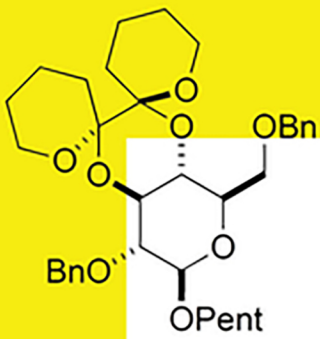
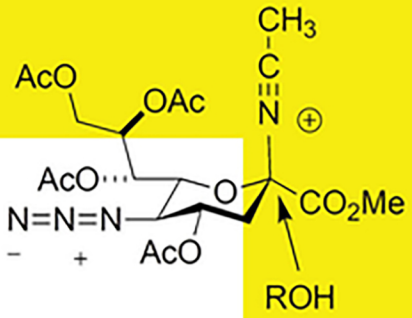




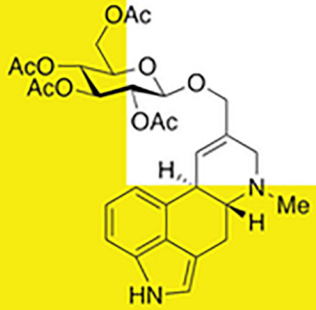
GREENE'S

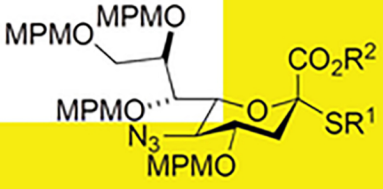
PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

Volumes 1–2

6th Edition

Peter G. M. Wuts





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GREENE'S PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

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Sixth Edition

VOLUME 1

PETER G. M. WUTS
Kalamazoo, Michigan, USA

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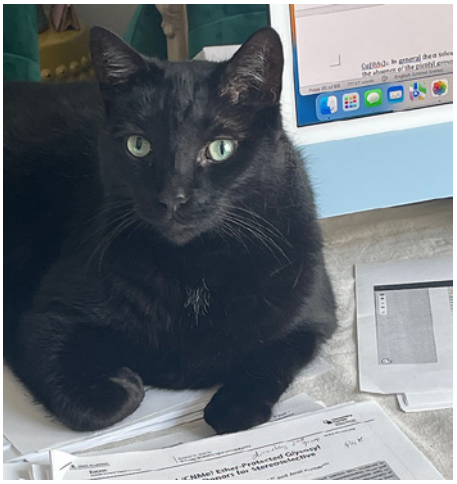
DEDICATION

This volume is dedicated to the memory of my loyal assistant Osiris Wuts.



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Volume 2

PREFACE

This edition has maintained the tradition of the previous five editions. The literature cutoff was the end of February 2024, which covers nearly 10 years since the last edition. I have processed over 4000 references of which a little over 3000 of these have been put in the new addition. I have been as all-inclusive as possible since this book is meant to provide as many options as possible for protection and deprotection.

Although there are numerous papers with titles like "Protecting group free synthesis of X," we have a long way to go before protecting groups will not be used in chemical synthesis.

This edition includes a new chapter on how protecting groups affect the glycosylation process, a subject that has interested me since I started working on the second edition. I have limited the chapter to carbohydrates due to the sheer volume of literature that would need to be covered. This new chapter is divided into sections that cover different situations where protecting groups influence reactivity and stereoselectivity. When going through the chapter the reader will find that there is some overlap between sections since the publications cited, often present information in multiple areas. I have included a number of tables illustrating how various protecting group arrangements influence reaction outcomes. Being an organic chemist looking at structures and drawing conclusions is much more instructive than trying to do this in print. I have tried to organize related systems together as much as possible to simplify the examination of a particular concept. For example, how do various conformational restraints influence the outcome of a glycosylation.

In conclusion, I thank Jonathan Rose my editor for giving me this opportunity during my so-called retirement. Again, I thank Jed Fisher, who gave me a copy of his extensive database which included many useful references. I must also thank Western Michigan University for giving me an Adjunct Professorship, allowing me access to their library which has helped me keep up with the literature. My greatest thanks must go to my wife, Lizzie, who has encouraged me to do this edition and who printed out over 3000 references since it is difficult to read papers on the computer. As always, she brings me a glass of wine at the end of my evening session of working on the book.

February 2025 PETER G. M. WUTS

ABBREVIATIONS

PROTECTIVE GROUPS

In some cases, several abbreviations are used for the same protective group. We have listed the abbreviations as used by an author in his original paper, including capital and lower-case letters. Occasionally, the same abbreviation has been used for two different protective groups. This information is also included.

