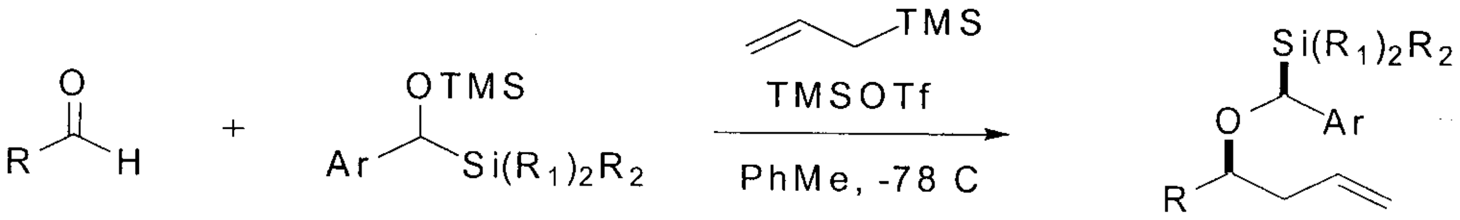
Synthesis of Optically Pure Arylsilylcarbinols and Their Use as Chiral Auxiliaries in Oxacarbenium Ion Reactions

Rychnovsky, S.D.; Huckins, J.R. *J. Org. Chem.* **2003**, ASAP



Current Literature

James Mignone

December 20, 2003

Introduction

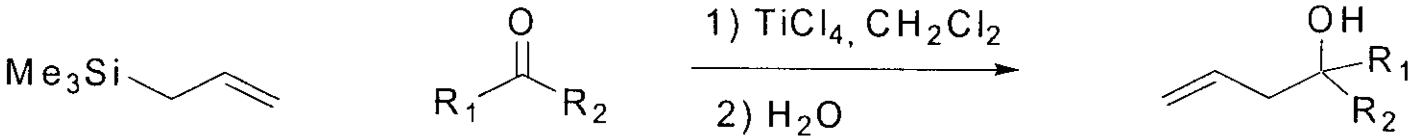
- Oxacarbenium ions are important intermediates in a variety of synthetic transformations including Prins cyclizations and many nucleophilic addition reactions which form new C-C bonds.

- Oxacarbenium ions are generated in the presence of Lewis acids but are not covalently bound to the Lewis acid – controlling enantiofacial addition via a chiral, catalytic Lewis acid is not feasible, so a chiral auxiliary is needed.

- Rychnovsky set out to develop a chiral auxiliary that:
  (a) promotes nucleophilic addition to one diastereotopic face
  (b) both enantiomers would be accessible
  (c) easily incorporated into oxacarbenium ion intermediates

Synthesis of α,β-Unsaturated Alcohols from Allysilanes and Carbonyl Compounds Using $TiCl_4$

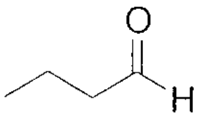
The Hosomi-Sakurai Reaction:



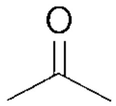
(1) Aliphatic, cyclic, and aromatic carbonyl compounds have been used

(2) Regiospecific transposition occurs in the allylic part

(3) Less satisfactory yields obtained with $AlCl_3$, $SnCl_3$, BF_3-OEt_2



(87%)



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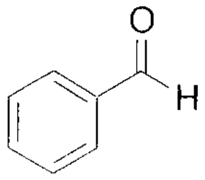
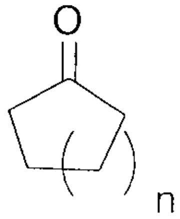


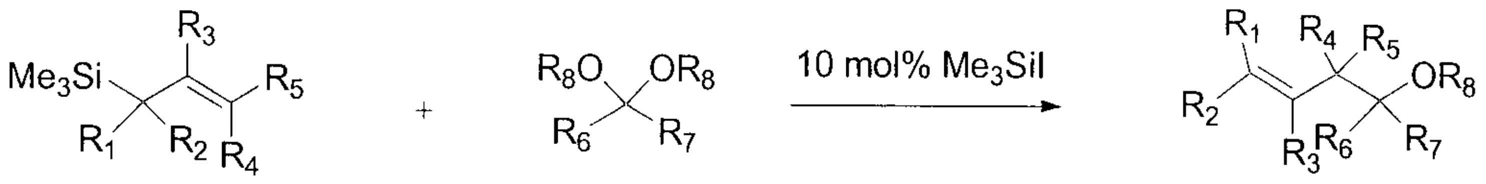
(58%)



