P-Menthane-3-carboxaldehyde: A Useful Chiral Auxiliary for the Synthesis of Chiral Quaternary Carbons of High Enantiomeric Purity

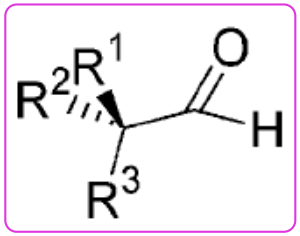
1. Spino, C.; Godbout, C.; Beaulieu, C.; Harter, M.; Mwene,T,M.; Boisvert, L. *J. Am. Chem. Soc*. **ASAP**.
2. Spino, C.; Granger, M. C.; Tremblay, M, C. *Org. Lett.* **2002**, *4.* 4735.
3. Spino, C.; Godbout, C. *J. Am. Chem. Soc.* **2003**, *125.* 12106.

Literature Presentation

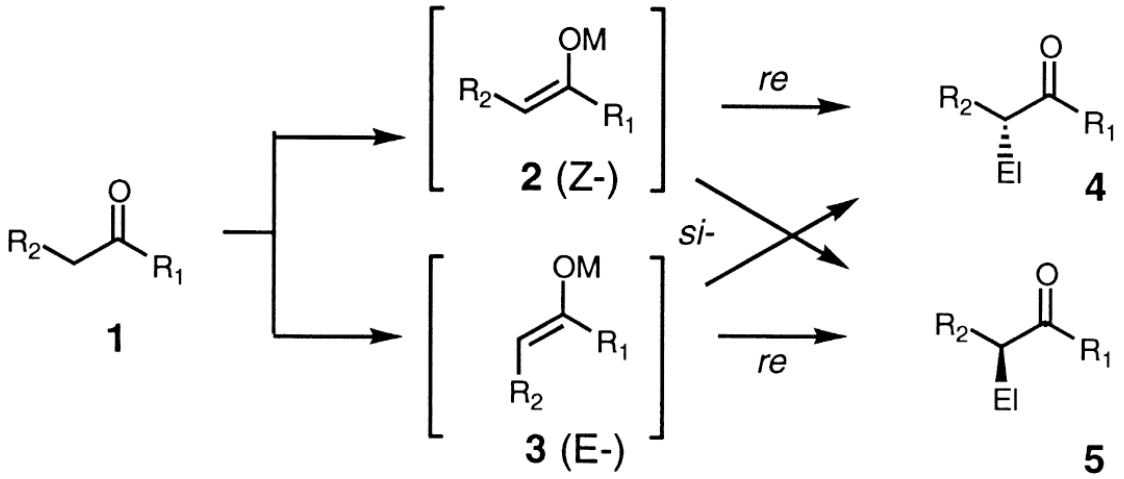
Zhenjie Lu

Oct 07, 2004

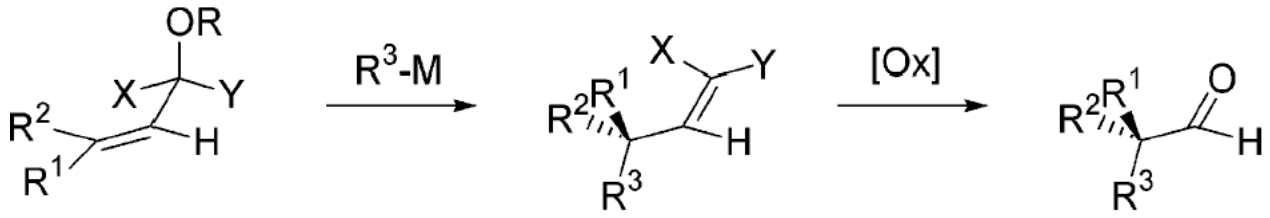
Attempts to Achieve Chiral Carbon Center



