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Aromatic and sterically hindered amines in aza-Michael reaction: solvent and high pressure effects

Alena Fedotova

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Pour obtenir le diplôme de doctorat

Spécialité (Chimie)

Préparée au sein de l'Université de Rouen Normandie
et de l'Institut Favorsky de l'Académie de Russie à Irkoutsk

Aromatic and sterically hindered amines in aza-Michael reaction: solvent and high pressure effects

Présentée et soutenue par
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Thèse soutenue publiquement le 22 mai 2018
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It is dedicated to my lovely parents...

CHAPTER I. WEAK NUCLEOPHILES IN AZA-MICHAEL REACTION.

Review.

Introduction.

One of the most fundamental problems in modern organic synthesis is a development of methods allowing to obtain complex target molecules in high selectivity. Among of the most useful methods to create novel carbon-carbon and carbon-heteroatom bonds, the conjugate nucleophilic addition to activated alkenes and alkynes has a particular interest. Such reaction type is known since more than one hundred years. In the middle of 1880s an American chemist Arthur Michael reported about a successful addition of malonic acid and acetoacetic acid esters to alkenoates. Despite the fact, that some examples of similar transformation have been known in literature before, this kind of reactions today is deservedly named after him. A. Michael studied in detail the reaction of nucleophiles with unsaturated carbonyl compounds, determined the direction of nucleophilic attack and suggested a plausible mechanism of all transformation cascade. Among of all conjugate nucleophilic addition processes exactly the reaction of activated alkenes with *N*-nucleophiles (so-called aza-Michael reaction) attracted great attention. At the present time it is the most popular and effective method of C-N bond formation [1-3]. It would seem that aza-Michael reaction is well studied and further investigations are of little scientific interest. However, according to SciFinder several original articles about improving

already known methods of conjugate nucleophilic addition as well as about developing of new ones, satisfying environmentally friendly protocols, appear annually. Taking into account that every 7th reaction in pharmaceutical industry is related to carbon-nitrogen bond formation, the growing interest in research in this field becomes clear. Aza-Michael reaction is the shortest way to β -amino carbonyl compounds, including β -amino acid derivatives, which can be the valuable intermediates for synthesis of nitrogen-containing bioactive molecules and drugs. This reaction type often initiates domino transformations resulted in complex polyfunctional carbo- or heterocycles and natural products analogs.

It is well known, that high nucleophilic amines are added readily to electron poor alkenes but most of the methods developed for aliphatic amines cannot be successfully transposed to aromatic amines. Actually, there are just few examples about non-catalytic conjugate nucleophilic addition of arylamines. Therewith, some examples of using Lewis or Brønsted acids, as well as the transition metal salts as catalysts of conjugate addition of low nucleophilic amines to high active Michael acceptors. Unfortunately, these methods are characterized by low yields of target products, harsh experimental conditions and necessity of using cost and toxic catalysts. As a rule, involved Michael acceptors deal with only terminal alkenes.

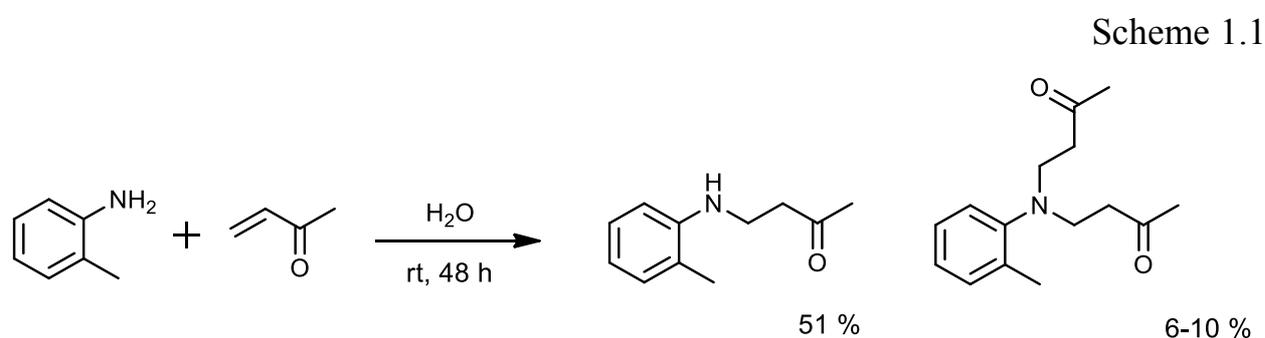
For the last decade significant progress has been made by using the new types of donors and Michael acceptors and developing of new ways to perform these reactions. The latest achievements in the study of aza-Michael reaction with weak *N*-nucleophiles (aromatic and heteraromatic amines, amides, carbamates, sulfonamides and etc.) and Michael acceptors containing terminal or internal double bond, published for the last 6 years (2011 – mid. 2017) are discussed in this review.

1.1 Aromatic and heteroaromatic amines

1.1.1 Non-catalytic aza-Michael reaction with (het)arylamines.

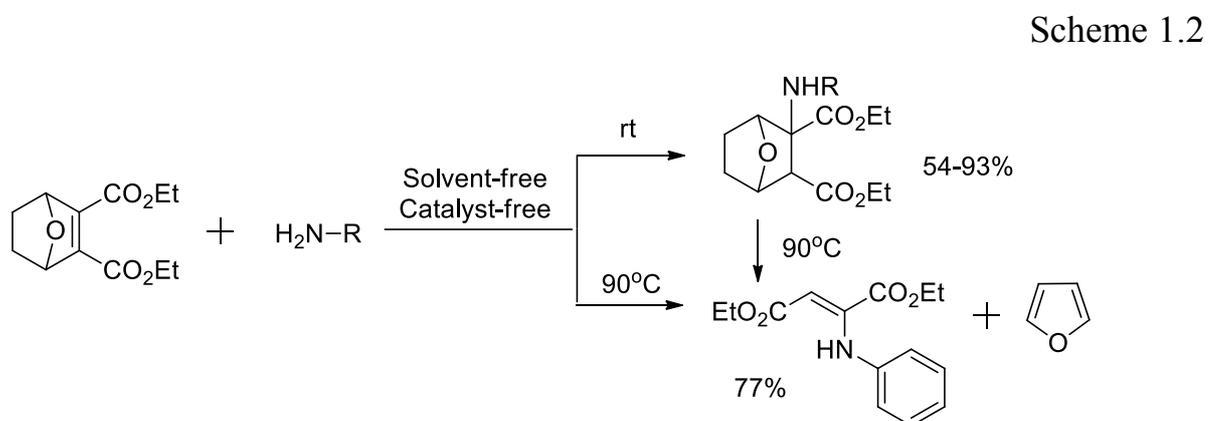
Aliphatic amines, as good nucleophiles, readily react with activated alkenes without a catalyst, while the reactions of less reactive aryl- or hetaryl amines require the additional activation, as expected. Indeed, the examples of non-catalytic conjugate addition of aromatic amines to Michael acceptors are rare, and the double bond of the latter must be strongly activated by the electron-withdrawing group (NO₂, C(O)R, SO₂R).

For example, *o*-toluidine readily adds to methylvinylketone in water already at room temperature [4] (Scheme 1.1).



It is worth to note when a double excess of ketone is used, the formation of a bis-adduct (6-10%) is observed. The monoadduct yield is slightly less with an equimolar ratio of reagents, but the formation of the undesired bis-adduct is practically reduced to zero.

A non-catalytic, "green" method to synthesize β -aminocarbonyl compounds based on oxonorbornene and arylamines is proposed by a group of scientists from China [5] (Scheme 1.2).

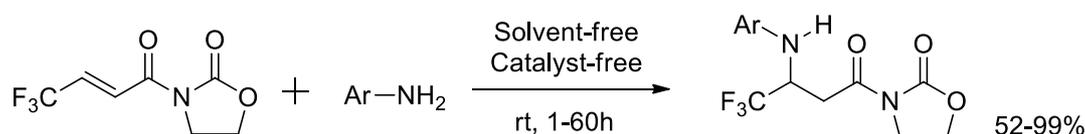


Amine: PhNH₂, 4-MeC₆H₄NH₂.

The authors point out the structure dependence of the reaction product on the experimental conditions. At room temperature, both alkyl- and arylamines form Michael adducts. When heated, the aromatic amine addition product is undergone to a Diels-Alder retro reaction to form a thermodynamically more stable β -aminofumarate.

Nucleophilic addition of arylamines to β -trifluoromethylacrylate derivatives is realized at room temperature without solvent and catalysts. It is not surprising, since the CF_3 group introduction in the vicinal position to EWG substantially increases the electrophilic nature of double bond, thereby facilitating the nucleophilic attack even by low-basic amines [6] (Scheme 1.3).

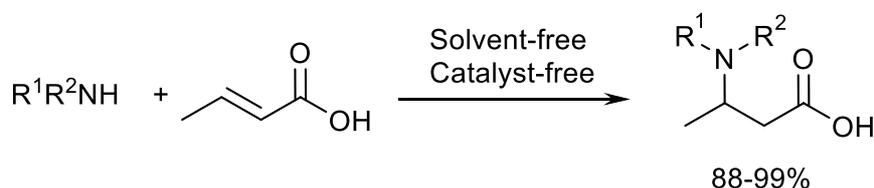
Scheme 1.3



Ar: Ph, 2-MeOC₆H₄, 2,4-(MeO)₂C₆H₃, 3-MeC₆H₄, 3-FC₆H₄, 3-ClC₆H₄, 3-BrC₆H₄, 3-CF₃C₆H₄, 4-EtC₆H₄, 4-^tBuC₆H₄, 4-FC₆H₄.

Simple and high effective method to synthesize the *N*-substituted β -alanine derivatives are suggested by authors from India [7]. Colleagues successfully add not only aromatic amines, but also heteroaromatic, when adducts with quantitative yields are resulted (Scheme 1.4).

Scheme 1.4



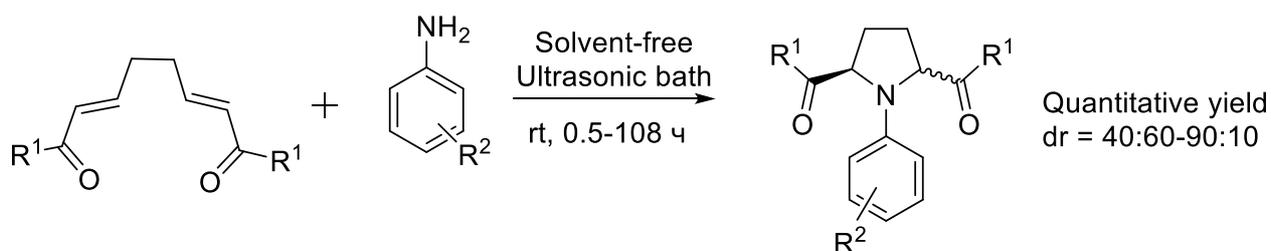
$\text{R}^1 = \text{H}, \text{R}^2 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-}i\text{-PrC}_6\text{H}_4;$
 $\text{R}^1\text{R}^2\text{NH} = \text{Ph(Me)NH}, 3\text{-H}_2\text{NPy}, 4\text{-H}_2\text{NPy}$

The authors observe that the substituent nature in the aromatic ring significantly affects the course of the conjugate addition reaction. As expected, electron-rich anilines (anisidine, toluidine) react rapidly, giving Michael adducts in quantitative

yield. The presence of strong electron-withdrawing substituents in the benzene ring of arylamines not only slows the reaction, but also significantly reduces the adduct yield. Here the reaction describes the nucleophilic addition and *N*-methylaniline, the conjugate addition of which proceeds not as easily as aniline because of the steric factor (methyl group). The technique proposed by the authors makes it easy to add secondary arylamine to crotonic acid, giving the target adduct in high yield (88%).

