

Léon Ghosez

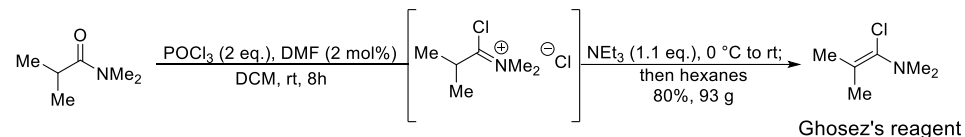
- Born: Belgium, 1934
- PhD: University of Louvain, Prof. G. Smets, 1958
- Postdoc: Harvard University, R.B. Woodward, 1960
- Currently a visiting scientist at the European Institute of Chemistry and Biology (IECB) and Prof. Emeritus at University of Louvain



<http://www.iecb.u-bordeaux.fr/index.php/fr/equipes/organic-a-medicinal-chemistry>

Ghosez's reagent (tetramethyl- α -chloroenamine, TMCE)

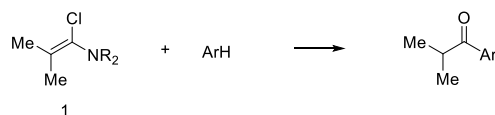
- Moisture-sensitive, colorless liquid
- Purified by distillation
- Readily converted to bromo, iodo, fluoro, and cyano analogs
- Sigma-Aldrich: \$183.00 for 5 mL



- Alternatively can be prepared using phosgene

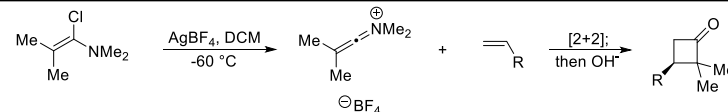
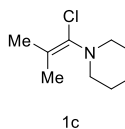
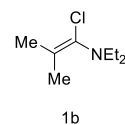
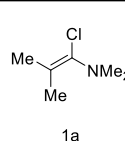
Ghosez, L et al. (2001). 1-Chloro-N,N,2-trimethylpropenylamine†. In Encyclopedia of Reagents for Organic Synthesis, (Ed.). <https://doi.org/10.1002/047084289X.rc155m>

Ghosez, 1972

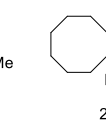
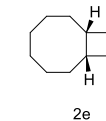
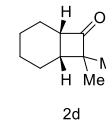
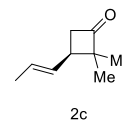
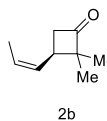
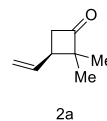


ArH	1	Yield (%)	Product
furan	1a	83	2-isobutrylfuran
furan	1b	85	2-isobutrylfuran
furan	1c	85	2-isobutrylfuran
pyrrole	1a	94	2-isobutrylpyrrole
pyrrole	1b	94	2-isobutrylpyrrole
pyrrole	1c	94	2-isobutrylpyrrole
N,N-dimethylaniline	1a	89	p-N,N-dimethylaminoisobutyrophenone
anisole	1a	0	n.p.
phenol	1a	0	n.p.

- No reaction with anisole; with phenol, exclusively aminoalkenylation at oxygen is observed
- No need for acid catalysis



ArH	Yield (iminium, %)	Yield (ketone, %)	Product
butadiene	84	86	2a
cis-piperylene	85	93	2b
trans-piperylene	82	89	2c
cyclohexene	83	89	2d
cis-cyclooctene	86	88	2e
trans-cyclooctene	85	87	2f

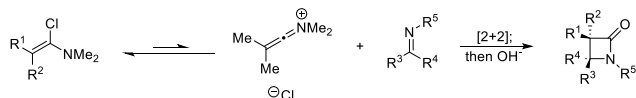


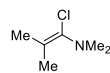




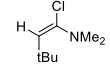

- Keteneiminium ions do not dimerize or polymerize like ketenes or keteneimines
- ZnCl₂ is a less expensive alternative to AgBF₄
- 1974: In presence of cis-fixed dienes: behaves as dienophile and reacts through C=N bond

- Ethylene: competent reaction partner at room temperature and atmospheric pressure
- More reactive than dimethylketene

of the week

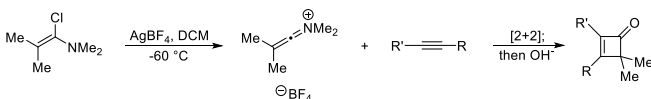
Ghosez, 1974



α -chloroamine	imine	Yield (iminium, %)	Yield (lactam, %)
		74	82
		47	68
		60	42
		65	70
		80	0

Angew. Chem. Int. Ed., **1974**, *13*, 267. <https://doi.org/10.1002/anie.197402672>

Ghosez, 1975

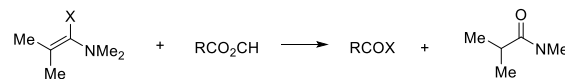


Acetylene	Lewis Acid	Yield (iminium, %)	Yield (ketone, %)
Ph—C≡C—Ph	AgBF ₄	82	90
Et—C≡C—Et	AgBF ₄	80	80
Et—C≡C—Et	ZnCl ₂	100	95
Me—C≡C—Me	ZnCl ₂	56	100
H—C≡C—H	AgBF ₄	77	0
H—C≡C—H	ZnCl ₂	80	0
H—C≡C—Me	AgBF ₄	80	0
H—C≡C—tBu	AgBF ₄	70	0

- For nonsymmetric acetylenes, the major product is the 3-subst. cyclobutenylideneiminium salt
- Acetylene and monosubst. acetylenes give ring-opened products upon hydrolysis

