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Aza-Michael reaction: achievements and prospects

A Yu Rulev

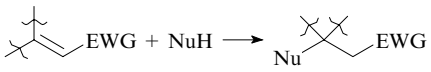
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Abstract. Data published in the last 10 years on the use of the aza-Michael reaction in organic synthesis are described systematically. The attention is focused on environmentally friendly processes following green chemistry principles and on methods for the synthesis of compounds that are difficult to access by other routes. The bibliography includes 269 references.

I. Introduction

In spite of great advances in chemistry and its benefits to mankind, chemophobia is widespread all round the world. The most common fear is related to environmental pollution from chemical and pharmaceutical waste products, whose amounts are often several dozen times higher than the amounts of useful products.[1] Hence, the main question is not which products should be produced but rather which processes should be used for this purpose. Evidently, key advances in organic synthesis can be achieved by the development of reliable elegant strategies following green chemistry principles. Undoubtedly, the addition of a carbanion (Michael reaction) and heteroatom-centred nucleophiles (hetero-Michael reaction) to alkenes activated by a strong electron-withdrawing group are such processes. They are characterized by the 100% atom efficiency and use cheap and easily available starting reagents. Hence, these approaches have become increasingly popular as fundamental methods for the construction of carbon – carbon and carbon – heteroatom bonds. In the 2000s, great efforts of the chemical community were focused on the search for efficient catalysts for the chemo- and stereoselective conjugate nucleophilic addition. Main advances were summarized in reviews concerned with the Michael reaction and hetero-Michael reaction,[2] including those with oxygen-,[3] sulfur-,[4,5] selenium-,[5] and phosphorus-centred nucleophiles.[6,7]



EWG = CO_2R, $C(O)NR_2$, C(O)R, CN, SO_2R, $P(O)R_2$;
Nu = NHR, NR_2, PR_2, OR, SR, SeR (R = Alk, Ar).

Among nucleophilic addition reactions with electron-deficient alkenes, the aza-Michael reaction is of particular interest, which is not surprising. Thus it is this reaction that is often the shortest route to β-amino acids and their derivatives, as well as to β-amino ketones, which are, as known, valuable starting compounds for the synthesis of various nitrogen-containing biologically active compounds, antibiotics, and other drugs. The versatility of this reaction is that it can occur with various N-nucleophiles (aliphatic and aromatic amines, amides, carbamates, and azides) and Michael acceptors (enones, acrylates, unsaturated nitriles, amides, sulfones, phosphonates, trifluoromethylalkenes, and nitroalkenes). Moreover, the aza-Michael reaction often initiates domino transformations resulting in the formation of polyfunctional derivatives, including heterocycles and analogues of natural substances.

The first report on the successful reactions of N-nucleophiles with conjugated acceptor systems dates back to 1874, when two Russian chemists, Academician N N Sokoloff and his follower P A Latschinoff, performed the addition of ammonia to mesityl oxide.[8] It should be mentioned that Arthur Michael discovered the reaction named after him almost 15 years later.[9] In spite of the considerable age, the aza-Michael reaction continues to attract the attention of synthetic chemists forcing them to search for new convenient and environmentally friendly ways to perform this reaction. The advances in this field were briefly considered relatively recently.[10,11] The present review summarizes the

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results of research into the conjugate addition of nitrogen-containing nucleophiles to electron-deficient alkenes obtained in the last decade. The emphasis is given to the synthetic aspect of the aza-Michael reaction, because its asymmetric version has been covered in several reviews.[12–16]

II. Various nucleophiles in the aza-Michael reaction

1. Aliphatic amines

The aza-Michael reaction is a particular case of the hydroamination of alkenes which is generally characterized by high activation barriers.[17] However, the introduction of an electron-withdrawing substituent into an alkene molecule facilitates the nucleophilic attack on the β-carbon atom of the double bond. Generally, the conjugate addition easily occurs in the presence of either base or acid catalysts. The former are used for the activation of the Michael donor; the latter, for the activation of the Michael acceptor. The choice of the catalyst is determined by the chemical activity of each reaction component.

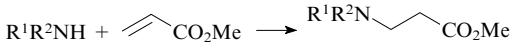
In some cases, the addition of highly nucleophilic aliphatic amines to conjugated systems occurs in the absence of a catalyst. Evidently, the higher the nucleophilicity of the Michael donor and the higher the electrophilicity and steric accessibility of the β-carbon atom of the starting alkene, the easier the reaction proceeds.

The data on the addition of secondary and primary aliphatic amines to various conjugated systems containing the terminal double bond are given in Tables 1–3. In spite of insignificant discrepancies, the results of investigations provide a fairly clear general idea of the process. Cyclic secondary amines (piperidine, morpholine, monosubstituted piperazine) easily add to alkyl acrylates, acrylonitrile, or methyl vinyl ketone to form Michael adducts in high yields. Their acyclic analogues are less reactive and their synthesis requires more drastic conditions and(or) a longer reaction time. In both cases, the reactions proceed so smoothly and selectively that there is often no need to additionally purify the reaction products. Amines containing long-chain (dioctylamine) (see Table 3) or branched (diisopropylamine) substituents (see Table 1) proved to be absolutely inactive under these conditions.

The reactions with primary amines are more complicated. For example, the reaction of *tert*-butylamine with diethyl vinylphosphonate at room temperature afforded the target aminophosphonate in 68% yield only after 70 h (see Table 3). The reaction of more nucleophilic benzylamine with the same substrate was completed within one day, whereas in boiling water the Michael adduct was formed in quantitative yield within less than one hour (see Table 3). In addition, it should be taken into account that the reactions of primary amines can give bis-adducts (see Tables 1–3).

In most cases, the noncatalytic aza-Michael reaction is restricted to alkenes containing the terminal double bond. The nucleophilic addition to β-substituted Michael acceptors is evidently more difficult to perform. For example, diethylamine surprisingly easily reacts with methyl acrylate (see Table 1), whereas the reaction of the same amine with ethyl crotonate afforded the product in 27% yield even when the reaction was performed for 20 h at room temperature.[23] Benzylamine gives the adduct with methyl acrylate (see Table 1), but does not react with its closest homologue.

Table 1. Addition of aliphatic amines to methyl acrylate.



Amine	Reaction conditions			Yield (%)	Ref.
	solvent	temperature /°C	time /h		
Piperidine	–	20	1	23	18
	–	20	3	60 [a]	19
	–	30–32	0.75	90	20
	MeCN	20	7	50	21
	H_2O	20	12	15 [a]	22
	H_2O	20	14	85 [a]	23
	H_2O	20	0.5	92	24
Morpholine	–	20	2	90 [b]	19
	–	20	6	90.7	25
	$Cl(CH_2)_2Cl$	83	3	38	26
	MeCN	20	20	50	27
Et_2NH	–	20	3	50 [b]	19
	–	20	3	95.5	25
	H_2O	20	0.5	86	24
Bu^n_2NH	MeOH	20	6	38	28
Pr^i_2NH	–	20	24	0	25
	$Cl(CH_2)_2Cl$	83	6	15	26
	MeCN	50	24	0	29
	MeCN	50	24	13 [c]	29
	H_2O	20	0.6	85	24
Bn_2NH	MeCN	20	6	3.8	30
$BnNH_2$	–	20	18	90 [d]	25
	MeCN	20	48	70	27
	H_2O	20	6	20 [e]	31
	H_2O	20	15	23 [a]	32

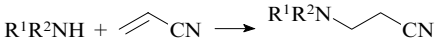
[a] Ethyl acrylate was used as the Michael acceptor; [b] the conversion is given; [c] the reaction was performed at 0.3 GPa; [d] the mixture (~3 : 1) of mono- and bis-adducts; [e] the mixture (35 : 65) of mono- and bis-adducts.

Thus methyl crotonate was completely recovered from the reaction mixture after its stirring with amine in CH_2Cl_2 at room temperature for 12 h.[41]

Therefore, as is shown with the most active aliphatic amines, the search for efficient catalysts for the aza-Michael reaction remains a challenge. Efforts of chemists are directed toward the development of a methodology best following green chemistry principles, in particular, such that it requires small amounts of catalysts (it is desirable that the catalyst can be regenerated) and does not require toxic solvents.

As can be seen from Tables 1–3, the addition of aliphatic amines to various conjugated systems proceeds much more rapidly if water is used as the solvent. It should be noted that the reactions of acrylic acid derivatives with primary amines in an aqueous medium give only mono-adducts.[24] It is well known that water can act as a catalyst for organic reactions by increasing the reactivity of the reactants and enhancing the selectivity of the reaction.[42,43] Apparently, this is associated with the ability of H_2O molecules to form hydrogen bonds with both the strongly electronegative atom of the activating group (through hydrogen atoms) and the NH or NH_2 groups (through the

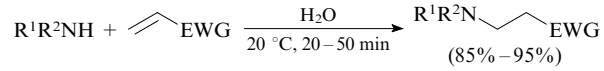
Table 2. Addition of aliphatic amines to acrylonitrile.



Amine	Reaction conditions			Yield (%)	Ref.
	solvent	temperature /°C	time /h		
Piperidine	–	20	3	52 [a]	19
	H_2O	20	0.4	90	24
Morpholine	–	30 – 32	2	91	20
	MeCN	20	20	45	27
	H_2O	20	0.5	90	24
N-Phenyl-	THF	20	48	19	33
piperazine	PEG-400	20	0.6	99	34
Et_2NH	–	20	3	90.6	25
	–	30 – 32	3	75	20
	PhMe	30	2	83 [b]	35
	H_2O	20	0.5	88	24
Pr^i_2NH	–	20	16	62	31
	–	50	16	69	31
	PhMe	30	3	74 [b]	35
$BnNH_2$	–	20	18	93 [c]	25
	PhMe	30	2	92 [b]	35
	H_2O	20	0.5	85	24

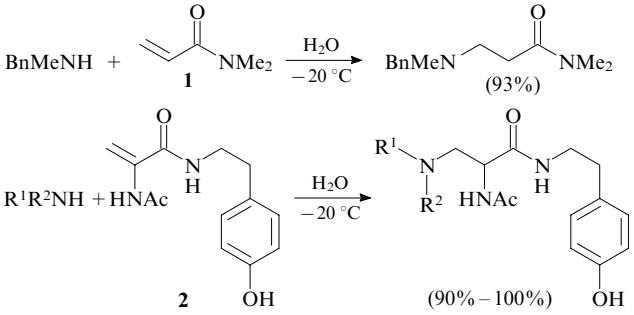
Note. PEG is polyethylene glycol. [a] The conversion is given; [b] GLC data; [c] the mixture (99 : 1) of mono- and bis-adducts.

oxygen atom). In the former case, the electrophilicity of the β-carbon atom of alkene increases; in the latter case, the nucleophilicity of the amine nitrogen atom is enhanced. Therefore, water substantially facilitates the reactions of Michael donors with Michael acceptors by activating both reactants.



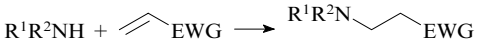
EWG = Ac, CO_2Me, CO_2Et, $C(O)NH_2$, CN;
R^1R^2N = Bu^nNH, BnNH, CyNH, Et_2N, Pr^i_2N, $(CH_2)_4N$, $(CH_2)_5N$, $O(CH_2CH_2)_2N$, $PhN(CH_2CH_2)_2N$; Cy is cyclohexyl.

It is surprising that the aza-Michael reaction can occur even in frozen water![44] For example, amines taken in an excess smoothly add to acrylamide derivatives **1** and **2** in dilute aqueous homogeneous solutions frozen to −20 °C to form Michael adducts in high yields.



R^1R^2N = Me_2N, $HOCH_2CH_2(Me)N$, $O(CH_2CH_2)_2N$.

Table 3. Addition of aliphatic amines to activated alkenes.