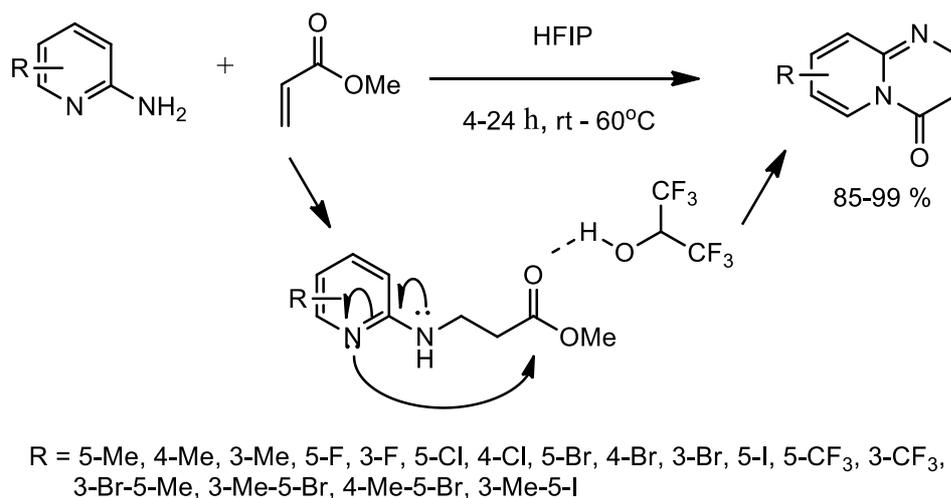
Nucleophilic addition of arylamines without a solvent and with ultrasonic action, is proposed [8]. The authors successfully add both electron-saturated (toluidine, anisidine, hydroxyaniline) and low-basic (*para*-nitroaniline) amines to dieneones, obtaining pyrrolidine derivatives in moderate yields (Scheme 1.5).

Scheme 1.5



One-pot synthesis of nitrogen-containing bicyclic compounds has been proposed [9] (Scheme 1.5). The non-catalytic synthesis of dihydropyrimidinones is based on the reaction of substituted 2-aminopyridines with methyl acrylate. In this case Michael addition is effectively promoted by strong proton-donor solvent (1,1,1,3,3,3-hexafluoroisopropanol, HFIP) (Scheme 1.6).

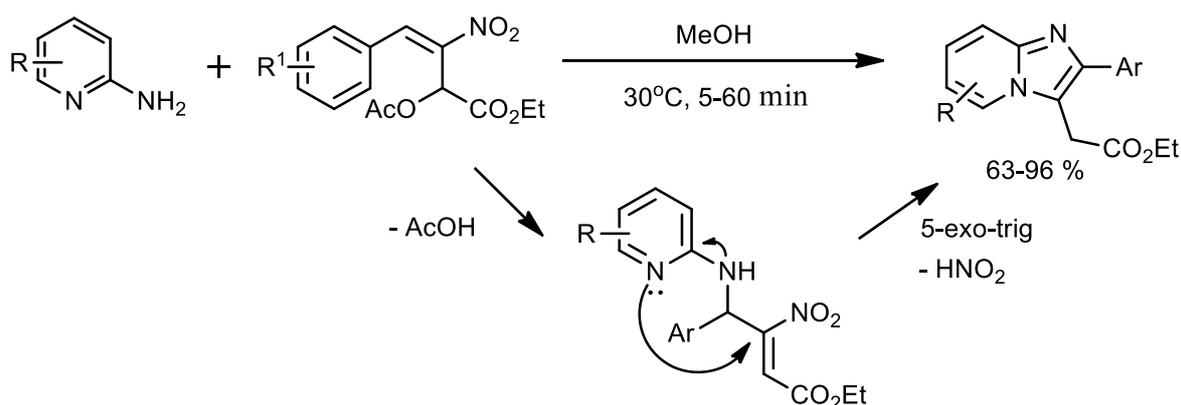
Scheme 1.6



The authors specify exactly the application of fluorine-containing alcohol makes it possible to easily obtain the target bicyclic compounds in high yield. Screening of such proton-donor solvents as methanol, ethanol, propanol, acetic acid has shown their ineffectiveness for the addition of aminopyridines to methyl acrylate. In all the listed solvents, the conversion of the initial reagents is zero. The catalytic action of the fluorinated alcohol is based on the formation of an intermolecular hydrogen bond with the carbonyl oxygen atom, thereby activating the double bond of the electrophile and facilitating the nucleophilic addition of hetarylamine to the acceptor. In the second stage activating the carbonyl group HFIP catalyzes intramolecular cyclization due to nucleophilic attack by the more basic pyridine nitrogen atom per carbon atom of the carbonyl group.

Another method for the synthesis of bicyclic aza-heterocycles is based on the reaction of 2-aminopyridines with nitroalkenes (Morita-Baylis-Hillman acetates) [10] (Scheme 1.7).

Scheme 1.7



R = 3-Me, 4-Me, 5-Cl, 5-Br;

R¹ = 3,4-(OMe)₂, 3,4,5-(OMe)₃, 4-Me, 4-Cl, 3-Br, 2-NO₂, 2-furyl, 2-thienyl

One-pot synthesis of imidazopyridines involves the conjugate addition of aminopyridine to the nitroolefin by the primary amino group followed by the elimination of the acetate ion (S_N2' mechanism) in the first stage; and in the second stage, regioselective intramolecular 1,4-addition by endocyclic nitrogen to β -carbon at the ethoxycarbonyl group. Why is the nucleophilic attack aimed at α -carbon in the nitro group? It would seem that the acceptor ability of the nitro group is much higher than alkoxy carbonyl radical one. Probably, the resulting heterocycle is a thermodynamic reaction product, which is an aromatic annelated structure. At the nucleophilic attack on β -carbon with respect to the nitro group, we do not obtain an aromatic structure that is less preferable.

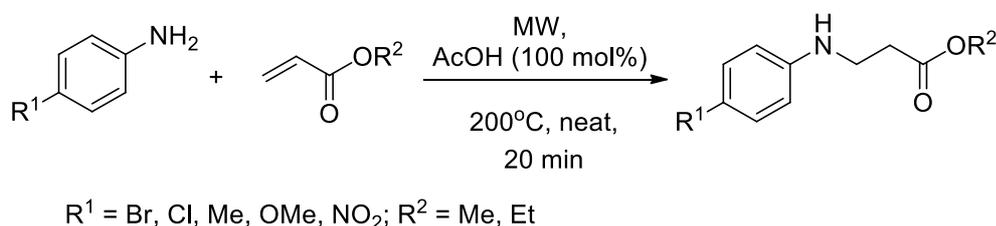
Thus, hetaryl amines are added to Michael acceptors even in the absence of a catalyst, but using additional activation (for example, physical one) provided that the double bond has a strongly pronounced electrophilic character. It is easily achieved by using terminal alkenes with strong acceptor group as electrophiles, or by introducing an additional activating group into the geminal or vicinal positions with respect to the first EWG.

1.1.2. Acid-base catalysts of aza-Michael reaction.

Acid catalysis plays a key role in modern organic synthesis. Conventional acid catalysts include both inorganic (H_2SO_4) and organic acids (TFA, *p*-TSA), as well as it concerns the aza-Michael reaction. It is not always possible to efficiently carry out the aza-Michael reaction with weak or sterically hindered nucleophiles or electrophiles without a catalyst. Brønsted and Lewis acids are widely used as a catalyst for the reaction of conjugate amine addition to activated alkenes. But one of the significant disadvantages of this catalysis method is the side reactions, which chemists try to avoid, improving this kind of catalysis.

A simple and completely environmentally friendly method of synthesis of β -aminoester derivatives is proposed recently [11]. The authors successfully add substituted anilines to α,β -unsaturated esters by heating to 200°C in the presence of an equimolar amount of acetic acid and under microwave irradiation (Scheme 1.8).

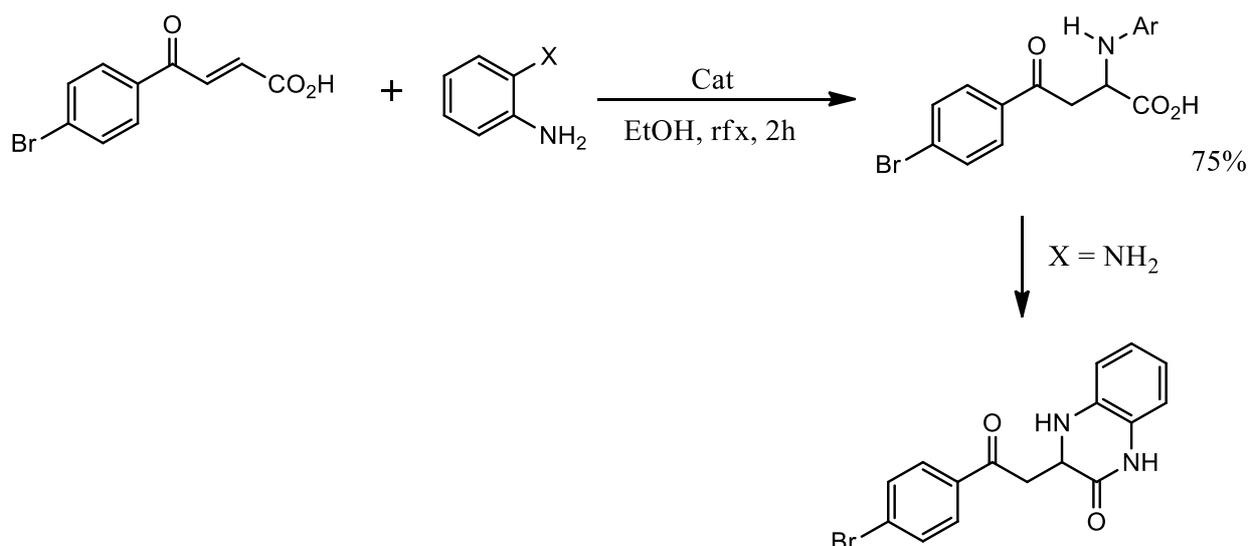
Scheme 1.8



It should be noted that the authors have managed to involve even a weak nucleophile, such as *para*-nitroaniline, in the reaction, that is undoubtedly one of the advantages of this technique.

The regioselective addition of anthranilic acid and *o*-phenylenediamine to β -aroylacrylic acid proceeds efficiently in boiling ethanol with a catalytic amount of acetic acid [12] (Scheme 1.9).

