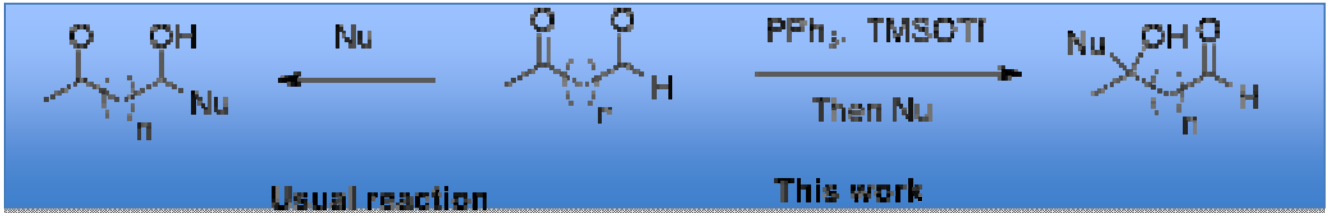
Reversing the reactivity of carbonyl functions via Phosphonium Salts: Enantioselective total synthesis of (+)-Centrolobine

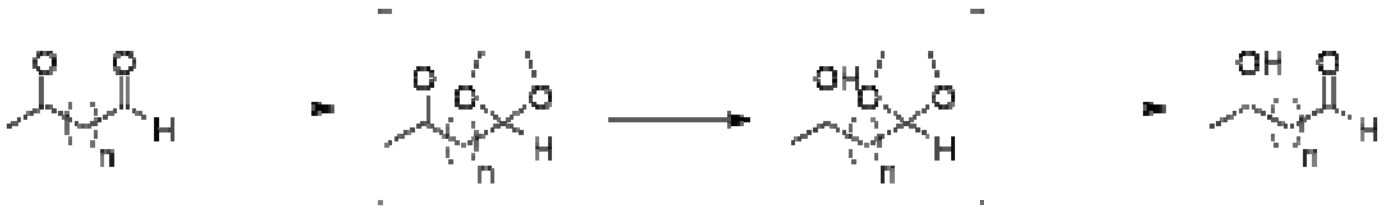
ACIE, **2011**, *50*, 1

TCR fabien



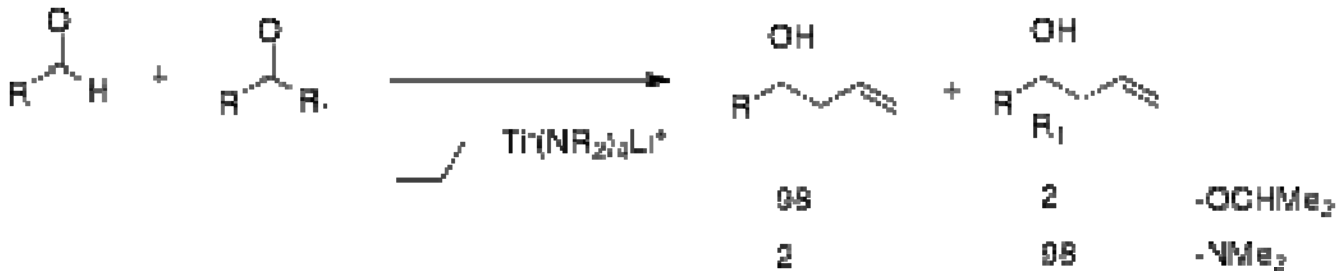
A bit of History……

Luche and Gemal[1]



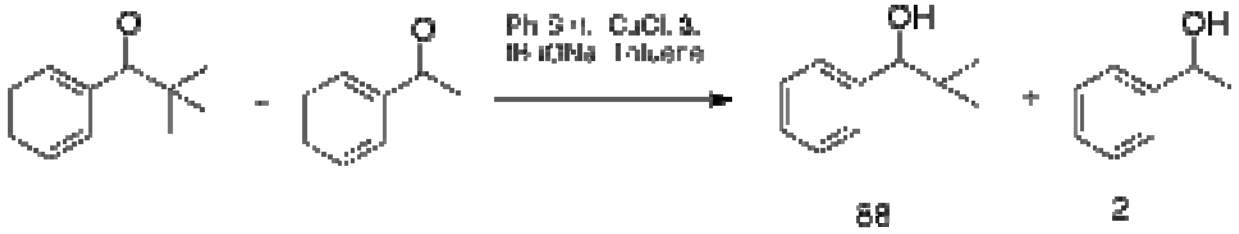
Non general
limit to reductions

Wenderoth *et al*[2]