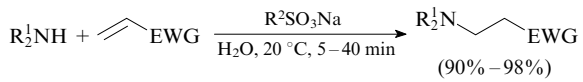


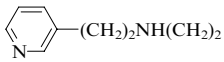
Amine	EWG	Reaction conditions			Yield (%)	Ref.
		solvent	temperature /°C	time /h		
Piperidine	Ac	MeCN	20	20	40	27
	Ac	PEG-400	20	0.6	99	34
	$P(O)(OEt)_2$	H_2O	20	0.12	95	36
	SO_2Ar_F (see [a])	DMF	55 – 60	6	40 [b]	37
	$SO_2C_6F_{13}$-n	CH_2Cl_2	20	1	86	38
	$S(O)C_6F_{13}$-n	CH_2Cl_2	20	1	85	38
Morpholine	Ac	MeCN	20	20	40	27
	Ac	PEG-400	20	0.6	99	34
	$P(O)(OEt)_2$	–	70 – 100	see [c]	80.5	39
	$P(O)(OEt)_2$	H_2O	20	0.75	95	36
Et_2NH	Ac	PEG-400	20	0.6	99	34
	$P(O)(OEt)_2$	H_2O	20	0.75	92	36
	$SO_2C_6F_{13}$-n	CH_2Cl_2	20	1	see [d]	38
	$S(O)C_6F_{13}$-n	CH_2Cl_2	20	48	100	38
$(n\text{-}C_8H_{17})_2NH$	$P(O)(OEt)_2$	H_2O	20	see [c]	0	36
$BnNH_2$	$P(O)(OEt)_2$	H_2O	20	24	92	36
	$P(O)(OEt)_2$	H_2O	100	0.75	100 [e]	36
Bu^tNH_2	$P(O)(OEt)_2$	H_2O	20	70	68	36
Cyclam [f]	SO_2Ph	$Pr^iOH - H_2O$	20	17	68	40
	S(O)Ph	$Pr^iOH - H_2O$	65	24	75	40

[a] The substrate 1,4-$(CH_2{=}CHSO_2)_2C_6F_4$; [b] in the presence of an excess of amine, the fluorine atoms in the benzene ring are replaced; [c] the reaction time was not reported; [d] the yield was not reported; the mixture (46 : 54) of mono- and bis-adducts; [e] ^{31}P NMR data; [f] 1,4,8,11-tetraazacyclotetradecane.

The addition of primary and secondary aliphatic amines to nocathiacins containing the dehydroalanine moiety also easily occurs.

In spite of evident advantages, the use of water as the solvent has serious limitations. One of them is the low solubility of many organic compounds in water. An intelligent solution for this problem is to perform the reaction in the presence of surfactants capable of forming micelles.[45,46] Impressive results were obtained with the use of sodium dodecyl sulfate: the addition of secondary aliphatic amines to methyl vinyl ketone at room temperature was completed within 5–15 min and gave products in almost quantitative yield.[46] Some nitrogen-containing sulfonates, which are formed by the addition of amines to vinyl sulfonate, have high catalytic activity.[47] In the presence of this catalyst (3 mol.%), alkyl acrylates, acrylonitrile, and methyl vinyl ketone react with secondary amines to form Michael adducts in 90%–95% yields.[48] It should be emphasized that these reactions are more difficult to perform in organic solvents.



EWG = Ac, CO_2Me, CO_2Et, CN; R^1_2N = Me_2N, Et_2N, $(CH_2)_5N$, $O(CH_2CH_2)_2N$; R^2 = n-$C_{12}H_{25}O$, .

Another reason for the use of organic solvents is that some reagents and catalysts for the aza-Michael reaction are decomposed or deactivated by water. Candidates for the role of 'organic water' were found among hydroxy-containing solvents. Recently, the catalytic effect has been observed in polyethylene glycol (PEG-400)[34] (see Tables 2 and 3) and glycerol.[49] The use of these solvents is attractive from both synthetic and economic points of view. Both solvents are cheap and are produced on a large scale, allow the use of more hydrophobic reagents, and can be reused after the extraction of the target compound.

The question is which experimental conditions are favourable for the conjugate addition of aliphatic amines. Based on the common knowledge of the reaction mechanism, it would be expected that it is sufficient to activate the Michael acceptor for the efficient reaction with highly nucleophilic amines. When choosing the catalyst, one should bear in mind that the catalyst for the Michael reaction should not initiate side reactions, primarily, the polymerization of the starting alkene.

Since water is considered as an ideal solvent in green chemistry, particular attention was paid to the design of catalytic systems working in an aqueous medium.

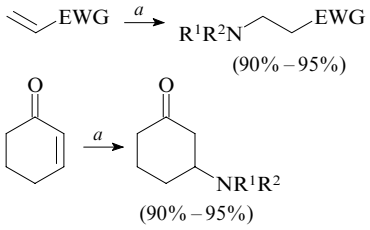
Transition metal salts and complexes were most often considered as potential catalysts for the conjugate nucleophilic addition of aliphatic amines. Certain Lewis acids, such as transition and main-group metal nitrates,[50] chlorides,[22,31,32,41,51–54] and triflates,[22,41,55–58] nickel[59] and copper[60] complexes, and the Zn/NH_4Cl system (zinc dust activated by a saturated NH_4Cl solution)[61] proved to be the most efficient catalysts. As can be seen from Table 4, various aliphatic amines form Michael adducts in high yield in the presence of 5 mol.%–20 mol.% of a Lewis acid. For example, the Cu^{2+} salt-catalyzed addition of piperidine or diethylamine to ethyl acrylate, acrylonitrile, and methyl vinyl ketone in water is completed in 12–15 h and gives products in quantitative yield (see Table 4). Apparently, lanthanide derivatives have the highest catalytic activity in water. For example, even 3 mol.% of cerium ammonium nitrate or samarium chloride are sufficient for the activation of the reactions of cyclic and acyclic amines with terminal alkenes containing the ethoxycarbonyl or cyano group (see Table 4). The addition of primary and secondary amines to acrylic acid derivatives in the presence of $RuCl_3$ (0.5 mol.%) occurs during heating in polyethylene glycol for 3–10 h (see Table 4). The report on the catalysis of these reactions with 0.2 mol.% of $LaCl_3$ is, apparently, erroneous; most likely, 10 mol.% of this salt (0.2 mmol of $LaCl_3$ per 2 mmol of each of the starting reactants) were used.[54] A similar inaccuracy was found when comparing the discussion of the results with the experiment described in the study.[53]

In some cases, not only terminal but also internal alkenes are involved in the aza-Michael reaction. The addition of amines easily occurs in various solvents, but it is most efficient in aqueous solutions (see Table 4).

In addition to Lewis acids, Brønsted acids, such as polystyrenesulfonic acid,[63] tungstophosphoric acid ($H_3PW_{12}O_{40}$),[64] and boric acid,[65] capable of catalyzing the aza-Michael reactions with aliphatic amines were mentioned in the literature. It is interesting that salts of boric acid [for example, borax (sodium tetraborate)] have catalytic activity comparable to that of the acid by itself.[66]

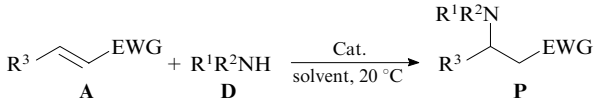
In spite of advantages (the versatility, mild conditions, the absence of organic solvents, high yields of Michael adducts), these methods are less attractive because of long reaction times, the toxicity of the catalyst, and its possible poisoning with amines. In addition, the reactions with primary amines are not always selective and often afford mixtures of mono- and bis-adducts.

That is why the use of transition metal salts on a polymer or mineral support becomes increasingly popular. This modification of catalysts has obvious advantages. First, the catalytic activity of such systems is higher and, as a consequence, the reaction time is considerably shorter and the selectivity of the addition is higher. Second, it is easier to regenerate the catalysts, due to which they can be reused. For example, polyaniline (PANI)-supported $InCl_3$ (Ref. 67) proved to be more efficient as the catalyst for the aza-Michael reaction (compared to individual indium chloride).[31] In the presence of this catalyst, even such amines as Pr^i_2NH and Bu^n_2NH react with methyl acrylate to form Michael adducts in 92%–95% yields. The reactions of primary amines are selective (the percentage of the bis-adduct in the mixture is at most 5%). In addition, not only terminal alkenes (esters and nitriles) but also cyclic enones act as Michael acceptors. Finally, the catalysts can be easily



EWG = CO_2Me, CN; R^1R^2N = BnNH, $(CH_2)_5N$, $O(CH_2CH_2)_2N$, Bu^n_2N, Pr^i_2N; (*a*) R^1R^2NH, $InCl_3$/PANI (10%), H_2O, 20 °C, 10–30 min.

Table 4. Lewis acid-catalyzed conjugate addition of aliphatic amines.



Catalyst (amount)	Michael acceptor (**A**)		Michael donor (**D**)	Ratio **A** : **D**	Reaction conditions		Yield of product (**P**) (%)	Ref.
	R^3	EWG			solvent	time /h		
$InCl_3$ (20 mol.%)	H	CO_2Me, CN	$BnNH_2$, $PhCH(Me)NH_2$, Me_2NH, Pr^i_2NH	1 : 1.2	H_2O	6 – 18	44 – 85 [a]	31
$Bi(NO_3)_3$ (10 mol.%)	H Me see [b]	Ac Bz	piperidine, $S(CH_2CH_2)_2NH$, Bn_2NH	1 : 1	CH_2Cl_2, Et_2O, MeOH, MeCN	12 – 15	64 – 79	50
$Bi(OTf)_3$ (2 mol.%)	H	CO_2Me	$BnNH_2$, $CyNH_2$, All_2NH, pyrrolidine, morpholine, piperazine	2 : 1	MeCN	0.5 – 3	54 – 98 [c]	55
$TiCl_4$ (10 mol.%)	Me	CO_2Et	$BnNH_2$	1 : 1.5	CH_2Cl_2	4.5	28 [d]	41
$FeCl_3 \cdot 7H_2O$ (10 mol.%)	H see [b]	CO_2Et, CN	$BnNH_2$, Bu^nNH_2, Et_2NH	1 : 1.2	H_2O	15	67 – 100 [e]	32
$Cu(OAc)_2$ (10 mol.%)	H	Ac, CO_2Et, CN	Et_2NH, piperidine	1 : 1.2	H_2O	15	100	32
$Cu(OAc)_2$ (5 mol.%)	H Me see [b]	Ac, CO_2Me, CO_2Et, CN CO_2Et	$BnNH_2$, Et_2NH, Pr^n_2NH, Bu^n_2NH, piperidine	1 : 1.2	H_2O	12	74 – 100 [e]	22
$CuCl_2$, $CuBr_2$, $Cu(ClO_4)_2$, $Cu(OTf)_2$, CuBr (5 mol.%)	H	CO_2Et	piperidine	1 : 1.2	H_2O	12	98 – 99	22
$ZrCl_4$ (10 mol.%)	H	Ac, CO_2Me CO_2Et, CN	$BnNH_2$, Et_2NH, Pr^i_2NH, pyrrolidine, piperidine, morpholine, *N*-phenylpiperazine	1.2 : 1	CH_2Cl_2	0.75 – 3	78 – 100 [c]	51
$RuCl_3$ (0.5 mol.%)	H	CO_2Et, CN	Pr^iNH_2, Bu^nNH_2, $BnNH_2$, $PhCH(Me)NH_2$, Bu^n_2NH, piperidine, morpholine	1 – 1.5 : 1	PEG-2000	3 – 10	90 – 100 [e, f]	62
$RuCl_3 \cdot 3H_2O$ (10 mol.%)	H	CO_2Et	piperidine	1 : 1.2	H_2O	12	78	52
$CdCl_2$ (20 mol.%)	H Ph	CO_2Et, CN CO_2Me, NO_2	$BnNH_2$, $BnCH_2NH_2$, Pr^i_2NH, pyrrolidine, morpholine, *N*-phenylpiperazine	1.1 : 1	CH_2Cl_2	2.5 – 4	84 – 93 [e]	53
$LaCl_3$ (0.2 mol.%) [g]	H	CO_2Et, CN	$BnNH_2$, $BnCH_2NH_2$, Pr^i_2NH, pyrrolidine, morpholine, *N*-phenylpiperazine	1 : 1	CH_2Cl_2	2 – 4	84 – 95 [c]	54
$La(OTf)_3$ (10 mol.%)	Me	CO_2Et	$BnNH_2$	1 : 1.5	CH_2Cl_2	6	95 [e]	41
CAN [h] (3 mol.%)	H	CO_2Et, CN	$BnNH_2$, $CyNH_2$, Me_2NH, All_2NH, Pr^i_2NH, Bn_2NH, pyrrolidine, piperidine, morpholine, piperazine, *N*-methyl- and *N*-phenylpiperazine	1 : 1.2	H_2O	12	55 – 99	52
$Sm(OTf)_3$ (10 mol.%)	H Ph	Ac, CO_2Et CN, $C(O)NH_2$ Bz, NO_2	$BnNH_2$, $BnCH_2NH_2$, $PhCH(Me)NH_2$, $PhCH(Pr^n)NH_2$, Bn(Me)NH, Et_2NH, pyrrolidine, morpholine, *N*-phenylpiperazine, $(4\text{-Py})CH_2NHEt$ (Py is pyridyl)	1 : 1	CH_2Cl_2	1.5 – 3	85 – 96 [e]	56
	Me	CO_2Et	$BnNH_2$	1 : 1.5	CH_2Cl_2	6	95 [e]	41

Table 4 (continued).