- Via enolate of defined geometry

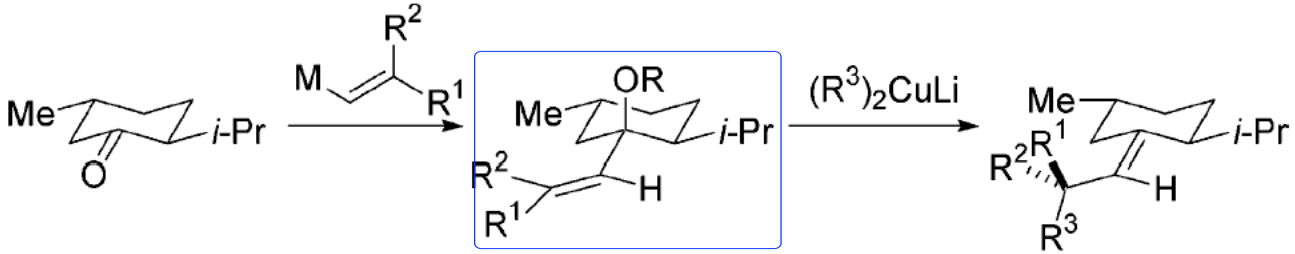


- Via SN2' displacement of an allylic leaving group



Menthone Chiral Auxiliary System

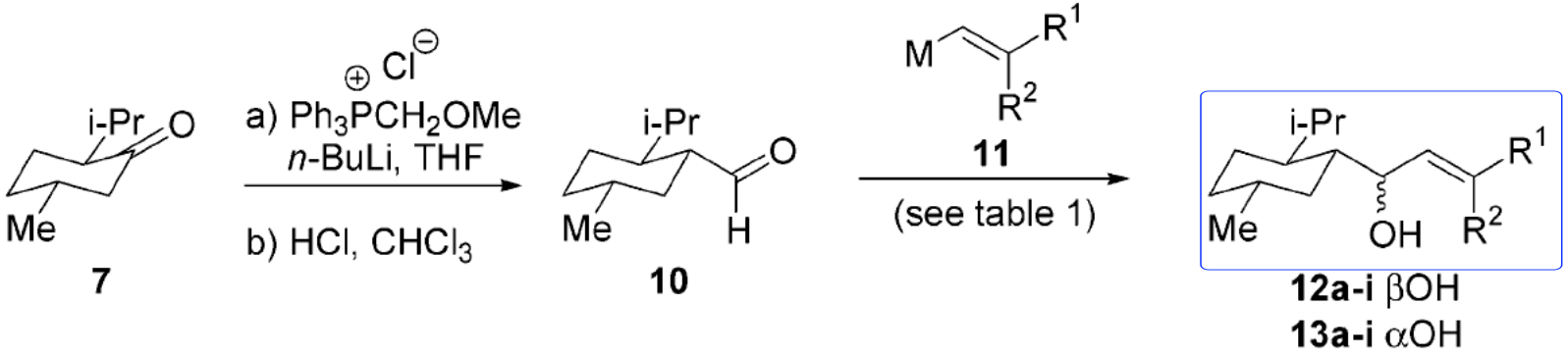
➢ Original menthone chiral auxiliary



7 **8a** R = H; **8b** R = CO_2Me **9**

• The displacement would not undergo if compound 8 is trisubstituted alkenes because of $A^{1,3}$ strain.

➢ Aldehyde as chiral auxiliary



7 **10** **12a-i** βOH; **13a-i** αOH

1. Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832.
2. Spino, C.; Beaulieu, C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1930.

Stereoselective Synthesis of β-Allylic Alcohols

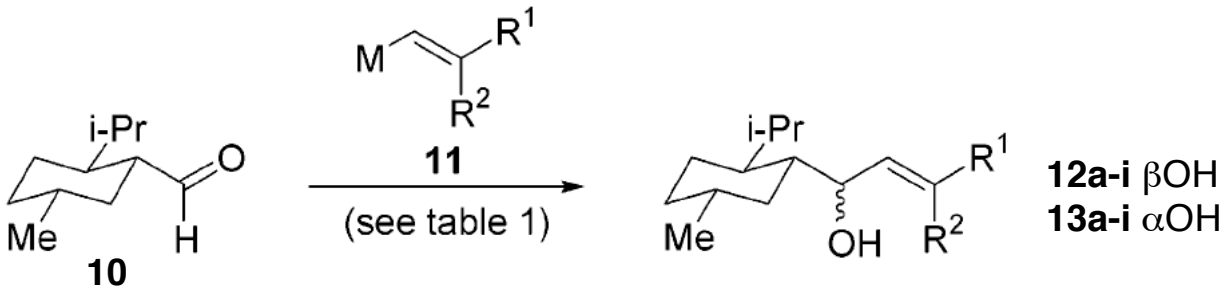


Table 1. Comparison of Ratios of Alcohols **12**:**13** Obtained by Two Different Methods Involving $AlMe_3$

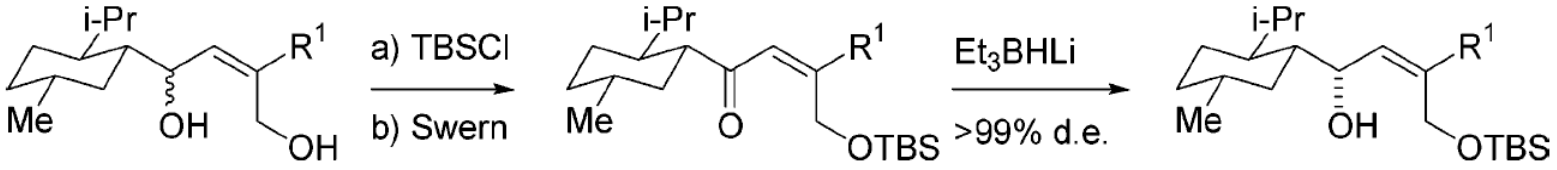
entry	**11**	R^1 (R^2 = Me)	**12/13**	**12:13** ratio[a] (% yield)[b] method A[c]	method B[d]
1	**11a**	*n*-Bu	**a**	12:1 (70)	
2	**11b**	*n*-Pen	**b**	9:1 (75)	80:1 (60)
3	**11c**	*c*-C_6H_{11}	**c**	14:1 (80)	
5	**11d**	Bn	**d**	11:1 (76)	
6	**11e**	CH_2OH	**e**	10:1 (quant)	
7	**11f**	$(CH_2)_3OTBS$	**f**	10:1 (71)	
8	**11g**	$(CH_2)_4OTBS$	**g**	11:1 (68)	
9	**11h**	Ph	**h**	18:1 (63)	34:1 (50)
10	**11i**	*p*-tolyl	**i**	24:1 (78)	39:1 (76)