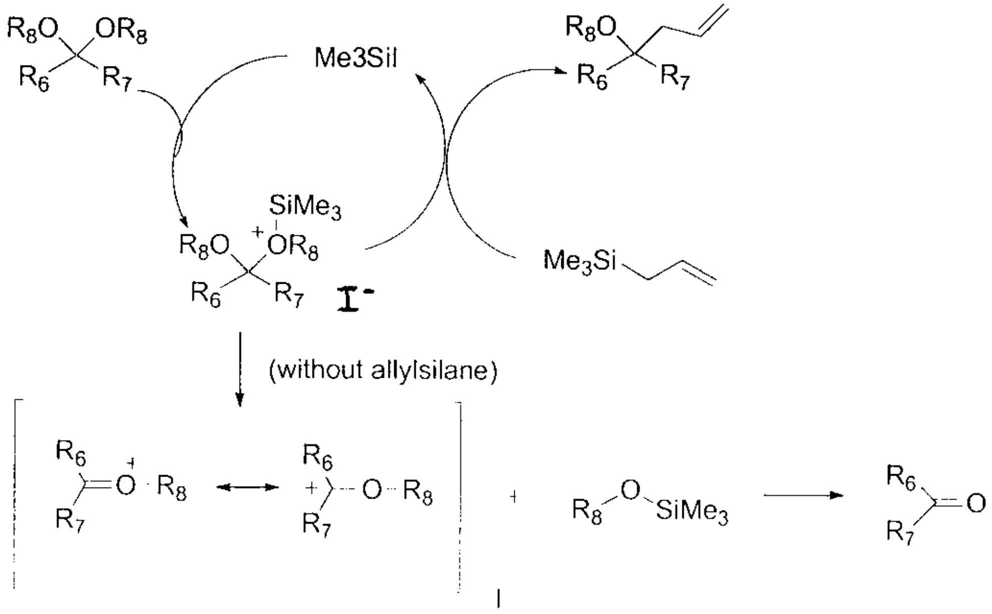
n=0 ; 44%
n=1 ; 70%

Sakurai, H.; Hosomi, A. *Tetrahedron Lett.* **1976**, *16*, 1295-1298

Me_3SiI Catalyzed Allylation of Acetals: Synthesis of Homoallylethers

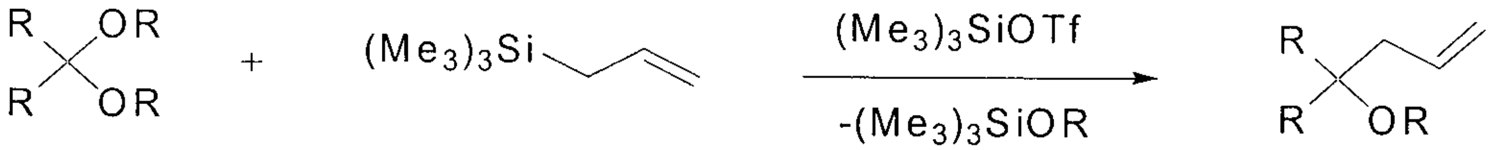


Catalytic Cycle of the Allylation

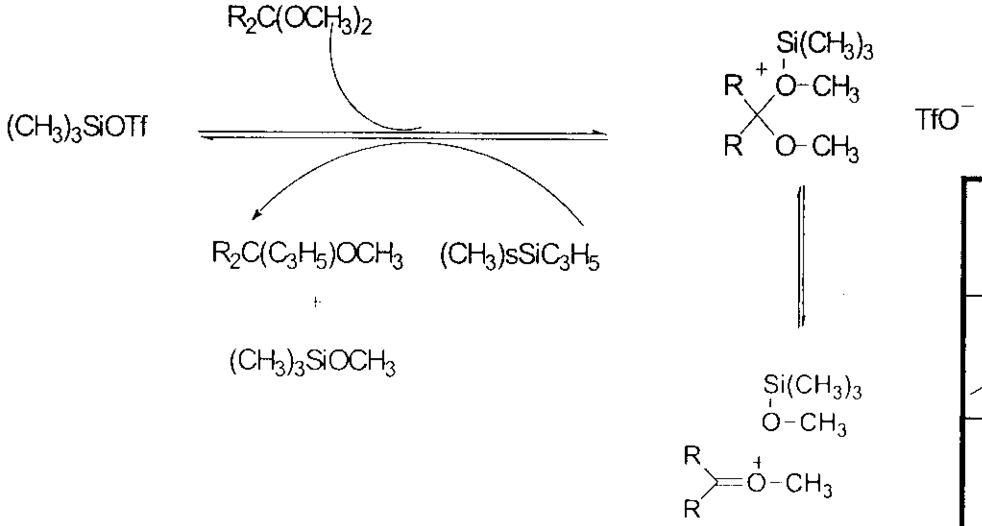


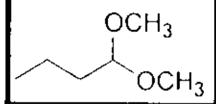
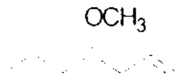
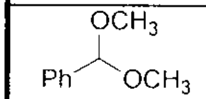
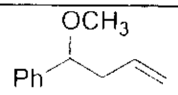
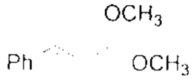
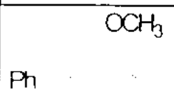
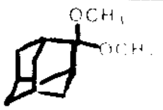
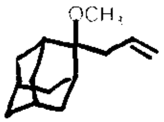
Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745-748