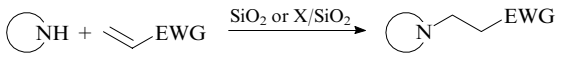
Catalyst (amount)	Michael acceptor (**A**)		Michael donor (**D**)	Ratio **A** : **D**	Reaction conditions		Yield of product (**P**) (%)	Ref.
	R^3	EWG			solvent	time /h		
$SmCl_3 \cdot 6H_2O$ (3 mol.%)	H	CO_2Et	piperidine	1 : 1.2	H_2O	12	72	52
$Yb(OTf)_3$ (10 mol.%)	Me	CO_2Et	$BnNH_2$, pyrrolidine	1 : 1.5	THF, EtOH, PhMe	6	92 – 97 [e]	41

[a] The reactions of primary amines give mixtures of mono- and bis-adducts; [b] cyclohex-2-enone is the Michael acceptor; [c] the reactions of primary amines afford only bis-adducts; [d] in addition to the Michael adduct, crotonic acid benzylamide was isolated (26%); [e] the reactions of primary amines give exclusively monoadducts; [f] the reaction was carried out at 50 °C; [g] probably, erroneous data (see the text); [h] CAN is cerium ammonium nitrate $(NH_4)_2[Ce(NO_3)_6]$.

removed after the completion of the reaction by the simple filtration and can be reused without loss of activity.[67]

Silica gel is an impregnating agent of choice. It should be noted that silica gel can, by itself, catalyze the Michael addition of amines. Generally, the reaction proceeds smoothly both in solvents[68] and in the absence of a solvent.[69] Derivatives of acrylic (esters, nitriles, amides) and methacrylic (esters) acids were used as Michael acceptors. Secondary and primary amines served as donors. The latter compounds gave mono- or bis-adducts depending on the nature of the substrate. The reactions of amines containing branched or bulky substituents (Pr^i_2NH, Cy_2NH) afforded addition products in good yields. After the regeneration, silica gel was reused without a considerable decrease in catalytic activity.

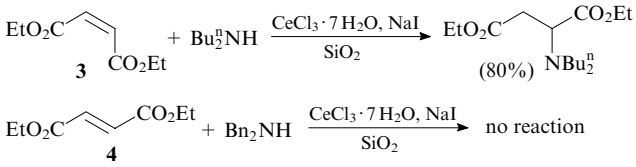
This method was further developed by using silica gel impregnated with Lewis or Brønsted acids as the catalyst.[70 – 74] For example, the deposition of $AlCl_3$ (Ref. 70) or $HClO_4$ (Ref. 71) onto SiO_2 made it possible to prepare highly efficient regenerable heterogeneous catalysts. A comparison of their activity was made by an example of the addition of cyclic amines to activated alkenes.



Amine	EWG	Yield of the product on different catalysts (%)		
		SiO_2 (see [a])	$AlCl_3/SiO_2$ (see [b])	$HClO_4/SiO_2$ (see [c])
$(CH_2)_5NH$	CN	87	72.5	92
	CO_2R (R = Me, Et)	–	100	95
	Ac	–	77.5	95
$O(CH_2CH_2)_2NH$	CN	96	86	90
	CO_2R (R = Me, Et)	–	100	92
	Ac	–	90	95
$(CH_2)_4NH$	CN	–	–	90
	CO_2R (R = Me, Et)	93	100	96

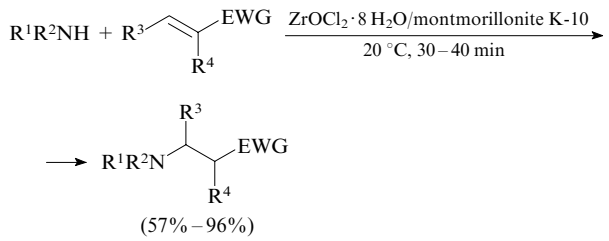
[a] Reaction conditions: 40 – 50 °C, 1 h;[69] [b] reaction conditions: 20 °C, 2 h;[70] [c] reaction conditions: 20 °C, 0.75 h.[71]

A mixture of $CeCl_3 \cdot 7H_2O$ and NaI deposited on an inorganic support proved to be a good catalyst for the aza-Michael reaction.[73 – 76] Thus, silica gel impregnated with this mixture catalyzes the addition of secondary amines to enones and acrylic acid derivatives.[73,74] However, a long time (5 – 10 h) and an equimolar amount of the catalyst are required for the completion of the reaction. In addition, the reaction is very sensitive to the stereochemistry of the starting alkene. For example, the addition of Bu^n_2NH to diethyl maleate (**3**) affords the reaction product in high yield, whereas diethyl fumarate (**4**) does not react with Bn_2NH under these conditions. This result was attributed to the retro-Michael reaction that proceeds on silica gel and dominates over the conjugate addition.



The use of neutral aluminium oxide as a support made it possible to perform the reactions with Michael acceptors having the *E* configuration.[75] In the absence of Al_2O_3, the target adducts were obtained in substantially lower yields due to side reactions.

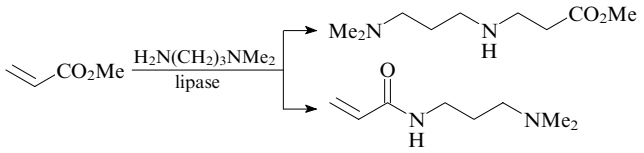
Aluminosilicates, such as zeolites and natural clays, have long been used as mineral supports in organic reactions. Some of these compounds proved to be efficient heterogeneous catalysts for the aza-Michael reaction.[26] Montmorillonite K-10 characterized by excellent adsorption and ion-exchange properties has become the most popular catalyst. It was found that the addition of enones and derivatives of α,β-unsaturated acids to amines easily occurs in the presence of $ZrOCl_2 \cdot 8H_2O$ supported on this mineral.[18] Only acrolein reacts exclusively at the formyl group. This method appeared to be efficient for both derivatives containing the terminal double bond and (which is particularly important) for β-methyl- and β-phenyl-substituted homologues. In all cases, the reactions proceed under mild conditions and are completed within a few minutes to form Michael adducts in high yield.



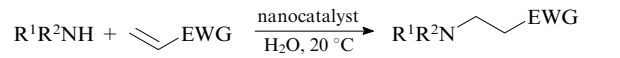
R^1R^2N = Bu^nNH, BnNH, CyNH, Et_2N, $(CH_2)_4N$, $(CH_2)_5N$, $O(CH_2CH_2)_2N$; R^3 = H, Me, Ph; R^4 = H, Me; EWG = CO_2Me, CO_2Et, CN, Ac, $C(O)NH_2$.

Other simple compounds and composites on mineral or polymer supports also exhibit different catalytic activity: I_2 on aluminium oxide,[77] $[Ti_4H_{11}(PO_4)_9]\cdot n\,H_2O$ on titanium oxide,[19] sulfated zirconium(IV) oxide,[78] polymer-supported $Gd(OTf)_3$,[79] polymer-supported azaphosphatrane nitrate,[27] polyaniline and cellulose, impregnated CuI (Ref. 80) and Cu (Ref. 81), as well as heterogeneous catalysts based on ion-exchange resins,[82–84] hydroxyapatites,[85] and hydrotalcites.[28,86]

Biocatalysts, for example, lipases characterized by high activity and stability in organic media have found use in the aza-Michael reaction along with mineral catalysts. In the presence of biocatalysts, the addition of primary and secondary amines to acrylonitrile[35,87] or methyl acrylate[88–90] occurs 2–100 times more rapidly than in non-catalytic conditions. The enzyme can be used many times without loss of activity. The aminolysis of the methoxycarbonyl group is the only complication in the reaction with methyl acrylate. The ratio of the competitive reactions depends on the experimental conditions and the amount of the biocatalyst.



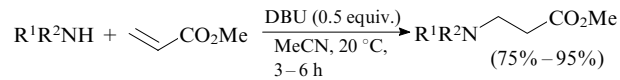
The extensive development of nanotechnologies gave impetus to the use of nanosized catalysts in organic synthesis. Impressive results have been recently obtained for the aza-Michael reaction catalyzed by copper nanoparticles,[33] copper(II) oxide nanoparticles,[91] or monodisperse SiO_2@Cu core–shell nanoparticles,[92] and nanoferrite-anchored glutathione.[93,94] It is hardly probable that there are other catalytic systems comparable in efficiency of the activation of the conjugate addition of aliphatic amines to different Michael acceptors. The reactions with terminal alkenes are completed within 1–20 min, and the yields of adducts are up to 80%–98%. Moreover, the use of water as the solvent allows the catalyst to be esily regenerated, the activity of the latter remaining unchanged for at least five cycles.



Amine	EWG	I		II		III	
		time /min	yield (%)	time /min	yield (%)	time /min	yield (%)
Piperidine	CO_2Me	5	90	30	92	420	50
	CO_2Me	–	–	–	–	1200	50
	CN	1	95	30	90	–	–
Morpho-	CO_2Me	5	90	–	–	–	–
line	CN	4	98	30	90	1200	45
	Ac	20	80	–	–	1200	40
$BnNH_2$	CO_2Me	10	90 [a]	360	20	2880	70
	CN	5	90	30	85	–	–
	CN	10	90 [a]	–	–	–	–

Note. (I) the catalyst SiO_2@Cu, H_2O;[92] (II) in the absence of a catalyst, H_2O;[24,31] (III) in the absence of a catalyst, MeCN.[21,27] [a] 2 equiv. of the Michael acceptor; only the bis-adduct was obtained.

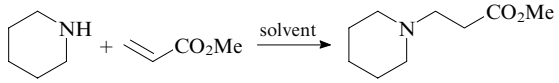
There are a few examples of the conjugate addition of aliphatic amines in the presence of base catalysts. When taken in an excess amount, amines are generally readily involved in the aza-Michael reaction and seemingly do not require additional bases. However, the recent publications[95–97] cast doubt on this statement. For example, acrylamides containing an electron-donating substituent in the α position are often inert Michael acceptors. Only amides of dehydroamino acids containing the geminal electron-withdrawing CF_3 group add to amines in the presence of base catalysts.[98] Some metal oxides[99,100] (including metal oxide-supported potassium fluoride),[101] poly(vinyl pyridine),[102] modified polyacrylamide,[103] and some organic bases[30] exhibit high catalytic activity. For example, the addition of various amines to methyl acrylate readily occurs in the presence of 0.5 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Weaker Lewis bases[104] are much less efficient catalysts. Apparently, the catalytic action of base catalysts is associated with the activation of the Michael donor. It should be noted that the authors of the study[30] stated that it is difficult to explain the role of DBU in the aza-Michael reaction only in terms of the base catalysis.



R^1R^2N = BnNH, BnMeN, Bn_2N, $(CH_2)_5N$, $O(CH_2CH_2)_2N$.

In spite of the efficiency of the methods discussed above, a serious drawback of some of them is that they use toxic solvents (MeCN, CH_2Cl_2). Hence, the selection of catalysts was accompanied by the search for appropriate solvents. Ionic liquids came to the attention of the chemical community more than 25 years ago as technologically efficient solvents following green chemistry principles because they are nontoxic, nonvolatile, and incombustible.

Due to high solvation ability and the possibility of regeneration, ionic liquids are an excellent alternative to conventional organic solvents both in laboratory practice and industry. Moreover, it was found that in some cases ionic liquids serve two functions being simultaneously convenient solvents and efficient catalysts. It is not surprising that chemists try to perform almost all known processes in these solvents. The aza-Michael reaction is not an exception. It appeared that ionic liquids can catalyze the conjugate addition of amines to activated alkenes. The efficiency of the reaction depends on the nature of both the cation and the anion. Examples of the successful use of alkylimidazolium,[105, 106] polyalkylammonium,[107] and hydroxyethylammonium [108] ionic liquids in the aza-Michael reaction were documented. Recently, first well working basic ionic liquids containing a strongly basic organic cation or the hydroxide anion have been described.[109–111] The use of various ionic liquids was shown by an example of the addition of piperidine to methyl acrylate at room temperature. The results of investigation of this reaction in organic solvents (THF, DMSO) are given for comparison.



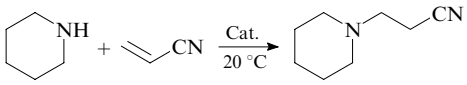
Solvent	Time /min	Yield (%)	Ref.
[bmim]OH	10	98	111
[emim]OH	10	94	111
[bdmim]OH	10	95	111
[H-DBU]OAc	90	92	110
$[HO(CH_2)_2NH_3]HCO_2$	20	90 [a]	108
$[bmim]PF_6$	10	55	111
$[bmim]BF_4$	420	95 [a]	106
	10	60	111, 112
THF	48 h	15	111
DMSO	48 h	30	111

Note. bmim is 1-butyl-3-methylimidazolium, emim is 1-ethyl-3-methylimidazolium, bdmim is 1-butyl-2,3-dimethylimidazolium, H-DBU is protonated DBU. [a] Ethyl acrylate was used.