[a] All ratios measured by G. C. or NMR of the crude mixtures. [b] Isolated yield of pure **12**. [c] Method A: alkyne, Cp_2ZrCl_2 (cat.), $AlMe_3$, CH_2Cl_2, aldehyde **10**. [d] Method B: vinyllithium, $AlMe_3$, ether, aldehyde **10**.

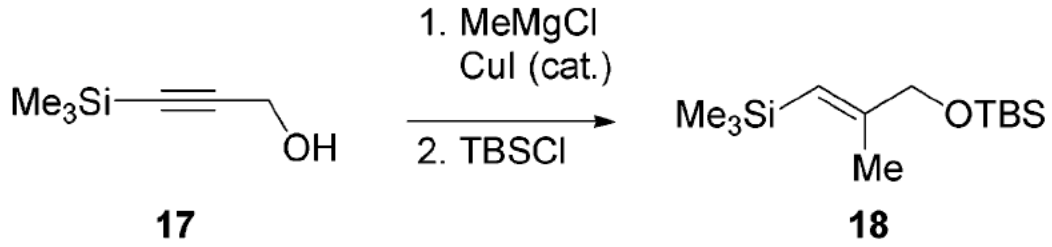
Spino, C.; Granger, M. C.; Tremblay, M, C. *Org. Lett.* **2002**, *4.* 4735.

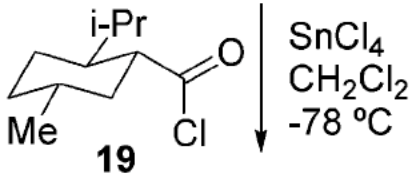
Stereoselective Synthesis of α-Allylic Alcohols

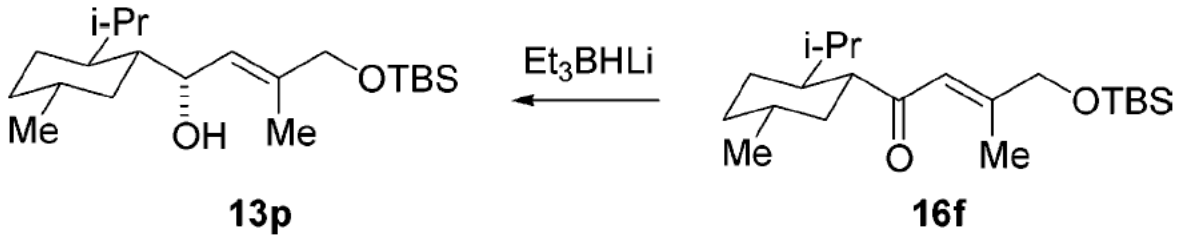
- From the diastereomers.



- From acyl chloride with vinylsilane

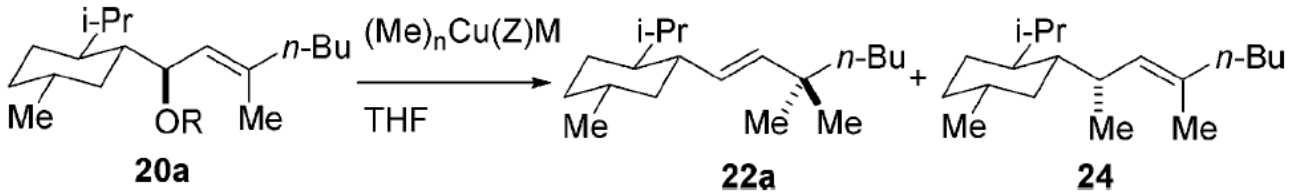






yield: 70-75%

Quaternary Chiral Center Formation by SN2' Displacement



- Regioselectivity was strongly dependent on the nature of the leaving group and of the cuprate reagent.

