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Substitution at the α-carbons of α,β-unsaturated carbonyl compounds: *anti*-Michael addition

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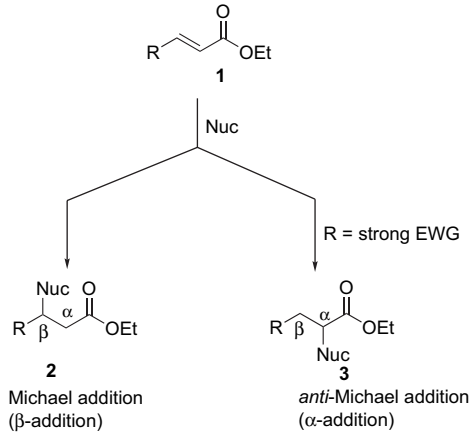
1. Introduction

The conjugate addition of nucleophilic species to α,β-unsaturated systems is a fundamental concept in organic chemistry and is considered as one of the most versatile methods in organic synthesis. Among the manifold of carbon–carbon bond-forming reactions, the Michael addition, also termed 1,4-addition, is especially valuable for selectively creating a new bond at the β-position of activated olefins **1** (Scheme 1).[1] In some circumstances, addition at the carbonyl atom occurs, i.e., 1,2-addition. The versatility of the conjugate additions is mainly due to the large variety of nucleophiles (organometallic reagents, other carbanions, heteroatom Michael donors) and acceptors (α,β-unsaturated carbonyl compounds, nitriles, esters, phosphates, sulfones, nitroalkenes and alkynoates among others) that can be employed. The vast chemistry related to the Michael reaction has been the subject of numerous reviews.[2]



Scheme 1. Regiospecific C–C (or C–heteroatom) bond formation of an activated olefin.

Keywords: *Anti*-Michael addition; *Contra*-Michael addition; Abnormal Michael reaction; Substitution at carbon-α.
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Among the variety of synthetic transformations, an improvement in synthetic design would occur if the reactivity of Michael acceptors could be altered so that 1,4-addition could be circumvented in favour of the α-position of an α,β-unsaturated system. This is known as *anti*-Michael addition, *contra*-Michael addition, abnormal Michael reaction or substitution at carbon-α. The regioselectivity of the classical Michael reaction can be inverted by groups with strongly electron-withdrawing properties at carbon-β and give rise to the α-substitution product **3** (Scheme 1). During our theoretical and synthetic work on the regioselectivity of the Michael reaction (α-addition vs conjugated β-addition), we noticed that reports on nucleophilic α-addition are scattered throughout the literature. The literature in this area is quite rare and it would therefore be worth whole complementing the vast literature on the conjugated Michael addition.

In this Report, I will discuss the synthetic approaches towards addition to the α-carbons of α,β-unsaturated carbonyl compounds, which can be divided into four categories:

- addition of nucleophiles to α,β-unsaturated alkenoates and related compounds in which polarity of the double bonds is redirected by strong electron-withdrawing substituents at carbon-β;
- double addition to α,β-unsaturated alkynoates in which the regioselectivity is redirected to an overall α-addition mode by utilization of a phosphine base;
- carbon–carbon bond formation at the α-position of Michael acceptors by palladium-mediated reactions;
- utilization of organometallic reagents as tools for controlling the regioselectivity of Michael additions.

2. Addition to α,β-unsaturated alkenoates with EWG groups at the β-position

Walborsky and Schwarz[3] in 1953 first mentioned the possibility of forming an *anti*-Michael product in the addition reaction to ethyl 4,4,4-trifluorocrotonate. They expected that polarization of the double bond in ethyl 4,4,4-trifluorocrotonate could be redirected by the trifluoromethyl group through an inductive or hyperconjugative effect, as illustrated in structure **4** (Fig. 1). In the competition between a single trifluoromethyl group and the carboxyl group, the latter could determine the regioselectivity of the addition, giving the same product as its nonfluorinated analogue. The trifluoromethyl group was unable to exert enough influence to reverse the normal mode of addition.

The inverted polarization of the double bond in β,β-bis-(trifluoromethyl)acrylic acid and its esters has been observed by Knunyanta and Cheburkov in the addition of ammonia, piperidine and water (Scheme 2).[4] They reported the isolation of *anti*-Michael products **6**, **7a** and **7b** from the reaction mixtures. Adducts of the type **7** were isolated by others[5] using secondary amines such as dimethylamine to form product **7c**, pyrrolidine and 2,2-dimethylaziridine. When methanol was used, adduct **7d** was obtained with 55% yield in the presence of a catalyst (KF/Al_2O_3) at a higher temperature (Scheme 2).[5]

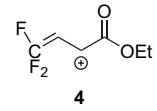

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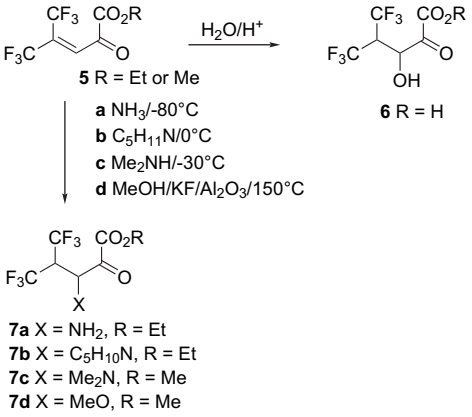
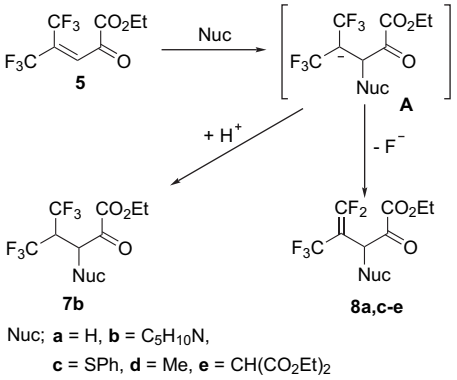
Figure 1.



Scheme 2.

Martin et al.[6] showed that the reduction of β,β-bis-(trifluoromethyl)acrylic ester **5** (R=Et) by lithium triethoxyaluminium hydride at −78 °C in ether provided compound **8a** in 77% yield resulting from the α-addition of hydride followed by fluoride ion elimination (Scheme 3). This addition–elimination reaction was extended to various nucleophiles such as sodium diethyl malonate, sodium phenyl sulfide and methyllithium and was applied as a convenient route to the synthesis of α-perfluoroisopropenyl α-substituted acetic acid esters **8c–e**. It was also noticed that using piperidine as a nucleophile allowed the isolation of only the α-addition product **7b** as previously reported.[4] Interestingly, ^{19}F NMR spectra indicated the formation of **8b** as a major product at the beginning of the reaction.[6] This means that compound **7b** could be considered as the thermodynamic product. These observations can be explained by the formation of the carbanionic intermediate **A** which, in the absence of a proton, eliminates fluoride ion to form **8** (Scheme 3). In the case of piperidine, a piperidinium hydrofluoride salt is formed and the fluoride ion becomes sufficiently nucleophilic to add to the double bond of the kinetic product **8b**, leading to **7b**. An analogous α-addition of nucleophiles followed by halide ion elimination has been observed with hindered γ-bromo-α,β-unsaturated esters.[7]



Scheme 3.

2.1. Theoretical calculation and synthetic answers

In the literature, there have been a few theoretical studies and deliberations on the factors controlling the regiochemistry of nucleophilic additions at carbon-β versus carbon-α of α,β-unsaturated carbonyl compounds possessing electron-withdrawing substituents at the β-carbon atoms. A theoretical calculation to rationalize the preference for α-addition to 3,3-bis(trifluoromethyl)acrylate ester **5** (R=Et) has been reported by Shinohara et al. (Fig. 2).[8] They performed MOPAC calculations for **5** along with its nonfluorinated prototype, ethyl crotonate, and 3-trifluoromethyl acrylate for both LUMO energy levels and p_z orbital coefficients. The results indicated that the α-position of compound **5** has a larger absolute value of the orbital coefficient than the β-position, which clearly explains its *anti*-Michael addition preference (Fig. 2).

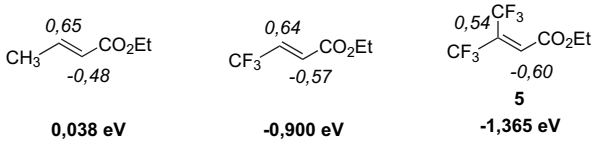
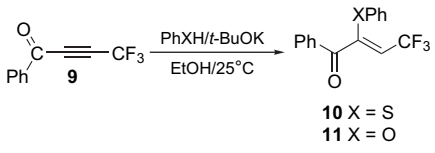


Figure 2. p_z Coefficients are in italics, LUMO energy levels are in bold.