An advantage of ionic liquids is also the ease of the extraction of reaction products. The latter are most often isolated by either the extraction or distillation. In the latter case, the use of organic solvents is completely excluded even in the step of the preparative isolation. The remaining ionic liquid can be reused in the reaction.

In addition to the above-mentioned examples, successful attempts were made to perform the aza-Michael reaction in functionalized ionic liquids [112–115] combined with microwave radiation [116, 117] and ultrasound.[118]

The use of environmentally safe solvents seems to be an ideal (or almost ideal) way of performing these reactions. A few years ago, it was suggested that the aza-Michael reaction might be performed in the absence of a solvent. This approach is attractive from both economic and environmental points of view and it has gained popularity in the last decade. Advantages of this procedure can be clearly shown by an example of the synthesis of 3-piperidinopropionitrile.

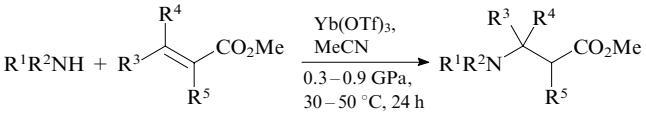


Catalyst [amount (mol.%)]	Solvent	Time /h	Yield (%)	Ref.
$Me_2S^+ Br\ Br^-$ (5)	–	< 0.1	99	119
$ZrClO_4 \cdot 8\,H_2O$/montmorillonite [a]	–	0.25	94	18
$SiCl_4$ (2)	–	1–4	94	120
$VO(OAc)_2$ (5)	–	0.7	88	121
$LiClO_4$ (100)	–	1	80	122
CAN (10)	THF [b]	0.3	96	123
H_3BO_3 (10)	H_2O	1.5	95	65
Borax (10)	H_2O	2	90	66
β-Cyclodextrin (100)	H_2O	6	84	124
–	–	3	52 [c]	19

[a] 0.75 g mol^{-1}; [b] the reaction was activated by ultrasound; [c] the conversion is given.

Actually, in some cases the reactions performed in the absence of a solvent made it possible to substantially reduce the reaction time, decrease the amount of the catalyst, and increase the yield of the target product. Since the differences are small, the economic and environmental characteristics are of most interest, due to which preference is most often given to reactions occurring in the absence of a solvent. An exception is $LiClO_4$. This method is of little use because it requires equimolar amounts of highly explosive perchlorate.

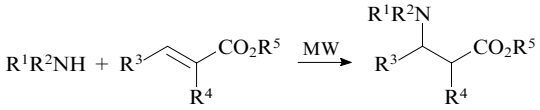
Jenner proposed a radically new strategy for the aza-Michael reaction.[29] The simultaneous use of the classical (Lewis acids) and nonclassical (high pressure) activation made it possible to perform the addition of branched primary and secondary aliphatic amines to α,β-unsaturated acid esters and prepare β-amino esters, which are difficult (if at all possible) to synthesize by conventional methods.



(10%–100%)

R^1R^2N = Pr^iNH, Bu^tNH, BnNH, Pr^i_2N, Pr^iMeN;
R^3, R^4, R^5 = H, Me.

Another nonclassical method of activation of the aza-Michael reaction, *e.g.*, microwave radiation termed [125] 'Bunsen burner of the 21st century', is worthy of note. Impressive results of the use of microwave radiation in the synthesis of β-amino acid esters were obtained for the first time by chemists from the Lomonosov Moscow State University.[126]



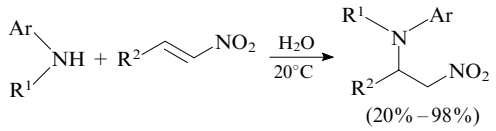
(31%–84%)

R^1R^2N = BnNH, PhCH(Me)N, $(CH_2)_5N$, $O(CH_2CH_2)_2N$;
R^3 = H, Me, Ph; R^4 = H, Me; R^5 = Me, Bu^n, Bu^s.

The reaction of morpholine with *sec*-butyl crotonate is a bright example. In the absence of a catalyst and a solvent, the reaction was completed within 5 days to give the target adduct in 17% yield. The prolonged reaction (9 days) of the reactants in the presence of $Yb(OTf)_3$ afforded amino ester in 60% yield. The microwave-assisted reaction was completed within 25 min and gave the Michael adduct in 72% yield. A similar effect of microwave radiation in the synthesis of amino esters has been recently confirmed.[127] Unfortunately, this method is inefficient if the Michael acceptor contains a substituent in the α position [126] or the branched substituent (PhCHMe) in the β position with respect to the activating group.[128] On the contrary, the sonochemical activation made it possible to perform the reaction of ferrocenylenones containing a β-aryl substituent.[129]

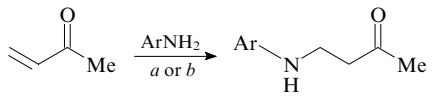
2. Aromatic amines

There are few examples of the noncatalytic conjugate nucleophilic addition of arylamines to electron-deficient alkenes. For the reaction to be successful, the Michael acceptor should contain a very active double bond as, for example, in ethenetricarboxylates,[130] nitroalkenes,[131] or enones.[46] Actually, highly reactive nitroalkenes readily form Michael adducts with aromatic amines.[131] Even weakly nucleophilic (nitroaniline) and secondary (*N*-methylaniline) amines are involved in the reactions, although in these cases the yields of the target compounds are substantially lower.



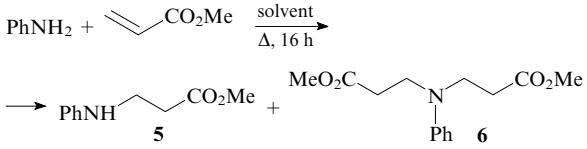
Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; R^1 = H, Me; R^2 = Ph, 2-$MeOC_6H_4$, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-thienyl.

Like nitroalkenes, methyl vinyl ketone easily reacts with anilines in pure water [132] or in the presence of surfactants.[46] In both cases, the reaction stops at the formation of the monoadduct even in the presence of a threefold excess of enone.[132]



(*a*) Surfactant, H_2O, 20 °C, 0.25 – 2 h: Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4; 85% – 92% yields;
(*b*) H_2O, 20 °C, 2 – 6 h: Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4; 65% – 83% yields.

It should be noted that all reactions under consideration were carried out in an aqueous medium. It is understandable because the nucleophilicity of aromatic amines strongly depends on the nature of the solvent and substantially increases in water.[133] However, even under these conditions, aniline remains inactive in reactions with weaker Michael acceptors (acrylates).[24] Another solvent (or a cosolvent catalyst), which can activate this reaction, was required. Such a solvent was found by French chemists.[132] They showed how not only the conjugate addition of arylamines can be activated but also its selectivity can be controlled. The authors found that methyl acrylate does not react with aniline during prolonged heating in CH_2Cl_2 or EtOH and that the conversion in water is at most 15%, and they performed the reaction with the use of a threefold excess of the ester in highly polar protic solvents (trifluoroethanol and hexafluoroisopropanol). It appeared that fluorinated alcohols facilitate not only the formation of monoadduct **5** but also its reactions with an excess of the ester. As a result, the fraction of bis-adduct **6** increases and reaches 96% in hexafluoroisopropanol. Similar results were obtained with methyl vinyl ketone.

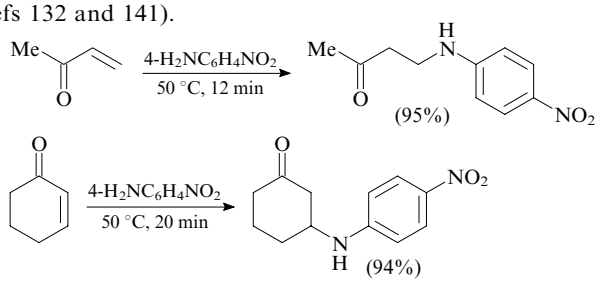


Solvent	Ratio **5** : **6**
H_2O	100 : 0
CF_3CH_2OH	71 : 29
$(CF_3)_2CHOH$	4 : 96

The authors of the above-described study believed that the activation of the Michael acceptor by fluorinated alcohols is a key step in the mechanism of the catalytic action of these alcohols.

As it was mentioned in Section II.1, many Lewis and Brønsted acids were studied as potential catalysts for the aza-Michael reaction. Some of these compounds chemoselectively catalyze the addition of only aliphatic amines, other compounds have a universal action and activate the reactions of various Michael acceptors with both aliphatic and aromatic amines.

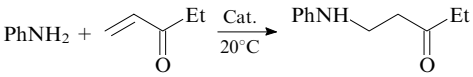
Transition metal salts and complexes, such as samarium iodide,[134 – 137] yttrium nitrate hexahydrate,[138] zirconium chloride,[139] and zirconyl chloride octahydrate,[140] exhibited high catalytic activity in the conjugate addition of aromatic amines to electron-deficient alkenes. As a rule, the reactions of anilines with enones and acrylic acid derivatives proceed slowly (require from several hours to several days) even in the presence of catalysts. However, impressive experimental results were reported recently.[140] Thus the addition of primary and secondary arylamines to cyclic and acyclic enones readily (2 – 20 min) occurs in the presence of 2 mol.% $ZrOCl_2 \cdot 8\,H_2O$ to give products in almost quantitative yields. This catalyst substantially accelerates the reaction of enones with such a weak nucleophile as *p*-nitroaniline. The reactions with methyl vinyl ketone and cyclohexenone were completed in 12 and 20 min, respectively. Generally, the reactions of this amine occur in rare cases even with terminal alkenes. If these reactions did proceed, the reaction time was several hours (see, for example, Refs 132 and 141).



The $RuCl_3$-catalyzed reaction of *p*-nitroaniline with cyclohexenone gave the target adduct in 87% yield after heating at 50 °C during several days.[62]

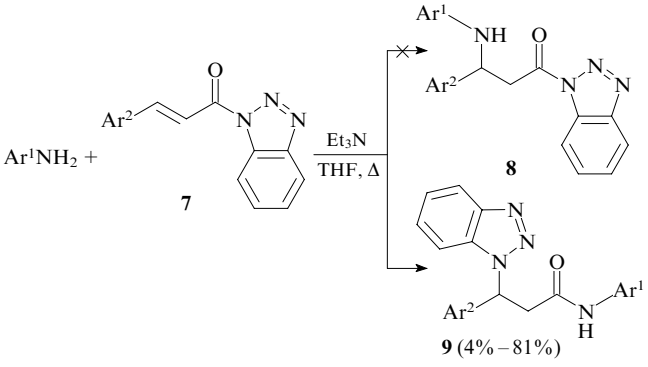
Copper [142] and palladium [143, 144] complexes proved to be efficient catalysts for the addition of aniline to unsaturated ketones, esters, and nitriles, including α- or β-substituted derivatives. Glacial acetic acid was used as the solvent in the reaction of arylamines with various Michael acceptors performed under reflux [145] or microwave radiation,[146] including in the template synthesis.[147] However, these studies dealt only with terminal alkenes. An attempt to perform the reaction with cinnamic acid ester failed.[146]

In 2006, the basic ionic liquid [bmim]OH was used for the first time as the catalyst for the conjugate addition of aromatic amines.[148] The adducts of aniline and its *para*-substituted derivatives with cyclic and acyclic enones were obtained in good yields (67%–98%), but the reaction time was very long (8–24 h). Studies in this field were continued and soon afterward it was found that other ionic liquids (primarily DBU derivatives) [149] and nanosized copper particles dispersed in ionic liquids [150] also have high catalytic activity.



Catalyst	Time /min	Yield (%)	Ref.
[H-DBU]O_2CCH(OH)Me	30	99	149
[H-DBU]OAc	40	96	149
[H-DBU]O_2CCF_3	40	96	149
[bmim]OH	480	98	148
[bmim]BF_4	40	55	149
DBU	40	43	149
–	40	37	149

The unusual reaction occurs between aromatic amines and α,β-unsaturated *N*-acylbenzotriazoles **7**. This reaction afforded isomeric β-benzotriazole amide **9** instead of the expected Michael adduct **8**.[151]



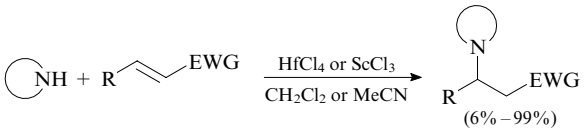
Ar^1 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 1-naphthyl; Ar^2 = Ph, 4-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-furyl.

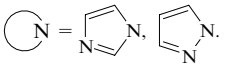
When receiving evidence that benzotriazole cannot add to cinnamanilide under these conditions, the authors concluded that amide **9** is formed as a result of the rearrangement of Michael adduct **8** that is initially formed.