Scheme 1.9

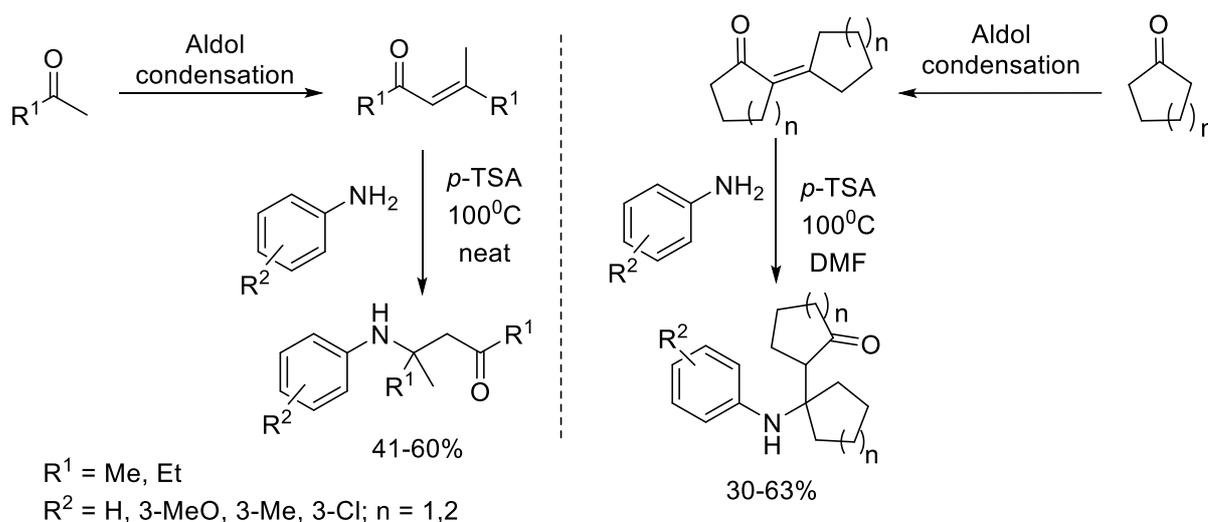


X = CO₂H, NH₂.

The nucleophilic attack is always directed towards α -carbon in the carboxyl group. The authors have assumed the formation of both 6- and 7-membered heterocyclic structures with an additional nucleophilic center in the diamine molecule (o-PDA). But as a result of the addition-dehydration reaction, only one product, the dihydroquinoxaline derivative, has been isolated.

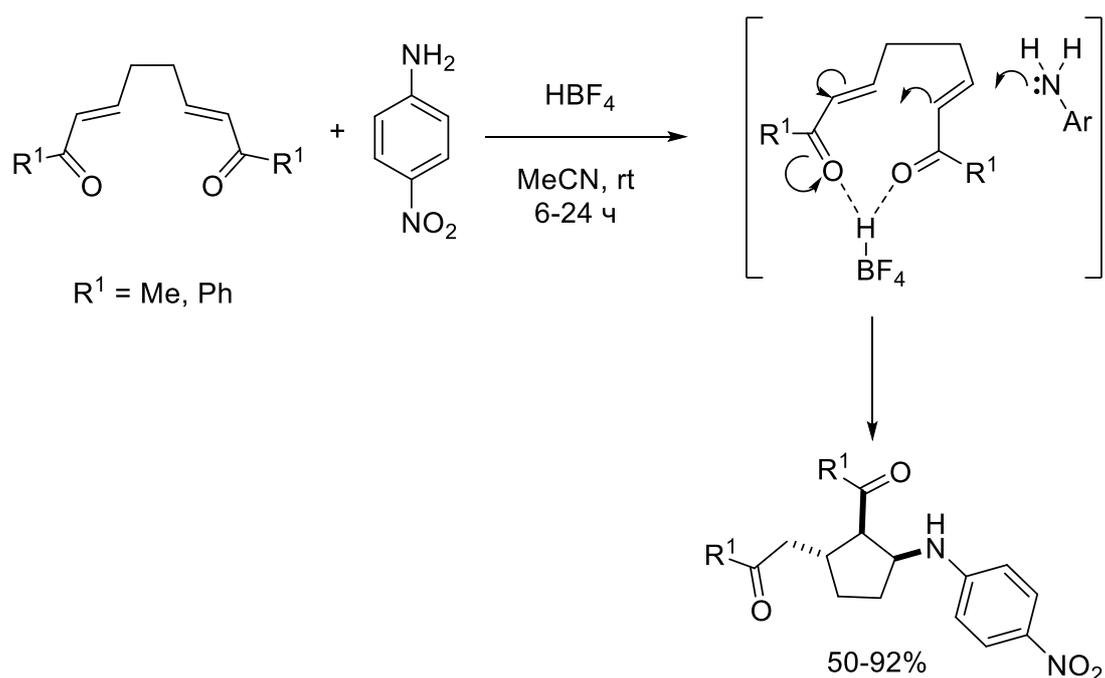
p-Toluenesulfonic acid as an effective catalyst in the reaction of the nucleophilic addition of substituted anilines to cyclic and acyclic ketones is proposed [13]. The authors have successfully synthesized new β -aminoketone derivatives containing a quaternary azacarbon center (Scheme 1.10).

Scheme 1.10



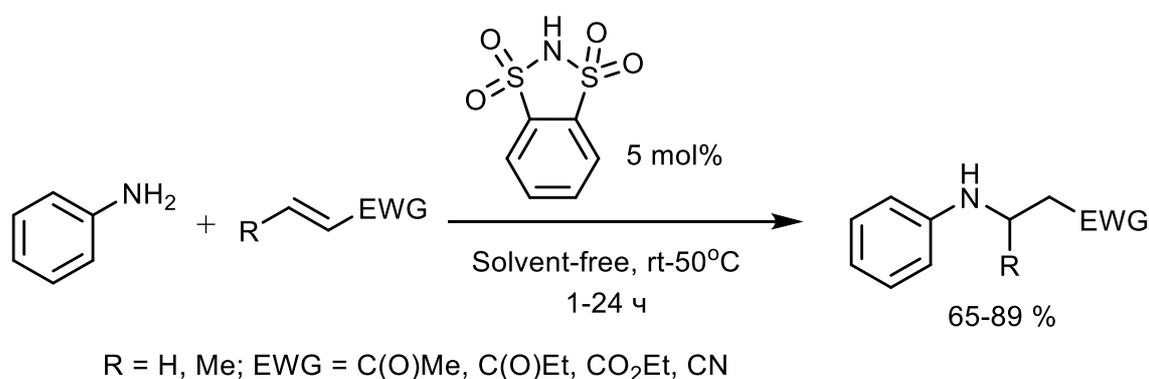
Earlier, in Section 1.1.1, it has been discussed [8], i.e. successful addition of *para*-nitroaniline to acyclic diketones without a catalyst, but with ultrasonic promotion. The authors have observed double Michael addition (nucleophilic attack by the primary amino group, then intramolecular addition of the formed secondary aminogroup to the second double bond) to form pyrrolidine. It has been required up to 108 hours of ultrasound. Further, the authors have decided to simplify the reaction – to use a strong acid - HBF_4 . At acid catalysis the aza-Michael reaction occurs only at the first stage of addition to a multiple bond, and then yields to the competitive addition according to its classical version. Due to the low nitrogen basicity the oxygen of the carbonyl group is protonated. The resulting enol undergoes intramolecular cyclization to form the cyclopentane derivative (Scheme 1.11).

Scheme 1.11



Italian chemists propose to use organic molecules having an NH-acid center as an effective regenerative catalyst for the reaction of conjugate aniline addition to unsaturated ketones, esters and nitriles [14] (Scheme 1.12).

Scheme 1.12

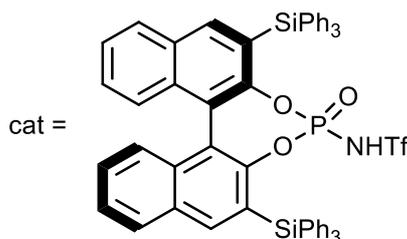
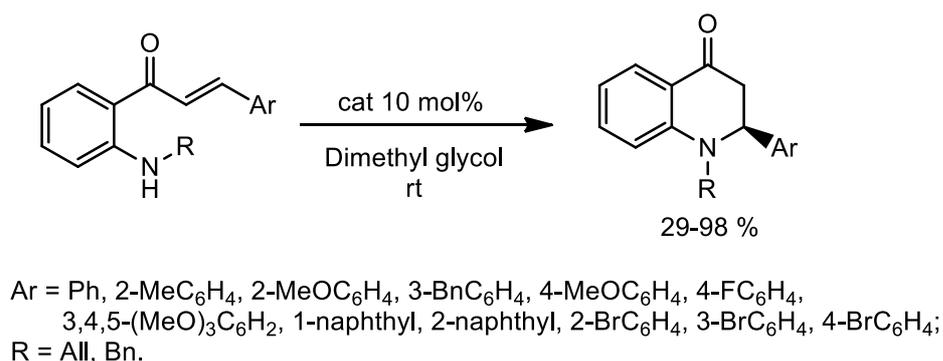


The authors suggest that in the first stage the amine is protonated with Brønsted acid to form a quaternary ammonium salt, which, in turn, is the protonating reagent in a carbonyl, alkoxy carbonyl or cyano group activation. To confirm or disprove this hypothesis, the colleagues have received separately an ammonium salt and have used it as a catalyst for the addition reaction of amine to the enoate. The reaction rate and product yield have been comparable to the results obtained earlier, that confirmed the

authors' hypothesis, although they have not exclude the possibility of the direct protonation by the disulfonimide of the carbonyl acceptor group in the presence of an amine.

Asymmetric synthesis of 2-aryldihydroquinolinones based on intramolecular aza- Michael reaction has been proposed in [15] (Scheme 1.13).

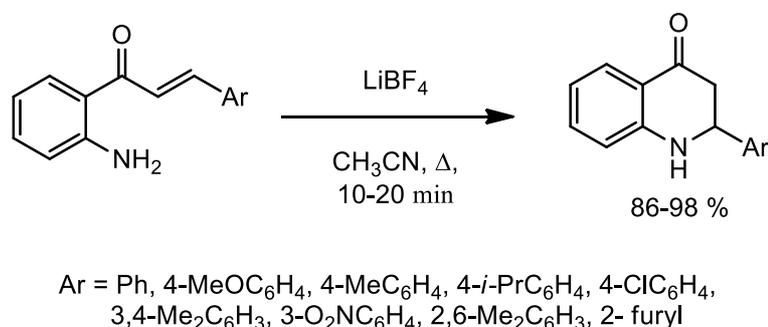
Scheme 1.13



The chiral Brønsted acid allows to get heterocyclic derivatives of dihydroquinolines in high enantioselectivity (*ee* 74-81 %).

Intramolecular conjugate addition effectively proceeds also under Lewis acid catalysis [16] (Scheme 1.14).

Scheme 1.14



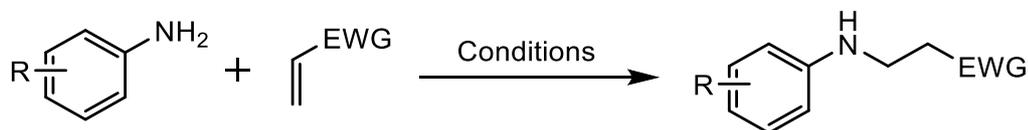
The authors have been firstly reported that LiBF₄ can successfully catalyze both intra- and intermolecular 1,4-addition of *N*-centered nucleophiles to wide spectrum of Michael acceptors (Scheme 1.15).

Scheme 1.15



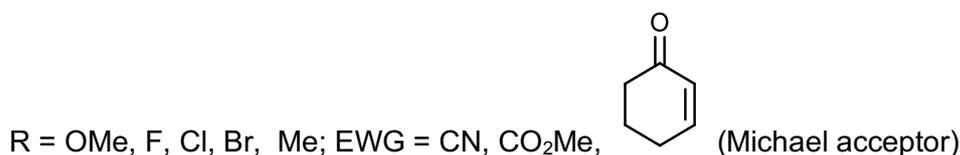
Reasonable and efficient synthesis method of β -aminocarbonyl and β -aminonitriles compounds is described [17, 18]. It is proposed to use Lewis acids (FeCl₃, SbCl₂), coated on a solid carrier (nanoclay or titanium oxide), as a heterogeneous catalyst. The reaction proceeds smoothly without a solvent and is completed after 1-7h (Scheme 1.16).