A theoretical explanation of the α-addition to benzoyl(trifluoromethyl)acetylene **9** as Michael acceptor in reactions with PhS^- and PhO^- was performed using MNDO molecular orbital calculations on $HCOC{\equiv}CCF_3$ (**A**) as a model compound.[9] As shown in Scheme 4, reaction of **9** with thiophenol or phenol in the presence of *t*-BuOK in ethanol led exclusively to the α-addition products **10** and **11**, respectively. The calculated charge densities on the acetylenic carbon atoms and coefficients of the acetylenic LUMO for theoretical model **A** are given in Figure 3. It can be seen that C_α has less negative charge density, so that a nucleophile will preferentially attack this position, leading to *anti*-Michael addition. A larger LUMO coefficient at carbon-α than carbon-β is also consistent with α-addition.



Scheme 4.

A very interesting observation was made during the utilization of α,β-unsaturated acids as Michael acceptors for the synthesis of thieno[2,3-*b*]thiopyrans.[10] The general approach of this method is a Michael reaction of alkyl- and arylacrylic acids with 2-mercaptothiophene to produce the Michael adducts and then cyclization to the corresponding thieno[2,3-*b*]thiopyran. It was found that 3-(4-pyridyl)propenoic acid (**12**) reacted with 2-mercaptothiophene in THF

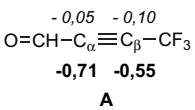
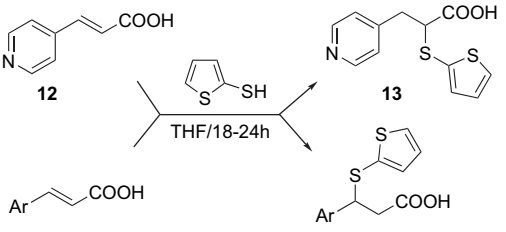


Figure 3. Charge densities are in italics, LUMO coefficients are in bold.

providing the α-addition product **13**. On the other hand, the β-addition products **15a** and **15b** were formed for the other acrylic acid derivatives such as 3-(3-pyridyl or 4-methoxyphenyl)propenoic acid **14a** and **14b** (Scheme 5). Surprisingly, the strong electron-withdrawing groups such as *p*-nitro and *o*-nitro present in cinnamic acid derivatives **14c** and **14d** failed to give the corresponding α-addition products **15c** and **15d**. Additionally, the Michael reaction of the silyl ester of compound **12** provided the normal β-adduct.



Compounds **14**,**15**: Ar; **a** = 3-pyridyl, **b** = *p*-MeO-C_6H_4, **c** = *p*-NO_2-C_6H_4, **d** = *o*-NO_2-C_6H_4

Scheme 5.

Ponticello et al.[10] presumed that a protonated intermediate such as **16** (Fig. 4) could be responsible for directing the addition of 2-mercaptothiophene to the α-position of **12**, affording **13**. The calculated AM1 proton affinities of **12**, **14a** and **14c** indicated that **12** has a higher value (212.7 kcal/mol) than either **14a** or **14c** (210.6 and 188.4 kcal/mol, respectively). In the case of silyl ester **17** (Fig. 4), the MNDO calculations predicted higher proton affinities (about 3.6 kcal/mol) at the carbonyl oxygen than at the pyridyl nitrogen. It seems that protonation at the carbonyl side increases the polarization of the carbon–carbon double bond (see atomic charges and LUMO coefficients for **17** and **12** in Table 1) and reinforces the preference for the Michael β-addition. In the case of **14a** and **14c**, the Michael addition presumably proceeds via the neutral species, the charge distributions of which are in agreement with the preferred β-addition. In addition, the calculations for two simple α,β-unsaturated

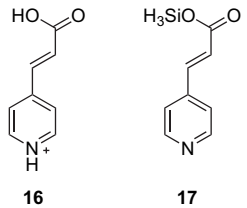


Figure 4.

Table 1

Compound	LUMO coefficients		Atomic charges	
	β	α	β	α
12	−0.46	0.45	−0.04	−0.18
14a	−0.43	0.43	−0.02	−0.20
14c	−0.01	0.19	−0.13	−0.07
16	−0.11	0.35	−0.14	−0.06
17	0.55	−0.19	0.12	−0.23
Acrylic acid	−0.66	0.48	−0.12	−0.19
Methyl acrylate	−0.65	0.48	−0.13	−0.19

systems such acrylic acid and its methyl ester correctly predicted the normal Michael addition.

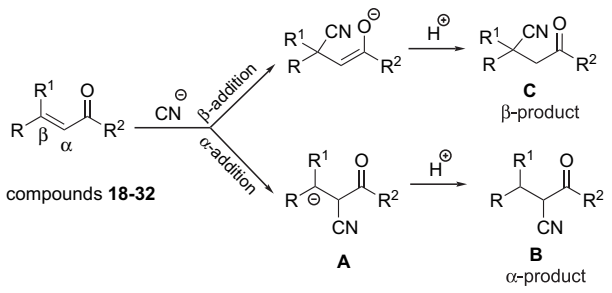
Chatfield et al.[11] have performed theoretical calculations [HF/6-31+G(d) and B3LYP//HF/6-31+G(d)] for the addition of cyanide ion to several α,β-unsaturated carbonyl compounds **18**–**32** (Table 2) in order to determine the trends of regioselectivity with respect to the electron-withdrawing properties of the substituents at the β-carbons. The general expectation was that the EWGs would stabilize the negative

Table 2

Compound	R	R^1	R^2	Gas phase ΔE^{TS}	Solution phase ΔE^{TS}
18	H	H	H	24.1	25.2
19	F	F	H	22.7	25.3
20	CF_3	H	H	8.7	7.7
21	CF_3	CF_3	OMe	−6.8	−4.1
22	NO_2	H	H	−1.3	−0.4
23	NO_2	H	OMe	−3.3	−5.0
24	CH_2=CH	H	H	8.9	12.0
25	CF_3(H)C=CH	H	H	10.5	14.6
26	NO_2(H)C=CH	H	H	−5.5	−4.6
27	Ph	H	H	5.9	10.5
28	2-NO_2–C_6H_4	H	H	−1.2	3.2
29	3-NO_2–C_6H_4	H	H	2.8	7.9
30	4-NO_2–C_6H_4	H	H	−0.7	3.1
31	2,4-$(NO_2)_2$–C_6H_4	H	H	−6.0	−2.9
32	2-NO_2–4-CF_3–C_6H_3	H	H	−3.8	0.1

Differences (kcal/mol) between energies of transition states ($\Delta E^{TS}=E_\alpha^{TS}-E_\beta^{TS}$) for α- versus β-addition in the gas and solution phases; R, R^1, R^2 are defined in Scheme 6.

charge at C_β for the intermediates of α-addition **A** by stabilizing the corresponding transition states (Scheme 6). The relative favourability of α- versus β-addition was found to depend primarily on the differences between the energies of the transition states ($\Delta E^{TS}=E_\alpha^{TS}-E_\beta^{TS}$) for α- and β-addition (if the reaction is under kinetic control) or between the energies of the corresponding products **B** and **C** ($\Delta E^{P}=E_\alpha^{P}-E_\beta^{P}$) (in the case of thermodynamic control).

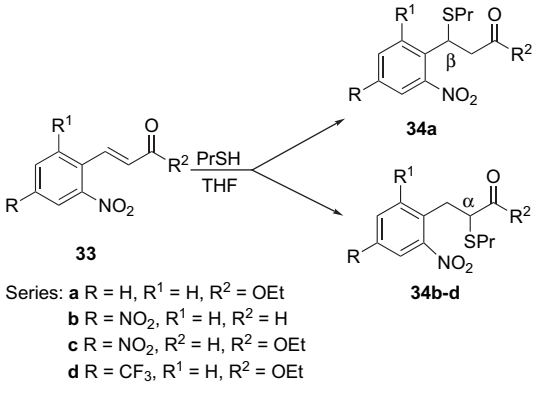


Scheme 6.

Based on these calculations, it was found that ΔE^{TS} rather than ΔE^{P} are predictive of the regioselectivity, which thus appears to be under kinetic control. The sign of ΔE^{TS} indicates which of the reactions are kinetically favoured (positive for β-addition and negative for α-addition). Table 2 demonstrates a clear trend for the values of ΔE^{TS}, as they decrease as the strength of the EWG increases (NO_2>CHO>CF_3>F). In particular, the results indicate that the presence of one nitro group or two trifluoromethyl groups at carbon-β reverses the polarity of the carbon–carbon double bond in acrolein acceptors (e.g., **21** and **26**) and thus redirects the regioselectivity of nucleophilic addition from the classical β-addition to an abnormal α-addition. Two nitro groups or one nitro and a trifluoromethyl group on a phenyl ring attached to carbon-β have the same effect on the nucleophilic addition to cinnamaldehydes or cinnamic esters (e.g., **31** and **32**). The difference between the reaction barriers for α- versus β-addition decreases as the strength of the electron-withdrawing groups increases until, for sufficiently strong electron-withdrawing groups, α-addition becomes favoured.