3. Aromatic aza heterocycles

β-Amino ketones and β-amino acid derivatives containing an aromatic N-heterocycle are considered as potential drugs. For this reason, the addition of imidazoles, pyrazoles, pyrroles, triazoles, and indoles to enones and acrylates has attracted particular attention. In spite of the fact that all these heterocycles are weak nucleophiles, they are involved in the aza-Michael reaction under certain conditions and form adducts in high yield.

It should be emphasized that in the absence of a catalyst, aromatic aza heterocycles do not react even with such powerful Michael acceptors as enones and enals. The action of some catalytic systems is selective and depends on the nature of the Michael donor and the Michael acceptor. For example, hafnium and scandium chlorides efficiently catalyze the addition of imidazole and pyrazole to enals and enones.[152] By contrast, imidazole does not react with methyl vinyl ketone in the presence of any of these salts. Unlike chlorides, triflates of the same metals do not exhibit catalytic activity in the reactions with pyrazole. In these reactions, pyrrole acts as the C-nucleophile.



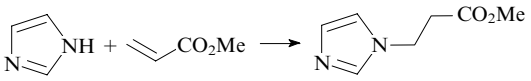
EWG = CHO, Ac, Bz; R = H, Me, Et; 

As mentioned above, potassium fluoride supported on some metal oxides activates the addition of aliphatic amines to acrylates.[101] It was found that KF/Al_2O_3 can catalyze the addition of much less nucleophilic imidazole, pyrazole, and pyrrole to the same substrates, pyrrole acting as the N-nucleophile.[153] The yields of the reaction products were up to 42%–98% and were lower if enones act as Michael acceptors.

Clays impregnated with Li^+ and Cs^+ salts were used as base catalysts.[154] Their efficiency increases under the simultaneous ultrasound activation.

Some alkaloids [155, 156] and enzymes [157–159] proved to be fairly efficient biocatalysts for the conjugate addition of N-heterocycles to alkyl acrylates and chalcones. The addition of imidazole and its derivatives to cycloalkenones and acrylates was assisted by UV [160] and microwave radiation.[161]

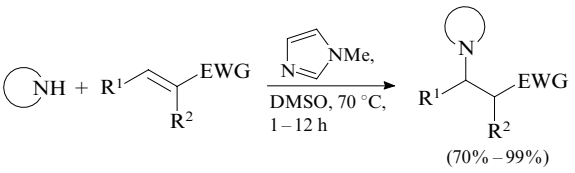
As in the series of aliphatic and aromatic amines, the aza-Michael reaction with aromatic N-heterocycles efficiently occurs in ionic liquids.[162–164] The best results were obtained with the use of basic ionic liquids. The efficiency of this method is so high that the reactions easily proceed even with imidazoles containing a strong electron-withdrawing group. For example, the reaction of 4-nitroimidazole with methyl acrylate in conventional organic solvents (THF, DMSO) at room temperature affords the Michael adduct in low yield (5%) after 48 h, whereas the reaction in the ionic liquid [bmim]OH is completed in one hour and gives the target compound in 95% yield.[162] The advantages of [bmim]OH as the catalyst and the medium are clearly manifested in the conjugate addition of imidazole to methyl acrylate.



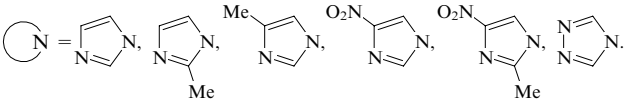
Catalyst	Reaction conditions	Yield (%)	Ref.
[bmim]OH	25 °C, 1 h	92	162
[bmim]BF_4	60 °C, 6 h	50	163
[bmim]BF_4	$Cu(acac)_2$ (2 mol.%), 60 °C, 6 h	90	163
[mipim]PF_6	PhMe, Et_3N, MW (200 °C), 2 min	75	164
–	Et_3N, MW (200 °C), 2 min	0	164

mipim is 1-methyl-3-isopropylimidazolium.

Taking into account the evident structural similarity of *N*-methylimidazole and cations of alkylimidazolium ionic liquids, Liu *et al.*[165] suggested that this compound can be used for the catalysis of the aza-Michael reaction. The idea was successful. Thus, in the presence of 5 mol.% of this catalyst, the reaction of 4-nitroimidazole with methyl acrylate afforded the adduct in quantitative yield upon heating in DMSO for one hour. In the absence of the catalyst, the yield of the target adduct was at most 4%. The reactions of 2- and 4-methylimidazoles and triazole with alkyl acrylates and methyl vinyl ketone are equally efficient. The reactions with α- or β-substituted acrylates were much more difficult to perform, and they were completed in 12 h.

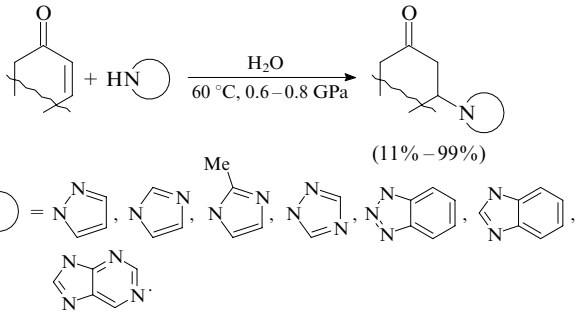


EWG = Ac, CO_2Me, CO_2Et, CO_2Bu^n; $R^1 = R^2 = H$, Me;

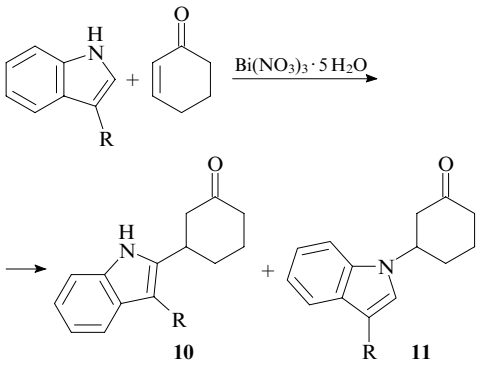


It was found that poly(*N*-vinylimidazole) also has high catalytic activity.[166] The addition reactions of various 1,2,4-triazoles (water, 20–25 °C, 2–48 h) with terminal alkenes (methyl vinyl ketone, methyl vinyl sulfone, methyl acrylate) and cyclohexenone readily proceed and give aza-Michael adducts in high yields.

Recently, a new original method has been developed for the conjugate addition of aromatic aza heterocycles to enones.[167] The reaction was carried out in water in the absence of a catalyst at a pressure of 0.6–0.8 GPa and at 60–80 °C and was completed in 20–40 h. The reactions of less reactive acyclic enones proceeded under more drastic conditions and required longer time to achieve satisfactory yields of Michael adducts.



The characteristic feature of aromatic N-heterocycles is that they can form both N- and C-addition products. For example, indole is involved in the aza-Michael reaction with methyl vinyl ketone and acrylic acid derivatives in the presence of base catalysts, such as KF/Al_2O_3 (Ref. 168) and DBU.[30] On the contrary, in the reactions catalyzed by Lewis acids, *viz.*, hafnium and scandium chlorides and triflates,[152] $InBr_3$,[169] $InCl_3$,[170] $Bi(NO_3)_3$,[50] $PhSO_3Na/SiO_2$ in [dbim]SbF_6 (dbim is 1-butyl-3-decylimidazolium),[171] and 2,4,6-trichlorotriazine,[172] indole and its derivatives react exclusively as C-nucleophiles. In attempting to reproduce the results of the study,[50] McCluskey and co-workers[173] unexpectedly found that cyclohexenone reacts with 3-substituted indoles in the presence of $Bi(NO_3)_3 \cdot 5H_2O$ to form C-adduct **10** along with N-adduct **11**. The authors performed a series of experiments and concluded that the chemoselectivity of the reaction depends on the substituent at the C(3) atom and the nature of the solvent. Thus polar solvents are favourable for the aza-Michael reaction.



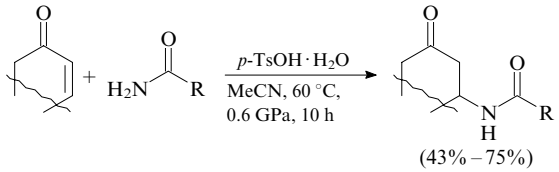
4. Amides and carbamates

The conjugate addition of amides and carbamates to enones and acrylates is the shortest route to β-aminocarbonyl derivatives containing the protected amino group. For this reason, the aza-Michael reaction with weak N-nucleophiles, such as amides and carbamates, has attracted great interest in the last decade.

To perform the conjugate addition of amides to various Michael acceptors, both conventional and nonclassical methods of activation were used. For example, in the presence of crown ether and Bu^tOK, secondary formamides added to nitroalkenes and gave Michael adducts in good yields.[174] Caesium carbonate exhibited the highest catalytic activity in the reactions of primary aromatic amides with alkyl acrylates. The reaction was carried out in the presence of Bu^n_4NBr and in the absence of a solvent under microwave irradiation.[174] The reactions of benzamide, acrylamide and cinnamide with cyclic and acyclic enones were catalyzed by palladium complexes.[175] The reaction with acetamide did not proceed.

The hyperbaric aza-Michael reaction of amides has recently been described by Kotsuki and co-workers.[176] The authors developed further the procedure proposed earlier by Jenner[29] and showed that the addition of aliphatic and aromatic amides to α,β-unsaturated ketones occurs at a

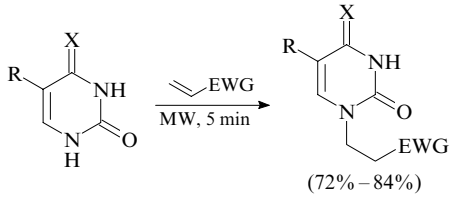
pressure of 0.6 GPa in the presence of Brønsted acids. It should be emphasized that the high pressure is the necessary condition for the reaction to occur. Unfortunately, in spite of the efficiency of the proposed method, the range of Michael acceptors is limited to enones, because acrylic and cinnamic acid esters do not react with benzamide.



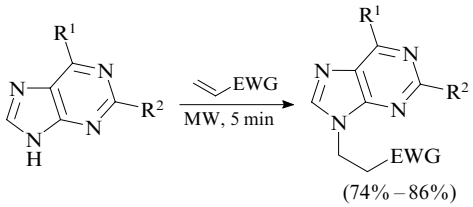
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, Bn, Pr^n, Bu^t.

The conjugate addition of amides is most often activated by base catalysts. For example, the reactions of sulfamides, succinimide, phthalimide, and saccharin with various Michael acceptors are catalyzed by alkali metal carbonates [K_2CO_3,[177–179] Cs_2CO_3 (Refs 180 and 181)], metal oxides (ZnO,[182,183] MgO,[184] the $KF-Al_2O_3$ system[185]), strong mineral [NaOH (Ref. 186)] and organic (1,4-diazabicyclo[2.2.2]octane[187,188]) bases. The best results were obtained in the reactions performed in the absence of a solvent or in ionic liquids, as well as under microwave irradiation.

Pyrimidine and purine bases were successfully used as Michael donors in the reactions with acrylates and acrylonitrile in the presence of base catalysts[189,190] or biocatalysts.[191,192] Triethylamine proved to be the mildest and most efficient base. Acyclic nucleosides can be synthesized rapidly and in high yield if the reaction is performed in water and assisted by microwave radiation.



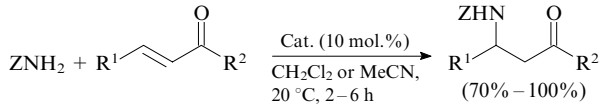
EWG = CN, CO_2Me, CO_2Et, CO_2Bu^t; X = O, S; R = H, Me, Cl, I.



EWG = CN, CO_2Me, CO_2Et, CO_2Bu^t; R^1 = Cl, NH_2, NHBn, $NH(CH_2)_2OH$; R^2 = H, F, Cl, NH_2.