Noyori's Elaboration of Sakurai's Results



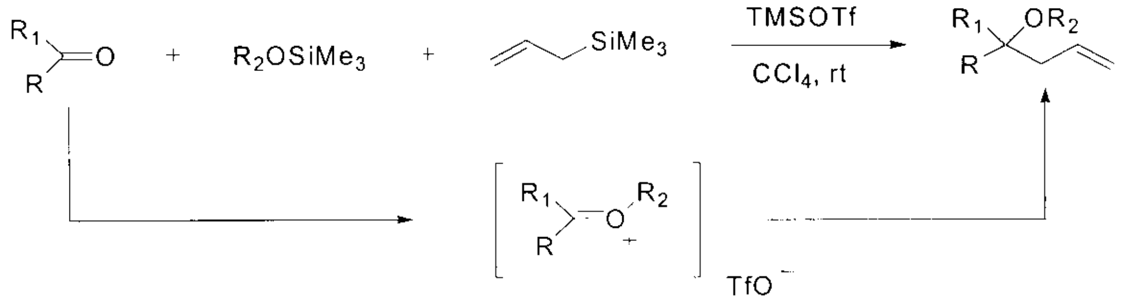
Proposed Mechanism:



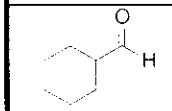
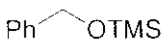
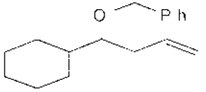
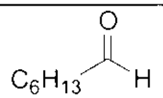
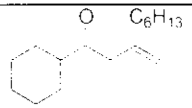
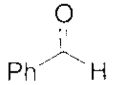
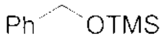
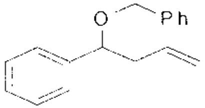
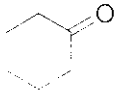
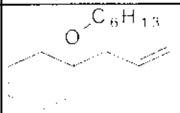
Acetal	mol % TMSOTf	Product	% Yield
	10		95
	10		90
	10		98
	10		78

Noyori, R.; et. al. *Tetrahedron Lett.* **1980**, 21, 71-74

The One-Pot Silyl Modified Sakurai (SMS) Reaction



"Catalytic, one-step, formation of homoallylic ethers from carbonyl compounds"

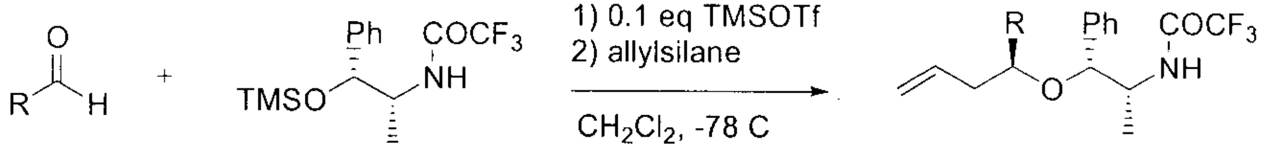
Substrate	Reagent	Product	Yield
			89
	$C_6H_{13}OTMS$		62
			92
	$C_6H_{13}OTMS$		68

-Success is independent of silyl ether but reaction does not proceed without it.

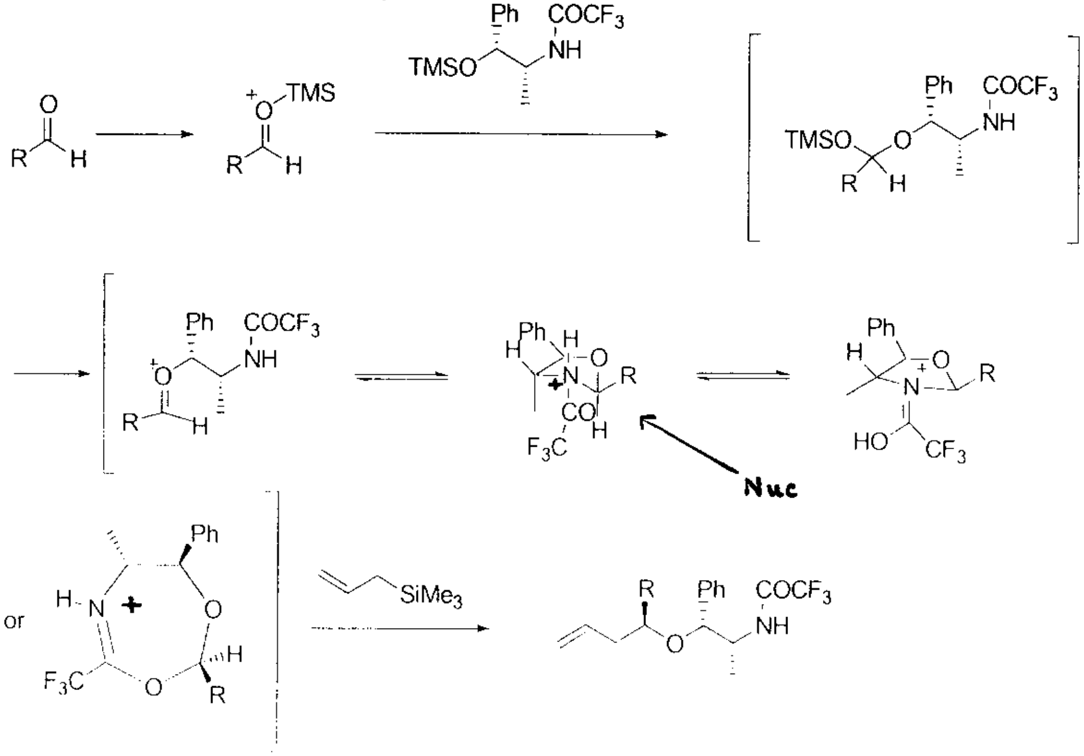
- Chiral silyl ethers were also explored.

Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1991**, *32*, 4779-4782

Enantiopure Homoallylic Ethers by Diastereoselective Allylation of Aldehydes Using N-trifluoroacetylnorpseudoephedrine

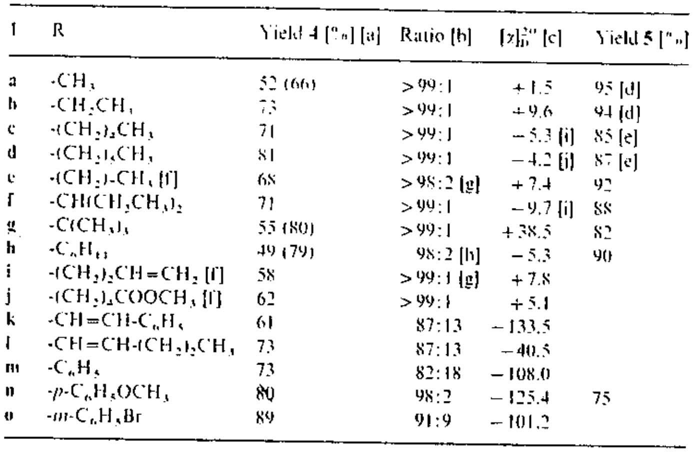


Proposed Mechanism:



Tietze, L.F.; et.al. *Chem. Eur. J*, **1996**, *2*, 1164-1168

Enantiopure Homoallylic Ethers by Diastereoselective Allylation of Aldehydes Using N-trifluoroacetylnorpseudoephedrine

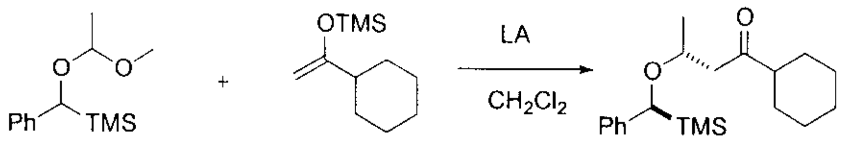


1	R	Yield 4 [%] [a]	Ratio [b]	$[\alpha]_D^{20}$ [c]	Yield 5 [%]
a	-CH$_3$	52 (66)	> 99:1	+ 1.5	95 [d]
b	-CH$_2$CH$_3$	73	> 99:1	+ 9.6	94 [d]
c	-(CH$_2$)$_2$CH$_3$	71	> 99:1	− 5.3 [i]	85 [e]
d	-(CH$_2$)$_4$CH$_3$	81	> 99:1	− 4.2 [i]	87 [e]
e	-(CH$_2$)-CH$_3$ [f]	68	> 98:2 [g]	+ 7.4	92
f	-CH(CH$_2$CH$_3$)$_2$	71	> 99:1	− 9.7 [i]	88
g	-C(CH$_3$)$_3$	55 (80)	> 99:1	+ 38.5	82
h	-C$_6$H$_{11}$	49 (79)	98:2 [h]	− 5.3	90
i	-(CH$_2$)$_2$CH=CH$_2$ [f]	58	> 99:1 [g]	+ 7.8	
j	-(CH$_2$)$_4$COOCH$_3$ [f]	62	> 99:1	+ 5.1	
k	-CH=CH-C$_6$H$_5$	61	87:13	− 133.5	
l	-CH=CH-(CH$_2$)$_2$CH$_3$	73	87:13	− 40.5	
m	-C$_6$H$_5$	73	82:18	− 108.0	
n	-*p*-C$_6$H$_4$OCH$_3$	80	98:2	− 125.4	75
o	-*m*-C$_6$H$_4$Br	89	91:9	− 101.2	

- Sterically hindered aldehydes can be allylated but reactions do not always go to completion.
- Due to stabilization of the oxonium ion intermediate, lower selectivity is observed for α,β-unsaturated and aromatic compounds.