Scheme 1.16



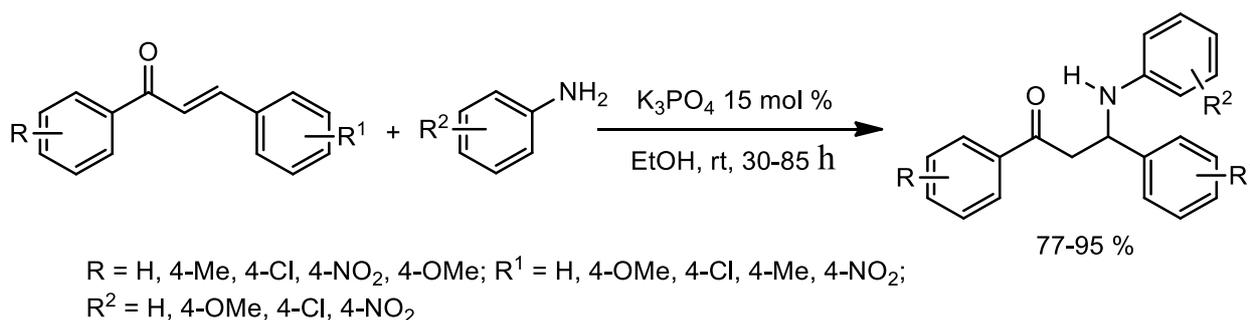
Conditions: FeCl₃-MontK10 10 mol%, 60°C, 1-7 h, 65-94% [17];

TiO₂-SO₃-SbCl₂ 2 mol%, 60°C, 1-3.5 h, 85-95% [18];



Other approach to obtain β -aminocarbonyl compounds is based on the Brønsted or Lewis bases. One-step synthesis of β -aminoketones based on conjugate addition of arylamines to chalcon derivatives catalyzed by potassium phosphate is described [19] (Scheme 1.17).

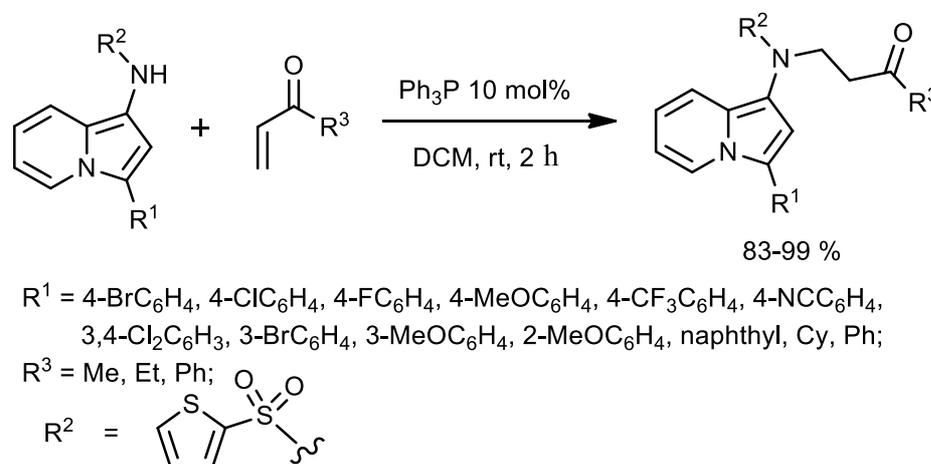
Scheme 1.17



It is worth to emphasize that a very weak nucleophile (nitroaniline) successfully reacts with the chalcon, obtaining the desired adduct with a rather high yield (81%). The authors believe that the action of potassium phosphate is activated by the potassium ion of the carbonyl group of the enon that increases the electrophilicity of the β -carbon atom. In turn, the phosphate ion being a strong base, deprotonates the amino group, increasing the amine nucleophilicity.

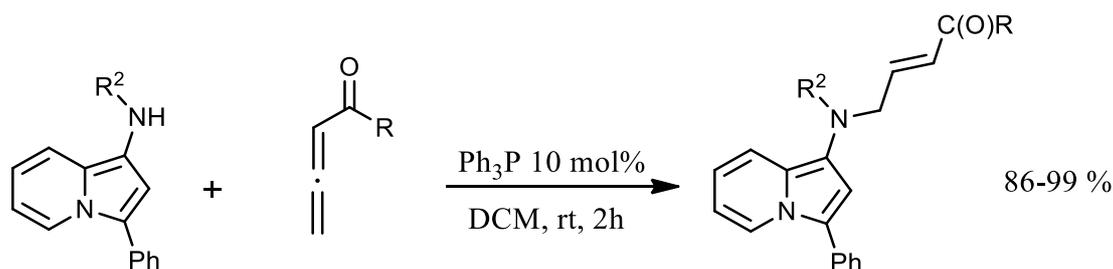
Successful use of triphenylphosphine as a catalyst of conjugate addition of aminoindolizines to activated ketones is described [20] (Scheme 1.18).

Scheme 1.18



The nature of the substituent of the nucleophile in the aromatic ring does not have a significant effect on the yield of the products formed. Both electron-saturated and electron-deficient aryl substituents lead to aza-Michael adducts in high yields (Scheme 1.19).

Scheme 1.19



R = Me, OEt.

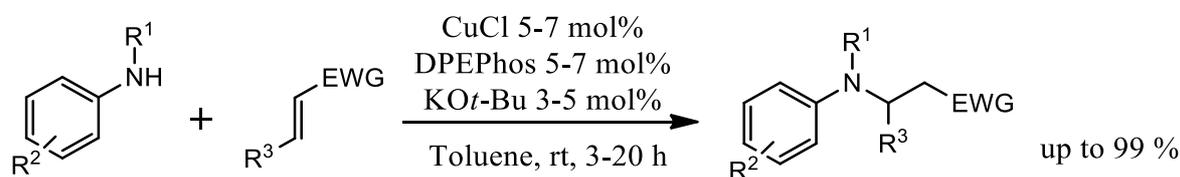
Extending the range of Michael acceptors, the authors have introduced acrolein and methyl acrylate into the reaction with the same nucleophiles. However, all these attempts have turned out, unfortunately, unsuccessful. On the contrary, the use of activated allenes as electrophiles make it possible to easily obtain Michael adducts in high yields.

1.1.3 Transition metal catalysis.

Salts of transition metals are actively synthesized in various β -aminocarbonyl compounds, catalyzing the conjugate addition of weak nucleophiles to conjugated systems.

Copper chloride (I) has recommended as an effective catalyst for the reaction of arylamines to α,β -unsaturated sulfones [21], ketones, esters, nitriles [22]. The reactions proceed at room temperature in toluene (Scheme 1.20).

Scheme 1.20



R¹ = H, Me, Ph;

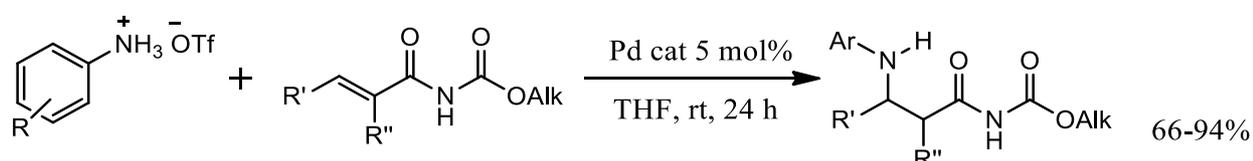
R² = 2-Me, 2-OMe, 4-Hal, 4-OMe, 4-Me, 4,5-(OMe)₂, 4-F, Br, 6-Cl;

R³ = H, Ph.

Several examples of palladium salts used as catalysts for conjugate addition reaction of low-basic amines to α,β -unsaturated activated alkenes are known in the literature.

It is firstly proposed to prepare a quaternary triflate salt of aniline and only then to add a substrate and a palladium salt to obtain a palladium catalyst [23,24]. The authors suggest that the palladium salt addition directly to the amine can deactivate the catalyst (the metal cation act as acid, the amine - as Lewis base). The effective addition of arylamines to α, β -unsaturated carbamates is shown [25] (Scheme 1.21).

Scheme 1.21

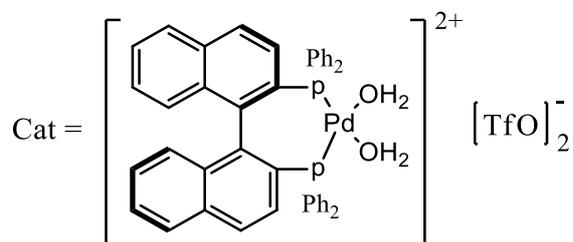
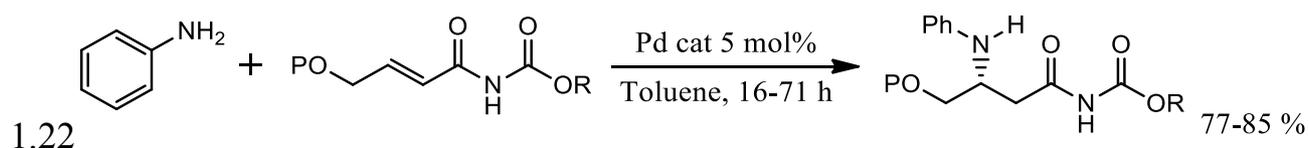


R = 4-CF₃, 4-Hal, 4-OMe;

R' = Me; R'' = Me, Et, *i*Pr, Bn, Ph.

Enantioselective aza-Michael reaction catalyzed by complex palladium salts is described [26] (Scheme 1.22).

Scheme



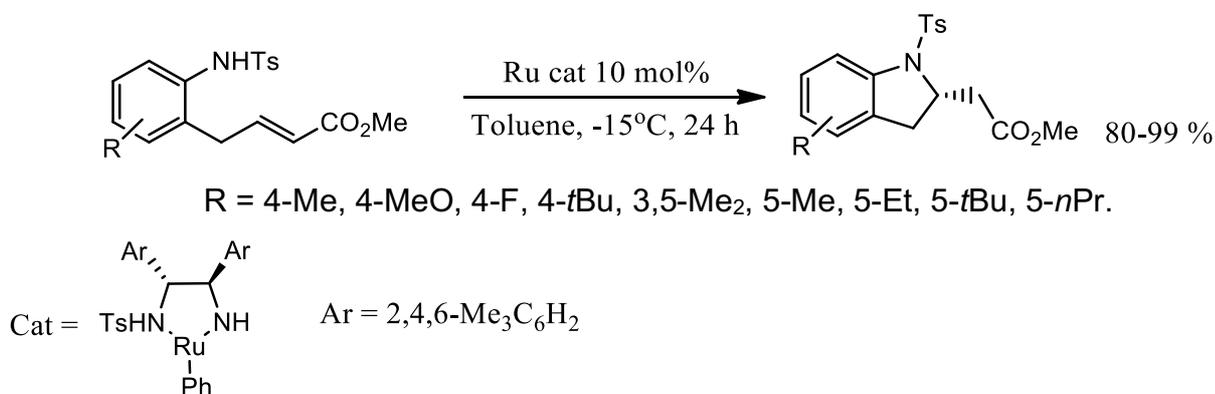
P = Bn, TBDPS; R = Me, Bn.

The obtained aminocarbamates are successfully used in the synthesis of analogues of natural compounds.

The aza-Michael reaction is successfully catalyzed with arylamines or salts of indium [27], zirconium [28], nickel [29], ruthenium [30]. The metal complex catalysis is used to synthesize new β -alanine derivatives with high enantioselectivity, in a short time, even such low reactivity reagents as nitroanilines and β -substituted Michael acceptors can enter the reaction (Table 1).

