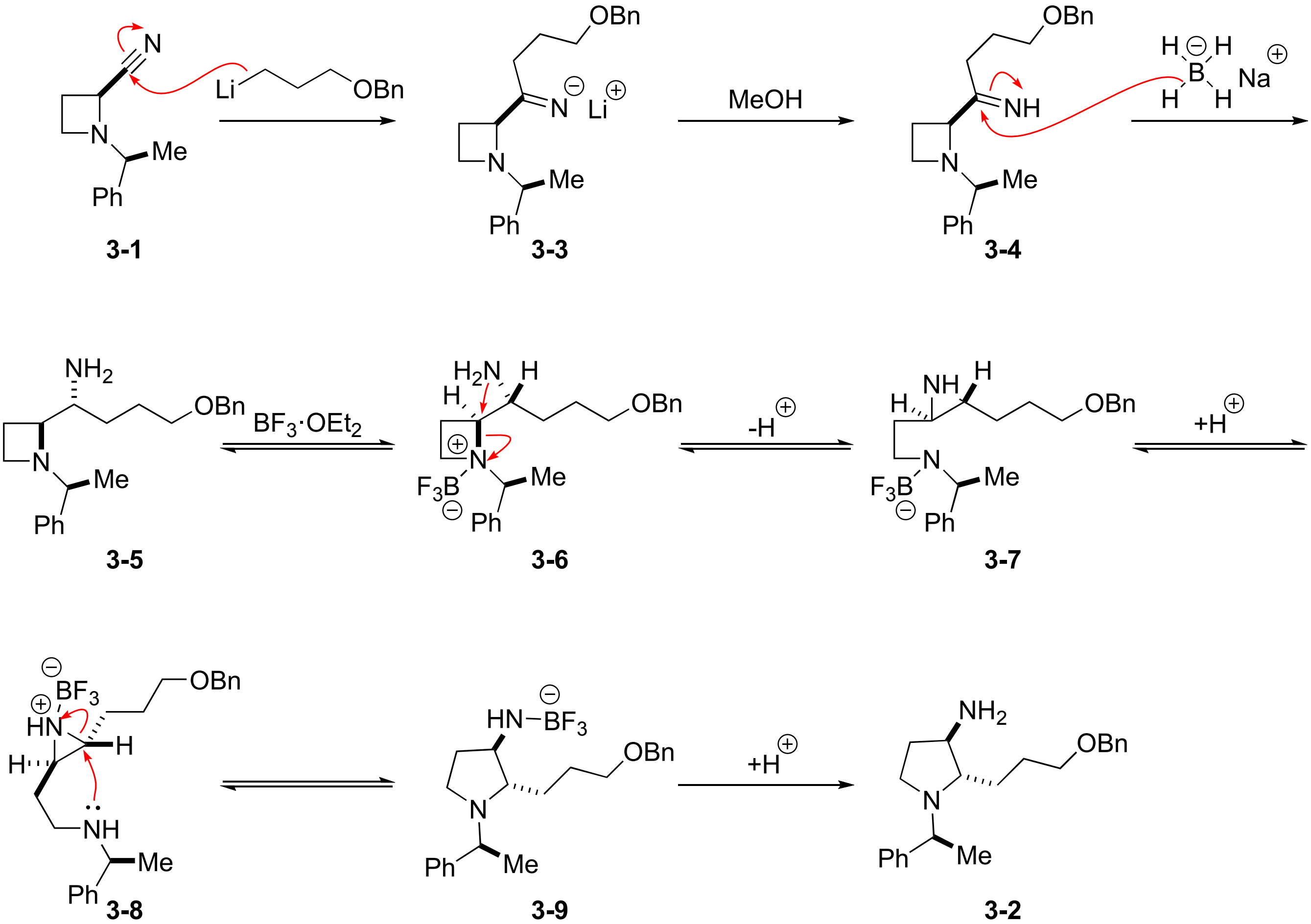
3)