Angew. Chem. Int. Ed., **1975**, *14*, 569. <https://doi.org/10.1002/anie.197505691>

Ghosez, 1979

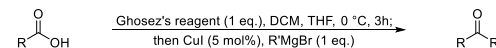


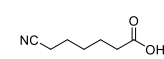

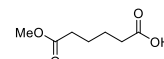

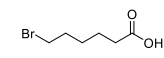

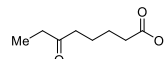

R	X	Yield (%)	R	X	Yield (%)
Cl ₃ C	Cl	100	Cl ₃ C	F	100
tBu	Cl	100	tBu	F	100
CH ₂ =CH-	Cl	96	Ph	F	100
1,3-dithiolan-2-yl	Cl	100	Cl ₂ CH	F	98
N ₂ CH	Cl	100	MeCH=C(Me)	F	97
(MeO) ₂ CH	Cl	94	H	F	100
HCO	Cl	96	tBu	Br	100
MeCO	Cl	100	CH ₂ =CH	Br	100
PhCO	Cl	80	H	Br	100
pyrrol-2-yl	Cl	100	Me	I	100
furan-2-yl	Cl	100	Ph	I	100
H	Cl	94	tBu	I	100
			H	I	100

- Mild acidity and absence of racemization lends well to peptide synthesis
- Excellent yields, unreactive isobutyramide byproduct obviates the need for purification

J. Chem Soc., Chem. Commun., **1979**, 1180 <https://doi.org/10.1039/C39790001180>

Fujisawa, 1983

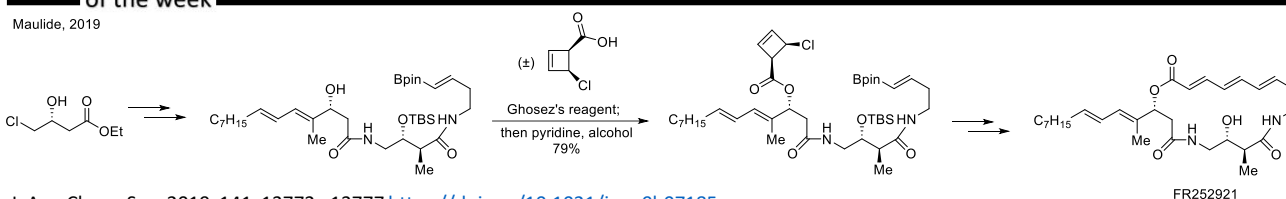


Carboxylic Acid	Grignard Reagent	Yield (%)	Carboxylic Acid	Grignard Reagent	Yield (%)
	PhCH ₂ CH ₂ MgBr	88		PhCH ₂ CH ₂ MgBr	80
	PhCH ₂ CH ₂ MgBr	82		PhCH ₂ CH ₂ MgBr	83
	PhCH ₂ CH ₂ MgBr	87		PhCH ₂ CH ₂ MgBr	83
	PhCH ₂ CH ₂ MgBr	80		EtMgBr	80

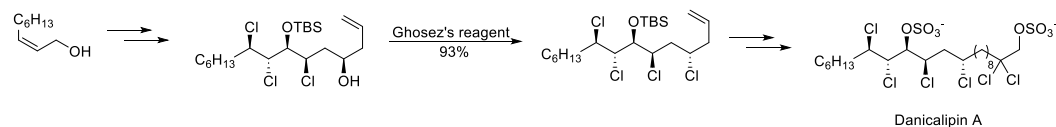
- Equimolar Grignard reagents to carboxylic acids, high chemoselectivity, one-pot operation

Chem. Lett., **1983**, *12*, 11, 1791. <https://doi.org/10.1246/cl.1983.1791>

Maulide, 2019



Carreira, 2015



Summary

- In synthesis, Ghosez's reagent often sees use in the middle to late stages due to exceedingly mild reaction conditions, where conventional reagents and their byproducts would promote undesired reactivity
- Some of the more unique chemistry of TMCE is underrepresented in synthesis
- However, the chemistry of α -haloenamines largely is well explored

Miscellaneous reactivity not covered:

- Diastereoselective keteneiminium [2+2] cycloadditions
- Coupling of allylic alcohols with organometallic compounds (Grignard reagents)
- Coupling of allylic alcohols with lithium enolates of dithioesters
- Aminoazirine synthesis from sodium azide
- Invertive halogenation of phosphorothioic acid & phosphorus oxyacids

Reviews and Lectures

- α -Chloroenamines: New Reagents for Organic Synthesis
<https://doi.org/10.1002/anie.197208522>
- 1-Chloro-N,N,2-trimethylpropenylamine†
<https://doi.org/10.1002/047084289X.rc155m>
- Amide activation: an emerging tool for chemoselective synthesis
<https://doi.org/10.1039/C8CS00335A>

Chem. Soc. Rev., 2018, 47, 7899–7925 <https://doi.org/10.1039/C8CS00335A>

Chem. Lett., 1985, 14, 10, 1453–1456, <https://doi.org/10.1246/cl.1985.1453>

Angew. Chem., Int. Ed. Engl. 1972, 11, 852–853 <https://doi.org/10.1002/anie.197208522>

Tetrahedron Lett., 1982, 23, 999–1002 [https://doi.org/10.1016/S0040-4039\(00\)87004-5](https://doi.org/10.1016/S0040-4039(00)87004-5)

Synthesis 2005, 11, 1765–1770 <https://doi.org/10.1055/s-2005-865363>

Ghosez, L et al. (2001). 1-Chloro-N,N,2-trimethylpropenylamine†. In Encyclopedia of Reagents for Organic Synthesis, (Ed.). <https://doi.org/10.1002/047084289X.rc155m>