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ABBREVIATIONS

18-c-6	18-crown-6
Ac	acetyl
Acac	acetylacetonyl
AcOH	acetic acid
AIBN	azo bis*iso*-butyronitrile
Am	amyl
An	4-anisyl
Aq.	aqueous
BIPY	4,4'-bipyridyl
Bn	benzyl
BTAF	benzyltrimethylammonium fluoride
Bu	butyl
BuLi	butyllithium
Bz	benzoyl
BzC	benzyloxycarbonyl
18-c-6	18-crown-6
Cat.	catalytic
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
CSA	camphor sulfonic acid
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	9,10-dicyanoanthracene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diastereomeric excess
DIA	di(*iso*-propyl)amine
DIEA	di(*iso*-propyl)ethylamine
DIBAL	di-*iso*butylalane
DMAP	4-N,N-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMM	dimethoxymethane
DMPS	dimethylphenylsilyl
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMTHF	2,5-dimethyltetrahydrofuran
DPMS	diphenylmethylsilyl
e.e.	enantiomeric excess
EBO	1-ethoxy-1-ethyl
EG	ethylene glycol
Eq	molar equivalent
Et	ethyl
FMN	fumaronitrile

HMPA	hexamethylphosphoramide
Hunig's base	N-ethyldiisopropylamine
i-	iso
Im	imidazole
Inv	inverse
LDA	lithium di-*iso*-propylamine
LSA	lithium N-trimethylsilylbenzylamine
Lig	ligand
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
MoOPH	Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide
MOM	methoxymethyl
n-	normal
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NEP	N-ethylpiperidine
NMO	N-methylmorpholine, N-oxide
o/n	overnight
OTf	trifluoromethanesulfonyl
Pent	pentyl
PDMS	phenyldimethylsilyl
Pip.	piperidine
Ra-Ni	Raney nickel
RAMP	(*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine
R.t.	room temperature
s	secondary
SAMP	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
t-	tertiary
tert-	tertiary
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tertiary*-butyldimethylsilyl
TBTMG	*ter*-butyltetramethylguanidine
TEAF	tetra-ethylammonium fluoride
TFA	trifluoroacetic acid
TfO	trifluoromethanesulfonyl
Th	2-thienyl
THF	tetrahydrofuran
Thiaz. cat	thiazolium catalyst
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TMSCN	cyanotrimethylsilane
TMSI	iodotrimethylsilane
TMEDA	tetramethylethylenediamine
TMG	tetramethylguanidine
TMS	trimethylsilyl
TMSI	iodotrimethylsilane
Tol	4-tolyl

TABLE OF CONTENTS

1 Organization of the book

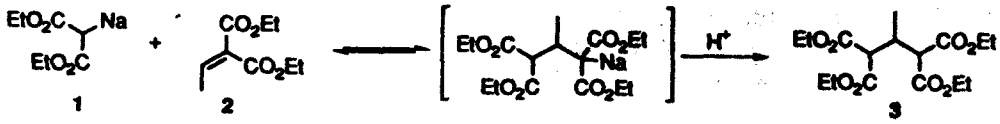
This book is divided into seven chapters, each based on a particular class of conjugate acceptor. Chapters 2, 3 and 4 are divided into two major sections, the first covering intermolecular reactions and the second intramolecular reactions. Each chapter is then divided into sections dealing with conjugate additions of individual classes of nucleophiles relevant to the chapter. In some of the larger sections of the book a further division, into various combinations of reaction partners on the basis of chirality, has been necessary. These are:

(a) The addition of achiral nucleophiles to achiral conjugate acceptors
(b) The addition of achiral nucleophiles to chiral conjugate acceptors
(c) The addition of chiral nucleophiles to achiral conjugate acceptors

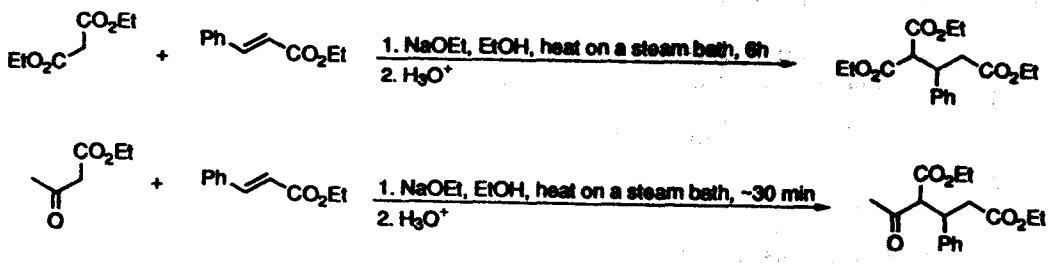
Where a chiral catalyst or ligand has been used this has been included, somewhat arbitrarily, in part (c).