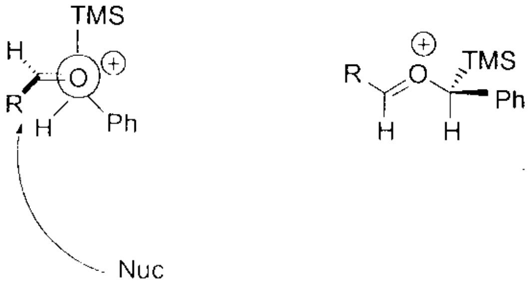
Tietze, L.F.; et.al. *Chem. Eur. J*, **1996**, *2*, 1164-1168

Stereoselective Nucleophilic Addition to Acyclic Acetals: The Linderman Model



Entry	Lewis Acid	Selectivity	Yield
1	$SnCl_4$	11.6:1	83
2	$TiCl_4$	11.6:1	86
3	BF_3-OEt_2	11.3:1	72
4	Et_2AlCl_2	11.7:1	86
5	$EtAlCl_2$	11.1:1	73
6	$AlCl_3$	11.6:1	76
7	TMSOTf	12.5:1	70
8	Ti(O*i*Pr)$_4$		0

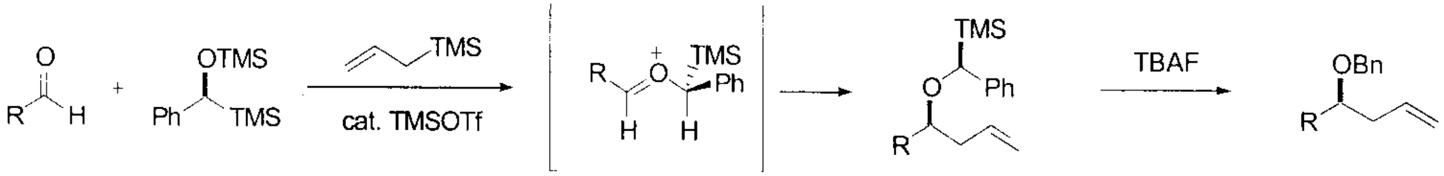
The Linderman Model

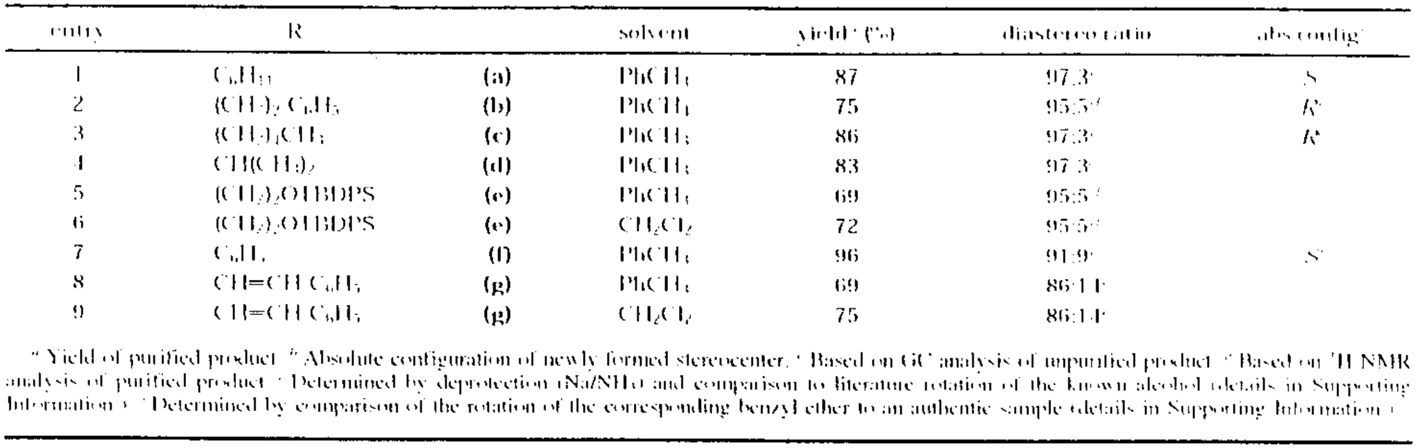


The α-silyloxocarbenium ion adopts a conformation that provides maximum overlap of σ C-Si and π C=O of the oxacarbenium ion.