R: CO-*t*-Bu
Cuprate: MeCu(CN)MgBr
22a:24 ratio: >99:1

Scheme 6. SN_2' Displacement of pivalates **20** or **21** with cuprate reagents

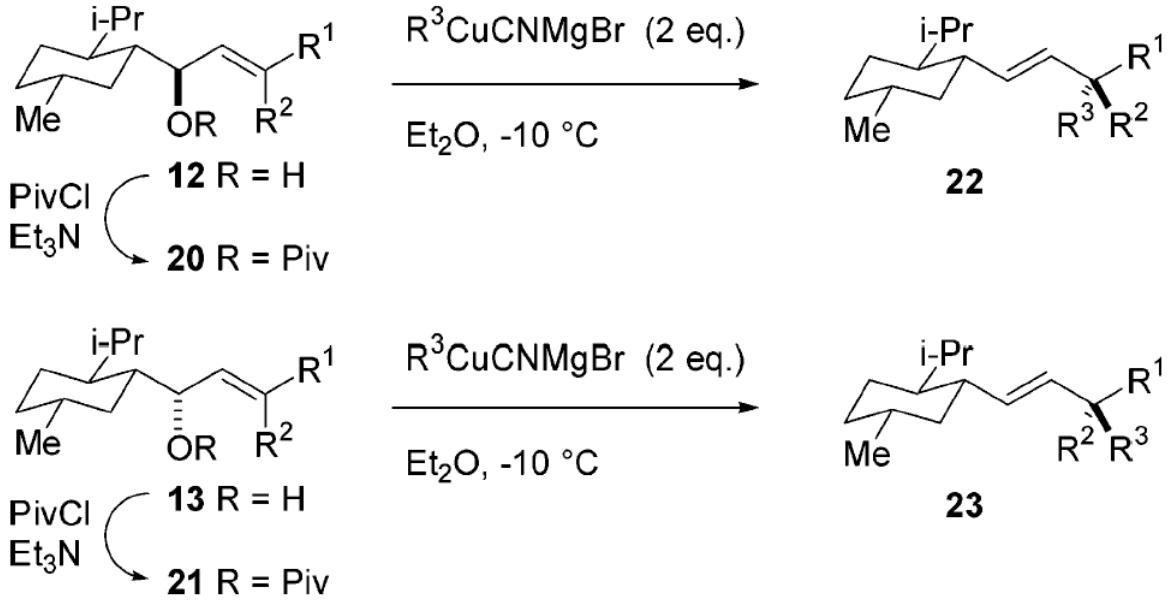
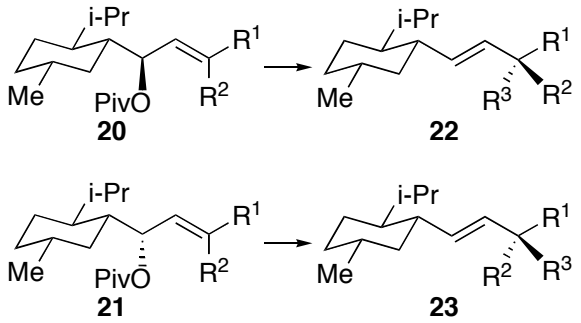


Table 3. Yields and Ratios of Cuprate Addition on Allylic Pivalate Esters **20** or **21**

entry	piv.[a]	R^1	R^2	R^3	maj. prd.	**22:23**[b] (% yield)[c]
1	**20a**	*n*-Bu	Me	*i*-Pr	**22b**	>98:2 (90)
2	**20a**	*n*-Bu	Me	Et	**22c**	>98:2 (98)
3	**20a**	*n*-Bu	Me	*n*-Hep	**22d**	>98:2 (97)
☞ 4	**20a**	*n*-Bu	Me	*t*-Bu or Ph		(0)
5	**20c**	*c*-C_6H_{11}	Me	*i*-Pr	**22e**	>98:2 (95)
6	**20d**	CH_2Ph	Me	*i*-Pr	**22f**	>98:2 (92)
7	**20d**	CH_2Ph	Me	$H_2C{=}CH(CH_2)_2$	**22g**	>98:2 (88)
8	**20d**	CH_2Ph	Me	$H_2C{=}CH(CH_2)_3$	**22h**	>98:2 (91)
9	**21r**[d]	CH_2OH	Me	*i*-Pr	**23i**	>99:1 (98)
10	**21s**[e]	CH_2OSEM	Me	*i*-Pr	**23j**	>99:1 (57)
11	**21t**[e]	CH_2OBn	Me	*i*-Pr	**23k**	>99:1 (8)
☞ 12	**21p**	CH_2OTBS	Me	*i*-Pr		(0)
13	**20p**	CH_2OTBS	Me	$H_2C{=}CH(CH_2)_2$	**22l**	>99:1 (80)
14	**20f**	$(CH_2)_3OTBS$	Me	*i*-Pr	**22m**	>98:2 (95)
15	**20f**	$(CH_2)_3OTBS$	Me	Et	**22n**	>98:2 (89)
16	**20f**	$(CH_2)_3OTBS$	Me	$H_2C{=}CH(CH_2)_2$	**22o**	>98:2 (82)
17	**20g**	$(CH_2)_4OTBS$	Me	$H_2C{=}CH(CH_2)_2$	**22p**	>98:2 (41)
☞ 18	**20h**	Ph	Me	*i*-Pr	**22q**	91:1 (90)
19	**20n**	Ph	CH_2OH	*i*-Pr	**22r**	>99:1 (73)
20	**20o**	*m*-MeO-Ph	CH_2OH	Et	**22s**	>99:1 (86)
☞ 21	**21m**	*t*-Bu	CH_2OH	*i*-Pr or Et		(0)
22	**21n**	Ph	CH_2OH	*i*-Pr	**23r**	>1:99 (77)
23	**21o**	*m*-MeO-Ph	CH_2OH	Et	**23s**	>1:99 (64)