ABO	2,7,8-trioxabicyclo[3.2.1]octyl
Ac	acetyl
ACBZ	4-azidobenzyloxycarbonyl
ACE	*O*-bis(2-Acetoxyethoxy)methyl
AcHmb	2-acetoxy-4-methoxybenzyl
Acm	acetamidomethyl
a-CNV-OPh	α-carboxy-6-nitroveratryl
Ad	1-adamantyl
ADMB	4-acetoxy-2,2-dimethylbutanoate
Adoc	1-adamantyloxycarbonyl
Adpoc	1-(1-adamantyl)-1-methylethoxycarbonyl
AIBN	Azobisisobutyronitrile
Alloc or AOC	allyloxycarbonyl
AOC or Alloc	allyloxycarbonyl
Allocam	allyloxycarbonylaminomethyl
Als	allylsulfonyl
AMB	2-(acetoxymethyl)benzoyl
AMPA	(2-azidomethyl)phenylacetate
AN	4-methoxyphenyl or anisyl
Ans	anisylsulfonyl
Anpe	2-(4-acetyl-2-nitrophenyl)ethyl
p-AOM	*p*-anisyloxymethyl or (4-methoxyphenoxy)methyl

APAC	2-allyloxyphenylacetate
Aqmoc	anthraquinone-2-ylmethoxycarbonyl
Azb	*p*-azidobenzyl
Azm	azidomethyl
AZMB	2-(azidomethyl)benzoate
Bam	benzamidomethyl
BBA	butane-2,3-bisacetal
Bbc	but-2-ynylbisoxycaronyl
BDIPS	biphenyldiisopropylsilyl
	benzoyldiisopropylsilyl
BDMS	biphenyldimethylsilyl
	benzyldimethylsilyl
Bdt	1,3-benzodithiolan-2-yl
Betsyl or Bts	benzothiazole-2-sulfonyl
Bhcmoc	6-bromo-7-hydroxycoumarin-4-ylmethoxycarbonyl
BHQ	8-bromo-7-hydroxyquinoline-2-ylmethyl
BHT	2,6-di-*t*-butyl-4-methylphenyl
BIBS	di-*t*-butylisobutylsilyl
Bic	5-benzisoxazolylmethoxycarbonyl
Bim	5-benzisoazolylmethylene
Bimoc	benz[*f*]inden-3-ylmethoxycarbonyl
BIPSOP	*N*-2,5-bis(triisopropylsiloxy)pyrrolyl
Bloc	1-buten-4-yl
BMB	*o*-(benzoyloxymethyl)benzoyl
Bmpc	2,4-dimethylthiophenoxycarbonyl
Bmpm	bis(4-methoxyphenyl)-1′-pyrenylmethyl
Bn	benzyl
Bnf	fluorousbenzyl
Bno	tri-*n*-butylmethyl
Bnpeoc	2,2-bis(4′-nitrophenyl)ethoxycarbonyl
Bns	benzylsulfonate
BOB	Benzyloxybutyrate
BOC	*t*-butoxycarbonyl
Bocdene	2-(*t*-butylcarbonyl)ethylidene
BOM	benzyloxymethyl, beer of the month
bpa	bispicolylamide
Bpoc	1-methyl-1-(4-biphenyl)ethoxycarbonyl
BSB	benzostabase
Bsmoc	1,1-dioxobenzo[*b*]thiophene-2-ylmethoxycarbonyl
BTM	*t*-butylthiomethyl
Bts or Betsyl	benzothiazole-2-sulfonyl
B′SE	2-*t*-butylsulfonylethyl
Bts-Fmoc	2,7-bis(trimethylsilyl)fluorenylmethoxycarbonyl
Bum	*t*-butoxymethyl
Bus	*t*-butylsulfonyl
t-Bumeoc	1-(3,5-di-*t*-butylphenyl)-1-methylethoxycarbonyl
Bz	benzoyl
Bz-NPPOC	2-(5-benzoyl-2-nitrophenyl)propyl
CAEB	2-[(2-chloroacetoxy)ethyl]benzoyl