Linderman, R.J.; Anklekar, T.V *J. Org. Chem.* **1992**, *57*, 5078-5080

Optically Pure α-(Trimethylsilyl)benzyl Alcohol via Oxocarbenium Ion Auxiliary





entry	R		solvent	yield[a] (%)	diastereo ratio	abs config[b]
1	C_6H_{11}	**(a)**	$PhCH_3$	87	97:3[c]	*S*[e]
2	$(CH_2)_2C_6H_5$	**(b)**	$PhCH_3$	75	95:5[d]	*R*[f]
3	$(CH_2)_4CH_3$	**(c)**	$PhCH_3$	86	97:3[c]	*R*[e]
4	$CH(CH_3)_2$	**(d)**	$PhCH_3$	83	97:3[c]	
5	$(CH_2)_2OTBDPS$	**(e)**	$PhCH_3$	69	95:5[d]	
6	$(CH_2)_2OTBDPS$	**(e)**	CH_2Cl_2	72	95:5[d]	
7	C_6H_5	**(f)**	$PhCH_3$	96	91:9[c]	*S*[f]
8	$CH{=}CH\,C_6H_5$	**(g)**	$PhCH_3$	69	86:14[c]	
9	$CH{=}CH\,C_6H_5$	**(g)**	CH_2Cl_2	75	86:14[c]	

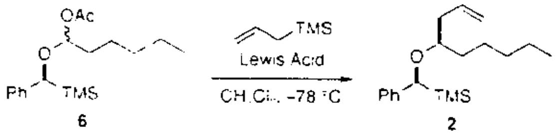
[a] Yield of purified product. [b] Absolute configuration of newly formed stereocenter. [c] Based on GC analysis of unpurified product. [d] Based on ^1H NMR analysis of purified product. [e] Determined by deprotection (Na/NH$_3$) and comparison to literature rotation of the known alcohol (details in Supporting Information). [f] Determined by comparison of the rotation of the corresponding benzyl ether to an authentic sample (details in Supporting Information).

- α-(trimethylsilyl)benzyl alcohol auxiliary leads to high levels of diastereoselectivity , especially when used with alkyl oxocarbenium ions

- Observed selectivities were explained via the Linderman model

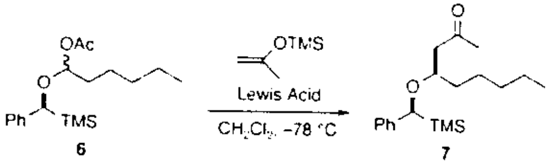
Rychnovsky, S.D.; Cossrow, J. *Org. Lett.* 2002, *4*, 147-150

Diastereoselective Additions of Nucleophiles to α-Acetoxy Ethers Using the α-(Trimethylsilyl)benzyl Auxiliary



entry[a]	Lewis acid (equiv)	yield (%)[b]	dr[c]
1	TMSOTf (0.2)	87	47:1
2[e]	**TMSOTf (1.1)**	**93**	**44:1**
3[d]	TMSOTf (0.2)	83	65:1
4	TfOH (0.2)	97	28:1
5	$SnCl_4$ (1.1)	93	13:1
6	$BF_3 \cdot OEt_2$ (1.3)	67	8:1
7	$TiCl_4$ (1.3)	76	5:1

[a] With 1.1 equiv of nucleophile used. [b] Yield of purified product. [c] Determined by GC analysis of unpurified product. [d] Result for (S)-6 in toluene. [e] With 2 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) added.



entry[a]	Lewis acid (equiv)	yield (%)[b]	dr[c]
1	TMSOTf (0.1)	98	30:1
2	TMSOTf (1.1)	93	28:1
3[d]	TMSOTf (1.1)	69	67:1
4[e]	**TMSOTf (0.2)**	**95**	40:1
5	TfOH (0.2)	61	23:1
6	$SnCl_4$ (1.1)	100	13:1
7	$BF_3 \cdot OEt_2$ (1.1)	64	8:1
8	$TiCl_4$ (1.1)	90	4:1

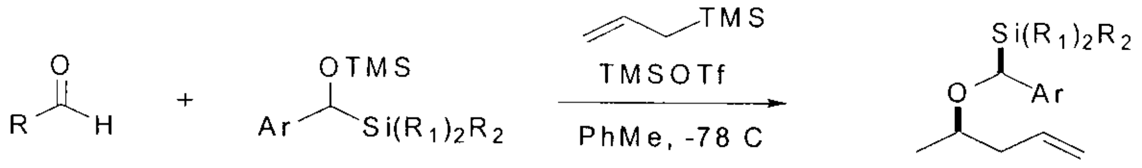
[a] With 1.1 equiv of nucleophile used. [b] Yield of purified product. [c] Determined by GC analysis of unpurified product. [d] Result for (S)-6 in toluene. [e] With 2 equiv of DBMP added.