3-1 **3-2**

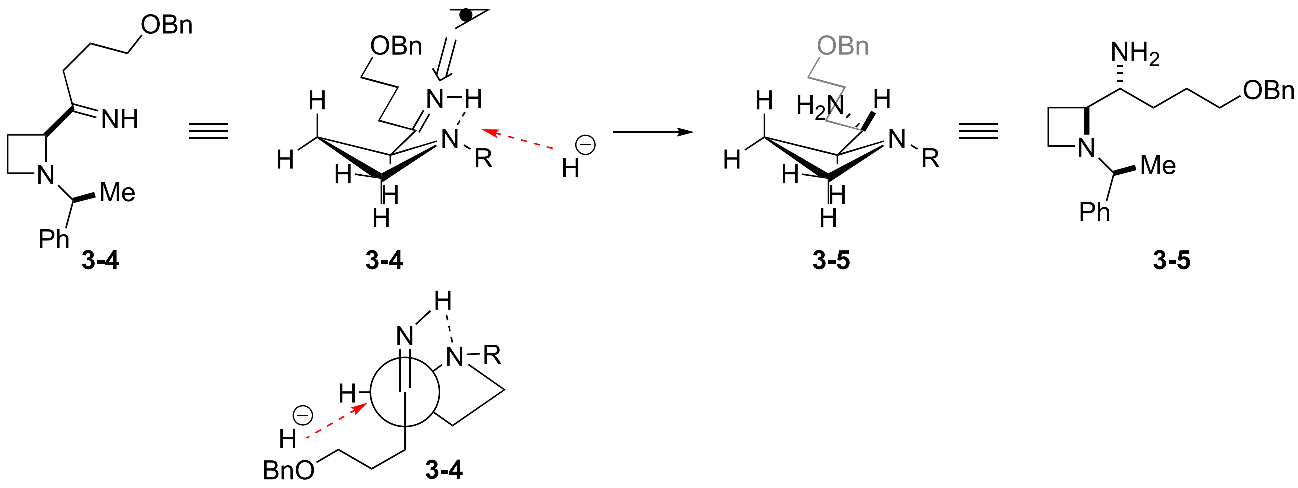
Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861.

Proposed mechanism:



Discussion:

1. Diastereoselectivity in $NaBH_4$ reduction



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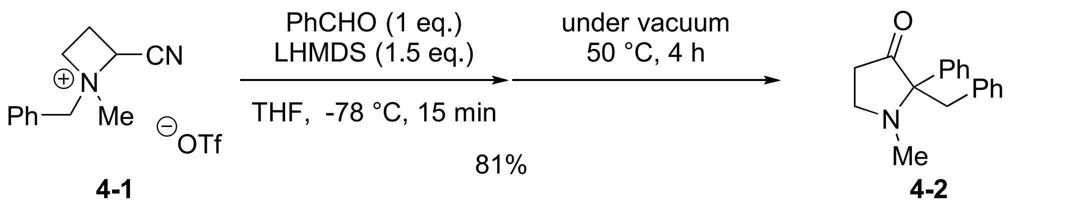
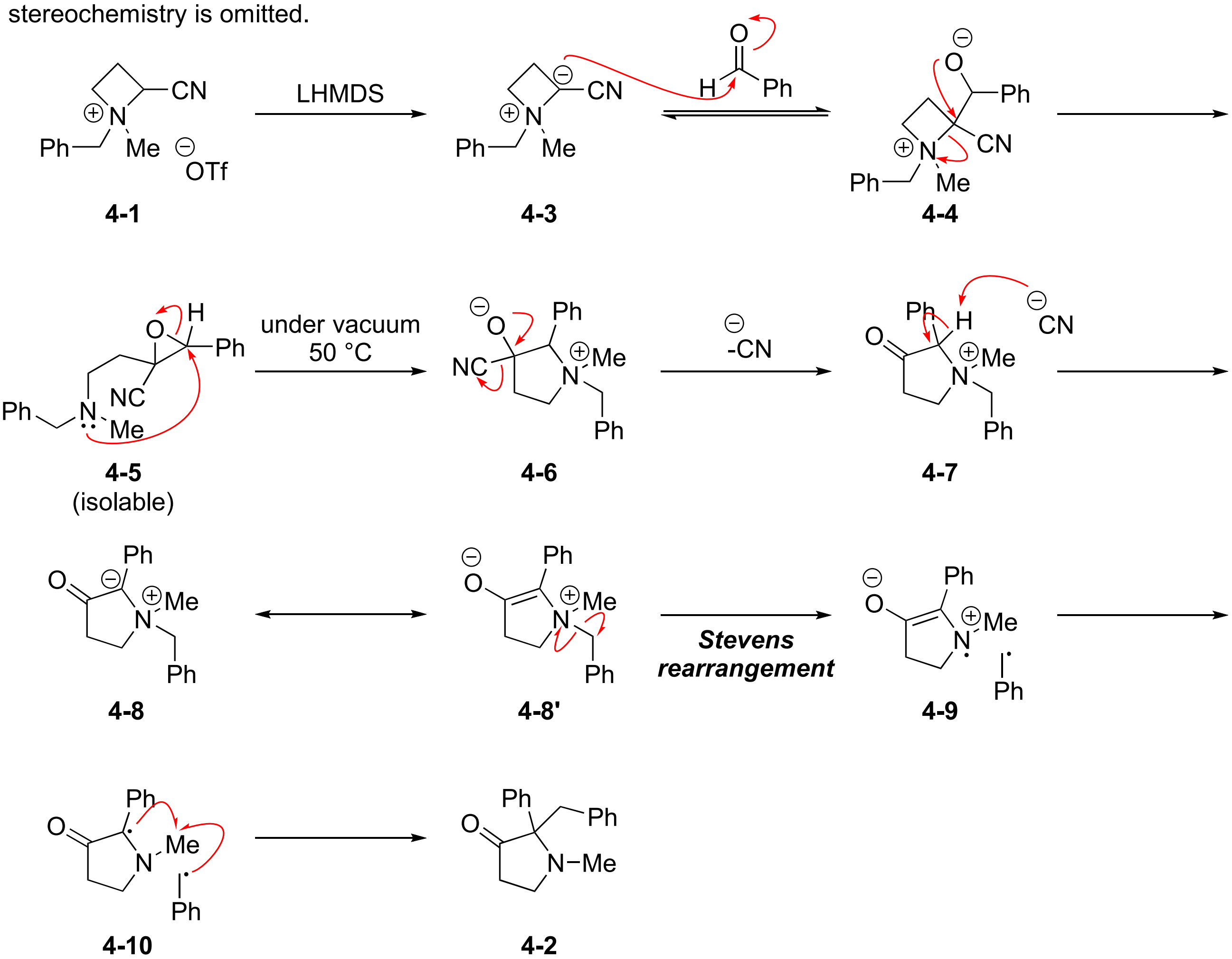
4)



Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* **2007**, 2500.