Cam	carboxamidomethyl
CAMB	2-(chloroacetoxymethyl)benzoyl
Cbz or Z	benzyloxycarbonyl
CEM	2-cyanoethoxymethyl
CDA	cyclohexane-1,2-diacetal
CDM	2-cyano-1,1-dimethylethyl
CE or Cne	2-cyanoethyl
Cee	1-(2-chloroethoxy)ethyl
CEE	1-(2-cyanoethoxy)ethyl
Ceof	cyclic ethyl orthoformate
cHex	cyclohexyl
cHBS	di-*tert*-butyl(cyclohexyl)silyl
Chx	cyclohexyl
Cin	cinnamyl
ClAzab	4-azido-3-chlorobenzyl
Climoc	2-chloro-3-indenylmethoxycarbonyl
Cms	carboxymethylsulfenyl
CNAP	2-naphthylmethoxycarbonyl
Cne or CE	2-cyanoethyl
Coc	cinnamyloxycarbonyl
CPC	*p*-chlorophenylcarbonyl
CPDMS	(3-cyanopropyl)dimethylsilyl
Cpeoc	2-(cyano-1-phenyl)ethoxycarbonyl
Cpep	1-(4-chlorophenyl)-4-methoxypiperidin-4-yl
CPTr	4,4′,4″-tris(4,5-dichlorophthalimido)triphenylmethyl
CTFB	4-trifluoromethylbenzyloxycarbonyl
CTMP	1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl
Cyclo-SEM	5-trimethylsilyl-1,3-dioxane
Cys	cysteine
DAM	di-*p*-anisylmethyl or bis(4-methoxyphenyl)methyl
	2′-*O*-{[2,2-dimethyl-2-(2-nitrophenyl)acetyl]oxy}methyl
DATE	1,1-di-*p*-anisyl-2,2,2-trichloroethyl
DB-*t*-BOC	1,1-dimethyl-2,2-dibromoethoxycarbonyl
DBD-Tmoc–NR2	2,7-Di-*t*-butyl[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl Carbamate
DBS	dibenzosuberyl
DCP	dichlorophthalimide
Dcpm	dicyclopropylmethyl
Ddm or Dmbh	bis(4-methoxyphenyl)methyl
Dde	2-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl
Ddz	1-methyl-1-(3,5-dimethoxyphenyl)ethoxycarbonyl
DEABn	3-diethylaminobenzyl
DEAPE	1-(3-(diethylamino)phenyl)ethyl
DEM	diethoxymethyl
DEIPS	diethylisopropylsilyl
Desyl	2-oxo-1,2-diphenylethyl
Dim	1,3-dithianyl-2-methyl
DIMON	1,4-dimethoxynaphthalene-2-methyl
DMA	dimethylacetamide
Dmab	4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl

Dmaoc	*N,N*-dimethylamonoxy
DMATr	(3-(dimethylamino)phenyl)diphenylmethyl
DMB	3′,5′-dimethoxybenzoin
Dmb	2,4-dimethoxybenzyl
DMBM	[(3,4-dimethoxybenzyl)oxy]methyl
dMDmoc	2-(1,3-dithian-2-yl)propan-2-yl
Dmepa	dimethylaminoethylpicolylamide
DMIPS	dimethylisopropylsilyl
DMN	2,3-dimethylmaleimide
Dmoc	dithianylmethoxycarbonyl
Dmp	2,4-dimethyl-3-pentyl
Dmp	dimethylphosphinyl
DMP	dimethoxyphenyl
	dimethylphenacyl
DMPM	3,4-dimethoxybenzyl
DMTC	dimethylthiocarbamate
DMT or DMTr	di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl
DMTr or DMT	di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl
DNAP	2-(dimethylamino)-5-nitrophenyl
DNB	*p,p′*-dinitrobenzhydryl
DNMBS	4-(4′,8′-dimethoxynaphthylmethyl)benzenesulfonyl
DNP	2,4-dinitrophenyl
Dnpe	2-(2,4-dinitrophenyl)ethyl
Dnpeoc	2-(2,4-dinitrophenyl)ethoxycarbonyl
DNs	2,4-dinitrobenzenesulfonyl
DNse	2-(2,4-dinitrophenylsulfonyl)ethoxycarbonyl
Dnseoc	2-dansylethoxycarbonyl
Dobz	*p*-(dihydroxyboryl)benzyloxycarbonyl
Doc	2,4-dimethylpent-3-yloxycarbonyl
Dod	bis(4-methoxylphenyl)methyl
DOPS	dimethyl[1,1-dimethyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]silyl
DPA	diphenylacetyl
Dpaa	2-(di(pyridin-2-yl)amino)acetamide
DPIPS	diphenylisopropylsilyl
DPM or Dpm	diphenylmethyl
DPMS	diphenylmethylsilyl
Dpp	diphenylphosphinyl
Dppe	2-(diphenylphosphino)ethyl
Dppm	(diphenyl-4-pyridyl)methyl
DPSE	2-(methyldiphenylsilyl)ethyl
DPSide	diphenylsilyldiethylene
Dpt	diphenylphosphinothioyl
DPTBOS	*t*-butoxydiphenylsilyl
DPTBS	diphenyl-*t*-butoxysilyl or
	diphenyl-*t*-butylsilyl
Dtb-Fmoc	2,6-di-*t*-butyl-9-fluorenylmethoxycarbonyl
DTBMS	di-*t*-butylmethylsilyl
DTBS	di-*t*-butylsilylene