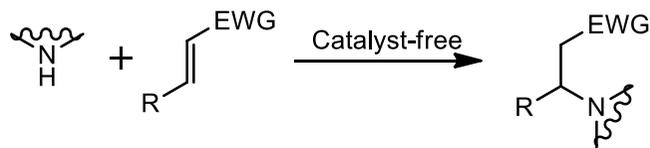
There is an example of enantioselective synthesis of indolines, initiated by intramolecular aza-Michael reaction. Such process proceeds at catalysis by amide complex of ruthenium [30] (Scheme 1.23).

Scheme 1.23



Thus, transition metal catalysis is actively used for both inter- and intramolecular addition of low-nucleophilic amines to conjugated alkenes.

Table 1.



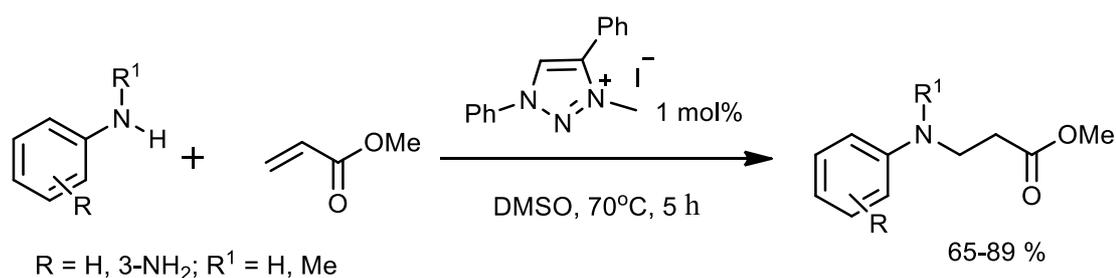
Michael acceptor		Michael donor	Reaction conditions				Yield, %	Ref.
R	EWG		Catalyst	Solvent	Temp., °C	Time, h		
4-ClC ₆ H ₄ ; 4-O ₂ NC ₆ H ₄ ; 4-MeC ₆ H ₄ ; 4-MeOC ₆ H ₄	C(O)Ar	 Ar = 4-ClC ₆ H ₄ , 4-O ₂ NC ₆ H ₄ , 4-MeOC ₆ H ₄	InCl ₃ /Zn 10 mol%	H ₂ O	60	80-105	72- 80(95/5- 97/3 <i>de</i>)	27
H	CN, CO ₂ Me	PhNH ₂ , 4-MeOC ₆ H ₄ , 4-ClC ₆ H ₄	Zr(OTf) ₂ 5 mol%	C ₆ D ₆	25-60	0.1-1	12-75	28
H, Me	CN	PhNH ₂ , 4-FC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 2,5-Me ₂ C ₆ H ₄	Ni(II) 1 mol%, Et ₃ N	THF	50	2	-	29

H	CN	PhNH ₂ , 4-MeC ₆ H ₄ , 4-ClC ₆ H ₄ , 2,4,6-Me ₃ C ₆ H ₄ , 2,5-Me ₂ C ₆ H ₄	Ni(II) 1 mol%	Toluene	50	3	-	29
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1.1.4 Organocatalytic aza-Michael reaction

It is known that the addition of arylamines readily proceeds in ionic liquids, including imidazolium [31,32]. The authors propose to use an imidazolium salt in the catalysis of 1,4-addition of arylamines to methyl acrylate, obtained *in situ* based on the “click”-reaction of phenylacetylene and phenylazide in the presence of a copper catalyst [33] (Scheme 1.24).

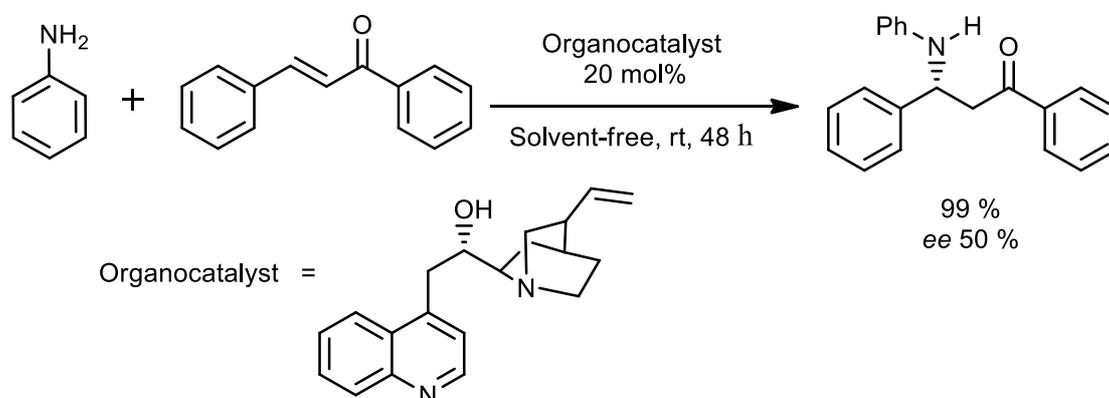
Scheme 1.24



It should be noted that the triazole itself does not catalyze the reaction (the adduct yield is only 20% after 5 hours at 70°C). Using the same salt (essentially, ionic liquid) obtained by N-alkylation of triazole with methyl iodide under the same conditions makes it possible to significantly increase the yield of the desired product (up to 89%).

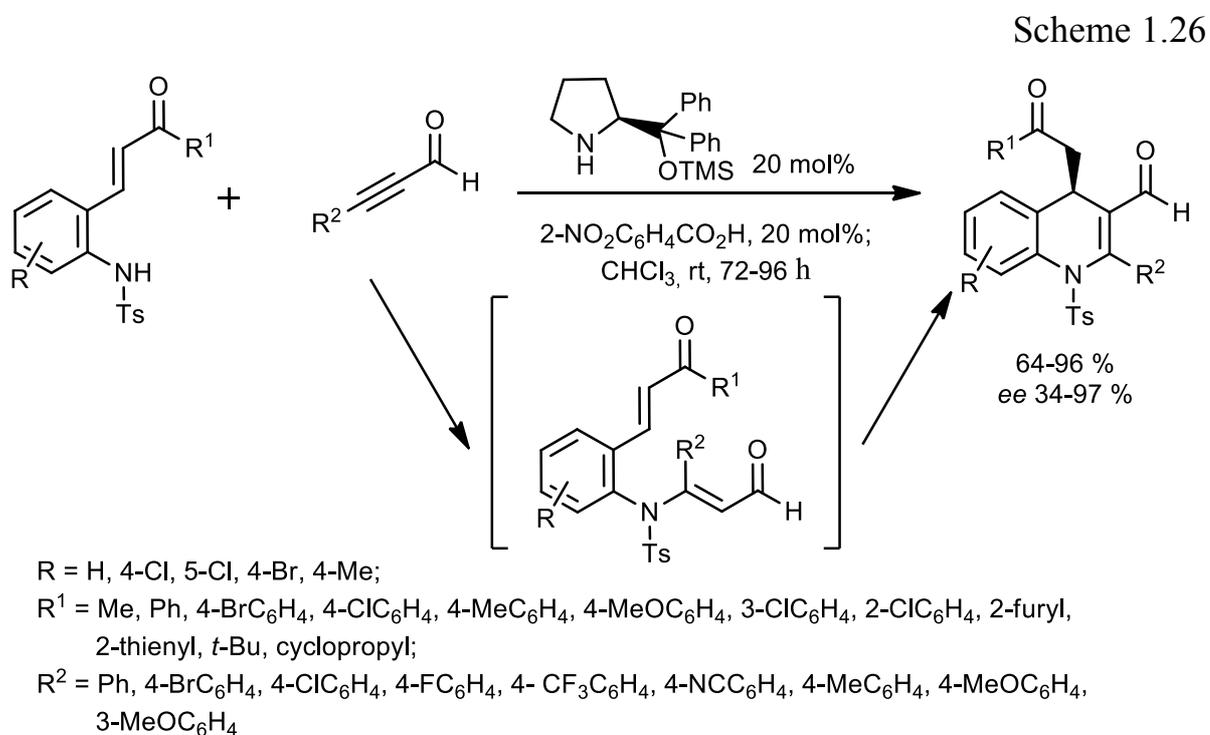
The enantioselective nucleophilic addition to the chalcon proceeds easily at twofold excess of aniline without a solvent during the catalysis of the quinine derivative [34] (Scheme 1.25).

Scheme 1.25



The catalytic action of quinine is based on the nucleophile activation by deprotonation of primary amino group by the more basic tertiary nitrogen of the catalyst and by the increase of the multiple bond electrophilicity due to the formation of the hydrogen bond of the hydroxyl proton with oxygen of the carbonyl group.

The asymmetric assembly of the 1,4-dihydroquinoline nucleus initiated by the aza-Michael reaction is proposed [35]. Silyl ether of diphenylprolinol acts as a catalyst, activating the substrate both at the stage of conjugate aniline addition to alkyne via the formation of an immonium intermediate, and at the stage of intramolecular Michael reaction with the formation of a heterocycle (Scheme 1.26).

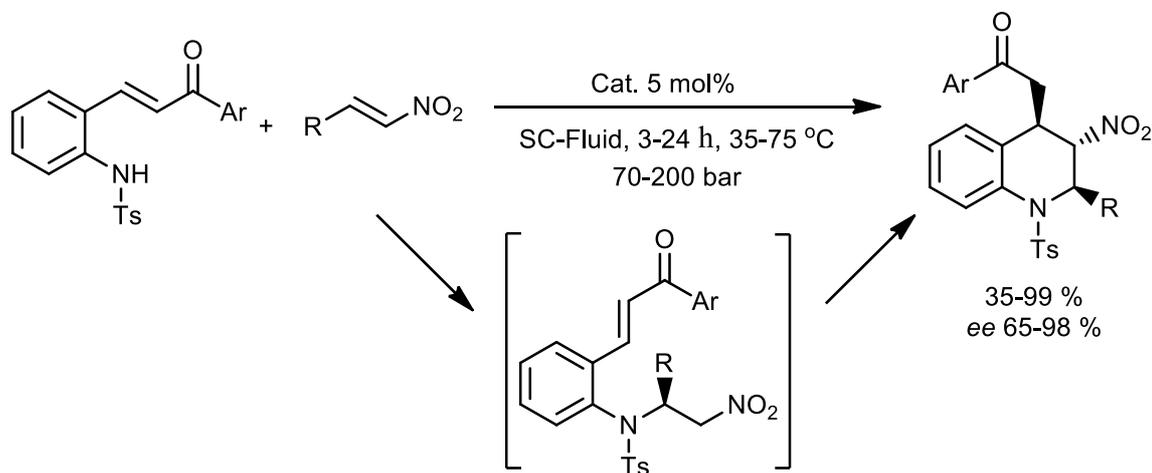


It is found that the substituent nature in the aromatic ring of the amine or in the electrophilic carbon of the substrate does not have a significant effect on the reaction rate and the product yield.

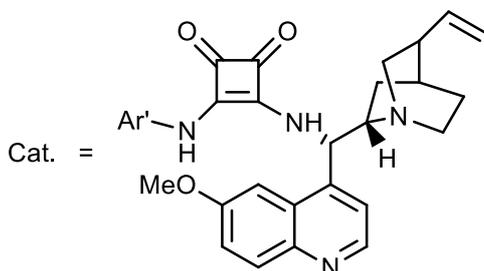
The first case of using bifunctional quinine in a supercritical fluid as an effective catalyst for asymmetric synthesis of functionalized tetrahydroquinolines has been proposed [36]. The conjugate addition of arylamine to nitroalkene initiates a domino-transformation followed by the intramolecular cyclization to a heterocycle.