Harsh conditions
Need to

Tsuji *et al*[3]



Concept

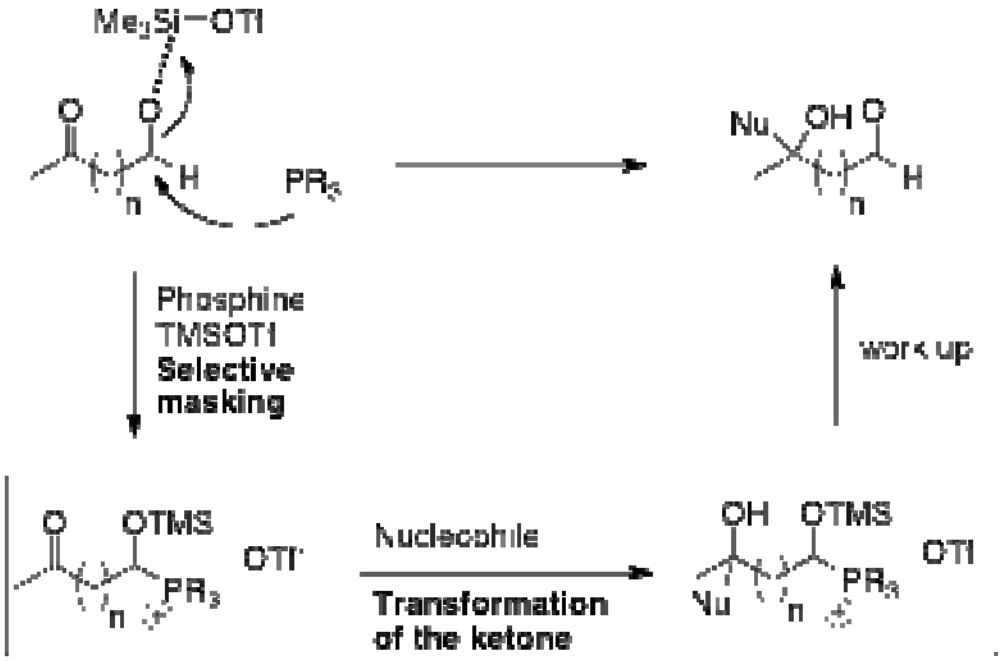
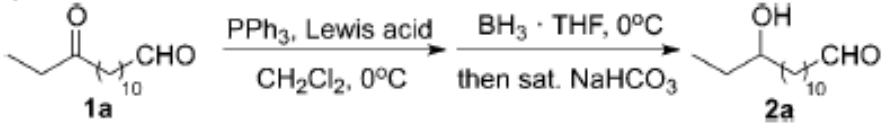

Me3Si—OTf
PR3
Phosphine
TMSOTf
Selective
masking
work up
OTMS
OTf
PR3
Nucleophile
Transformation
of the ketone
OH
OTMS
OTf
Nu
PR3

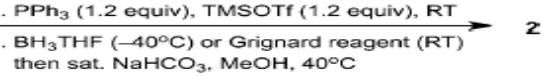
Table 1: Optimization of the reaction conditions.[a]



Entry	Lewis acid (equiv)	Equiv PPh_3	Equiv BH_3·THF	Yield [%][b]
1	TMSOTf (2.0)	3.0	4.0	90
2[c]	TESOTf (2.0)	3.0	4.0	86
3[c]	TBSOTf (2.0)	3.0	4.0	94
4	BF_3·Et_2O (2.0)	3.0	4.0	trace
5[d]	TMSOTf (1.2)	1.2	1.5	88
6[d,e]	TMSOTf (1.2)	1.2	1.5	96
7[f]	–	–	1.2	0

[a] Reaction conditions: **1a** was treated with PPh_3 and Lewis acid in CH_2Cl_2 (0.1 M) at 0 °C for 1 h. Then, BH_3·THF was added at 0 °C. After the reaction was completed, the mixture was treated with sat. $NaHCO_3$ (unless stated otherwise). [b] Yield of isolated product **2a**. [c] TBAF (3.0 equiv) was used for the work-up. [d] PPh_3 and TMSOTf were added at RT. [e] Reduction was performed at −40 °C. [f] Reaction was performed in the absence of Lewis acid and PPh_3. TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, THF = tetrahydrofuran.