DTE	2-(hydroxyethyl)dithioethyl or "dithiodiethanol"
Dts	dithiasuccinimidyl
E-DMT	1,2-ethylene-3,3-bis(4′4″-dimethoxytrityl)
EDT	ethane-1,2-dithiol
EE	1-ethoxyethyl
EOM	ethoxymethyl
Epin	1,1,2,2-Tetraethylethylene glycol
^{F}Cbz	fluorous benzyloxycarbonyl
Fcm	ferrocenylmethyl
Flu	fluorenyl
Fm	9-fluorenylmethyl
Fmoc	9-fluorenylmethoxycarbonyl
Fpmp	1-(2-fluorophenyl)-4-methoxypiperidiny-4-yl
Fsec	2-[4-fluorophenyl)-sulfonyl]ethyl
GUM	guaiacolmethyl
HAPE	1-[2-(2-hydroxyalkyl)phenyl]ethanone
HBn	2-hydroxybenzyl
Hdoc	hexadienyloxycarbonyl
HFB	hexafluoro-2-butyl
HFIA	dimethyl 2-(alkoxyoxymethoxy)isophthalate
HIP	1,1,1,3,3,3-hexafluoro-2-phenylisopropyl
Hoc	cyclohexyloxycarbonyl
HSDIS	(hydroxystyryl)diisopropylsilyl
HSDMS	(hydroxystyryl)dimethylsilyl
hZ or homo Z	homobenzyloxycarbonyl
ICPrc	3-isocyanopropyl
IDTr	3-(imidazol-1-ylmethyl)-4′,4″-dimethoxytriphenylmethyl
IETr	4,4′-dimethoxy-3″-[*N*-(imidazolylethyl)carbamoyl]trityl
iMds	2,6-dimethoxy-4-methylbenzenesulfonyl
Ipaoc	1-isopropylallyloxycarbonyl
Ipc	isopinocampheyl
IPDMS	isopropyldimethylsilyl
LED	Light emitting diode
Lev	levulinoyl
LevS	4,4-(ethylenedithio)pentanoyl
LevS	levulinoyldithioacetal ester
LMM*o*(*p*)NBz	6-(levulinyloxymethyl)-3-methoxy-2-nitrobenzoate
MAB	2-{{[(4-methoxytrityl)thio]methylamino}methyl}benzoate
MAQ	2-(9,10-anthraquinonyl)methyl or 2-methyleneanthraquinone
MBE	1-methyl-1-benzyloxyethyl
Mbh	bis(4-methylphenyl)methyl
mBhc	6-bromo-7-hydroxy-3-methyl-4-((alkylthio)methyl)-2*H*-chromen-2-one
MBF	2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl
MBS or Mbs	*p*-methoxybenzenesulfonyl
MCPM	1-Methyl-1′-cyclopropylmethyl
Mds	2,6-dimethyl-4-methoxybenzenesulfonyl
MDPS	methylene-bis-(diisopropylsilanoxanylidene
Me	methyl

ME	methoxyethyl
MEC	α-methylcinnamyl
Mee	methoxyethoxyethyl
MeOAc	methoxyacetate
MeO-CyHO	4-methoxy-(8-cyano-7-hydroxyquinolin-2-yl)methyl
MEM	2-methoxyethoxymethyl
Menpoc	α-methylnitropiperonyloxycarbonyl
MeO-NDBF	7-methoxy-2-(1-(alkylthio)ethyl)-3-nitrodibenzo[*b,d*]furan
MeOZ or Moz	*p*-methoxybenzyloxycarbonyl
Mes	mesityl or 2,4,6-trimethylphenyl
MIP	methoxyisopropyl or 1-methyl-1-methoxyethyl
MM	menthoxymethyl
MMT or MMTr	*p*-methoxyphenyldiphenylmethyl
MMTr or MMT	*p*-methoxyphenyldiphenylmethyl
MMPPOC	2-(3,4-methylenedioxy-6-nitrophenypropyloxycarbonyl
Mmsb	3-methoxy-4-methylsufinylbenzyl
MNPPOC	2-(3,4-methylenedioxy-6-nitrophenylpropyl
MOB	2-{[(4-methoxytritylthio)oxy]methyl}benzoate
Mocdene	2-(methoxycarbonyl)ethylidene
MoEt	2-*N*-(Morpholino)ethyl
MOM	methoxymethyl
MOMO	methoxymethoxy
Moz or MeOZ	*p*-methoxybenzyloxycarbonyl
MP	*p*-methoxyphenyl
Mpe	3-methyl-3-pentyl
MPM or PMB	*p*-methoxyphenylmethyl or *p*-methoxybenzyl
Mps	*p*-methoxyphenylsulfonyl
Mpt	dimethylphosphinothioyl
Ms	methanesulfonyl or mesyl
MSE	2-(methylsulfonyl)ethyl
Msib	4-(methylsulfinyl)benzyl
Mspoc	2-methylsulfonyl-3-phenyl-1-prop-2-enyloxy
Msz	4-methylsulfinylbenzyloxycarbonyl
MTAD	4-methyl-1,2,4-triazoline-3,5-dione
Mtb	2,4,6-trimethoxybenzenesulfonyl
Mte	2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl
MTHP	4-methoxytetrahydropyranyl
MTM	methylthiomethyl
MTMB	4-(methylthiomethoxy)butyryl
MTMECO	2-(methylthiomethoxy)ethoxycarbonyl
MTMT	2-(methylthiomethoxymethyl)benzoyl
Mtpc	4-(methylthio)phenoxycarbonyl
Mtr	2,3,6-trimethyl-4-methoxybenzenesulfonyl
Mts	2,4,6-trimethylbenzenesulfonyl or Mesitylenesulfonyl
Mtt	4-methoxytrityl
	4-methyltrityl
Nap	2-napthylmethyl
NAPOM	2-naphthylmethoxymethyl
NBOM	nitrobenzyloxymethyl