The regioselectivity has been quantitatively related to charges and frontier-orbital influence. The analysis has been based on correlating the values of ΔE^{TS} by simple expression in terms of partial atomic charges and contributions of frontier orbitals, thus providing parameters that can be used to predict the regioselectivity from easily calculated properties of reactants that could be applicable to a variety of α,β-unsaturated carbonyl compounds. The study demonstrates a relatively simple way to predict likely candidates for α-addition and also suggests that the regioselectivity may be sensitive to the solvent polarity or the choice of the nucleophiles.

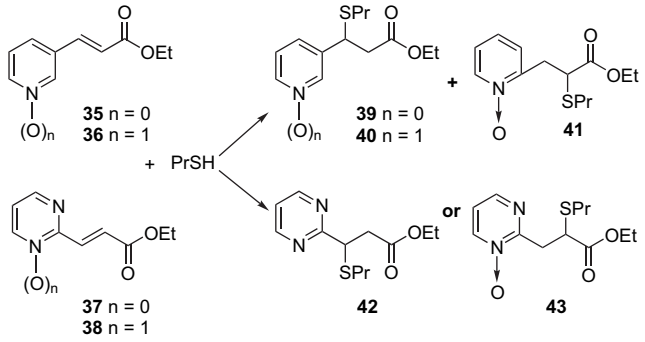
The theoretical results were found to be in agreement with the experimental outcomes in such systems like cinnamic aldehyde **33b** and esters **33c**–**d** (Scheme 7).[11,12] As an example, the reactions of **33b**–**d** with propanethiol yielded the α-addition products **34b**–**d**, confirming the theoretical predictions, whilst on the other hand, one nitro group in the phenyl ring was not able to redirect the nucleophilic addition of thiols, providing the conjugated product **34a** (Scheme 7).[12] The study demonstrates that appropriate electron-withdrawing groups (EWG) can be chosen to effect the desired nucleophilic addition at either the α- or the β-carbon atoms in the α,β-unsaturated carbonyl compounds. The calculations also confirm the experimental data reported by others[4–6] (see Schemes 2 and 3).



Scheme 7.

It has been also shown that pyridin-3-yl and pyrimidin-2-yl rings attached to the β-carbon atoms of propenoate esters **35** and **37** are able to redirect the Michael β-addition to α-substitution (Scheme 8).[13] In particular, propanethiolate addition to **35** or **37** results in the usual formation of the β-adduct **39** or **42**, while the addition to the more π-deficient *N*-oxide **38** occurs at the α-carbon atom to give **43**. Treatment of **36** with propanethiolate gives a mixture of α- and

β-carbon adducts **41** and **40**. The density functional theory (DFT) and Hammett constants were generally consistent with these results. In particular, the Hammett constants σ^- are correlated with the experimental regioselectivity and can be predictive. In general, increasing the electron deficiency of the aromatic ring improves the favourability of the α-addition with respect to the β-addition and can be understood in terms of stabilization of the resonance structure depicted in Figure 1.



Scheme 8.

The experimentally observed change from β- to α-addition was found to be correlated with both increasing σ^- and with decreasing transition-state energies E_α^* (Table 3). While the calculations and experimental results are in agreement with addition to **35** and **38**, the results with **36** and **37** contradict the theoretical predictions. The energy differences between the calculated transition states for the α- and β-addition in the gas phase are however, small and are close to the computational uncertainty for the method. These findings also suggest a significant solvent contribution to the regioselectivity.

Table 3

Compound	σ[a]	E_α*,[b]	E_β*,[b]
35	0.76	17.9	13.0
36	2.25	15.2	12.6
37	1.98	15.9	17.3
38	3.47	14.0	19.0

[a] Hammet constants.
[b] Transition-state energies [kcal/mol] for α-, β-addition.

Additional factors affecting the regioselectivity may be the LUMO coefficients and partial atomic charges for the possible site of nucleophilic attack (C_α vs C_β). It has been shown that there is not a clear correlation between the charges and the regioselectivity, but the LUMO contributions are clearly correlated with ΔG^* (Table 4).[13] In every case, the carbon atoms with the largest $|2p_z|$ have the smallest ΔG^*. Thus, the reactions appear to be under frontier-orbital control.

2.2. Application to organic synthesis

From a synthetic point of view, the most useful Michael acceptors which lead to the formation of α-addition products are β-nitro- and β,β′-ditrifluoromethyl-α,β-unsaturated alkenoates. The α-addition of nucleophiles to 3-nitro-2-

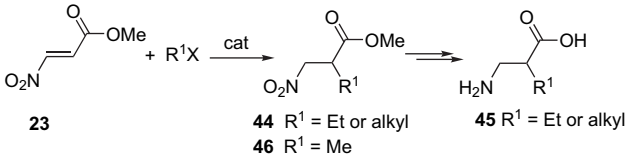
Table 4

Compound	$\lvert 2p_z\rvert$		Q		ΔG^*[B3LYP] TS_α
	C_α	C_β	C_α	C_β	
35	0.26	0.29	−0.41	−0.00	4.95
36	0.27	0.28	−0.36	−0.05	2.83
37	0.27	0.24	−0.22	−0.28	−1.16
38	0.27	0.22	−0.23	−0.19	−4.97

Absolute value of coefficient of $2p_z$ orbital ($|2p_z|$) in LUMO, ChelpG charges (Q) for the possible sites of nucleophilic attack (C_α, C_β) and ΔG^* transition-state free energies relative to β-transition states (298 K, kcal/mol, gas phase, TS_β=0.00).

alkenoates allows a convenient access to 2-substituted 3-nitroalkanoates that are versatile intermediates in organic synthesis. In addition, the nitro functionality can be easily transformed into an amine, oxime, ketone or carboxylic acid, providing a wide range of synthetically interesting compounds. Among these, the β-nitroacrylates are highly reactive compounds that are important building blocks for the synthesis of practically useful structures, including fragments of natural products and biologically active compounds.

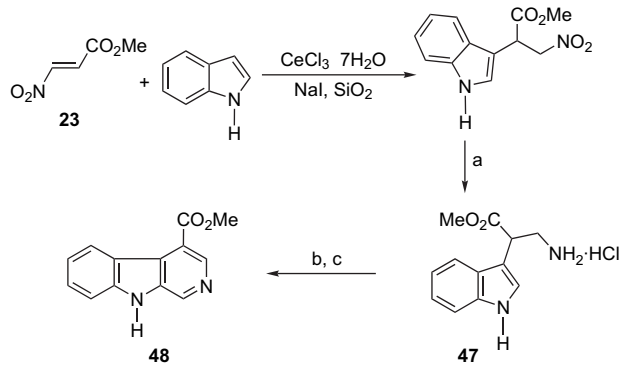
The β-nitroacrylates have been used as precursors in the stereoselective synthesis of 2-branched-β-amino acids.[14,15] Rimkus and Sewald[14] have described an enantioselective addition of diethylzinc or mixed diorganozinc compounds to the methyl 3-nitropropenoate (**23**) catalyzed by copper(I) complexes with BINOL-phosphoramidite ligands, giving rise to the formation of 2-alkyl-3-nitropropanoates **44** with enantioselectivities up to 92% and chemical yields up to 94% (Scheme 9, route a). The β-nitroesters **44** can be easily reduced by catalytic hydrogenation and subsequently hydrolysed to give the β-amino acids **45**. This approach has been extended[15b] to the trialkylaluminium donors, yielding the corresponding 2-substituted 3-nitropropionic acid esters such as **46** (Scheme 9, route b) with good enantiomeric excess and chemical yields.



Scheme 9. Route a: R^1X=Et_2Zn, cat $Cu(OTf)_2$/ligand (BINOL-based phosphoramidite). Route b: R^1X=Me_3Al, cat Cu(I)/ligand (BINOL-based phosphoramidite).

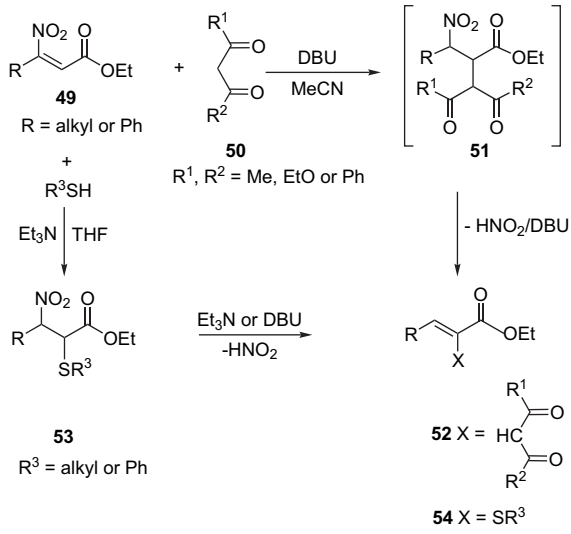
Lewis acid-promoted [cerium(III) salt in solvent-free conditions] α-addition of indoles to β-nitroacrylate **23** has been utilized as a convenient method for the preparation of β-substituted tryptamines such as **47** (Scheme 10).[16] This synthetic route has been further employed for the preparation of 4-substituted β-carboline derivative **48** in 83% isolated yield, that is, otherwise difficult to prepare. Ethyl 3-nitropropenoate reacts with indole and 1-ethylindole without catalysts to yield the α-adducts.[17]

Ballini and co-workers[18] showed that the nitro group in the β-nitro acrylic esters can not only serve as an electron-withdrawing group to promote α-addition, but also as a good leaving group in their synthetic approaches for the preparation of



Scheme 10. Reagents and conditions: (a) H_2, rt; (b) (i) 37% aq HCHO, MeOH, rt; (ii) 6% aq K_2CO_3, EtOAc, rt; (c) Pd/C.