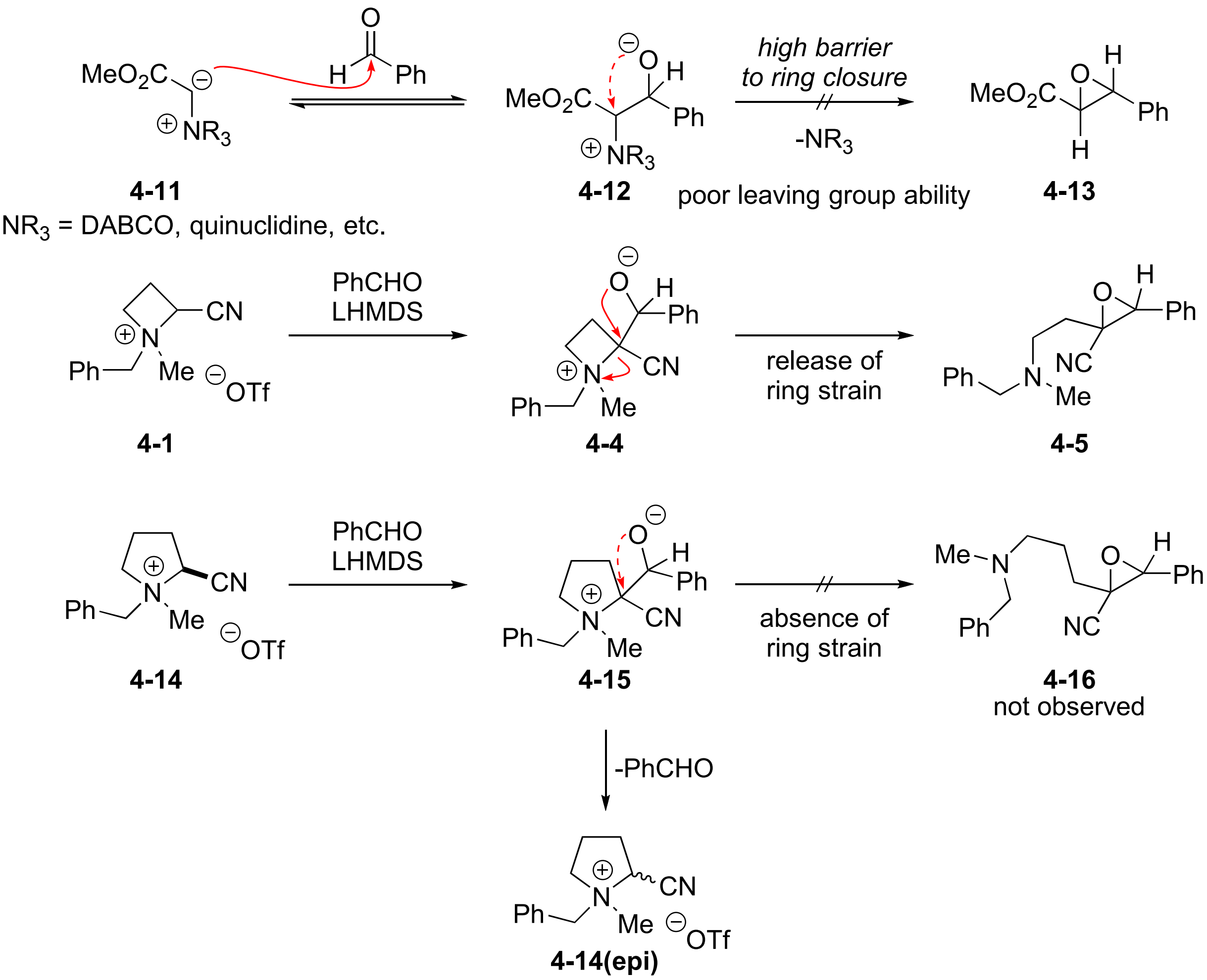
Proposed mechanism:

stereochemistry is omitted.