NBM	nitrobenzyloxymethyl
NDBF	2-(1-(alkylthio)ethyl)-3-nitrodibenzo[*b,d*]furan
NDMS	2-norbornyldiemethylsilyl
Ne	2-nitroethyl
NNM	3-nitro-2-naphthylmethyl
Noc	4-nitrocinnamyloxycarbonyl
Nosyl or Ns	2- or 4-nitrobenzenesulfonyl
Npb	3-(2-nitrophenyl)butan-2-ol
Npe or npe	2-(nitrophenyl)ethyl
Npeoc	2-(4-nitrophenyl)ethoxycarbonyl
Npeom	[1-(2-nitrophenyl)ethoxy]methyl
Npes	2-(4-nitrophenyl)ethylsulfonyl
Nph	6-hydroxy-5-(2-nitrophenyl)heptanoic
Npp	2-(2-nitrophenyl)propyl
NPPOC	2-(2-nitrophenyl)propyloxycarbonyl
NPS or Nps	2-nitrophenylsulfenyl
NpSSPeoc	2-[(2-nitrophenyl)dithio]-1-phenylethoxycarbonyl
Npys	3-nitro-2-pyridinesulfenyl
Ns or Nosyl	2- or 4-nitrobenzenesulfonyl
Nse	2-(4-nitrophenylsulfonyl)ethoxycarbonyl
NVOC or Nvoc	3,4-dimethoxy-6-nitrobenzyloxycarbonyl or 6-nitroveratryloxycarbonyl
OBO	2,6,7-trioxabicyclo[2.2.2]octyl
O-DMT	3,3′-oxybis(dimethoxytrityl)
ONB	*o*-nitrobenzyl
oNv	(4,5-dimethoxy-2-nitrophenyl)methylthio
PAB	*p*-acylaminobenzyl
PAB	acetoxybenzyl
PAC_H	2-[2-(benzyloxy)ethyl]benzoyl
PAC_M	2-[2-(4-methoxybenzyloxy)ethyl]benzoyl
Paloc	3-(3-pyridyl)allyloxycarbonyl or 3-(3-pyridyl)prop-2-enyloxycarbonyl
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PDNO	2,6-pyridinedicarboxylic acid *N*-oxide
PeNB	pentadienylnitrobenzyl
PeNP	pentadienylnitropiperonyl
Peoc	2-phosphonioethoxycarbonyl
Peoc	2-(triphenylphosphonio)ethoxycarbonyl
Pet	2-(2′-pyridyl)ethyl
Pf	9-phenylfluorenyl
Pfp	pentafluoropenyl
Phamc	phenylacetamidomethyl
PhAc	4-phenylacetoxybenzyloxycarbonyl
Phedec	phenyldithioethyl
Phenoc	4-methoxyphenacyloxycarbonyl
PhS-NPPOC	2-(4-ethyl-2-nitro-5-(phenylthio)phenyl)propyl
Pic	picolinate
Pim	phthalimidomethyl
PIP	2-(piperidine-1-yl)-ethyl
Piv	pivaloyl