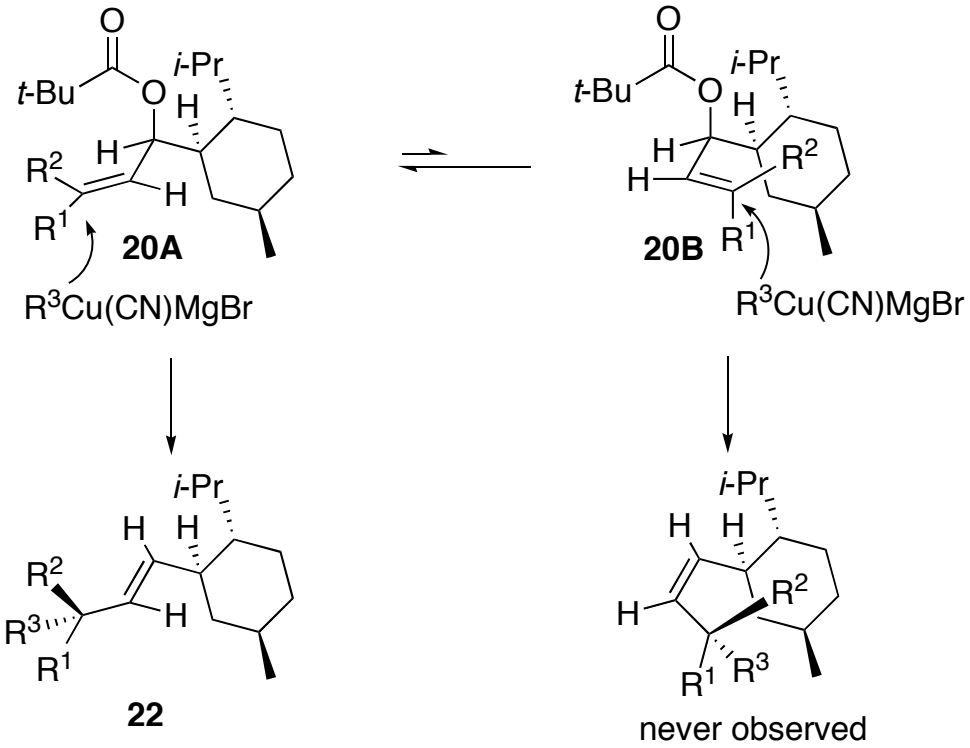
[a] For clarity, the pivalates bear the same letter as the alcohol they were formed from. [b] All ratios measured by G. C., HPLC, or NMR of the crude mixtures. [c] Isolated yields. [d] Obtained from the deprotection of **21p**. [e] Obtained from the protection of **21r**.



Conclusions:

1. It's General for primary or secondary alkylcuprates.
2. The same level of chirality transfer for **20** and **21** observed.
3. Bulky or less-reactive cuprates didn't work.
4. Bulky substituent should preferably be part of the allylic alcohol.
5. There is no reaction when both R^1 and R^3 are bulky.