Table 2: Selective one-pot transformation of carbonyl groups in the presence of aldehydes.[a]



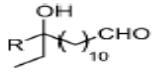
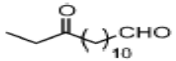
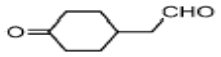
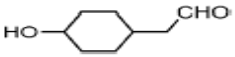
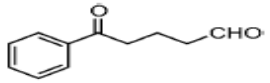
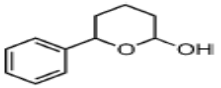
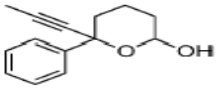
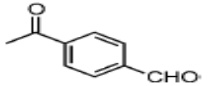
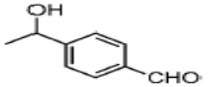
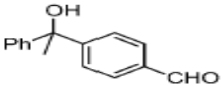
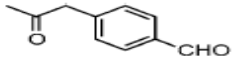
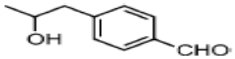
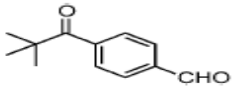
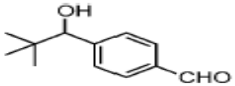
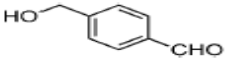
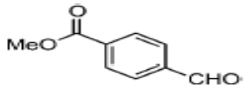
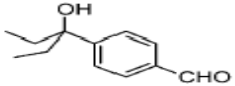
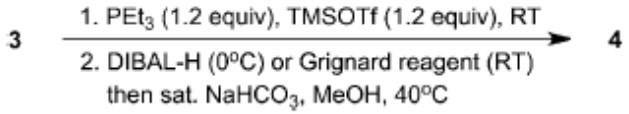
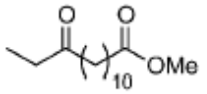
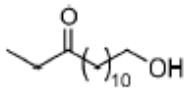
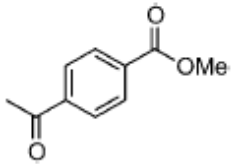
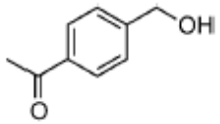
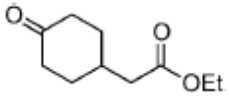
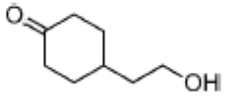
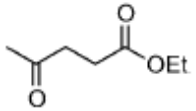
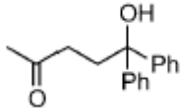
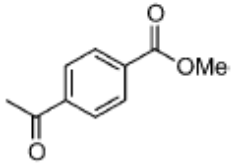
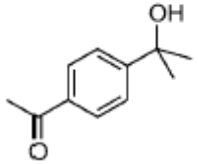
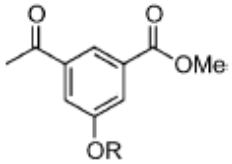
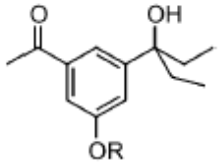
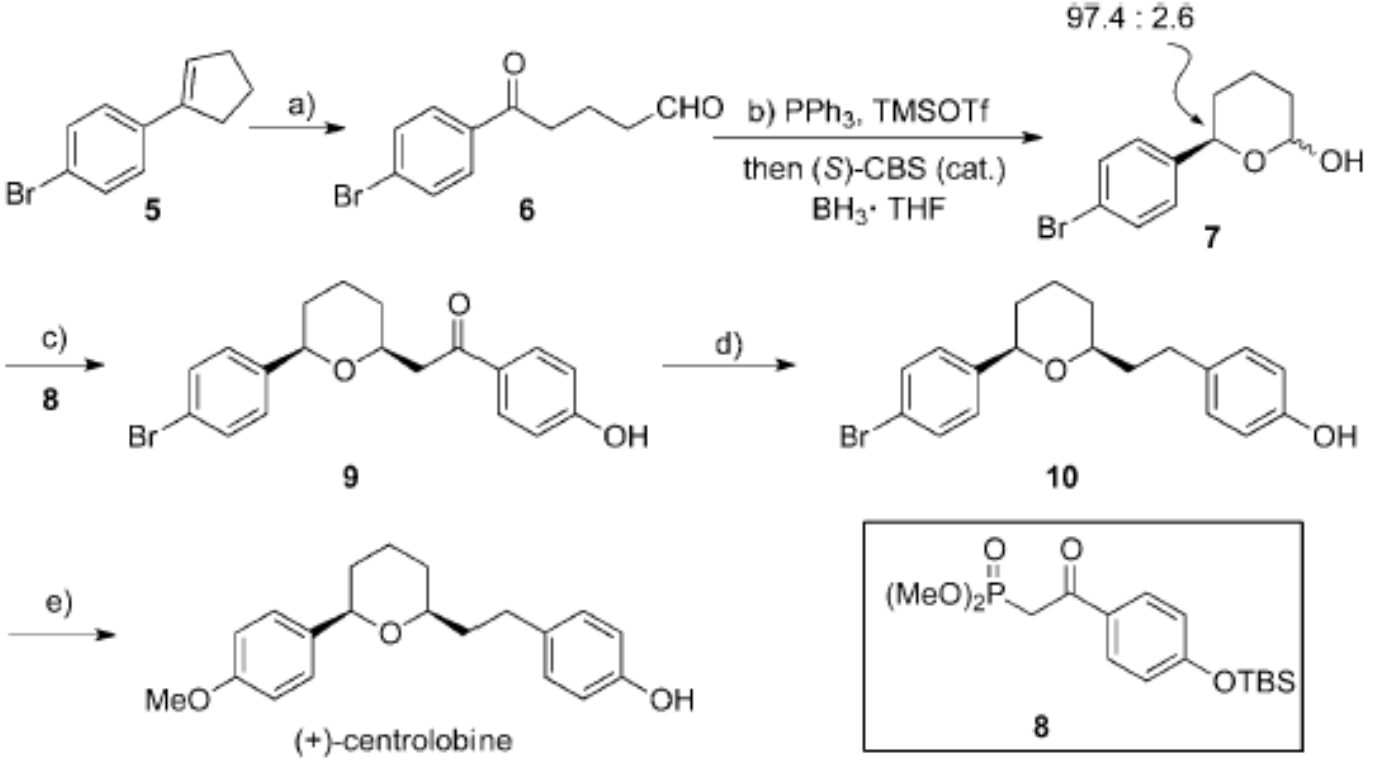
Entry	Substrate	Reagent (equiv)	Product	Yield [%][b]
				