The technique proposed by the authors makes it possible to obtain valuable tetrahydroquinoline structures with high diastereo- and enantioselectivity (Scheme 1.27).

Scheme 1.27

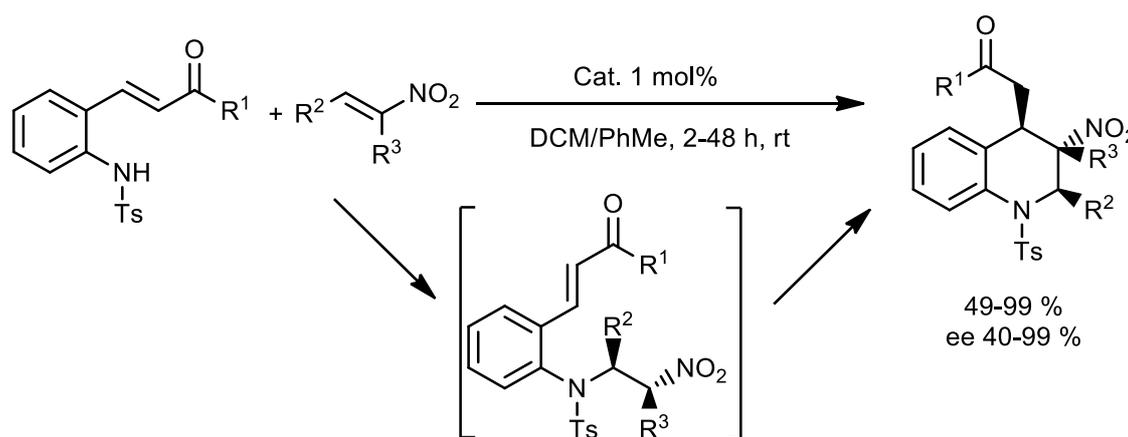


SC-Fluid = CHF₃, CO₂; Ar' = 3-F₃CC₆H₄;
 R = 2-ClC₆H₄, 2-BrC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 2,4-Cl₂C₆H₃, 2-MeOC₆H₄, 3-MeOC₆H₄,
 4-MeOC₆H₄, 3-BuOC₆H₄, 4-MeC₆H₄, 3-O₂NC₆H₄, 4-O₂NC₆H₄, 2-thienyl;
 Ar = 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 4-ClC₆H₄, 2-ClC₆H₄



The same catalyst is also appropriate for β-nitrostyrenes [37]. The authors propose an enantioselective synthesis of tetrahydroquinolines, initiated by the 1,4-addition of *N*-tosylaniline derivatives to nitrostyrenes (Scheme 1.28).

Scheme 1.28



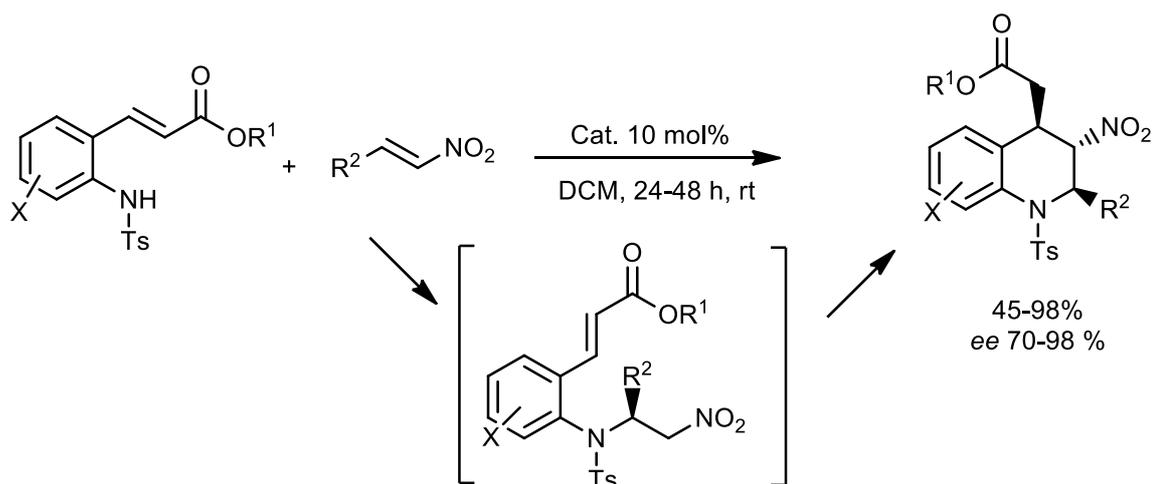
R^1 = Me, OEt, *t*-Bu, 2-MeOC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 4-ClC₆H₄; R^3 = H, Me, Et;
 R^2 = Ph, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 2-ClC₆H₄, 2-MeOC₆H₄,
 furyl, *i*-Pr

The authors indicate that the presence of alkyl substituent in nitrostyrene does not have a significant effect on the yield of the target heterocycle. When the presence of electron-donating (Me-, MeO-) or acceptor (Cl-, Br-, F-) substituents in the aromatic ring of styrene gives an insignificant difference in the yields of the reaction products. In all cases, the derivatives of tetrahydroquinolines have been obtained in high yields and stereoselectivity.

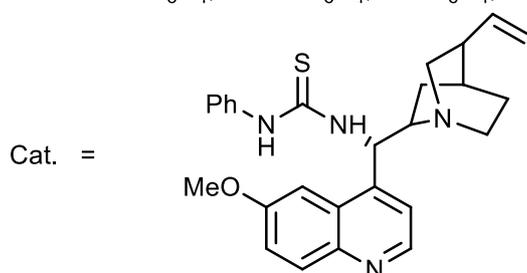
The authors have continued the study of the organocatalytic addition of *N*-tosylanilines to nitroolefins [38]. Bifunctional quinine-based catalyst containing a thiourea fragment perfectly catalyzes the domino-aza-Michael/Michael reaction, giving tetrahydroquinoline derivatives. Varying the amino group protection, the authors have found that derivatives containing ethoxy-, *tert*-butoxy- or benzyloxycarbonyl groups do not react with β -nitrostyrene at all. On the contrary, at using the tosyl protecting group, the reaction cascade has proceeded smoothly, then, forming the desired tetrahydroquinolines in high yield and stereoselectivity. Moreover, high diastereoselectivity has been achieved due to the presence of the tosyl group. The nature of the solvent significantly affects the process course: in proton-donor solvents (MeOH), the reaction almost does not occur, while in toluene or dichloromethane a high yield of adducts has been observed. It is possible that when methanol is used as a

solvent, the catalyst deactivation takes place by protonation of the most basic nitrogen atom. Thus, the quinine derivative cannot catalyze the conjugate addition of arylamine. I admit that the proton of the amino group of aniline is more acidic than methanol, but the latter is taken in a considerable excess compared to the nucleophile (Scheme 1.29).

Scheme 1.29

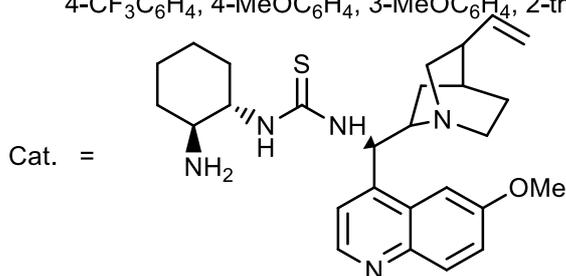
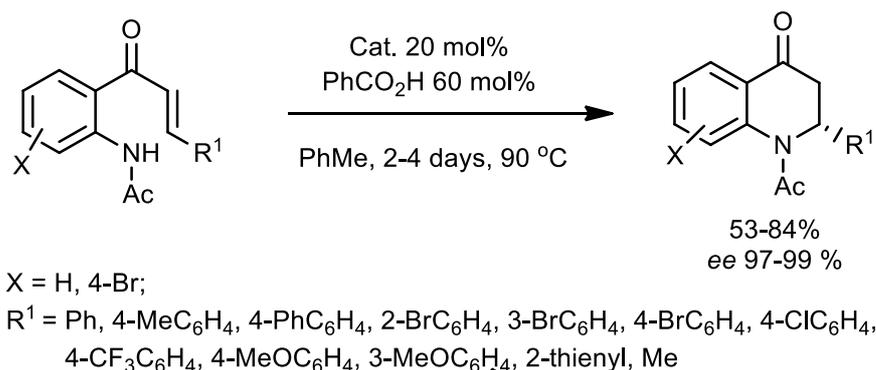


X = H, 4-Me, 6-Me, 4-Cl, 5-Cl, 4-Br; R¹ = Me, Et, *t*-Bu, Bn;
 R² = Ph, 4-MeOC₆H₄, 4-MeC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 4-O₂NC₆H₄, 3,4-(MeO)₂C₆H₃,
 3-MeOC₆H₄, 2-MeOC₆H₄, 2-ClC₆H₄, 2-BrC₆H₄, 2-thienyl, *i*-Pr



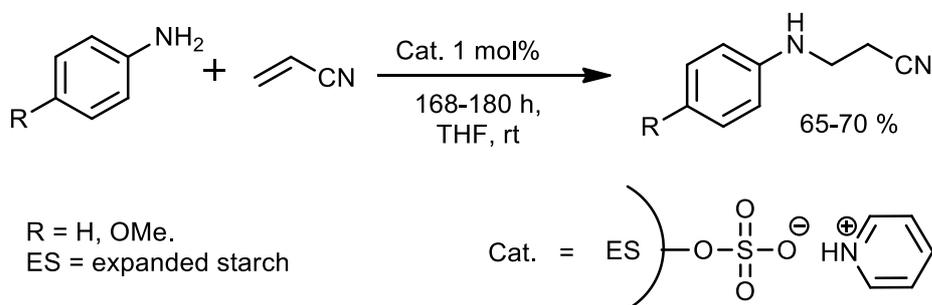
Enantioselective synthesis of azaflavonones or tetrahydroquinolines, valuable biologically active compounds, is proposed on the basis of intramolecular aza-Michael reaction [39]. The quinine-based catalyst has already two additional functions: a thiourea fragment and a primary amino group. The mechanism proposed by the authors includes the formation of an immonium salt in the result of the nucleophilic attack of the primary amino group of the catalyst on the keto group, the donor activation proceeds through the formation of a hydrogen bond between the aniline proton and the tertiary nitrogen atom of the bicyclic quinine fragment (Scheme 1.30).

Scheme 1.30



Recently, a modified swollen corn starch has been proposed as an environmentally safe, readily available and efficient catalyst for the conjugate addition of alkyl and arylamines to activated olefins. Among its unconditional advantages there are biodegradability, possibility of reuse and high catalytic activity. Unfortunately, the reaction proceeds easily only with aliphatic amines; aniline and *para*-anisidine react much more slowly, and the yields of Michael adducts are lower (65-70%) [40] (Scheme 1.31).

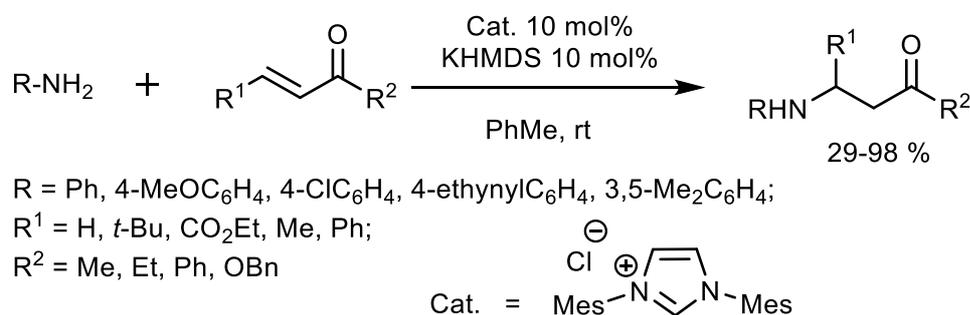
Scheme 1.31



The authors suggest that the catalyst has a double activating power: an acidic proton activates the electron-withdrawing group, while the sulfonate group increases the nucleophilicity of the amino group.