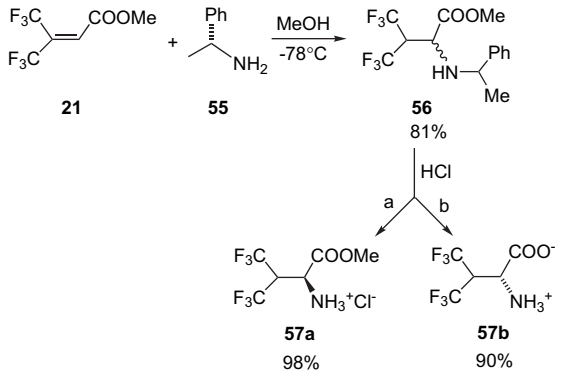
polyfunctionalized α,β-unsaturated esters. The procedure was based on an α-addition of the activated methylene derivatives **50** to β-nitro-α,β-unsaturated alkenoates **49**, which leads to the formation of the intermediate **51**. Subsequent in situ base-induced elimination of nitrous acid gave the α-substituted α,β-unsaturated products of the type **52** (Scheme 11).



Scheme 11.

The application of β-nitroacrylates as α-Michael acceptors has been also utilized in a new approach for the synthesis of α-alkyl(or aryl)thio α,β-unsaturated alkenoates.[19] This method involves the formation of β-nitro-α-thio intermediates **53** via an α-addition of the thionucleophiles to β-nitroalkenoates **49**. Subsequent in situ elimination of nitrous acid from the resulting α-adduct in basic conditions provided products of the type **54**.

The α-addition of (*R*)-1-phenylethylamine (**55**) to methyl bis(trifluoromethyl)acrylate **21** has been applied for the synthesis of enantiomerically pure methyl hexafluorovalinate (Scheme 12).[20,21] Thus, the addition of (*R*)-**55** to **21** led to a mixture of diastereomeric (*S*,*R*) and (*R*,*R*)-adducts **56**. Upon addition of excess hydrochloric acid to the resulting mixture, one diastereomer precipitated and hydrogenolysis provided access to the enantiomerically pure hydrochloride adduct of (*S*)-hexafluorovalinate ester **57a**. Treatment of (*R*,*R*)-adduct **56** with BBr_3 gave (*R*)-hexafluorovaline **57b**.



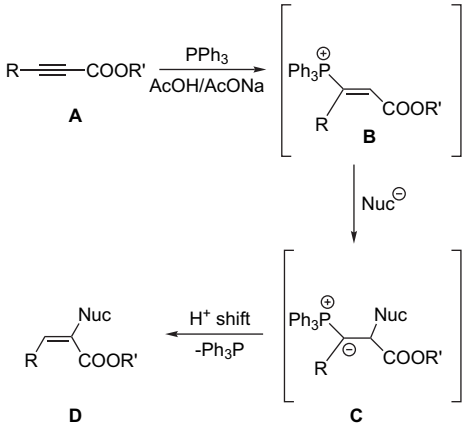
Scheme 12. Reagents and conditions: (a) Pt–C/H_2/MeOH; (b) BBr_3/CH_2Cl_2.

3. Addition to α,β-unsaturated alkynoates redirected by phosphine bases

3.1. *N*-Nucleophile donors

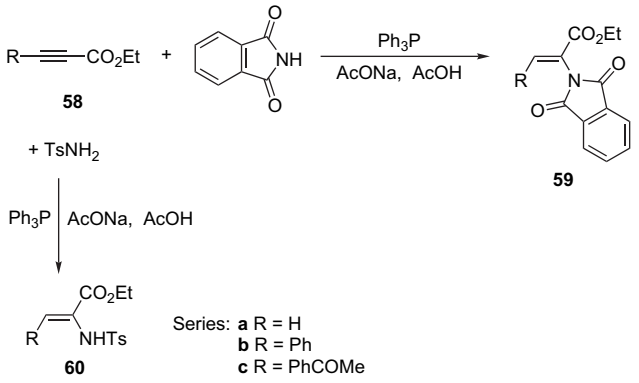
Conjugated acetylenes undergo Michael addition with nucleophiles to give the expected β-adduct. Trost's group[22] described a new pattern of reactivity for alkynoates, showing that the regioselectivity of Michael additions can be redirected from the classical β-addition to the abnormal α-addition when triphenylphosphine is used as a catalyst. They have shown that PPh_3-catalyzed addition of nucleophiles to 2-alkynoate esters **A** occurs at the α-carbon to give 2-alkenoates **D**. The overall α-addition resulted from β-addition of PPh_3 to alkynoates **A**, which led to the formation of the vinylphosphonium intermediate **B**. The latter serves as an α-Michael acceptor (relative to the carbonyl group) and reacts with the nucleophile to give intermediate **C**, which after elimination of triphenylphosphine furnishes the products **D** with an overall α-substitution (Scheme 13). It was shown that triphenylphosphine could serve as a general base catalyst for Michael additions.

Treatment of ethyl propiolate (**58a**) with phthalimide in the presence of a catalytic amount of triphenylphosphine as well as 50 mol % of acetic acid and 50 mol % of sodium acetate in toluene at 105 °C gave the adduct **59a** in 95% isolated yield (Scheme 14). Sulfonamides also acted as good



Scheme 13. α-Addition of nucleophiles to 2-alkynoates in the presence of PPh_3.

nucleophiles for **59a–c** yielding under identical conditions the α-adducts **60a–c**. The stereochemistry of the α-adducts **59** or **60** has been established as *Z*-isomers. The α-adducts further served as a source of dehydroamino acids and their derivatives. This methodology has also been utilized as a convenient access to the natural and unnatural α-amino acids via rhodium-catalyzed conjugated addition of α-adducts of the type **59** with organotin reagents.[23]



Scheme 14.

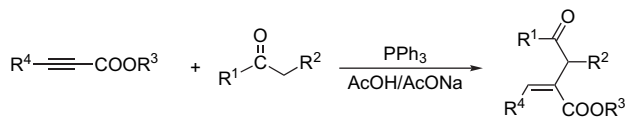
Other alkynoates that do not undergo phosphine-catalyzed redox isomerization[24] to 2,4-dienoates or γ-addition[25] also serve as α-Michael acceptors. Among these derivatives, aryl propynoates and substituted aryl propynoates led to the formation of single α regioisomers.[22]

The annulation of thiobenzamide and ethyl 2-pentynoate in the presence of tributylphosphine is an example of an α-addition of an *N*-nucleophile, which is dominant over γ-addition.[26] Nucleophilic addition of N–H acids such as pyrrole, indole, imidazole or benzimidazole to alkyl propynoates using triphenylphosphine as a catalyst is a good example of the utilization of Trost's procedure, which provides access to the α-*N*-substituted alkyl acrylates.[27]

3.2. *C*-Nucleophile donors

Based on Trost's concept,[22] α-addition of activated methylenes to alkynoates has been developed.[28] Using the PPh_3/AcOH/AcONa system reported for nitrogen-based nucleophiles, activated methylene derivatives **62a–h** were found to react with alkyl (or aryl) propynoates **61a–h** providing the α-addition products **63a–h** in moderate to good yields (Table 5). This simple one-pot methodology represents an improvement for the synthesis of α-functionalized acrylic esters. When, β-oxodithiobutyric acid methyl ester (**64**) was used as

Table 5

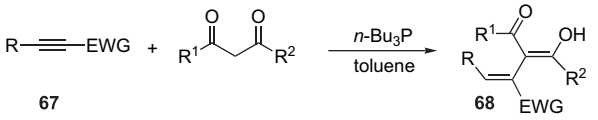


R^1	R^2	R^3	R^4	Product (yield %)
Me	COMe	Et	H	**63a** (88)
Me	COMe	Bn	H	**63b** (85)
Me	COMe	*t*-Bu	H	**63c** (83)
Me	COOEt	Et	H	**63d** (56)
OEt	COOEt	Et	H	**63e** (60)
Ph	$PO(OEt)_2$	Et	H	**63f** (71)
Me	COMe	Et	Ph	**63g** (62)
Ph	$PO(OEt)_2$	Et	Ph	**63h** (50)

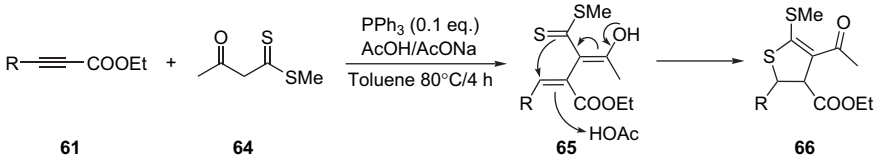
nucleophile, the phosphine catalyst was able to direct the addition reaction to alkynoates **61a**,**g** in favour of the α-*C*-addition to form **65a**,**g** (Scheme 15). The product **65** underwent further cyclization to yield dihydrothiophenes **66a**,**g**.