1.1 History

Conjugate additions have a relatively long history. The first example of a conjugate addition was reported by Komnenos in 1883.[1,2] This publication described the addition of diethyl sodiomalonate (1) to diethyl ethylidenemalonate (2).



However, the chemistry of conjugate additions really began soon after, with the work of the American,[3] Arthur Michael.[4] His early publications (the first appeared in 1887) on the reaction focussed on the base-promoted additions of the sodium salts of malonates and β-ketoesters to ethyl cinnamate.[5]



Since that early work was done many stabilized carbanions have been used in the reaction.[6] One of the most important applications of the Michael reaction (using ketone enolates, rather than the more stabilized malonate and acetoacetate carbanions) came with Robinson's introduction of his annulation reaction (see section 2.1.1.1). Since then numerous classes of nucleophiles have been used in conjugate additions. The next major

class of nucleophile to be introduced into conjugate addition chemistry, after π-stabilized carbanions, was the (still growing) multitude of organocopper reagents. The success of many total syntheses of important natural products, such as the prostaglandins (section 3.1.2), has hinged on such conjugate additions.

Some of the more significant carbon nucleophiles which have followed include silyl enol ethers, ketene acetals and allyl silanes. There has also been something of a renaissance in the conjugate addition of other organometallic reagents. Organic free radical chemistry is now also an important element in conjugate additions, especially with regard to intramolecular additions. With many of these reactions, high levels of stereocontrol can be achieved by judicious choice of reaction partners. Much is now known about the stereoselectivity of the Michael reaction itself.[7] Because so many of these reactions do show good stereoselectivity, most authors offer their ideas on the likely transition states. Wherever possible, these have been included in this book.

1.2 Nomenclature, classification of reaction types and survey of conjugate acceptors

1.2.1 Nomenclature of reaction types

In searching the literature for reactions relevant to this book it became clear that the use of the terms "Michael addition", "Michael reaction" and "conjugate addition" were often used without any particular system in mind. In this book, the following conventions have been observed:

"Conjugate addition" (or 1,4-addition, see section 1.2.2) refers to the addition of *any* class of nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group. (This is a slightly restricted definition as it does not include the 1,4-addition of, say, bromine across 1,3-butadiene).

"Heteroconjugate addition" is a term coined by Isobe for conjugate additions to alkenes activated by heteroatom-containing functional groups other than carbonyl derivatives.[8] This seems slightly unfortunate as the term could just as easily and, perhaps more appropriately, be applied to the conjugate addition of heteronucleophiles. Consequently, the use of the term has been avoided in this book.

"Michael addition" refers to the addition of *carbanions* to unsaturated systems in conjugation with an activating group.

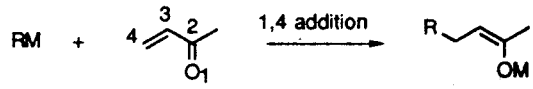
"The Michael reaction" refers to the addition of *stabilized carbanions* to unsaturated systems in conjugation with a *carbonyl* group.

The term "Michael addition" has not been used in this book. Instead, the term "conjugate addition" has been used throughout and the use of "Michael" has been restricted to the Michael reaction as defined above.

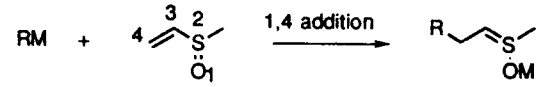
"Cyanoethylation" is often used to describe the conjugate addition of nucleophiles to propenenitrile.[9] In this book the reaction will be found in the appropriate sections of Chapter 4.

1.2.2 1,2 *vs* 1,(2n+2) addition (n = 1,2 etc)

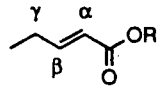
Conjugate addition refers to the addition of a nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group (**A**). Originally, these ideas were applied to additions to α,β-unsaturated carbonyl compounds. As a result, a numbering scheme was developed for these substrates with the numbering beginning at the carbonyl oxygen (C3 and C4 correspond to the α- and β-positions, respectively):



Conjugate addition may take place at any site 2n atoms distant from the carbonyl *carbon*, n = 0,1,2.. etc, with n = 1 being by far the most common. As many other **A**'s also activate unsaturated systems towards conjugate addition, this numbering system has been extended and position "2" refers to the atom within **A** directly attached to the unsaturated system. For example, in alkenylsulfoxides the sulfur atom occupies the "2" position:



Thus 1,4-addition originally referred to the addition of a carbon nucleophile to positon no. 4 and a metal ion to position no. 1 (and similarly for 1,6- or 1,8-additions). It is also sometimes useful to designate positions using the Greek alphabet:



Some examples, which display the structural diversity of conjugate acceptors currently so far designed, are given below.