Limitation:

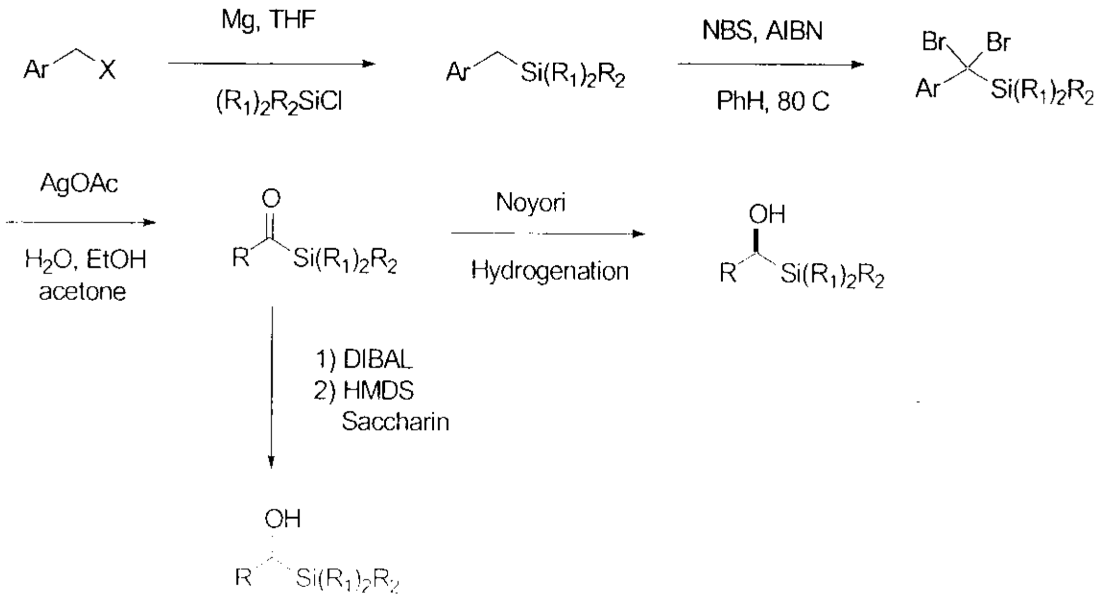
-Nucleophilic sp and sp^3 carbon atoms proceed in excellent yield but suffer from poor selectivity

Rychnovsky, S. D.; Cossrow, J. *Org. Lett.* 2003, 5, 2367-2370

Synthesis of Optically Pure Arylsilylcarbinols and Their Use as Chiral Auxiliaries in Oxacarbenium Ion Reactions

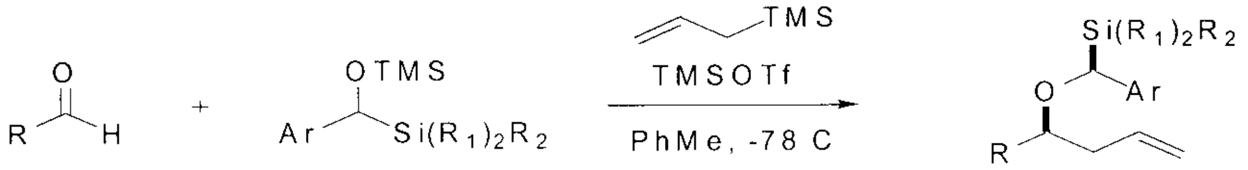


Preparation of Racemic and Chiral Auxiliaries:



Rychnovsky. S.D.: Huckins. J.R. *J. Org. Chem.* 2003, ASAP

Synthesis of Optically Pure Arylsilylcarbinols and Their Use as Chiral Auxiliaries in Oxacarbenium Ion Reactions



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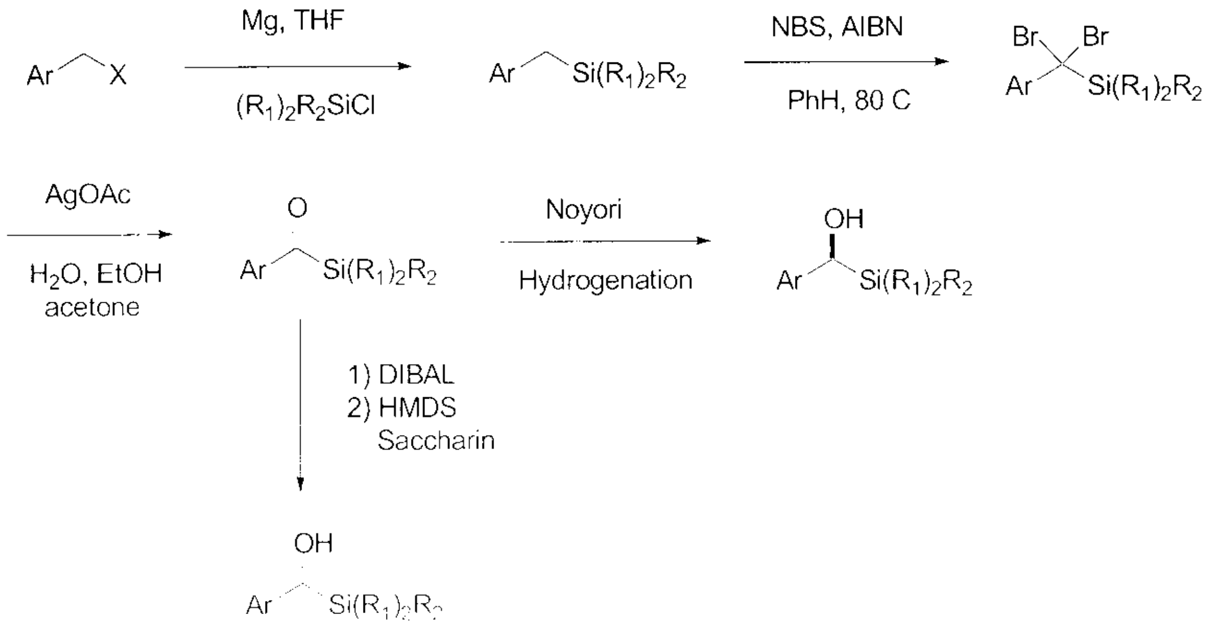
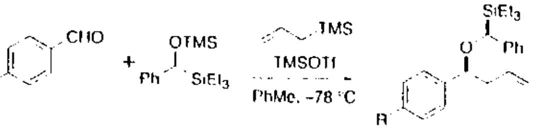