The phosphine-catalyzed α-addition was also shown to be applicable for a variety of 1,3-dicarbonyl compounds and electron-deficient alkynes.[28b] As shown in Table 6, various electron-deficient alkynes **67a–g** serve as α-Michael acceptors to produce the corresponding conjugated 1,3-diketones **68a–g** (observed exclusively in the enolic form) as the *E* isomers in good yields. The synthesis has been improved using tributylphosphine in toluene without the presence of acetic buffer[28b] or using triphenylphosphine in methylene chloride at room temperature.[29] The Ph_3P in CH_2Cl_2 was able to redirect the nucleophilic addition of phenols, such as 1-naphthol, to *tert*-butyl propynoate (**69**), providing the α-*C*-adduct **70** and the conjugated O-addition product **71** in a 1:1 ratio

Table 6



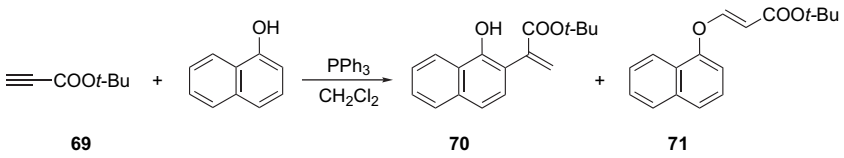
Entry	R	EWG	R^1	R^2	Product (yield %)
1	Ph	CO_2Et	Me	Me	**68a** (75)
2	Ph	CO_2Et	Me	OEt	**68b** (77)
3	Ph	CO_2Et	OEt	OEt	**68c** (78)
4	Ph	CO_2Et	Et	Et	**68d** (95)
5	PhOMe	CO_2Et	Me	Me	**68e** (80)
6	Ph	COPh	Me	Me	**68f** (80)
7	Ph	COMe	Me	Me	**68g** (90)



61a R = H
61g R = Ph

66a R = H (60%)
66g R = Ph (55%)

Scheme 15.



Scheme 16.

(Scheme 16).[30] A mixture of α-addition and conjugated O-addition products was also observed with 2-naphthol and 3-hydroxybenzaldehyde, while, in the case of phenol or 3-hydroxy-4-methoxybenzaldehyde, the conjugated O-addition products of the type **71** were exclusively formed.

4. Addition at the α-position of Michael acceptors catalyzed by palladium complexes

The use of transition metals for carbon–carbon bond formation reactions is very popular because the metal activates the ligated organic moiety intrinsically and facilitates the desired reaction. Among the various metals, palladium is regarded as one of the most often used, because palladium complexes display a wide reactivity and a higher selectivity than other transition metals. In particular, π-allylpalladium complexes (Fig. 5) are very useful reaction intermediates. In general, they are electrophilic and react with various nucleophiles to construct novel carbon–carbon or carbon–heteroatom bonds.

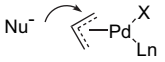
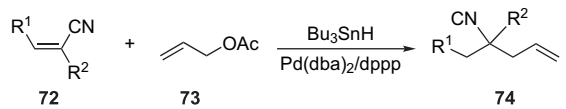


Figure 5.

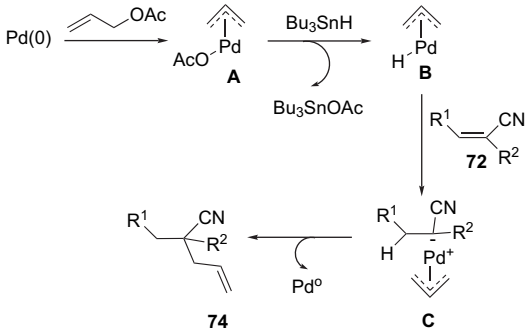
Trost and Yamamoto and their co-workers have developed a method, which afforded the formation of two new carbon–carbon bonds at the β- and α-positions of Michael acceptors via the reaction of activated olefins and bis-π-allylpalladium complexes.[31] Based on the original findings, Shim et al. reported a highly regiospecific carbon–carbon bond formation at the α-position of activated olefins.[32] They found that palladium catalyzed a three-component reaction between Michael acceptors **72a–j**, allyl acetate **73** and Bu_3SnH to give the α-addition products **74a–j** in good yields (Table 7). The

Table 7



Entry	R^1	R^2	Compound **74** (yield %)
1	Ph	CN	**a** (97)
2	2-Furfuryl	CN	**b** (83)
3	3-Tolyl	CN	**c** (97)
4	4-Tolyl	CN	**d** (97)
5	2-Naphthyl	CN	**e** (92)
6	*t*-Bu	CN	**f** (72)
7	2-Anisyl	CO_2Et	**g** (73)
8	3-Anisyl	CO_2Et	**h** (72)
9	Ph	CO_2Et	**i** (77)
10	Ph	SO_2Ph	**j** (91)

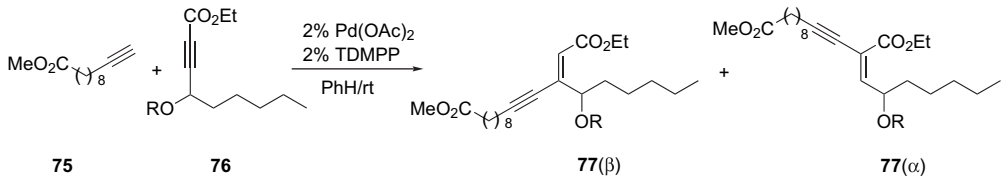
new carbon–carbon bond has been constructed regioselectively at the α-position of Michael acceptors containing two CN or one CN and COOEt or SO_2Ph as electron-withdrawing groups with electron-rich or electron-neutral substituents at the β-position. One of the possible mechanisms for this transformation is shown in Scheme 17. Thus, the oxidative addition of Pd(0) to allyl acetate led to the formation of a π-allylpalladium acetate complex **A**. Transmetalation of **A** with Bu_3SnH followed by hydropalladation of the resulting intermediate **B** to Michael acceptors **72** affords palladium complex **C**. The reductive elimination of Pd^0 from **C** gave the corresponding addition products **74**.



Scheme 17.

The excellent coordinating ability of alkynes for transition metals has been utilized in β-additions of terminal alkynes to Michael acceptors catalyzed by palladium complexes.[33a] The *contra*-Michael-type regioselectivity in the Pd-catalyzed cross coupling of alkynes has been observed by Trost et al. during the synthesis of *Z*-enediynes.[33b] Thus, the addition of alkyne **75** to protected γ-hydroxy alkynoates **76a**,**b** catalyzed by palladium in the presence of an electron-rich ligand such as tris(2,6-dimethoxyphenyl)phosphine (TDMPP) provided a mixture of two regioisomeric products **77a**,**b** (α and β) (Scheme 18). It appears that steric effect plays a significant role, because the free hydroxy group **76c** gave only the β-addition product **77c**(β).

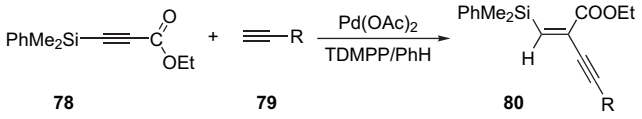
The formation of a C–C bond exclusively at the α-carbon of Michael acceptors was studied in the reaction of 3-(dimethylphenylsilyl)propynoate (**78**) with terminal alkynes **79** (Table 8).[33c] The reaction occurs with the exclusive formation of the α-addition product **80**. The regioselectivity-determining step was suggested to be the migratory insertion step, which led to the formation of the adducts **A** and **B**, as depicted in Scheme 19. The polarization of the transition state during migration favours placing the palladium complex at the α-position of the Michael acceptor **78**, providing the complex **A**. When R^1 in **78** is sterically very bulky, however, complex **B** is favoured, leading to an overall α-substitution.



	Yield of **77** (%)	Ratio β/α
a R = TBDMS	80	66/34
b R = PMB	83	77/23
c R = H	78	100/0

Scheme 18.

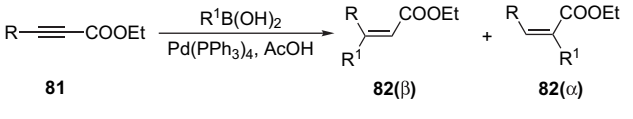
Table 8



R	Yield of **80** (%)
Ph	86
$CH_2CH(CO_2Me)_2$	66
$(CH_2)_3CHO$	73
CH_2CH_2OAc	48
	99
	93

Palladium-catalyzed α-hydroarylations and α-hydroalkenylations of alkynes with organoboronic acid derivatives have recently been reported.[34] The addition of a series of alkenyl and aryl organoboronic acids to various alkynes conjugated with electron-withdrawing groups (e.g., alkynoates **81**) gave a mixture of two regioisomeric products **82**(α) and **82**(β) (Table 9).