The addition of dihydropyrimidinones to ethyl acrylates and acrylonitrile occurs regioselectively and affords exclusively 3-substituted derivatives.[193]

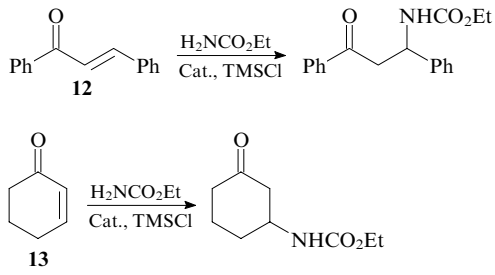
Researchers encountered many problems in trying to initiate the aza-Michael reaction with carbamates. Many catalysts, which generally activate the conjugate addition of amines, appeared to be inactive or poorly active in related reactions with these weak nucleophiles. For example, contrary to expectations, copper, iron, indium, and lanthanum halides and triflates do not catalyze the reactions of ethyl and benzyl carbamates with enones.[194,195] These obstacles were overcome with the use of strong Brønsted and Lewis acids as catalysts; the latter should contain fifth or sixth period transition metals in high oxidation states. For example, $IrCl_3 \cdot n H_2O$, $ReCl_3$, and $PtCl_2$ proved to be inefficient catalysts for the reaction of benzyl carbamate with enones, whereas higher chlorides of the same metals ($IrCl_4 \cdot n H_2O$, $ReCl_5$, and $PtCl_4 \cdot 5 H_2O$) efficiently catalyze this reaction resulting in the formation of Michael adducts in quantitative (or nearly quantitative) yields.[195] The conjugate addition of carbamates easily occurred in the presence of $OsCl_3 \cdot 3 H_2O$, $RhCl_3 \cdot 3 H_2O$, $AuCl_3 \cdot 3 H_2O$,[195] $VO(OTf)_2$,[196] $ZrCl_4$,[195,197] and zeolite-supported $SnCl_4$.[198]



R^1 = H, Me, Et; R^2 = Me, Ph; Z is benzyloxycarbonyl.

The ability of some metals to catalyze the aza-Michael reaction with weak nucleophiles is associated with the presence of highly electron-deficient centre in their structures. For example, the addition of benzyl carbamates to enones easily occurs in the presence of 1 mol.% – 10 mol.% of palladium and rhodium complexes,[199–201] copper complexes,[201,202] and silver complexes.[201]

The efficiency of Lewis acids as catalysts for the conjugate addition of carbamates is substantially increased in the presence of Me_3SiCl (TMSCl).[194,203,204] This is clearly exemplified by the addition of ethyl carbamate to acyclic (**12**) and cyclic (**13**) enones.



Enone	Catalyst	Amount of TMSCl /equiv.	Solvent	Time /h	Yield (%)	Ref.
12	–	1	CH_2Cl_2	24	traces	203
	$FeCl_3$	0	CH_2Cl_2	24	0	203
	$FeCl_3$	1.1	CH_2Cl_2	24	48	203
	$FeCl_3 \cdot 6 H_2O$	0	CH_2Cl_2	12	0	194
	$FeCl_3 \cdot 6 H_2O$	1.1	CH_2Cl_2	12	50	194
	$InCl_3$	0	PhMe	120	0	203
	$InCl_3$	1.1	PhMe	24	68	203
	$RhCl_3 \cdot 3 H_2O$	0	CH_2Cl_2	24	0	204
	$RhCl_3 \cdot 3 H_2O$	1.1	CH_2Cl_2	24	65	204
13	$FeCl_3 \cdot 6 H_2O$	0.05	CH_2Cl_2	12	30	194
	$FeCl_3 \cdot 6 H_2O$	1.1	CH_2Cl_2	12	89	194
	PPh_3	0	CH_2Cl_2	24	0	205
	PPh_3	1.1	CH_2Cl_2	15	95	205
	PBu^n_3	0	CH_2Cl_2	24	0	205
	PBu^n_3	1.1	CH_2Cl_2	15	100	205

In the discussion of the mechanism of the PBu^n_3-catalyzed reaction, the authors hypothesized that the first step involves the addition of phosphine as a soft nucleophile to the Michael acceptor. The subsequent reaction of the resulting silylated enolate with carbamate and the elimination of the Me_3Si group afford the corresponding amino ketone.[205] The role of TMSCl in these reactions remains unclear. Taking into account that the reaction virtually does not occur in the absence of transition metal salts, it is reasonable to suggest that the role of TMSCl is not only to activate the enone carbonyl group. In the study,[203] it was hypothesized that the synergism of the components of the catalysts leads to the activation of both the Michael donor and the Michael acceptor.

When studying the mechanism of the conjugate addition of weak nucleophiles, Spencer and co-workers[206] found that the catalytic activity of transition metal salts in these reactions well correlates with their tendency to be hydrolyzed in organic solvents. Based on these observations, the authors drew an unexpected, at the first glance, conclusion that the aza-Michael reaction with weak nucleophiles is catalyzed by a proton rather than by a Lewis acid. To support this conclusion, the reactions of benzyl carbamate with acyclic enone were studied in the simultaneous presence of a Lewis acid (rhenium, rhodium, platinum, and gold chlorides, copper, indium, and iron triflates, and bismuth nitrate) and a Lewis base (2,6-di-*tert*-butylpyridine). The latter, as is known, can add a proton but cannot coordinate a metal ion. The fact that the reaction does not occur in all these cases unambiguously indicates that the proton acts as the catalyst for the aza-Michael reactions with carbamates in the presence of Lewis acids.

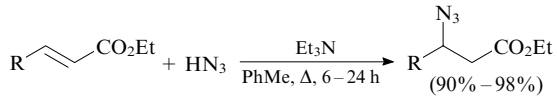
Actually, the addition of carbamates to enones easily occurs in the presence of strong Brønsted acids,[207] including polymer-supported acids.[208] Bis(trifluoromethanesulfonyl)imide, tetrafluoroboric acid, and tetrafluoromethanesulfonic acid proved to be the most efficient catalysts. In the presence of 10 mol.% of one of these catalysts, the addition of benzyl carbamate to enones easily occurs and is completed in 10 min to give the Michael adduct in high yield (86%–98%). By contrast, some carboxylic acids (CF_3CO_2H, AcOH),[207] HCl,[207] and H_3BO_3 (Ref. 66) do not have the catalytic activity.

It was found that KF/Al_2O_3 has versatile catalytic activity in the hetero-Michael reactions. This compound can equally efficiently activate the conjugate addition of aliphatic amines,[101] aromatic aza heterocycles,[153,168] and amides.[185] In the presence of this catalyst, the addition of oxazolidinone to esters, amides, and nitriles of acrylic acid occurs surprisingly easily.[153] The reactions proceeded at room temperature for 20–24 h, and the Michael adducts were obtained in 92%–97% yields. Unfortunately, the activity of the catalyst gradually decreased during the repeated use.

Finally, some ammonium salts catalyze the reactions of cyclic and acyclic enones, as well as of alkyl acrylates and crotonates, with carbamates and oxazolidinone in organic solvents[209,210] under phase-transfer catalysis conditions.[211] The metal oxide-catalyzed addition of ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = o-$O_2NC_6H_4SO_2$) to methyl acrylate containing the geminal CF_3 group was documented.[212]

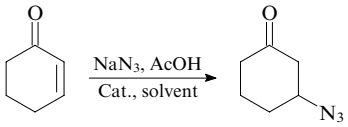
5. Other nucleophiles

First data on the addition of hydrogen azide to conjugated systems were published a century ago. However, no efficient methods for the synthesis of β-azidocarbonyl compounds have been available until recently. The problem of the synthesis of these derivatives was solved by performing the reaction in the presence of a Lewis base (Et_3N or pyridine).[213]



R = H, Me, Bn, $BnOCH_2$.

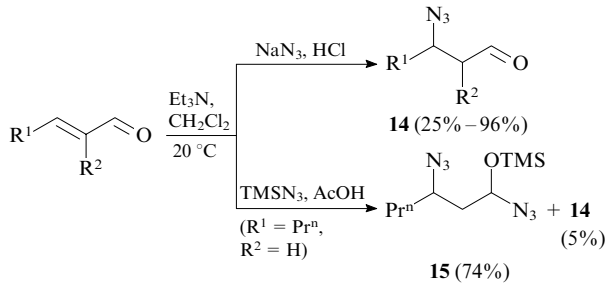
More recently, it was suggested that highly toxic and explosive acid HN_3 should be generated *in situ* from trimethylsilyl azide[214–216] or sodium azide.[217–219] For example, the treatment of NaN_3 with an equimolar amount of acetic or hydrochloric acid afforded HN_3, which reacted with enals, cyclic and acyclic enones, and derivatives of α,β-unsaturated carboxylic acids to form Michael adducts generally in good yields. The reactions readily proceeded in the presence of Lewis bases at room temperature in water,[217] organic solvents,[218] or ionic liquids.[219] The efficiency of this method can be exemplified by the synthesis of 3-azidocyclohexanone.



Catalyst	Solvent	Time /h	Yield (%)	Ref.
–	H_2O	24	60	217
–	[bmim]BF_4	20	90	219
–	[bmim]PF_6	20	89	219
Et_3N	H_2O	24	93	217
	CH_2Cl_2	24	35	217
	CH_2Cl_2	18	93	218[a]
	[bmim]PF_6	20	92	219
Pyridine	H_2O	24	92	217
	[bmim]BF_4	20	90	219
	[bmim]PF_6	20	95	219
N-Methylimidazole	H_2O	24	92	217
	[bmim]BF_4	20	13	219
	[bmim]PF_6	20	79	219
PBu^n_3	H_2O	24	94	217
	CH_2Cl_2	24	85	217

[a] In this case, concentrated HCl was used to prepare HN_3.

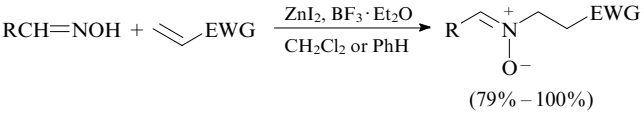
Unlike enones, α,β-unsaturated aldehydes were transformed into the corresponding azido aldehydes **14** only when sodium azide was used as a source of HN_3. Under these conditions trimethylsilyl azide formed mainly 1,2-addition product **15**.[218] Among Lewis bases, *N*-methylimidazole, Et_3N, and DBU proved to be the most efficient catalysts.



R^2 = H: R^1 = Me, Pr^n, Pr^i, Cy, Ph, $BnOCH_2$, $BzOCH_2$, $BzO(CH_2)_5$; R^1 = H, R^2 = Me.

Hydrazine, as well as hydrazones containing at least one free amino group, are involved in the aza-Michael reaction with various activated alkenes. If the electrophilicity of the β-carbon atom in the latter compounds is relatively high (for example, in nitroalkenes[220] or alkylidene malonates[221]), the addition occurs easily and in the absence of a catalyst. In other cases, the reaction is catalyzed by bases.[222,223]

Being bidentate nucleophiles, oximes are involved in oxo- or aza-Michael reactions depending on the reaction conditions; the former reaction proceeds in the presence of bases,[224] the latter is catalyzed by acids.[225,226] For example, the addition of aldoximes to various Michael acceptors catalyzed by a mixture of Lewis acids ZnI_2 and $BF_3 \cdot Et_2O$ affords *N*-alkylnitrones.[225] N-Alkylation products of oximes are formed in good yield in benzene at room temperature or under reflux in CH_2Cl_2 depending on the activity of the starting alkene.

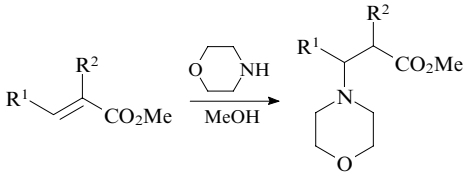


R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, n-C_7H_{15}, Bu^t, (*E*)-PhCH=CH, (*E*)-MeCH=CH, 2-thienyl, 2-furyl; EWG = H, Me, OMe, 2-oxo-3-oxazolidinyl.

III. Problem of the construction of the quaternary aza-carbon centre

Most of the above-considered aza-Michael reactions occur with either terminal or β-monosubstituted alkenes. The conjugate nucleophilic addition to their β,β-disubstituted analogues is one of challenges in organic synthesis. Numerous attempts to develop methods for the synthesis of β-aminocarbonyl compounds containing the quaternary aza carbon centre (*i.e.*, the quaternary carbon atom bound to the nitrogen atom) have been made. The catalytic addition of imidazole,[167] carbamates,[195,197,202] and azides[208,215,217] to enones, which are highly reactive Michael acceptors, was described in a few publications. Until recently, no examples of the addition of secondary amines to β,β-disubstituted derivatives of acrylic acid have been reported. It looked like that there is an insurmountable obstacle for the C–N bond formation based on the aza-Michael reaction.

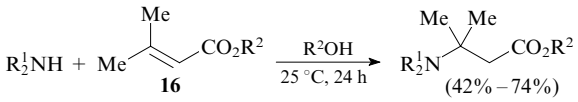
However, the problem has been solved. In the already classical study, D'Angelo and Maddaluno[227] showed that many conjugate addition reactions of primary amines with crotonates, which were difficult to perform using conventional activation methods, easily proceeded at high pressure (0.5–1.5 GPa). More recently, the author of the present review and co-workers[228] have found that the reactions of secondary amines also occur under these conditions.



R^1	R^2	Conditions	Yield (%)
Me	H	1×10^{-4} GPa, Δ, 24 h	82
Me	H	1.2 GPa, 25 °C, 6 h	91
Ph	H	1×10^{-4} GPa, Δ, 24 h	0
Ph	H	1.1 GPa, 25 °C, 24 h	62[a]
Et	Me	1.6 GPa, 25 °C, 24 h	70

[a] The recovery of the starting ester was 27%.