An interesting method for the synthesis of β -amino ketones based on the conjugate addition of arylamines to β -substituted unsaturated ketones is proposed in [41]. The *N*-heterocyclic carbene formed *in situ* from the imidazolium salt by a strong base (KHMDS) excellently catalyzes the addition of anilines to enones. Checking the necessity of using such a strong base, the authors have carried out the reaction with the imidazolium salt alone, but only the oligo- and polymerization processes have been observed (Scheme 1.32).

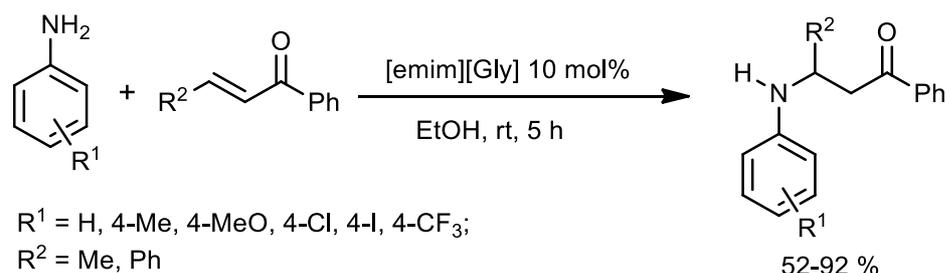
Scheme 1.32



The authors successfully have involved β -substituted ketones in the reaction, but, unfortunately, this method has proved to be unsuitable for reactions involving β,β -disubstituted enones. Also surprising fact is that terminal unsaturated aldehydes are also reluctant to react with arylamines, possibly due to oligo- and polymerization.

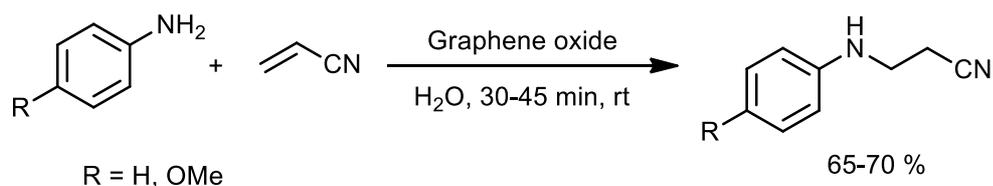
The imidazolium salt of glycine as a catalyst for the nucleophilic addition of arylamines to chalcones is suggested [42]. The authors have found that the presence of electron-withdrawing substituents in the benzene ring of the amine significantly reduces the reaction rate, even an increase of its duration does not allow increasing the adduct yield. The presence of electron-donating substituents on the carbonyl group (Me, 4-MeOC₆H₄) also significantly reduces the efficiency of the process: the reaction either does not occur or the products are formed in trace amounts (Scheme 1.33).

Scheme 1.33



The first example of the using graphene oxide in the synthesis of β -aminocarbonyl compounds is given [43]. The method proposed by the authors is excellent regarding alkylamines: the reactions have been carried out in an aqueous medium at room temperature in a comparatively short time (5-10 min). With the transition to weaker aromatic amines, the reaction rate falls significantly and the yield of the reaction product remains rather moderate after a long time (Scheme 1.34).

Scheme 1.34

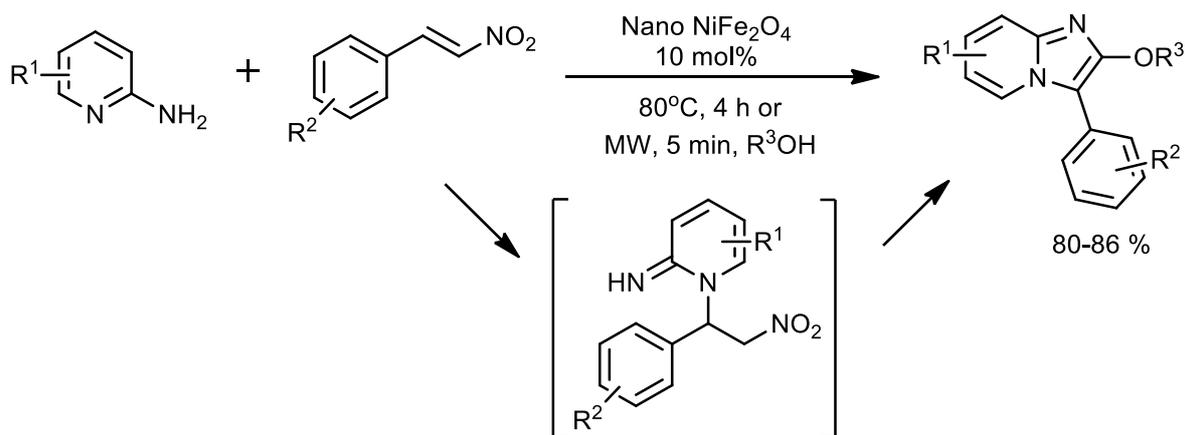


The authors still do not understand the mechanism of the catalytic action of graphene oxide. They suggest that the carboxyl and hydroxyl groups on the surface of the catalyst may be the source of an acidic proton, able to activate the carbonyl function of the Michael acceptor, thereby facilitating the reaction procedure.

1.1.5 Other methods of involving (het)arylamines in the aza-Michael reaction.

The authors successfully use the nanoparticles of the trevorite (NiFe_2O_4) as a catalyst in the conjugate addition of 2-aminopyridines to nitrostyrenes [44]. The authors suggest that the Michael addition is accelerated by the main Ni centers of the catalyst (Scheme 1.35).

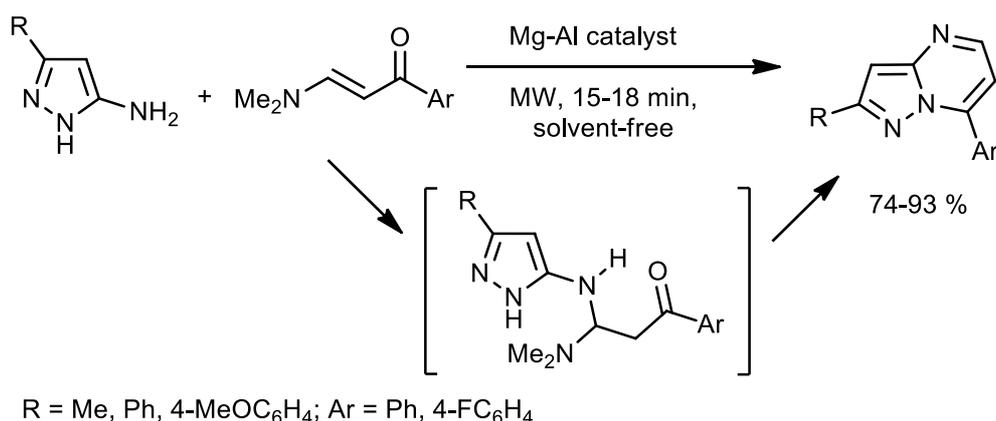
Scheme 1.35



R¹ = 3-Me, 4-Me, 6-Me; R² = 4-Cl, 4-Me, 4-OMe; R³ = Et, Pr, Bu

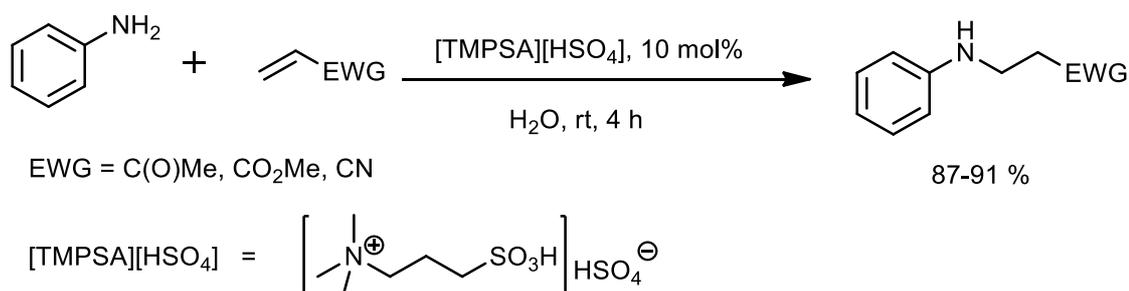
It is interesting to note that the nucleophilic attack on the double bond is carried out by the endocyclic nitrogen atom, the authors do not observe addition products due to the primary amino group. Relatively recently there have been reports of hydrotalcites, i.e. mixed hydroxides and magnesium and aluminium carbonates of the general formula Mg₆Al₂CO₃(OH)₁₆•4H₂O as new heterogeneous catalysts for the reactions of conjugate nucleophilic addition, including the aza-Michael reaction. According to the authors, this cheap porous material is the most effective among all the heterogeneous systems described so far, which catalyze the attachment of heteroaromatic amines to electron-deficient alkenes [45]. Its high activity is due to the joint activation of the substrate and the nucleophile with acidic and basic catalyst centers. The use of hydrotalcites allows obtaining the target adducts in high yields (up to 93%) in a short time (sometimes in 15-20 minutes) (Scheme 1.36).

Scheme 1.36



The authors propose to use an ionic liquid based on the ammonium salt in the reaction of 1,4-addition of primary arylamine to terminal acceptors of Michael [46]. Unfortunately, a number of aromatic amines are represented only by aniline (Scheme 1.37).

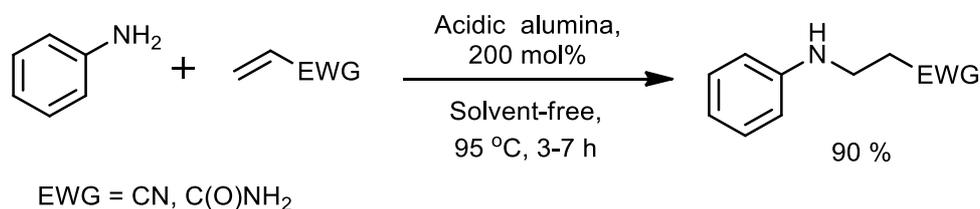
Scheme 1.37



The use of acidic aluminum oxide in the heterogeneous catalysis of aniline addition to unsaturated esters, nitriles and amides is proposed [47]. The authors have managed to selectively obtain monoadducts in the case of arylamines, whereas with aliphatic amines, the reaction has been complicated by the formation of bis-adducts, that could be probably explained by the higher nucleophilicity of alkylamines. A number of Michael acceptors for arylamines is limited only by terminal olefins. But, based on the fact that the authors have tried to involve such α - or β -substituted activated alkenes such as methyl crotonate, methyl methacrylate, cinnamic acid and nitrostyrene in the reaction with alkylamines, and the yields have turned out significantly lower even with prolonged heating, perhaps, due to spatial factors. I

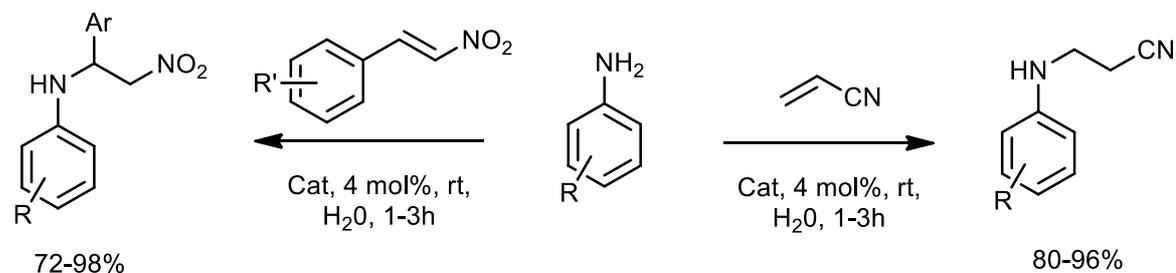
would venture to suggest that arylamines are significantly inferior to aliphatic amines, since they are weaker nucleophiles (Scheme 1.38).