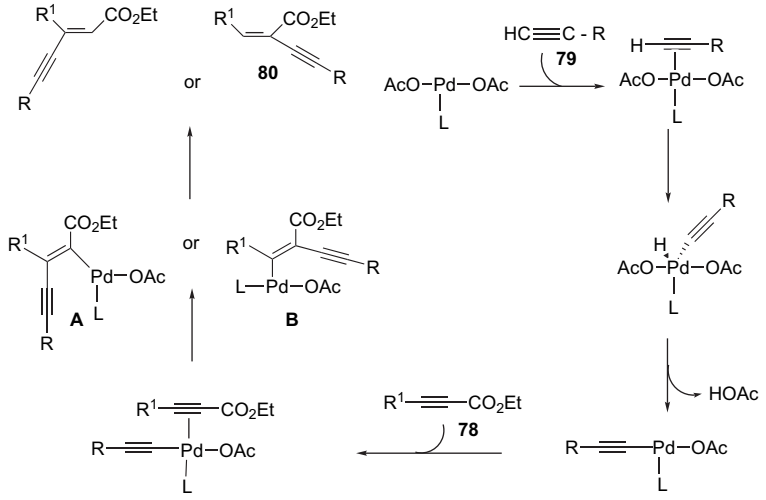
Table 9



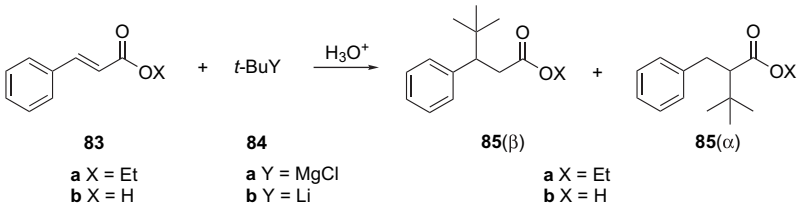
Entry	R	R^1	Ratio **82** β/α	Yield (%)
1	*n*-Bu	Ph	4:1	(80)
2	Ph	Ph	4:1	(84)
3	*n*-Bu	*n*-BuCH=CH	3:1	(85)
4	Ph	*n*-BuCH=CH	1:1	(78)

5. Controlling selectivity of the Michael reaction with organometallic reagents

Most additions of organometallic reagents to activated carbon–carbon double bonds lead to the formation of single regioisomers as products of the conjugated β-addition to Michael acceptors. Under some circumstances, the addition of organometallic reagents can occur at carbon-α of the Michael acceptor. The regioselectivity of this addition is determined by the nature of both the Michael acceptors and the organometallic reagents, as well as the reaction conditions.



Scheme 19.



Scheme 20.

Michael acceptors such as cinnamic acid and its esters, as well as primary and secondary amide derivatives, provide mixtures of 3- and 2-alkyl-substituted phenylpropionic acids **85**(β) or **85**(α) (or their corresponding derivatives) upon reaction with alkyllithium or Grignard reagents (Scheme 20). Crossland[35] first described the competition between conjugated addition and α-addition for the reaction of *tert*-butylmagnesium chloride (**84a**) with ethyl cinnamate (**83a**), which led to the formation of the corresponding **85a**(β) and **85b**(α) products as a 60/40 mixture (70%). In contrast to the ester **83a**, cinnamic acid **83b** underwent the conjugated addition under similar conditions yielding the β-adduct **85b** as the only product. The 60/40 mixture of the α and β regioisomers **85b** was later observed by Kruithof et al.[36] for the addition of *tert*-butyllithium (**84b**) to cinnamic acid **83b**. These findings were rationalized by assuming that the β-adduct **85** is a result of a single electron transfer (SET) from the metalloorganic reagents **84** to the cinnamic derivatives **83a** or **83b**, which in turn give rise to the radical anion **A** and radical cation **B** (Scheme 21).[35b] Both are formed within a cage and may rearrange to **C**. Diffusionless radical coupling between a *tert*-butyl radical and radical **C** (path a) produces the conjugated product **85**(β). On the other hand, the α-adduct **85** is formed by adding a 'diffused free' *tert*-butyl radical to the cinnamic derivative **D** (path b). The resulting benzyl radical **E** is further reduced by the radical **C** and then, finally, carbanion **F** is protonated to give the α-adduct **85**. This mechanism was confirmed by the fact that, in the presence of α-methylstyrene (as a radical trap), the amount of the α-adduct **85** was significantly lower.

The influence of the steric and electronic effects of Michael acceptors on the regioselectivity of the addition of organometallic reagents has been studied by Aurell et al.[37] The role of steric effects was shown in the reaction of 'flat' fluorenylideneacetic acid **A** (Fig. 6) with butyllithium, where a mixture of two regioisomers was obtained. In contrast, 3,3-diphenylpropanoic acid **B**, with at least one phenyl group deviating from the plane of the conjugated system, upon treatment with butyllithium exclusively gave the α-alkylated product. The electronic effect was examined with a number of *p*-, *o*- and *m*-substituted cinnamic acids as Michael acceptors. As shown in Table 10, the addition of *tert*-butyllithium to cinnamic acids **86a**–**g** favours the α-alkylated products **87a**–**g**(α) in the presence of electron-withdrawing groups, whereas the presence of strong electron-donating groups, e.g., **86h**, leads to the expected Michael β-adduct **87h** as the major product. Steric hindrance most likely also contributes to the regioselectivity of the addition to *o*- and *p*-methoxycinnamic acid (entry 3 vs 5). The difference is probably due to the additional complexation of the lithium cation on the benzylic anionic carbon with the methoxy group oxygen atom, which is

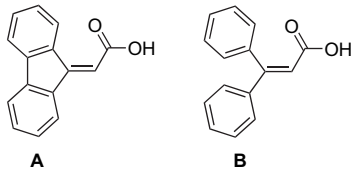
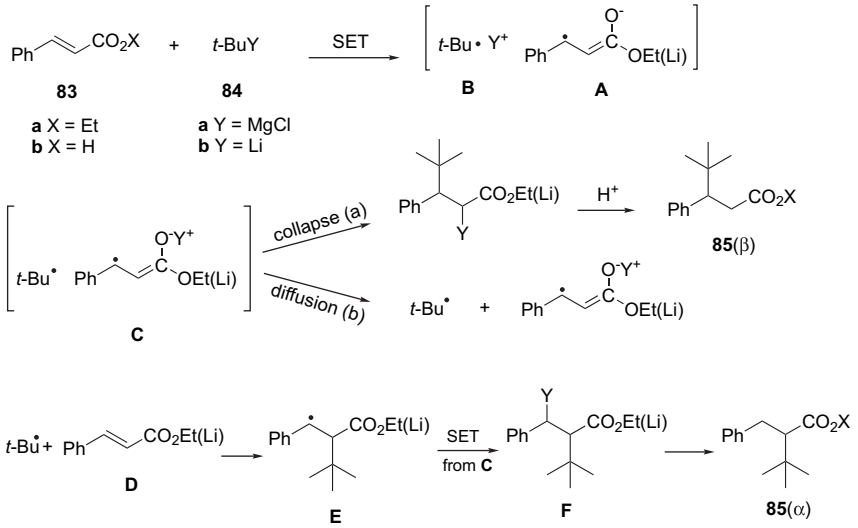
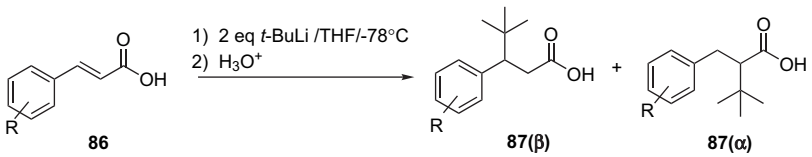


Figure 6.



Scheme 21.