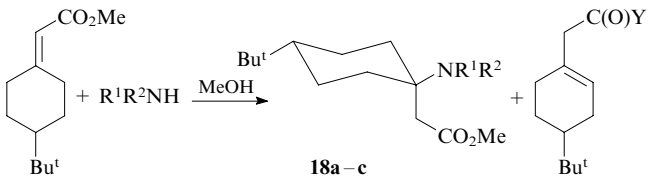
Being inspired with this discovery, we made an attempt to perform the aza-Michael reaction with β,β-disubstituted acrylates **16**. It appeared that cyclic (piperidine, morpholine) and acyclic (dimethyl- and diethyamine, *N*,*N*,*N*′-trimethylethylenediamine) amines react with alkyl β,β-dimethylacrylates **16** to form β-amino acid esters in good yields. Only in the reaction of diethylamine with methyl β,β-dimethylacrylate, the competitive oxo-Michael reaction with methanol used as the solvent is the major process; in this case, the aza-Michael adduct is formed in trace amounts.



16

R^1_2N = Me_2N, Et_2N, $(CH_2)_5N$, $O(CH_2CH_2)_2N$, $Me_2N(CH_2)_2NMe$; R^2 = Me, Et.

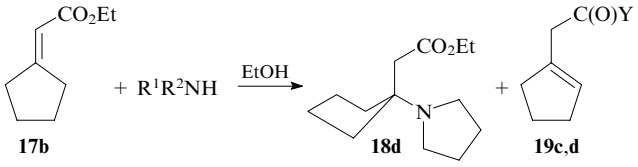
Similar results were obtained with alky(cycloalkylidene)acetates **17a**,**b**; the yields and the ratio of products **18** and **19** substantially depended on the reaction conditions.[228,229] For example, at high pressure ester **17a** was almost quantitatively transformed into Michael adduct **18c** with morpholine, whereas it remained inert under thermal activation. The addition occurred stereoselectively, *e.g.*, the amine moiety was in the equatorial position in the ring. The reaction of more nucleophilic piperidine, pyrrolidine, and benzylamine with the same Michael acceptors were complicated by the amidation and isomerization giving products



17a **18a–c** **19a**,**b**

R^1R^2N = BnNH (**a**), $(CH_2)_5N$ (**b**), $O(CH_2CH_2)_2N$ (**c**); Y = NHBn (**a**), OMe (**b**).

19a–d. In these processes, diethylamine served exclusively as the catalyst for the oxa-Michael reaction. In the absence of the latter, the starting ester **17b** did not react with alcohol.

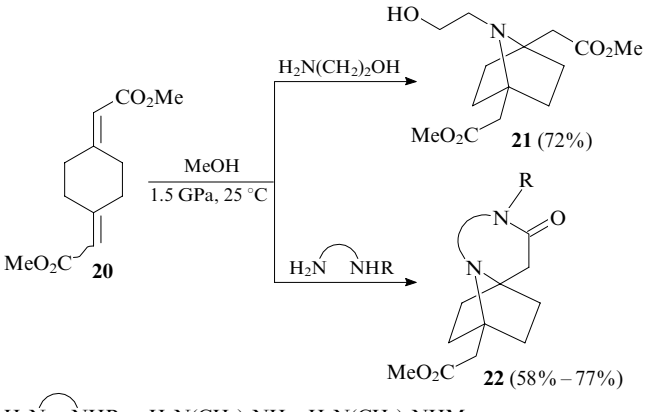


R^1R^2N = $(CH_2)_4N$, Et_2N; Y = OEt (**c**), $N(CH_2)_4$ (**d**).

Starting ester	R^1R^2N	Pressure /GPa	T/°C	Product [yield (%)]
17a	NHBn	1.5	25	**18a** (42) + **19a** (5)
	$N(CH_2)_5$	1.4	25	**18b** (17) + **19b** (65)
	$N(CH_2)_5$	1×10^{-4}	see [a]	**19b** (33) [b]
	$N(CH_2CH_2)_2O$	1.4	25	**18c** (98)
	$N(CH_2CH_2)_2O$	1×10^{-4}	see [a]	see [c]
17b	NEt_2	1.4	25	**19c** (44) [b]
	NEt_2	1×10^{-4}	see [a]	see [c]
	$N(CH_2)_5$	1.4	25	**18d** (38) + **19d** (37)

[a] The reaction was performed under reflux; [b] a large amount of the starting ester remained unconsumed; [c] the reaction did not occur.

The reactions of binucleophiles, for example, diamines, with the same substrates gave lactams (spirolactams) as the final products. The reactions simultaneously with a binucleophile and a bielectrophile serve as a route to complex polycyclic structures. Actually, diamines and amino alcohols containing a primary amino group reacted with diester **20** at high pressure to give azanorbornene derivatives **21** and **22** in good yield,[229] the cascade assembly of bi- and tricyclic structures being a one-pot reaction.

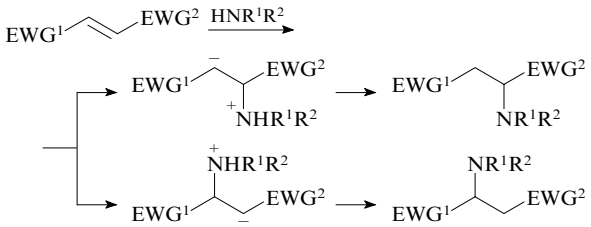


H_2N NHR = $H_2N(CH_2)_2NH_2$, $H_2N(CH_2)_2NHMe$, $H_2NCH_2CMe_2CH_2NH_2$.

Therefore, the hyperbaric noncatalytic version of the aza-Michael reaction substantially extends its scope, the reactions of β,β-disubstituted activated alkenes being possible to perform. Theoretical grounds of the use of high pressure for the aza-Michael reaction have been developed by Jenner.[230]

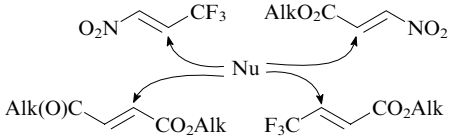
IV. Regioselectivity of the aza-Michael reaction

The conjugate addition of N-nucleophiles to alkenes containing one activating group occurs regioselectively and affords β-amino derivatives. However, the direction of the nucleophilic attack can be changed if the second electron-withdrawing substituent is present in the vicinal position with the respect to the first substituent (so-called pull-pull alkenes). In this case, the result of the reaction depends on the electron-withdrawing ability of both functional groups. Hence, the suggestion [231, 232] that the conjugate addition to these alkenes should be divided into the Michael and anti-Michael addition seems to be not always reasonable. Evidently, the regioselectivity of the addition is determined by the relative stability of the zwitterion that is formed in the first step. Consequently, the adduct containing the amino moiety in the β position with respect to the group most efficiently stabilizing the negative charge at the adjacent carbon atom is formed as the major product.



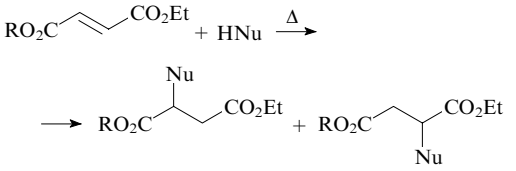
It is difficult to quantitatively estimate the electron-withdrawing ability of various functional groups because the inductive, mesomeric, and steric effects should be simultaneously taken into account. It was reported that the regioselectivity of the addition can be predicted based on the Hammett constants of various substituents. However, the published experimental data on the selectivity of the addition of various nucleophiles to alkenes containing two vicinal electron-withdrawing substituents provide evidence that the groups should be arranged in the order NO_2 > C(O)Alk > CO_2Alk > CF_3, which does not correlate with the Hammett constants.

For example, the addition of various N-nucleophiles to nitroalkenes containing the alkoxycarbonyl group in the β position always affords α-amino esters.[233–236] On the contrary, β-aminocarbonyl compounds are formed in the reactions of amines with β-trifluoromethyl acrylates.[237] The addition of alkenes containing the vicinal alkoxycarbonyl and carbonyl (formyl) groups to primary amines, aromatic aza heterocycles, or NaN_3 occurs selectively to give α-amino(azido) esters.[218, 238–241] Finally, the nucleophilic attack on trifluoromethyl-substituted nitroalkenes occurs at the carbon atom adjacent to the CF_3 group.[242, 243]

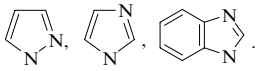


The regioselectively of the addition of azoles and primary amines to unsymmetrical fumaric acid esters also cannot be attributed exclusively to the electronic effects of the substituents.[244] In all cases, the nucleophilic attack

occurs mainly on the carbon atom bound to the bulkiest alkoxycarbonyl group. For example, the reaction of pyrazole with n-butyl ethyl fumarate gives an equimolar mixture of regioisomers, whereas the selectivity of the addition of the same azole to *tert*-butyl ethyl fumarate is 80%.



R = Bu^n, Cy, Bu^t; Nu = Bu^{n}NH, Bu^{s}NH, CyNH,

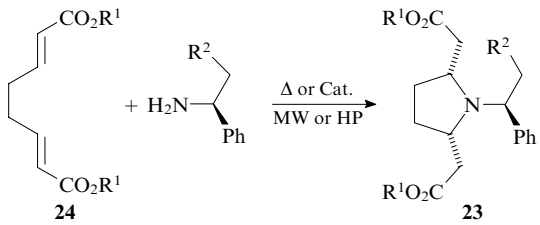


The above data show that the prediction of the regioselectivity of the addition to unsymmetrical alkenes containing two vicinal EWG groups is to a considerable extent based on the intuition and it is necessary to perform further studies of the influence of different factors (the nature of activating groups, the solvent, the catalyst, the reaction conditions) on the predominant direction of the nucleophilic attack.

V. Domino transformations including the aza-Michael reaction

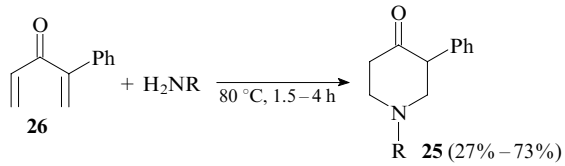
Domino reactions have been extensively developed in the last decades. This method makes it possible to minimize the number of synthetic operations, decrease the amount of by-products, and shorten the route to the target products.[245] A cascade of transformations is often initiated by the aza-Michael reaction.[246] Studies on the synthesis of heterocycles are of special interest. These transformations are known as aza-MIRC (aza-Michael Initiated Ring Closure). Since the detailed consideration of these reactions would unreasonably increase the volume of the review, only several examples will be mentioned.

A tandem of inter- and intramolecular aza-Michael reactions often plays a key role in the multistep synthesis of biologically active compounds and analogues of natural substances. For example, 2,5-disubstituted pyrrolidines **23**, which are structural fragments of widespread alkaloids, were synthesized in high yields and with high stereoselectivity by the reactions of primary amines with bis-α,β-unsaturated esters **24**.[247] The reactions can be activated by both conventional (heating, catalysts) and nonclassical (microwave radiation, high pressure) methods. The best results were obtained in the reactions performed under hyperbaric (HP) conditions.



R^1 = Me, Bu^t, Bn; R^2 = H, OH.

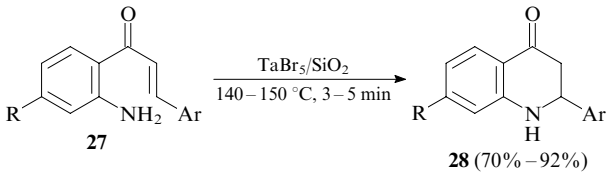
Piperidinones **25** were successfully synthesized by two successive aza-Michael reactions with the involvement of dialkenyl ketones and primary amines.[248, 249] For example, the one-pot aza-MIRC reaction of divinyl ketone **26** with aliphatic and aromatic amines gives target heterocycles **25** in good yield.[248] N-Unsubstituted piperidinone **25** (R = H) was synthesized with the use of an aqueous ammonia solution. The corresponding reaction with carbamates did not occur.



R = H, All, Bn, PhCH(Me), Ph.

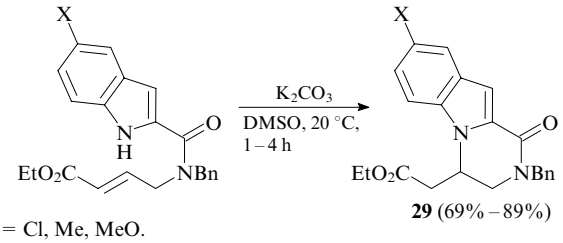
As can be seen, methods for performing inter- and intramolecular reactions have many features in common. Thus both processes can be catalyzed by acids or bases. The type of the catalyst is determined by the nature of the N centre.