Pixyl or Px	9-(9-phenyl)xanthenyl
PMB or MPM	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
PMBM	*p*-methoxybenzyloxymethyl
Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
pMCB	4-(alkoxymethyl)benzoate
Pme	pentamethylbenzenesulfonyl
PMNB	2-(4′-methoxy-4-nitro-[1,1′-biphenyl]-3-yl)propan-1-ol
PMP	*p*-methoxyphenyl
PMS	*p*-methylbenzylsulfonyl
Pms	2-[phenyl(methyl)sulfonio]ethoxycarbonyl
PNB	*p*-nitrobenzyl
	p-nitrobenzoate
*p*NBZ	*p*-nitrobenzoate
PNP	*p*-nitrophenyl
PNPE	2-(4-nitrophenyl)ethyl
PNZ	*p*-nitrobenzylcarbonyl
POC	propargyloxycarbonyl
POM	4-pentenyloxymethyl
POM	pivaloyloxymethyl
POM	[(*p*-phenylphenyl)oxy]methyl
POMB	2-(prenyloxy)methylbenzoate
Ppoc	2-triphenylphosphonioisopropoxycarbonyl
Pp	2-phenyl-2-propyl
Ppt	diphenylthiophosphinyl
Pre	prenyl
Preoc	prenyloxycarbonyl
Proc or Poc	propargyloxycarbonyl
PSB	*p*-siletanylbenzyl
PSE	2-(phenylsulfonyl)ethyl
Psoc	(2-phenyl-2-trimethylsilyl)ethoxycarbonyl
Psec	2-(phenylsulfonyl)ethoxycarbonyl
PTE	2-(4-nitrophenyl)thioethyl
PTM	phenylthiomethyl
PTMSE	(2-phenyl-2-trimethylsilyl)ethyl
Pv	pivaloyl
Px or pixyl	9-(9-phenyl)xanthenyl
Pydec	2-pyridyldithioethyl
Pyet	1-(α-pyridyl)ethyl
Pyoc	2-(2′- or 4′-pyridyl)ethoxycarbonyl
Qn	2-quinolinylmethyl
Qm	2-quinolinylmethyl
QUI	4-quinolinylmethyl
SATE	*S*-acetylthioethyl
Scm	*S*-carboxymethylsulfenyl
SEE	1-[2-(trimethylsilyl)ethoxy]ethyl
SEM	2-(trimethylsilyl)ethoxymethyl
SES	2-(trimethylsilyl)ethanesulfonyl
SIBA	1,1,4,4-tetraphenyl-1,4-disilanylidene
Sisyl	tris(trimethylsilyl)silyl

SMOM	(phenyldimethylsilyl)methoxymethyl
Snm	*S*-(*N*′-methyl-*N*′-phenylcarbamoyl)sulfenyl
SOB	4-trialkylsilyloxybutyrate
STABASE	1,1,4,4-tetramethyldisilylazacyclopentane
TAB	2-{[(methyl(tritylthio)amino]methyl}benzoate
Tacm	trimethylacetamidomethyl
TBDMS or TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
Tbf-DMTr	4-(17-tetrabenzo[*a*,*c*,*g*,*i*]fluorenylmethyl-4′,4″-dimethoxytrityl
Tbfmoc	17-tetrabenzo[*a*,*c*,*g*,*i*]fluorenylmethoxycarbonyl
TBDPSE	*t*-butyldiphenylsilylethyl
TBDS	tetra-*t*-butoxydisiloxane-1,3-diylidene
Tbe	2-(*tert*-Butyldisulfaneyl)ethyl
TBMPS	*t*-butylmethoxyphenylsilyl
TBS or TBDMS	*t*-butyldimethylsilyl
TBTr	4,4′,4″-tris(benzyloxy)triphenylmethyl
TCB	2,2,2-trichloro-1,1-dimethylethyl
TcBOC	1,1-dimethyl-2,2,2-trichloroethoxycarbonyl
TCP	*N*-tetrachlorophthalimido
Tcroc	2-(trifluoromethyl)-6-chromonylmethyleneoxycarbonyl
Tcrom	2-(trifluoromethyl)-6-chromonylmethylene
TDE	(2,2,2-trifluoro-1,1-diphenyl)ethyl
TDG	thiodiglycoloyl
TDS	thexyldimethylsilyl
	tris(2,6-diphenylbenzyl)silyl
Tempoc	2,2,6,6-tetramethylpiperidin-1-yloxy
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl
Tfacm	*S*-trifluoroacetamidomethyl
Tfav	4,4,4-trifluoro-3-oxo-1-butenyl
Tfe-Pocam	*S*-*N*-trifluoromethylphenyacyloxycarbamidomethyl
Thexyl	2,3-dimethyl-2-butyl
THF	tetrahydrofuranyl
THP	tetrahydropyranyl
TIBS	triisobutylsilyl
TIPDS	1,3-(1,1,3,3-tetraisopropyldisiloxanylidene)
TIPS	Triisopropylsilyl
TIPSH	triisopropylsilane
TIX	trimethylsilylxylyl
TLTr	4,4′,4″-tris(levulinoyloxy)triphenylmethyl
Tmb	2,4,6-trimethylbenzyl
Tmob	trimethoxybenzyl
TMPM	trimethoxyphenylmethyl
TMS	trimethylsilyl
Tms	(2-methyl-2-trimethylsilyl)ethyl
TMSE or TSE	2-(trimethylsilyl)ethyl
TMSEC	2-(trimethylsilyl)ethoxycarbonyl