Table 10



Entry	**86**	R	Crude yield (%)	Ratio **87** β/α
1	**a**	H	82	37:63
2	**b**	*p*-Me	91	51:49
3	**c**	*p*-MeO	88	75:25
4	**d**	*m*-MeO	84	36:64
5	**e**	*o*-MeO	88	42:58
6	**f**	*p*-Cl	89	38:62
7	**g**	*m*-Cl	88	31:69
8	**h**	*p*-NMe_2	79	84:16

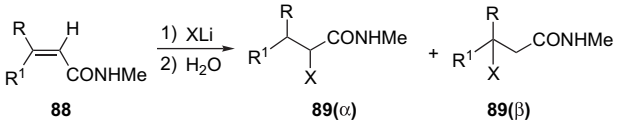
possible for the α-adduct of the *o*-methoxy-, but not the *p*-methoxy, substrate. On the basis of these findings, the authors postulated that a polar mechanism can be competing with the SET process of the addition of organolithium reagents to cinnamic acid.[37]

The nature of the organometallic reagents is also an important factor in controlling the regioselectivity of the addition of organolithium reagents to cinnamic acid. Kruithof et al.[36] found that the addition of *n*-butyllithium to cinnamic acid led mostly to the conjugated product with a very small amount (6%) of the α-alkylated adduct. These findings were confirmed by Aurell et al.,[37] who obtained the same distribution of products. In the case of *tert*-butyllithium, however, a mixture of Michael **87a**(β) and α-alkylated **87a**(α) adducts in a 37/63 ratio and in 82% yield was found (Table 10, entry 1). It was also shown that *sec*-butyllithium as reagent afforded the α and β regioisomers in a 60/40 ratio and phenyllithium provided exclusively the conjugated addition product. The formation of the α and β regioisomers has also been noted for the addition of *sec*- and *n*-butyllithium reagents to cinnamic acid by other workers.[38]

Klumpp et al. described the formation of the α-alkylated adducts in the reactions of organolithium reagents with α,β-unsaturated secondary amides **88a–c**.[39] The authors observed that secondary amides of the type **88a**,**b** react with an organic group of the lithium reagent to yield predominantly the α-addition product in 90% yield for **89b**(α) and 60% for **89a**(α) (Table 11). The α-adduct was only formed in 14% yield when R and R^1 were both phenyl rings, e.g., **89c**(α). The formation of the conjugated addition products as the sole products **89d**(β) or **89e**(β) was observed for **88d**,**e** (R=$SiMe_3$, R^1=H). Addition at the α-carbon atoms was also observed for the reaction of ynoates of the type **90a–h** with organolithium reagents (Table 12). In all cases α-alkylated products **91a–g**(α) were obtained as the major adducts except in the reaction of **90h** with *n*-BuLi, where the conjugated product **91h**(β) was dominant.

Klumpp et al. consider that neither the steric hindrance nor the carbanion-stabilization effect by the R group are major factors favouring the *anti*-Michael addition.[39] Although it is known that carbanion stabilization by the R group can induce 100% α-addition in the case of ynamides **90a–e** and **90g** (Table 12). In the enamide series **88a–e** (Table 11), however, even the presence of two carbanion-stabilizing groups was not sufficient enough to obtain exclusively the α-substitution product. The monosubstituted enamides **88d**,**e** underwent conjugated addition only. In the above reactions, the carbanion-directing effect of trimethylsilyl is slightly stronger than that of phenyl (towards the attached carbon), resulting in predominant α-addition. It is known that free-energy lowerings by *anti*-Michael addition are always larger for

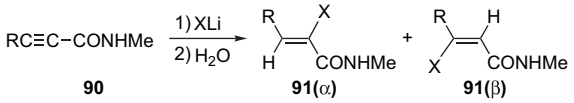
Table 11



Series	R	R^1	X	Yield (%)	Composition of product after hydrolysis (%)	
					89(α)	**89**(β)
a	$SiMe_3$	$SiMe_3$	Me	60	60	15[a]
b	$SiMe_3$	$SiMe_3$	*n*-Bu	65	90	10
c	Ph	Ph	*n*-Bu	80	14	37[a]
d	$SiMe_3$	H	*n*-Bu	75	—	100
e	$SiMe_3$	H	Me	74	—	100

[a] After hydrolysis, starting material was also detected.

Table 12



Series	R	X	Yield (%)	Composition of product after hydrolysis	
				91(α)	**91**(β)
a	$SiMe_3$	*s*-Bu	53	98	1
b	$SiMe_3$	Me	40	94	—
c	$SiMe_3$	*n*-Bu	58	92	—
d	$SiMe_3$	*t*-Bu	62	98	1
e	$SiMe_3$	Ph	17	100	—
f	Ph	Me	61	41	37[a]
g	Ph	*n*-Bu	92	100	—
h	*t*-Bu	*n*-Bu	60	10	90

[a] After hydrolysis, starting material was also detected.

the R–C≡C–C=O than for the RHC=CH–C=O system, while, for Michael addition, the opposite effect is true.[40] Presumably, these reactions are promoted by the formation of complexes between the organolithium reagent and the amide group, which most probably controls regioselectivity. Klumpp[39] postulated that the lithium compounds **A** and **B** (Fig. 7) are precursors for the α-alkylated products of the type **89**(α) and **91**(α). On the other hand, the allenoate **C** and enolate **D** were proposed to be intermediates for the conjugated addition pathway, which led to the formation of **89**(β) and **91**(β), respectively. The precoordination of the organolithium reagent by the substrate through CONLiMe species and lowering of the alkene (alkyne) LUMO energy was hypothesized as possible reason for the α-addition in these reactions. These findings showed that the formation of the CONLiMe could be utilized as a tool for controlling the reactivity and selectivity in organolithium chemistry.

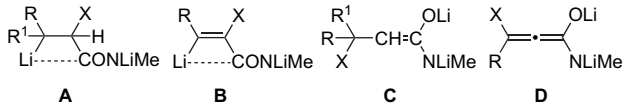
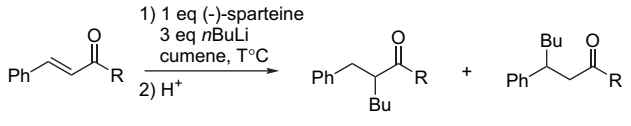


Figure 7.

Bermand et al.[41] observed predominant α-addition (vs conjugated addition) in the reaction of *n*-butyllithium with cinnamyl amides **92** at low temperature (Table 13). The best results were obtained using secondary amides as Michael acceptors, while a tertiary amide (Table 13, entry 4) led to the exclusive formation of the conjugated product **93**(**β**). It is worth noting that the addition of sparteine facilitated the formation of the α-alkylated secondary cinnamyl amides **93**(**α**) in nonpolar solvents. The procedure with (−)-sparteine as additive was further utilized in the diastereoselective synthesis of various α-alkylated amides.[41b] The formation of *anti*-Michael adducts has also been observed in the addition of lithium *tert*-butylcuprate to enynes.[42]

Table 13

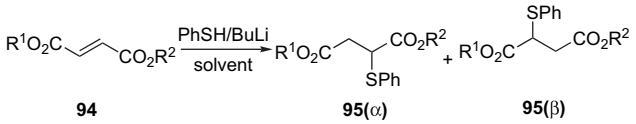


Entry	R	*T* (°C)	Time (h)	Ratios **α/β**	Yield of **93**(**α+β**) (%)
1	NH*i*-Pr	−20	5	70:30	67
2	NHMe	−30	24	63:37	49
3	NH_2	−40	5	66:34	44
4	NMe_2	−20	4	0:100	27

6. Miscellaneous Michael acceptors leading to *anti*-Michael addition

The presence of two electron-withdrawing groups, one at C_α and the other at C_β, in Michael acceptors usually enhances their reactivities. It also incurs regioselectivity problems unless the two groups are identical. The regioselectivity of the Michael addition of thiols to unsymmetrical fumaric derivatives was investigated by Kamimura et al.[43] They found that

Table 14



Series: **a** R^1 = Me, R^2 = Et
b R^1 = Et, R^2 = *t*-Bu

Entry	**94**	Solvent	**95** Yield (%)	Ratio **α/β**
1	**a**	THF	96	60:40
2	**a**	CH_2Cl_2	99	59:41
3	**b**	THF	75	92:8
4	**b**	DME	82	92:8
5	**b**	CH_2Cl_2	84	97:3

the regioselectivity of the Michael adducts of thiols with unsymmetrical fumaric diesters **94a**,**b** is efficiently controlled by the presence of a lithium cation in the non-coordinating solvent such as CH_2Cl_2 leading to the exclusive formation of one of the regioisomers **95a**,**b** (α) or (β) (Table 14).[43a] The best regioselectivity was observed in the addition of benzenethiol in the presence of BuLi to *tert*-butyl ethyl fumarate (**94b**) (Table 14, entry 5). In this case, the thiolate selectively attacked the *tert*-butoxycarbonyl site of the fumaric ester **94b**, leading predominantly to α-substitution with respect to the *tert*-butyl ester. Such results can be explained by the fact that the lithium cation is not soluble in CH_2Cl_2 and can act as a strong Lewis acid and likely coordinates to the carbonyl group from the ethyl ester **94b** (Fig. 8). Thus, due to the steric bulkiness of the *tert*-butyl group, the lithium cation selectively coordinated the ethoxycarbonyl group, which is then activated resulting in the formation of diastereomer **95b**(α) as the dominant one.

Kamimura et al. have also shown that the regioselectivity of the Michael addition to fumaric tertiary amide esters can be efficiently controlled by the presence or absence of base resulting in the formation of either of two isomers in a highly regioselective manner.[43b] Thus, the addition of benzenethiol to ethyl fumaric amide **96a** in the presence of a catalytic amount of Et_3N led to the formation of the adducts **97** in 85% yield as a mixture of two regioisomers. The β-addition product with respect to the ester group **97**(β) was found to be a major isomer (Table 15, entry 1). Without the aid of a base, the addition proceeded with a high level of regioselectivity affording the single isomer **97**(α) (Table 15, entry 2). The other tertiary amide derivatives, e.g., **96b**, also showed the same regiochemical behaviour. In the case of the secondary amides, e.g., **96c**, the same tendency was observed with

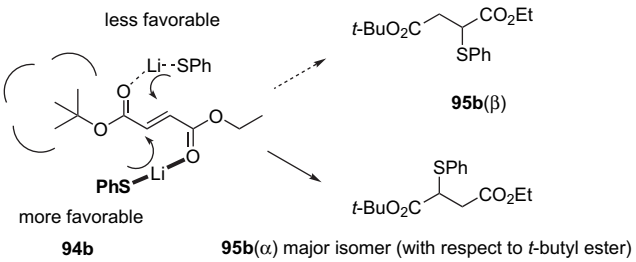
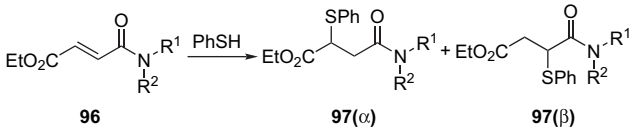


Figure 8.