1		BH_3·THF (1.5)	**2a** R = H	96
2		PhMgBr (3.0)	**2b** R = Ph	93
3	**1a** 	EtMgCl (1.5)	**2c** R = Et	87
4		allylMgBr (1.5)	**2d** R = allyl	75
5	**1b** 	BH_3·THF (1.5)	**2e** 	87
6	**1c** 	BH_3·THF (1.5)	**2f** 	89
7		 (3.0)	**2g** 	93
8	**1d** 	BH_3·THF (1.5)	**2h** 	96
9		PhMgBr (3.0)	**2i** 	85
10[c]	**1e** 	BH_3·THF (1.5)	**2j** 	87
11[d]	**1f** 	BH_3·THF (2.0)	**2k** 	74
12[e]		DIBAL-H (2.2)	**2l** 	80
13	**1g** 	EtMgCl (3.0)	**2m** 	76

Table 3: Selective one-pot transformation of esters in the presence of ketones.[a]



Entry	Substrate		Reagent (equiv)	Product		Yield [%][b]
1	**3a**		DIBAL-H (3.0)	**4a**		82
2	**3b**		DIBAL-H (3.0)	**4b**		93
3	**3c**		DIBAL-H (3.0)	**4c**		76
4	**3d**		PhMgBr (4.0)	**4d**		76
5	**3b**		MeMgBr (3.0)	**4e**		83
						
6	**3e**	R = MOM	EtMgCl (3.0)	**4f**	R = MOM	80
7	**3f**	R = TBS	EtMgCl (3.0)	**4g**	R = TBS	74

Total synthesis of (+)-Centrolobine



Scheme 3. Asymmetric synthesis of (+)-centrolobine. a) O_3, CH_2Cl_2, −78 °C; PPh_3, 99%; b) PPh_3, TMSOTf, CH_2Cl_2, RT; (*S*)-CBS (30 mol%), BH_3·THF, −40 °C, then aq sat. $NaHCO_3$/MeOH, 40 °C, 81%; c) **8**, LiOMe, MeOH, 0 °C→RT, 99%; d) $LiBH_4$, Et_2O, 0 °C; Et_3SiH, TFA, 0 °C→RT, 96%; e) CuI, NaOMe, DMF, 100 °C, 99%. DMF = *N*,*N*-dimethylformamide, TFA = trifluoroacetic acid.

Reference:

[1] J.L. luche, A. L. Gemal. *J. Am. Chem. Soc.* **1979**, *101*, 5848
[2] M. T. Reetz, B. Wenderoth, *Tetrahedron Lett.* **1982**, *23*, 5259
[3] T. Fujihara, Y. Tsuji, *Angew. Chem. Int. Ed*, **2010**, *49*, 1472