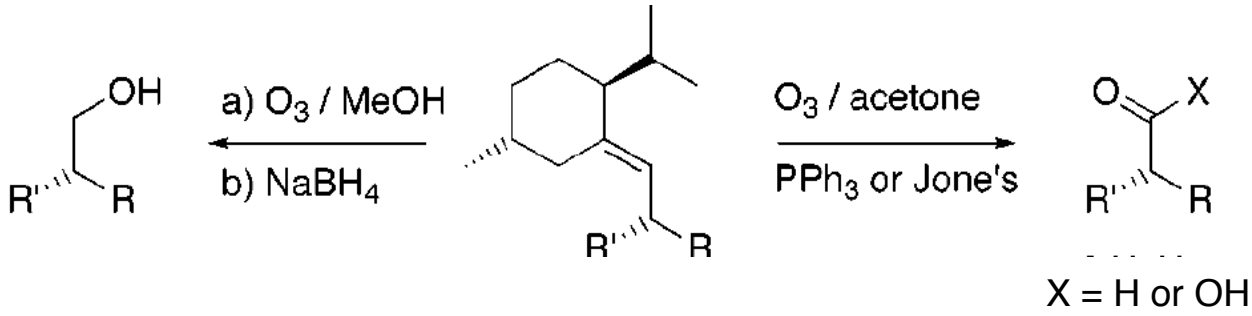
Conformational Biases of Pivalates 20



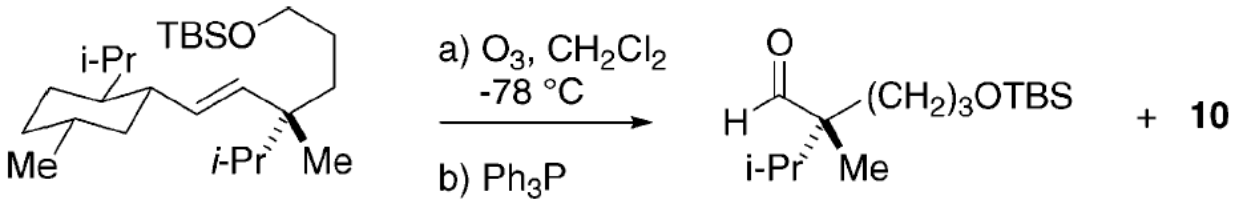
The controling elements in the transfer of chirality are:

- The anti-stereospecificity of the cuprate addition on allylic systems
- The conformational bias of the allylic ester toward conformations **20A** provided by $A^{1,3}$-strain (Adducts with a **Z** double bond, resulting from addition to conformer **20B**, have never been observed.)

Cleavage of the Auxiliary

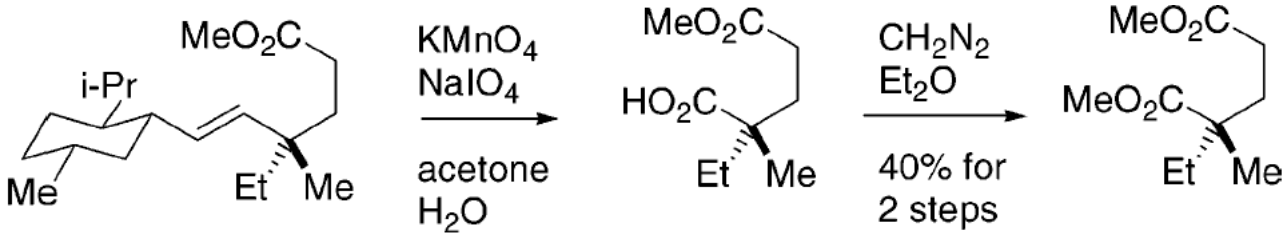


Example 1



22m **25**

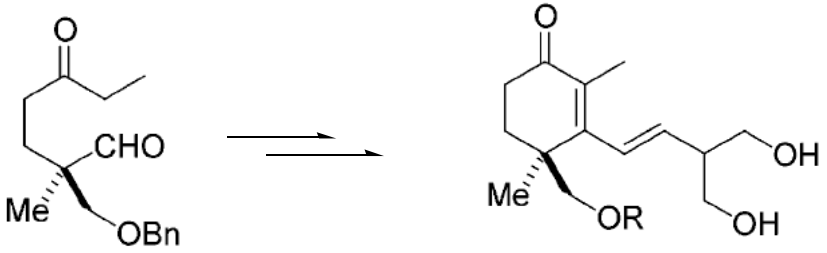
Example 2



26 **27** **28**

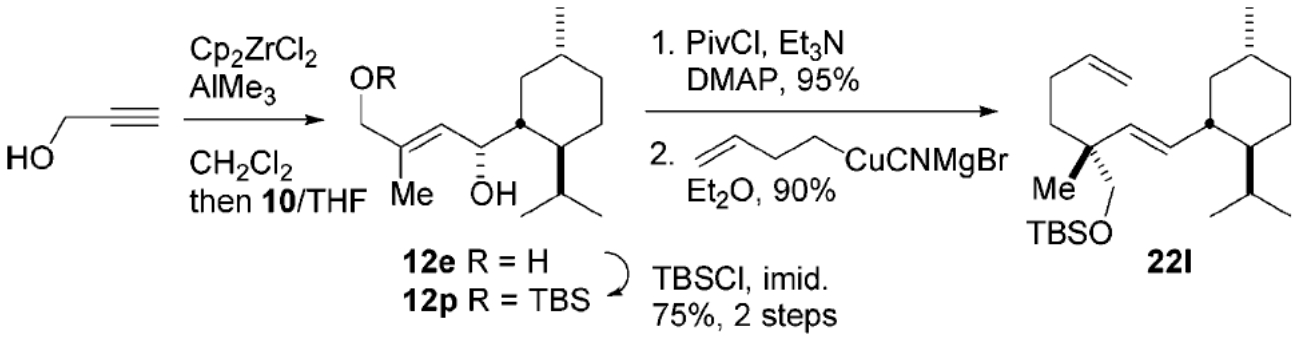
Spino, C.; Beaulieu, C.; Lafreniere, J. *J. Org. Chem.* **2000**, *65.* 7091.