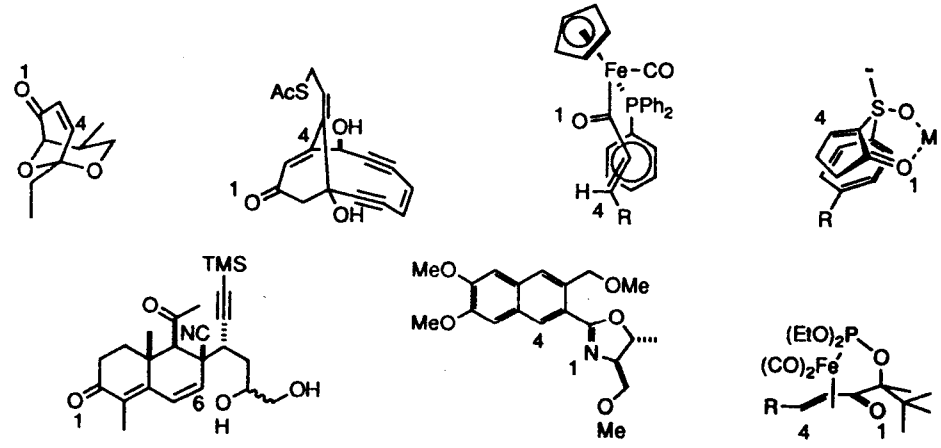


Figure 1.1 Some examples of conjugate acceptors

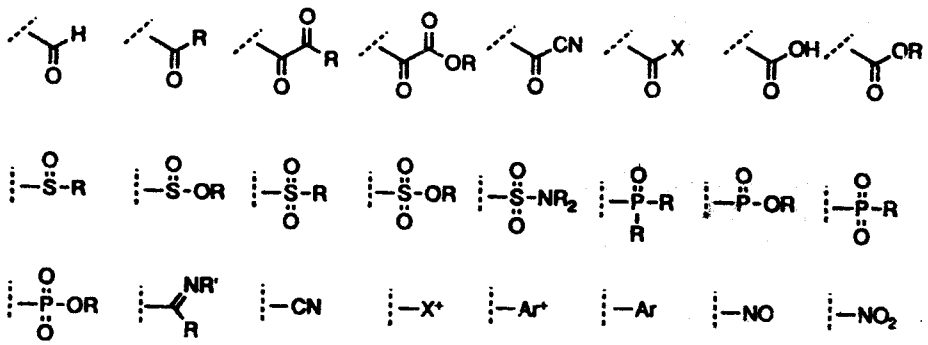
Since the inception of the Michael reaction many new types of conjugate acceptors have been prepared. Some of these consist of alkenes or alkynes activated by groups other than carbonyls or related functional groups. Often for these molecules the term "1,4" is not relevant as in the following example.

A set of stereochemical descriptors, based on the stereogenicity (or lack thereof) of the reacting centres, for describing all the possible combinations of reaction partners has recently been introduced by Oare and Heathcock.[10]

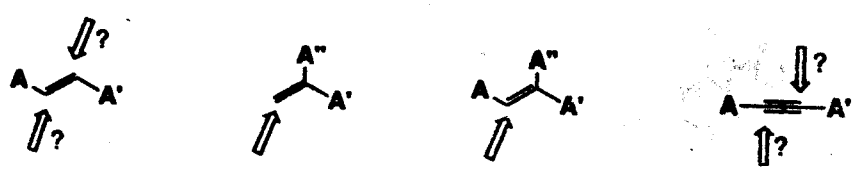
1.2.3 Survey of conjugate acceptors

There are two components in any conjugate acceptor, (i) the activating substituent (A) and (ii) the unsaturated system. The two archetypal conjugate acceptors are the activated alkene and alkyne structures shown below.

There are many examples of A, including:



It is also possible for the conjugate acceptor to contain two or more A groups acting in concert or opposition. This introduces a more subtle problem of regioselection. Which activating group has the stronger influence?



Although of only qualitative value, the relative activating power of these