TMSI	trimethylsilyliodide
TMSP	2-trimethylsilylprop-2-enyl
TMTr	tris(*p*-methoxyphenyl)methyl
TOB	2-{[(tritylthio)oxy]methyl}benzoate
Tos or Ts	*p*-toluenesulfonyl
Tom	triisopropylsilyloxymethyl
TPS	triphenylsilyl
TPTE	2-(4-triphenylmethylthio)ethyl
Tr	triphenylmethyl or trityl
$TrtF_7$	2,3,4,4′,4″,5,6-heptafluorotriphenylmethyl
Tritylone	9-(9-phenyl-10-oxo)anthryl
Troc	2,2,2-trichloroethoxycarbonyl
Ts or Tos	*p*-toluenesulfonyl
Tsc	2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl
TSE or TMSE	2-(trimethylsilyl)ethyl
Tse	2-(*p*-toluenesulfonyl)ethyl
Tsoc	triisopropylsiloxycarbonyl
Tsv	*p*-toluenesulfonylvinyl
VeZ	3-methoxy-4-(vinyloxy)benzyl
Voc	vinyloxycarbonyl
Xan	xanthenyl
Z or Cbz	benzyloxycarbonyl

ABBREVIATIONS REAGENTS

9-BBN	9-borabicyclo[3.3.1]nonane
bipy	2,2′-bipyridine
BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
Bt	benzotriazol-1-yl or 1-benzotriazolyl
BTEAC	benzyltriethylammonium chloride
CAL	Candida antarctica lipase
CAN	ceric ammonium nitrate
CMPI	2-chloro-1-methylpyridinium iodide
cod	cyclooctadiene
cot	cyclooctatetraene
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBAD	di-*t*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate

DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAC	*N,N*-dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DMDO	2,2-dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
DTE	dithioerythritol
DTT	dithiothreitol
EDC or EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (or 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide) hydrochloride
EDCI or EDC	1-ethyl-3-(3-(dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
HATU	*N*-[(dimethylamino)(3*H*-1,2,3-triazolo(4,5-*b*)pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate, previously known as *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.
HFIP	hexafluorisopropyl
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HOAt	7-aza-1-hydroxybenzotriazole
HOBT	1-hydroxybenzotriazole
Im	imidazol-1-yl or 1-imidazolyl
IPA	isopropyl alcohol
IPCF (=IPCC)	isopropenyl chloroformate (isopropenyl chlorocarbonate)
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDBB	lithium 4,4′-di-*t*-butylbiphenylide
MAD	methylaluminumbis(2,6-di-*t*-butyl-4-methylphenoxide
MCPBA	*m*-chloroperoxybenzoic acid
MoOPH	oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide
MS	molecular sieves
MSA	methanesulfonic acid
MTB	methylthiobenzene
MTBE	*t*-butyl methyl ether
NBS	*N*-bromosuccinimide
$Ni(acac)_2$	nickel acetylacetonate
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidinone
P	polymer support
Pc	phthalocyanine
PCC	pyridinium chlorochromate

$PdCl_2(tpp)_2$	dichlorobis[tris(2-methylphenyl)phosphine]palladium
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
PG	protective group
PhI(OH)OTs	[hydroxy(tosyloxy)iodo]benzene
PPL	porcine pancreatic lipase
PPTS	pyridinium *p*-toluenesulfonate
proton sponge	1,8-bis(dimethylamino)naphthalene
Pyr	pyridine
$Rh_2(pfb)_4$	rhodium perfluorobutyrate
ScmCl	methoxycarbonylsulfenyl chloride
SMEAH	sodium bis(2-methoxyethoxy)aluminum hydride
Su	succinimidyl
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TEBA or TEBAC	triethylbenzylammonium chloride
TEBAC or TEBA	triethylbenzylammonium chloride
TESH	triethylsilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFMSA or TfOH	trifluoromethanesulfonic acid
TfOH or TFMSA	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMOF	trimethyl orthoformate
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
TPPTS	sulfonated triphenylphosphine
TPS	triisopropylbenzensulfonyl chloride
$Tr^+BF_4^-$ or $Ph_3C^+BF_4^-$	triphenylcarbenium tetrafluoroborate
$TrS^-Bu_4N^+$	tetrabutylammonium triphenylmethanethiolate
Ts	toluenesulfonyl