Applications - Synthesis of an Analog of Taber's Intermediate 31

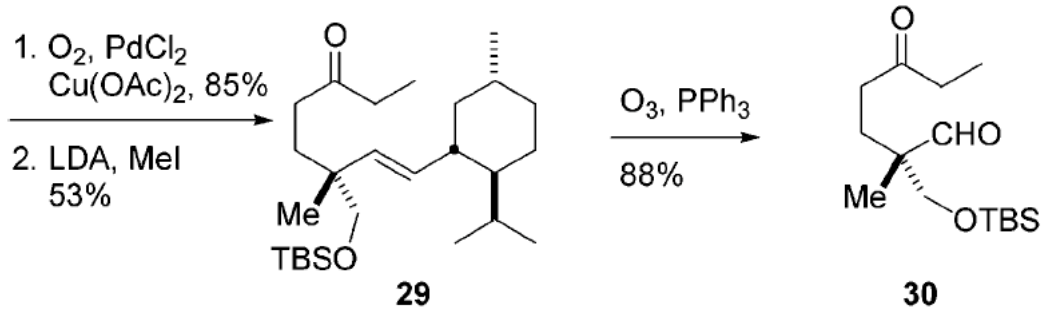


31

(+)-Cassioside 32a, R = Glu (Antiulcer agent, isolated in 1988.)
(+)-Cassiol 32b, R = H



22l

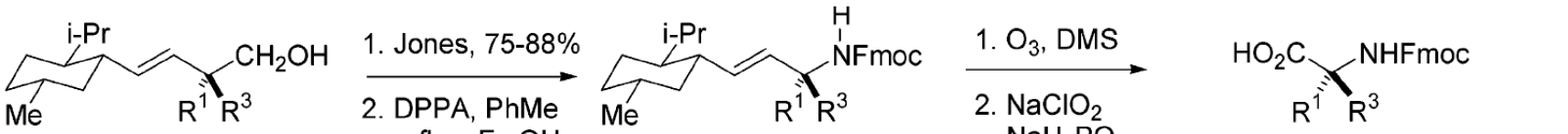


29 **30**

Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

Applications - Synthesis of α,α-Dialkylated Amino Acid

Route A:

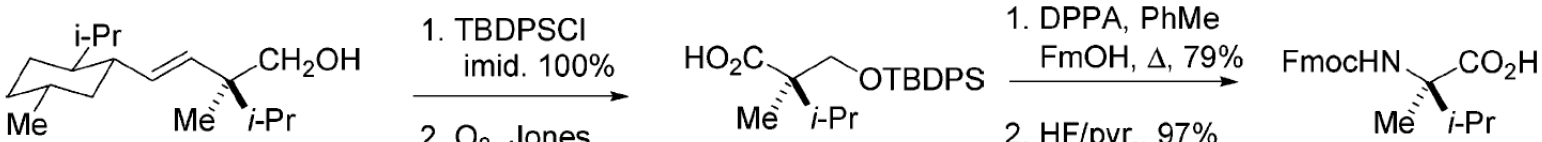


23i R^1=Me, R^3=*i*-Pr
23r R^1=Ph, R^3=*i*-Pr
23s R^1=*m*-MeOPh, R^3=Et

33a R^1=Me, R^3=*i*-Pr
33b R^1=Ph, R^3=*i*-Pr
33c R^1=*m*-MeOPh, R^3=Et

(*S*)-**34a** R^1=Me, R^3=*i*-Pr
(*R*)-**34b** R^1=Ph, R^3=*i*-Pr
(*R*)-**34c** R^1=*m*-MeOPh, R^3=Et

Route B: (Stereodivergent)



23i

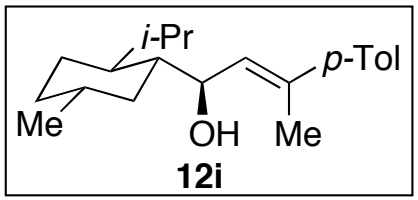
35

(*R*)-**34a**

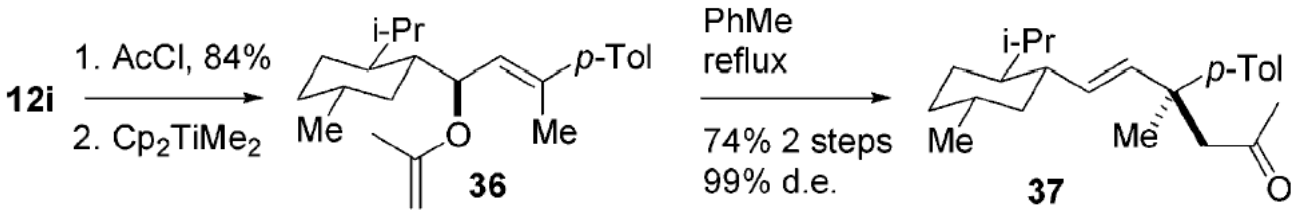
Spino, C.; Godbout, C. *J. Am. Chem. Soc.* **2003**, *125.* 12106.