For example, the formation of the dihydroquinoline moiety occurs during heating of 2′-aminochalcones **27** in the presence of silica gel-supported Lewis acids.[250] The reaction proceeds rapidly in the absence of a solvent and gives target heterocycles **28** in high yields. Attempts to prepare dihydroquinoline derivatives on pure silica gel in the absence of $TaBr_5$ failed. These compounds are formed in solution in the presence of this catalyst, but their yield is at most 30% – 40% even after prolonged (3 h) heating.



R = H, Br; Ar = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2,6-Cl$_2$C$_6$H$_3$, 2,6-(MeO)$_2$C$_6$H$_3$.

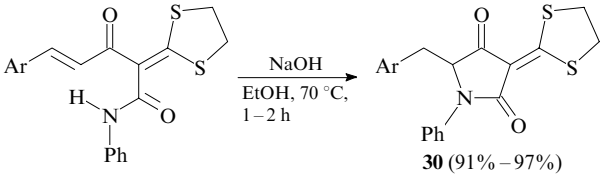
A convenient method was developed for the synthesis of polycyclic heteroaromatic compounds **29** based on the intramolecular 1,4-addition of a weakly nucleophilic nitrogen-containing moiety to the double bond activated by the ethoxy carbonyl group.[251] As in the intermolecular version of these reactions, the best results were obtained with the use of organic or mineral bases as the catalyst.



X = Cl, Me, MeO.

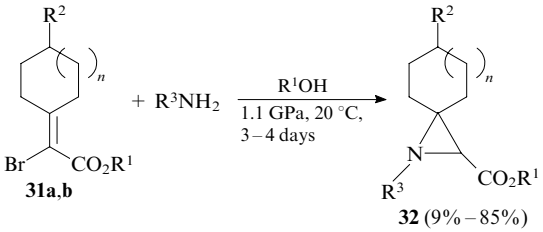
Finally, the unusual intramolecular cyclization that occurs as the anti-Michael addition (in this case, the term is correctly used) is worthy of note. In this reaction, the amide anion regioselectively attacks the α-carbon atom of the enone moiety.[252] This reaction proceeds under basic conditions (EtONa in ethanol) and gives tetramino acid

derivatives **30** as the final products in high yields. The 1,4-addition product was not detected even in trace amounts. The regioselectivity was attributed to the setereoelectronic structure of the amide anion, whose double bond is weakly polarized, as well as to the higher energy stability of the five-membered ring compared to the isomeric Michael adduct.



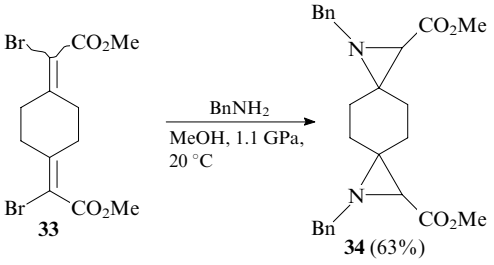
Ar = 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-Py.

The conjugate addition–nucleophilic substitution sequence is yet another cascade process often used in organic synthesis. Evidently, for this tandem reaction to be efficient, the initially formed Michael adduct should contain a good leaving group. This approach is at the basis of the synthesis of captodative† carbonyl-containing aminoalkenes,[253,254] various polycyclic compounds, including spiroheterocycles. For example, bicyclic α-keto aziridines were synthesized under mild conditions from 2-bromocyclopentenone and primary aliphatic amines.[255] Alkyl 2-bromo(cycloalkylidene) acetates **31a**,**b** react with primary amines at high pressure to give spiroaziridines **32**.[256,257] In most cases, aziridine carboxylates are formed in moderate or high yields, and the stereoselectivity of the reaction is 90%, the nucleophilic attack on the equatorial position of the ring being favourable.



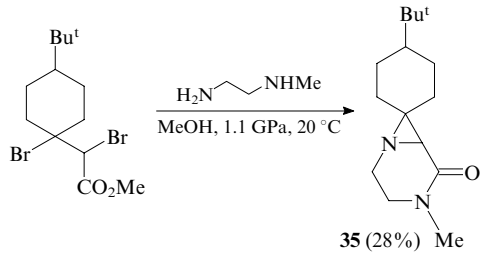
R^1 = Et, R^2 = H, n = 0 (**a**); R^1 = Me, R^2 = Bu^t, n = 1 (**b**);
R^3 = Pr^n, Pr^i, Bn, PhCH(Me), Ph.

An original idea to perform the tandem conjugate addition–nucleophilic substitution process was realized with the use of dibromo diester **33**, whose reaction with benzylamine at high pressure afforded bis-aziridine **34** as the final product.[256]

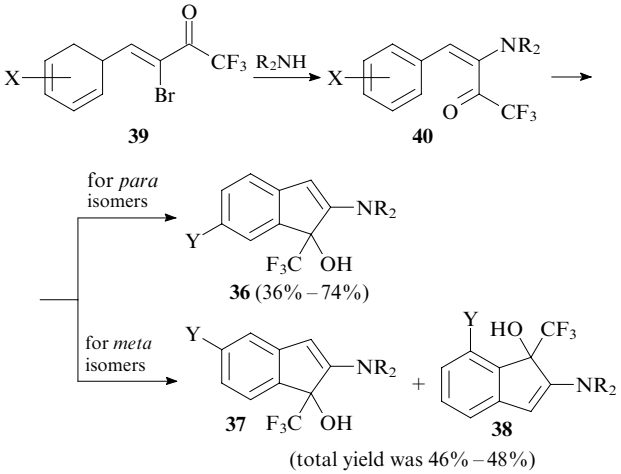


† This term refers to alkenes containing an electron-donating and electron-withdrawing substituents at the same carbon atom of the double bond.

The reactions with the use of bidentate nucleophiles can lead to additional transformations. For example, the cascade of transformations initiated by the aza-Michael reaction of the precursor of bromo(cyclohexylidene)acetate **31b** with *N*-methylethylenediamine is completed with the condensation at the alkoxycarbonyl group giving spirocyclic lactam **35**.[258]



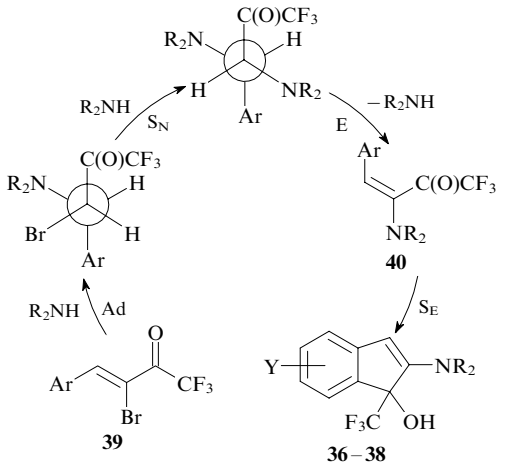
Recently, an elegant one-pot method was developed for the synthesis of polyfunctional indenols **36**–**38** from 2-bromoalkenyl trifluoromethyl ketones **39**.[259,260] The reaction proceeds at room temperature in the absence of a catalyst. The intramolecular cyclization with *meta*-substituted bromo enones **39** affords a mixture of isomeric indenols **37** and **38**.[260] A substantial predominance of isomer **37** is apparently attributed to the steric effect of the *meta* substituent. It is interesting that the cascade of the reactions of bromo enones which do not contain the trifluoromethyl group stops at the formation of captodative aminoalkene **40**.[261]



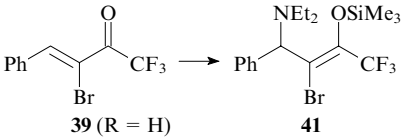
X = 3-Me, 4-Me, 3-MeO, 4-MeO; R_2N = Et_2N, Pr^n_2N, Bu^n_2N;
Y = Me, MeO.

These results can be interpreted based on the multistep scheme of transformations of bromo enones **39** in the presence of secondary amines (Scheme 1). The Michael addition (Ad) of amine to the conjugated C=C–C=O system is a key step of this scheme. The subsequent substitution (S_N) of the bromine atom with the amino group of the newly formed tetrahedral carbon atom, the elimination (E) of amine giving captodative system **40**, and the intramolecular electrophilic aromatic substitution (S_E) are the final steps of the synthesis giving indenol derivatives **36**–**38**.

Scheme 1

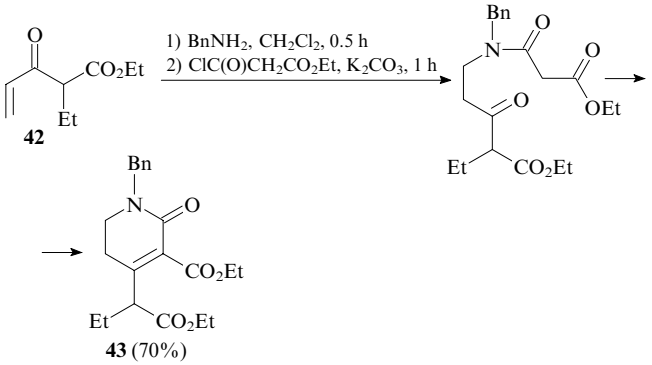


The postulated scheme of $Ad-S_N-E-S_E$ transformations was confirmed by the detection of some intermediates by NMR monitoring. Moreover, a convincing argument in favour of the initial aza-Michael reaction, which initiates the cascade of transformations, was obtained with the use of trimethylsilyl derivatives of secondary amines as nucleophiles.[259] The formation of adduct **41** is strong evidence in support of the fact that the aza-Michael reaction is a key step in the synthesis of indenols.

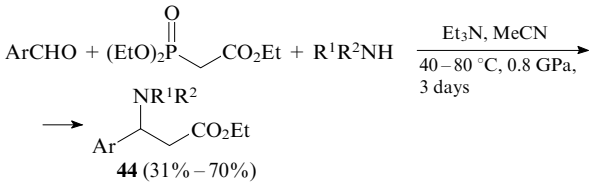


Examples of the reactions of trifluoromethyl alkenyl ketones involving the conjugate addition of nitrogen-containing nucleophiles as the initial step were given in reviews.[262–264]

Basic conditions used in the aza-Michael reaction with amines are favourable for the aldol condensation. This tandem sequence is often used for the construction of complex cyclic structures. Recently, this process has been used for the synthesis of camptothecin synthons, *viz.*, alkaloids having antitumour properties.[265] The addition of benzylamine to enone **42**, the reaction of the Michael adduct with ethyl malonyl chloride, and the subsequent intramolecular aldol condensation giving the desired heterocycle **43** are key steps in the synthesis.



The aza-Michael reaction can not only initiate the cascade of transformations but also be the final step in these transformations. For example, Reiser and co-workers[266] performed the three-component synthesis of β-amino esters by combining the Horner–Wadsworth–Emmons reaction with the subsequent Michael addition of amines. The developed domino reaction proceeds only at high pressure to give target compounds **44** in good yield.



Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$;
R^1R^2N = $(CH_2)_5N$, BnMeN, Pr^n_2N.

Finally, to complete the consideration of cascade transformations, it should be noted that in the recent past the aza-Michael reaction has found wide use in the synthesis of polymeric biomedical and pharmaceutical agents, as well as of various composites for microelectronics. The architecture of the resulting polymers varies from linear thermoplastic polymers to branched and network structures, including dendrimers. The obvious advantages of the aza-Michael reaction over other methods are that a wide range of monomers can be used and the synthesis of macromolecular structures can be performed under mild conditions. The recent advantages in this field are discussed in the review.[267]

VI. Conclusions

According to the data of the Pfizer Inc., which is the world leader in pharmaceutical industry, the molecules of more than 90% of all drugs contain at least one nitrogen atom,[268] and each seventh reaction in pharmaceutical industry involves the formation of the carbon–nitrogen bond.[269] Hence, it is not surprising that the aza-Michael reaction is one of the most widely used reactions in modern organic synthesis of biologically active compounds. In the last decade, great advances were made in the investigation of the conjugate addition of nitrogen-containing nucleophiles. First, a range of potential Michael donors and Michael acceptors was substantially extended. Due to the successful search for new catalytic systems and the development of methods for performing this reaction, it became possible to carry out the reactions with weak nucleophiles, such as carbamates or amides, as well as alkenes containing bulky substituents. The problems of the regioselectivity of the addition, the involvement of alkenes containing a weakly activated double bond in these reactions, and the development of methods for the cascade synthesis of complex molecules involving the conjugate addition of N-nucleophiles as a key step remain open.

Nowadays, the aza-Michael reaction is a powerful tool for constructing the C–N bond following green chemistry principles. Although there are no versatile catalysts equally suitable for the whole range of Michael acceptors and Michael donors, the analysis of all *pro et contra* in each particular case will allow one to choose an adequate procedure for performing the reactions and achieve the target.

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