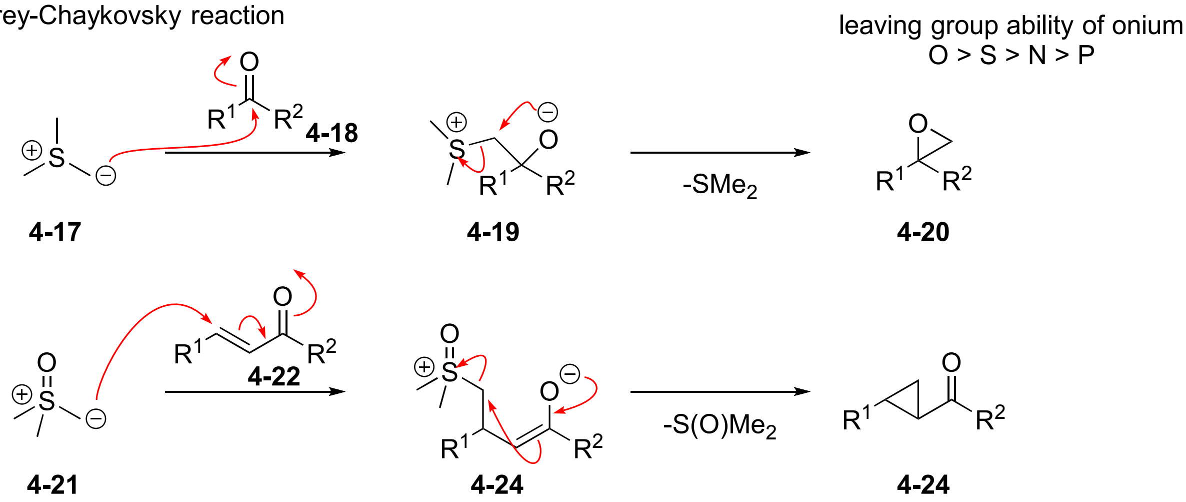


Discussion:

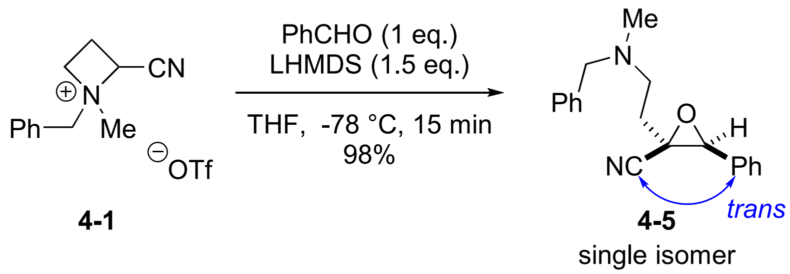
1. Ring strain enables the epoxidation



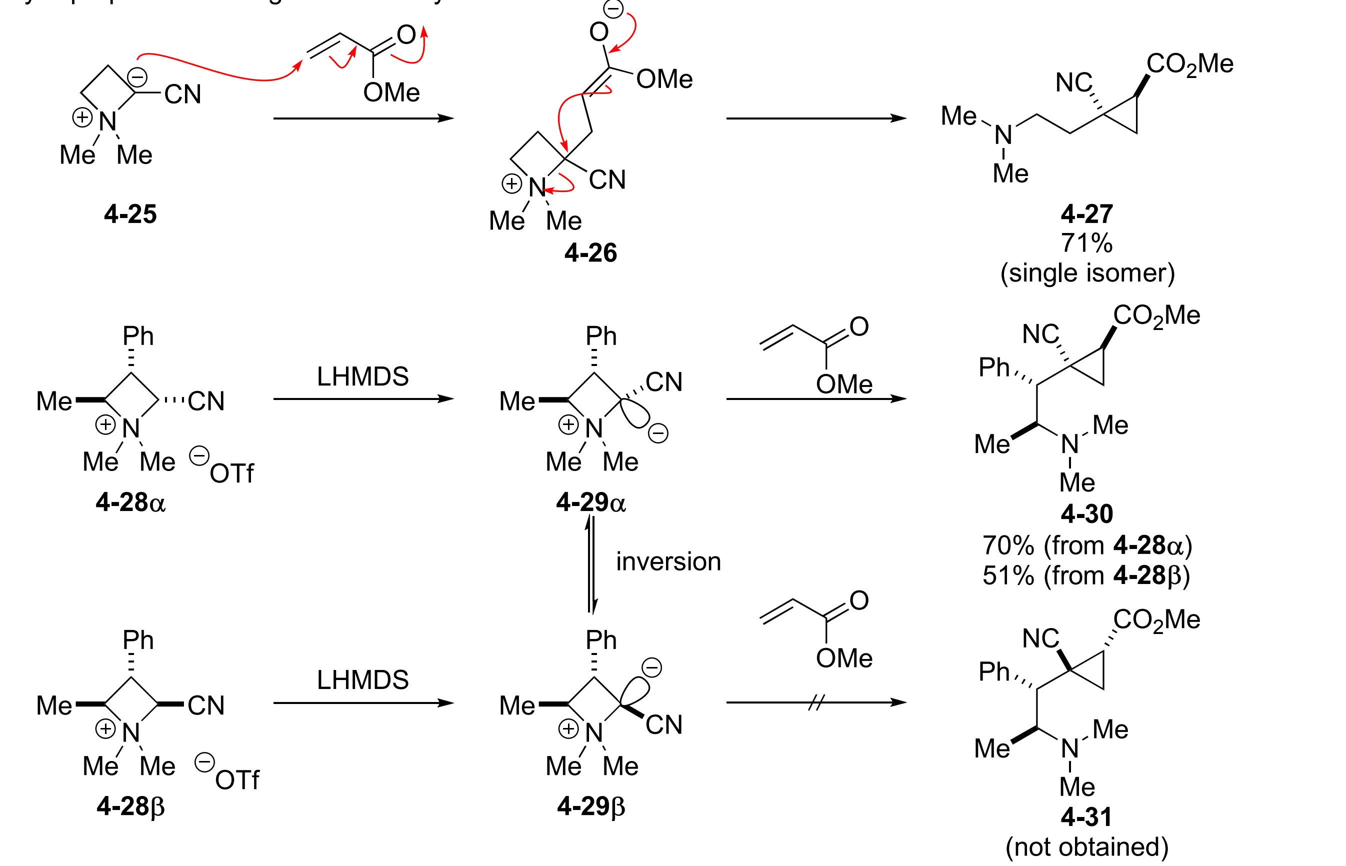
cf. Corey-Chaykovsky reaction



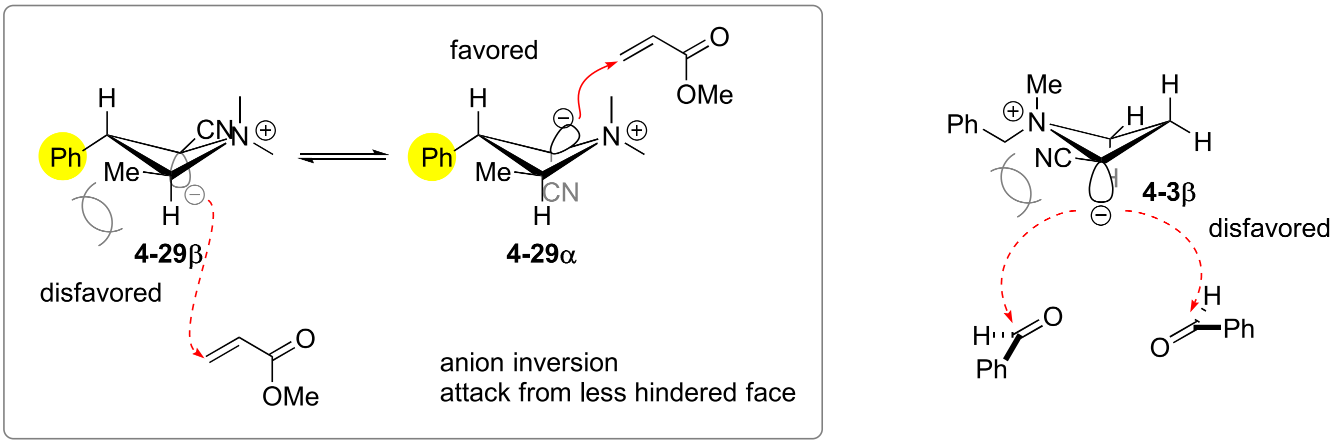
2. Stereochemistry of epoxide formation

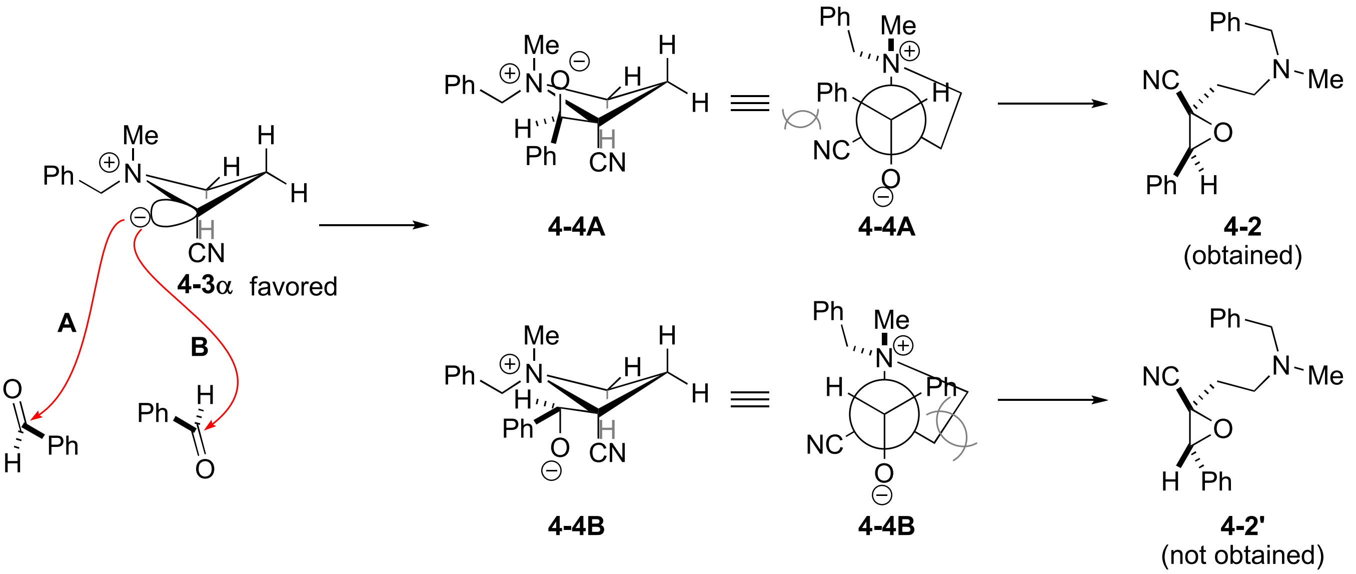