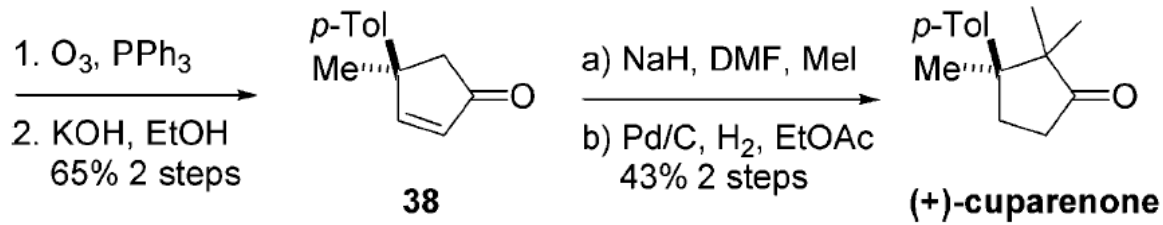
Applications - Claisen Rearrangement

- Synthesis of (+)-Cuparenone



12i



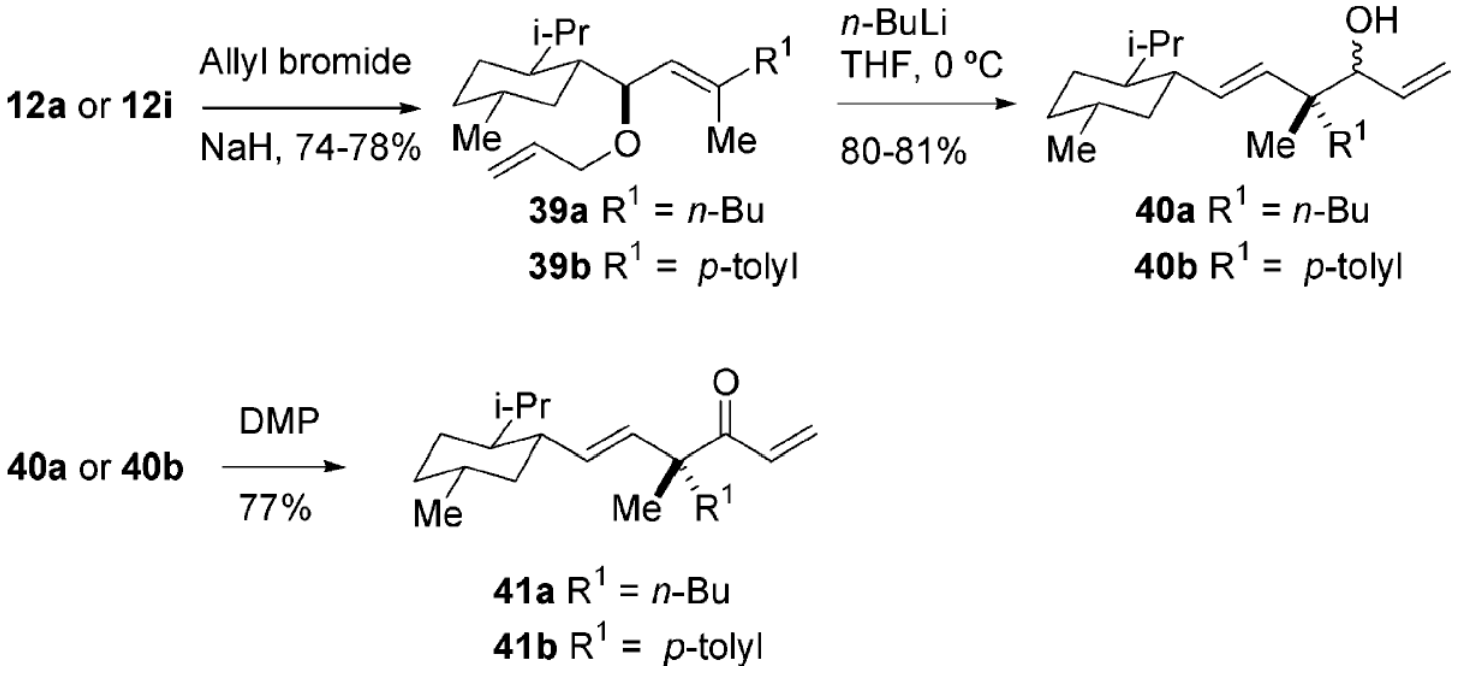


(+)-cuparenone

Antitumor effect

Isolated in 1976

Applications - [2,3] Wittig Rearrangement



Conclusion - Versatile Methodologies