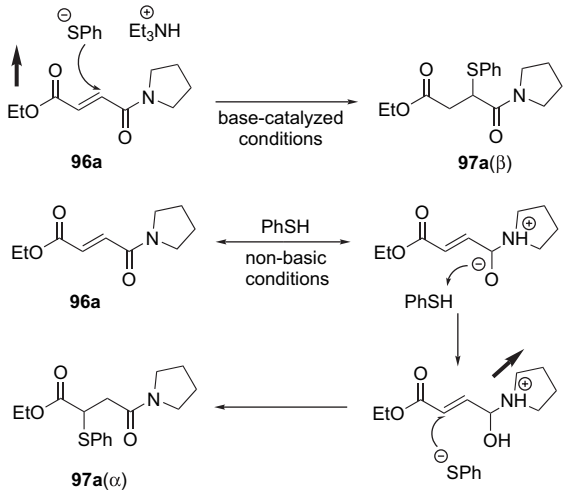
Table 15



Series: **a** $R^1 = R^2 = -(CH_2)_4-$
b $R^1 = R^2 = Bn$
c $R^1 = Bn$, $R^2 = H$

Entry	**96**	Conditions	**97** Yield (%)	Ratio **α/β**
1	**a**	X	85	10:90
2	**a**	Y	86	99:1
3	**b**	X	46	13:87
4	**b**	Y	91	>98:2
5	**c**	X	77	2:98
6	**c**	Y	20	83:17

Conditions: X, Et_3N/EtCN; Y, CH_2Cl_2, without base.



Scheme 22.

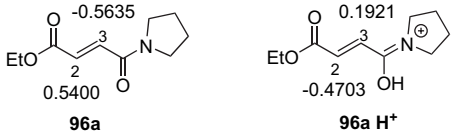


Figure 9.

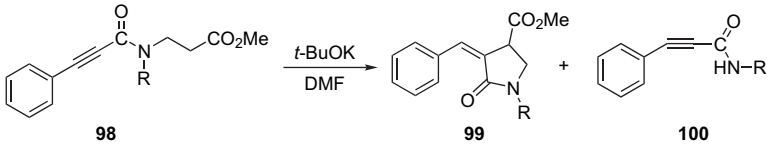
respect to the formation of the regioisomer **97**(β) in basic condition (Table 15, entry 5), but the formation of **97**(α) in non-basic conditions occurred in low yield (Table 15, entry 6).

These results showed that nucleophilic attack of thiolates prefers the β-carbon to the ester group under conventional basic conditions, while attack of thiols occurs at the α-carbon to the ester group in the absence of base. The basic conditions efficiently generate thiolate anions that add to the β-carbon with respect to the ester group, yielding product **97**(β), since the ester group usually acts as a much stronger electron-withdrawing group than the amide (Scheme 22). In the absence of base, the amide carbonyl acts as a Lewis base, which coordinates to the acidic proton in benzenethiol to form an iminium ion intermediate.[43] The protonated amide group becomes a stronger EWG than the ester and addition takes place at the α-carbon with respect to the ester group to give predominantly regioisomer **97**(α). To support the observed regioselectivity for the addition of thiols to **96**, the authors executed a PM-3 level semiempirical calculation.[43c] The coefficients of LUMO at C2 and C3 of the optimized structure **96a** indicated that C3 is the reactive carbon under basic conditions (Fig. 9). For the protonated amide carbonyl, however, the LUMO coefficient for C2 was calculated and C2 was found to be more reactive towards nucleophilic attack, in agreement with the experimental results.

A few examples of intramolecular Michael addition of nucleophiles to form α-addition products have also been reported.[44,45] The application of ynamides **98a–c** (Table 16) for the synthesis of pyrrolidine derivatives **99a–c** represents an example of the intramolecular α-addition of a carbanion to an α,β-acetylenic species.[45] Thus, treatment of acetylenic tertiary amide **98a** with potassium *tert*-butoxide afforded the elimination product of methyl acrylate to produce the secondary amide **100a** and a novel five-membered ring product **99a** resulting from the α-addition of the ester enolate to the ynamide moiety (Table 16). The substituent, which suppressed elimination, most efficiently was found to be a *tert*-butyl group affording 89% of the α-addition product **99c**. It is noteworthy that, during the course of the reaction the formation of the six-membered ring product via β-addition to the ynamide was not observed.

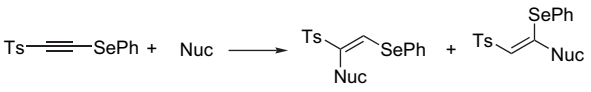
Unsaturated sulfones can serve as Michael acceptors and are known to undergo nucleophilic addition at the β-position.[46] The sulfone group like the carbonyl group has an activating effect upon an adjacent carbon–carbon double or triple bond with respect to the conjugated additions. Back et al.[47] found that substituted acetylene sulfones with a phenylseleno

Table 16

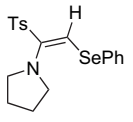
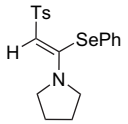
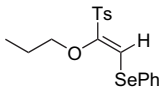
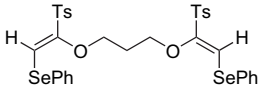
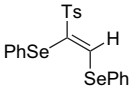
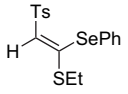


Series	R	**99** yield (%)	**100** yield (%)
a	Me	48	39
b	$CHPh_2$	31	52
c	*t*-Bu	89	5

Table 17



101 **102** **103**

Entry	Nucleophile	Products (isolated yield %)	
1	Pyrrolidine	 **102a** (66)	 **103a** (32)
2	PrONa	 **102b** (92)	
3	$NaOCH_2CH_2CH_2ONa$	 **102c** (63)	
4	NaSePh	 **102d** (62)	 **103d** (32)

group at carbon-β undergo unexpected α-addition of heteronucleophiles. Thus, the reaction of sulfone **101** with pyrrolidine afforded two regioisomers: the unexpected **102a** as a product of α-addition (66% yield) and the expected conjugated product **103a** (32% yield) (Table 17, entry 1). The addition of a hard nucleophile such as alkoxide (PrONa) produced the corresponding α-addition product **102b** as a single isomer in excellent yield, while sodium 1,3-propanedialkoxide gave the α-adduct **102c** as a dimmer (entries 2 and 3). Employing the soft nucleophiles such selenoates (NaSePh) provided the α-addition adduct **102d** as a major product and conjugated analogue **103d** as a minor product (entry 4). These reactions suggest that the phenylseleno groups are effective as activating groups in conjugated additions, competing effectively with the *p*-toluenesulfonyl group. The authors have also shown that acetylene selenides of the type PhSeC≡CH underwent the conjugated addition with heteroatom nucleophiles.[47b]

7. Conclusions

This review is a first attempt to compile the literature on the subject of α-Michael addition known also as α-substitution, *anti*-Michael addition, abnormal Michael reaction or *contra*-Michael addition. The examples presented in this report have shown that *anti*-Michael addition can be utilized in the synthesis of various compounds and has successfully been employed as the critical steps in the preparation of an important class of compounds such as α- and β-amino acids.

The number of factors which control the regioselectivity of addition varies from the presence of strong electron-withdrawing groups in Michael acceptors to the simple application of the coordination effects with metals. In many cases, 'delicate' manipulations with these factors allowed the synthesis of a single α-adduct regioisomer to be achieved. This review demonstrates that *anti*-Michael additions continue to emerge as an important complement to the fundamental 'traditional' Michael additions.

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Biographical sketch

Elzbieta Lewandowska received her Ph.D. in 1988 from the Adam Mickiewicz University in Poznan working under the direction of Professor S. Kinastowski at University of Agriculture in Poznan. During her research carrier, she did postdoctoral research with Professor D. Fiat at University of Illinois at Chicago (1990) and with Professor Morris J. Robins at Brigham Young University in Provo (1993) working on the synthesis of 2′,3′-didehydro-2′,3′-dideoxy nucleosides. In 2001 and 2003, she was a visiting professor at the Florida International University working in the field of nucleoside compounds (Prof. S. F. Wnuk) and on the regioselectivity of Michael addition (Prof. D. C. Chatfield). Recent research has focused on the nucleophilic α-addition to alkenoates.