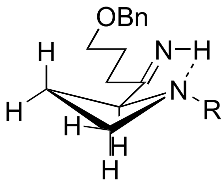
cyclopropanation using azetidinium ylide

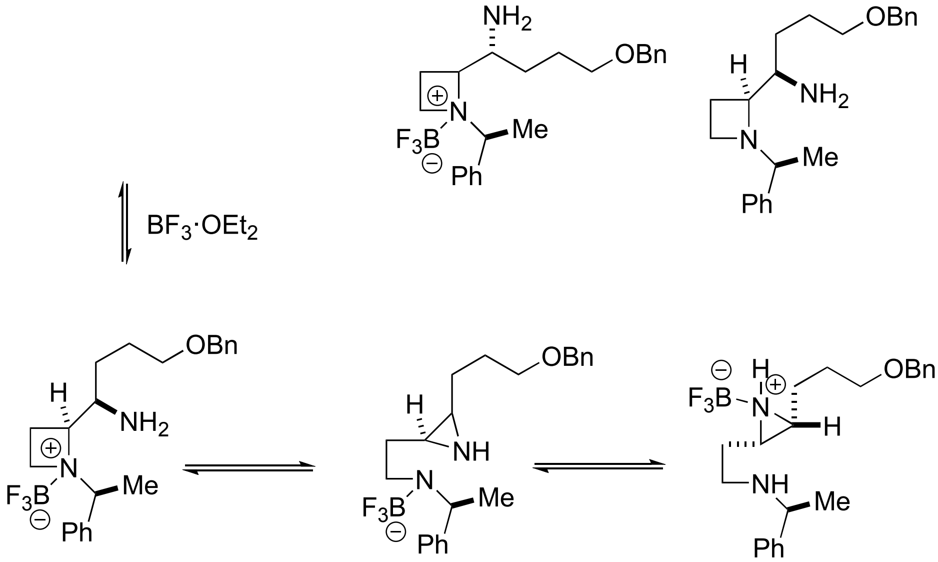


Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058.





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