Rychnovsky, S.D.; Huckins, J.R. *J. Org. Chem.* **2003**, ASAP

Substrate Limitations

- Aliphatic aldehydes lead to very good yields and diastereoselectivities with the previous auxiliaries but the selectivities for aromatic aldehydes aren't as good.

- Rychnovsky believed that the aromatic ring stabilizes the oxacarbenium ion, reducing the selectivity.

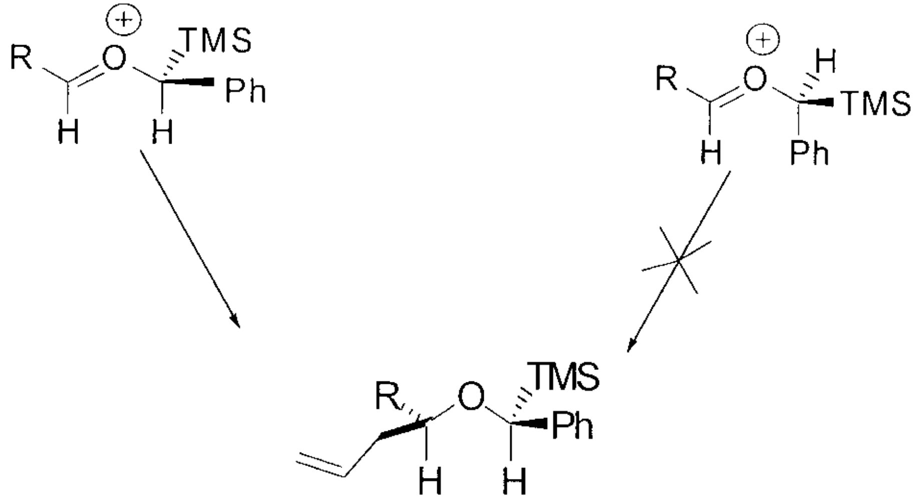


23 19a 24

entry	R	σ_p^+	yield (%)[a]	dr[b]
1	OMe	−0.648	60	11:1
2	F	−0.247	99	14:1
3	H	0.000	98	14:1
5	CN	0.674	76	22:1
6	NO_2	0.740	64[c]	19:1[c]

[a] Yield of the purified product. [b] dr based on the GC analysis of the crude product. The ratio is the average of the two experiments. [c] This reaction was very messy, and many side products were observed.

Rychnovsky, S.D.; Huckins, J.R. *J. Org. Chem.* 2003, ASAP



Linderman Model:
Si (front) attack

Oxacarbenium
Conformation:
Re (rear) attack

(Minimum energy at
B3LYP/6-31G*)

-The Linderman Model predicts the correct product for all auxiliaries but according to this model as the bulkiness of the Si-group increases so should the selectivity- this was not observed.

-The Linderman Model does not represent the realistic conformational minimum-energy. The Oxacarbenium conformation is at least 4 kcal/mol more stable, but this model predicts the wrong face of attack.

-Failure of the calculated model is due to the limitations of “ground state” analysis and a transition state analysis would be more appropriate.

Rychnovsky, S.D.; Huckins, J.R. *J. Org. Chem.* 2003, ASAP

Conclusion

- The synthetic utility of reactions involving oxacarbenium ion intermediates has prompted many groups to develop reactions that incorporate such intermediates.
- Rychnovsky has shown that α-trimethylsilyl benzyl is a practical chiral auxiliary for oxacarbenium ion reactions, yielding homoallylic ethers in good yield and high diastereoselectivity.
- The Linderman Model successfully predicts the selectivity in these reactions but the this model does not represent the minimum-energy conformation of the oxacarbenium intermediate.
- These reactions are currently being performed with carbon nucleophiles other than allyltrimethylsilane.