1

THE ROLE OF PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

PROPERTIES OF A PROTECTIVE GROUP

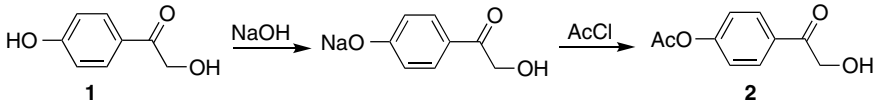
When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being, developed for this purpose. A protective group must fulfill several requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reaction conditions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should form a derivative (without the generation of new stereogenic centers) that can easily be separated from side products associated with its formation or cleavage. The protective group should have a minimum of additional functionality to avoid further sites of reaction. All things considered; no protective group is the best protective group. Currently, the science and art of organic synthesis, contrary to the opinions of some, has a long way to go before we can call it a finished and well-defined discipline, as amply illustrated by the extensive use of protective groups during the synthesis of multifunctional molecules. A greater number of protective group-free syntheses have been accomplished since the last edition of this book, but in some cases, this is the result of a suitable target choice rather than a fundamental advance in organic chemistry. Greater control over the chemistry used in the building of nature's architecturally beautiful and diverse molecular frameworks, as well as unnatural structures, is needed when one considers the number of protection and deprotection steps often used to synthesize a molecule. Peptides,[1] carbohydrates, and polyketides are among the classes of compounds that still require extensive use of protective groups whereas the synthesis of alkaloids appears to be less dependent upon protective group use.

HISTORICAL DEVELOPMENT

Since a few protective groups cannot satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and, indeed, are available. In early syntheses, the chemist chose a standard derivative known to be stable to the subsequent reactions. In a synthesis of callistephin chloride, the phenolic–OH group

Greene's Protective Groups in Organic Synthesis, Volume 1, Sixth Edition. Peter G. M. Wuts.

in **1** was selectively protected as an acetate.[2] In the presence of silver ion, the aliphatic hydroxyl group in **2** displaced the bromide ion in a bromoglucoside. In the final step, the acetate group was removed by basic hydrolysis.



1 **2**

Other classical methods of cleavage include acidic hydrolysis (eq. 1), reduction (eq. 2), and oxidation (eq. 3):

(1) $ArO–R \rightarrow ArOH$

(2) $RO–CH_2Ph \rightarrow ROH$

(3) $RNH–CHO \rightarrow [RNHCOOH] \rightarrow RNH_3^+$

Some of the original work in the carbohydrate area, in particular, reveals extensive protection of carbonyl and hydroxyl groups. For example, a cyclic diacetonide of glucose was selectively cleaved to the monoacetonide.[3] A summary[4] describes the selective protection of primary and secondary hydroxyl groups in a synthesis of gentiobiose, carried out in the 1870s, as triphenylmethyl ethers.

DEVELOPMENT OF NEW PROTECTIVE GROUPS

As chemists proceeded to synthesize more complicated structures, they developed more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds. At first, a tetrahydropyranyl acetal was prepared,[5] by an acid-catalyzed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild acid hydrolysis, but the formation of this acetal introduces a new stereogenic center. The formation of the 4-methoxytetrahydropyranyl ketal[6] eliminates this problem.

Catalytic hydrogenolysis of an *O*-benzyl protective group is a mild, selective method introduced by Bergmann and Zervas[7] to cleave a benzyl carbamate ($R_2NCO–OCH_2C_6H_5 \rightarrow R_2NH$) prepared to protect an amino group during peptide syntheses. The method also has been used to cleave alkyl benzyl ethers; stable compounds prepared to protect alkyl alcohols; benzyl esters are cleaved by catalytic hydrogenolysis under neutral conditions.

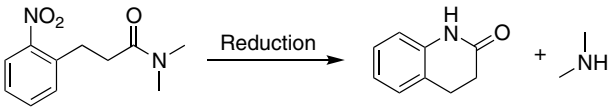
Three selective methods to remove protective groups have received attention: "assisted," electrolytic, and photolytic removal. Four examples illustrate "assisted removal" of a protective group. A stable allyl group can be converted to a labile vinyl ether group (eq. 4)[8]; a β-haloethoxy (eq. 5)[9] or a β-silylethoxy (eq. 6)[10] derivative is cleaved by the attack at the β-substituent; and a stable *o*-nitrophenyl derivative can be reduced to the *o*-amino compound, which undergoes cleavage by nucleophilic displacement (eq. 7)[11]:

(4) $ROCH_2CH{=}CH_2 \xrightarrow{t\text{-BuOK}} [ROCH{=}CHCH_3] \xrightarrow{H_3O^+} ROH$

(5) $RO-CH_2-CCl_3 + \xrightarrow{Zn} RO^- + CH_2{=}CCl_2$

(6) $RO-CH_2-CH_2-SiMe_3 \xrightarrow{Bu_4NF} RO^- + CH_2{=}CH_2 + FSiMe_3$
R=alkyl, aryl, R′CO–, or R′NHCO–

(7)



The design of new protective groups that are cleaved by "assisted removal" is a challenging and rewarding undertaking.

Removal of a protective group by electrolytic oxidation or reduction is useful in some cases. An advantage is that the use and subsequent removal of chemical oxidants or reductants (e.g., Cr or Pb salts; Pt− or Pd−C) are eliminated. Reductive cleavages have been carried out in high yield at −1 to −3 V (versus standard calomel electrode (SCE)) depending on the group; oxidative cleavages in good yield have been realized at 1.5–2 V (versus SCE). For systems