Scheme 1.38



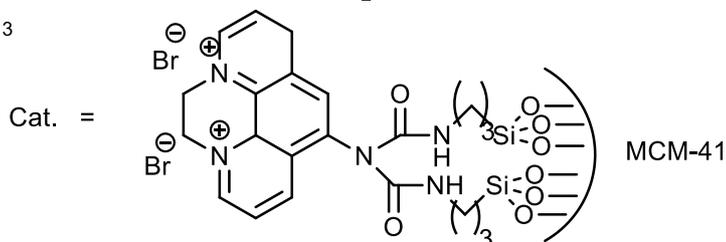
Heterogeneous catalysis for the 1,4-addition of anilines to α , β -unsaturated nitriles and nitroalkenes is proposed [48]. The authors of the paper use dibromide phenanthroline, supported on mesoporous silica gel. The reaction takes place in water at room temperature. This is certainly an advantage of this technique, since one of the main limitations of using water as a solvent is to achieve homogeneity of the reaction medium. The authors attempted to carry out the reaction without using a mesoporous material. As a result of homogeneous catalysis problems arose with the release of the catalyst, although the yields of the reaction product are comparable to the case of heterogeneous catalysis (Scheme 1.39).

Scheme 1.39



R = H, 2-OMe, 2-NH₂, 3-OMe, 4-OMe, 4-Me, 4-OH, 4-Cl, 4-NO₂;

R' = H, 4-Br, 4-NO₂, 4-CN, 4-CH₃

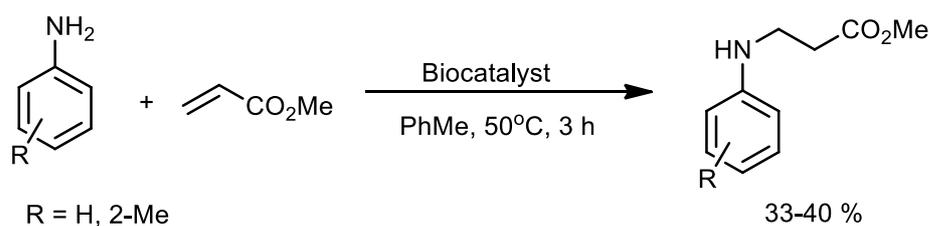


With the broadening of a number of nucleophiles, the authors have found that the nature of the substituent in the aromatic ring of amines exerts a significant

influence. As would be expected, alkyl and alkoxy substituents increase the rate of product formation, while electron-withdrawing substituents decrease the nucleophilicity of the amino group and, consequently, the reaction rate.

A biocatalytic method for the synthesis of β -aminocarbonyl compounds is proposed [49]. The authors describe the use of enzymes supported on a solid carrier as catalysts (Scheme 1.40).

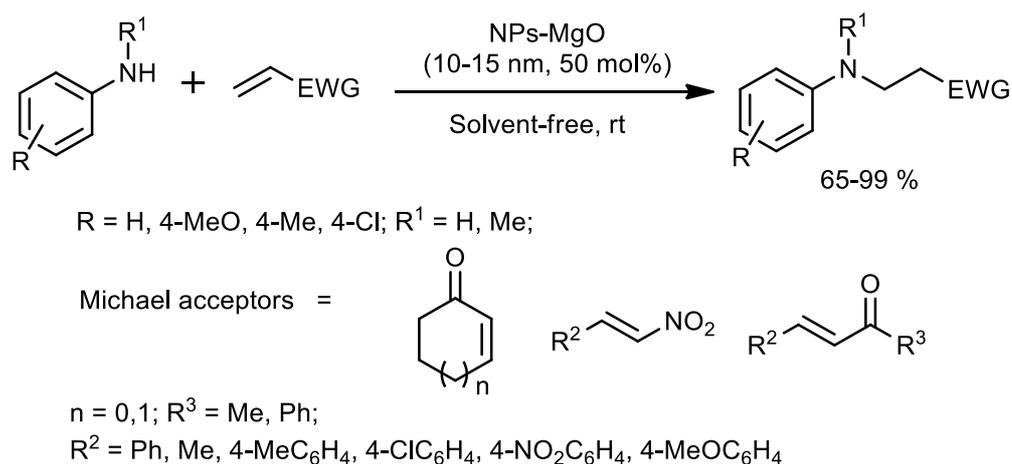
Scheme 1.40



The action of the catalyst is based on the simultaneous activation of both the donor and the Michael acceptor due to the presence of basic and acidic centers in the structure of the enzyme. A number of nucleophiles are represented by only two examples of primary arylamines (aniline and *o*-toluidine). The reaction proceeds chemoselectively to form a mono-adduct. The effectiveness of the use of lipase applied to the modified cellulose is proved by the reaction without a catalyst. The yield of reaction products in this case is lower by more than three times (10-13%)

The use of magnesium oxide nanoparticles as a catalyst allows to involve a wide range of primary and secondary arylamines in the reaction with various Michael acceptors [50] (Scheme 1.41).

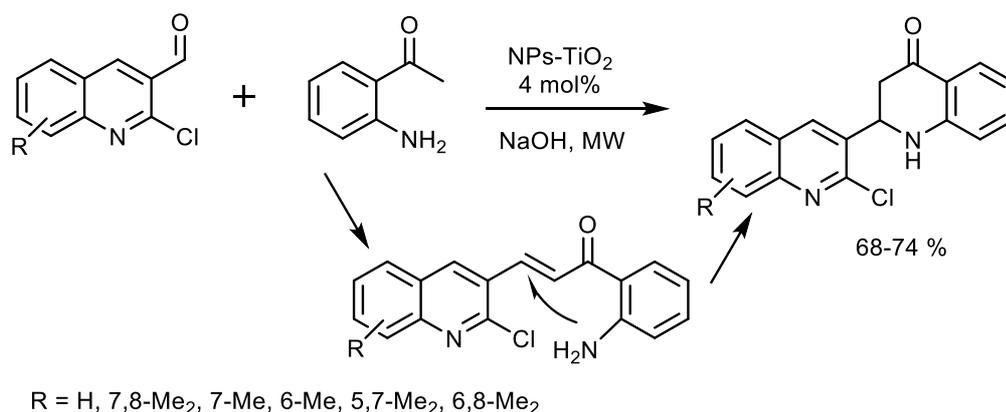
Scheme 1.41



The authors have used cyclic and acyclic enones, as well as β -substituted nitro olefins as activated alkenes. The action of the catalyst is based on an electrophilicity increase of the double bond of enon by forming a coordination bond between the magnesium ion and the oxygen of the carbonyl group, and, as a result, facilitating the nucleophilic attack even by such weak amines as anilines. Availability, stability, non-toxicity and low cost of the catalyst along with the possibility of its re-use are the most important advantages of the proposed method. Among the oxides of various metals - titanium, iron, zinc, aluminum and niobium – exactly, magnesium oxide has exhibited the highest activity in the reaction of aniline with chalcon. Moreover, the nanoscale catalyst nature is also important: the catalytic activity of commercially available magnesium oxide is twice lower.

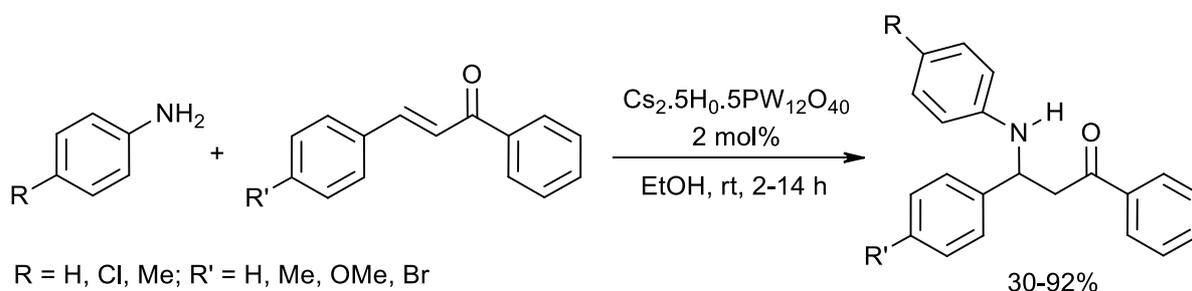
Continuing to use catalysis with metal oxide nanoparticles, the authors have proposed a one-reactor synthesis of dihydroquinolinone derivatives catalyzed by titanium oxide [51]. The process involves an intramolecular version of aza-Michael reaction, where titanium oxide activates the carbonyl function, making easier the attack of the amino group on the β -carbon atom (Scheme 1.42).

Scheme 1.42



Synthesis of β -aminoketones from *para*-substituted anilines and chalcones catalyzed by nanoparticles is proposed [52]. The catalyst based on the cesium and phosphotungstic acid salt contains in its structure both the Brønsted and Lewis acid sites, which effectively activates the carbonyl group of the ketone, making the beta carbon atom more reactive for the nucleophilic attack (Scheme 1.43).

Scheme 1.43

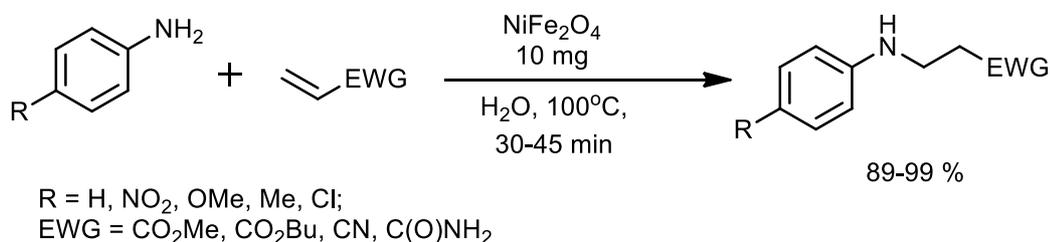


The authors have also compared the effect of a catalyst that does not contain nanoparticles and a nanocatalyst and have found that at using the latter, the reaction rate is much higher than in the former one. Moreover, the use of the proposed catalyst in selected conditions avoids the side processes - polymerization, the formation of the 1,2-addition product or the bis-adduct.

An interesting use of magnetic nanoparticles as catalysts for the nucleophilic addition of substituted anilines to activated alkenes is proposed in [53]. The authors

have managed to involve even such a weak amine as *para*-nitroaniline in the reaction with the unsaturated ester and amide and obtain the target adducts in high yields (89%) (Scheme 1.44).

Scheme 1.44



An additional advantage of the proposed catalyst is its ease of removal from the reaction medium: it is sufficient to only use a magnet, and the catalyst nanoparticles can be re-involved. It is worth noting the high chemoselectivity of the reaction: neither the products of bis-addition nor the products of transamidation have been observed by the authors.

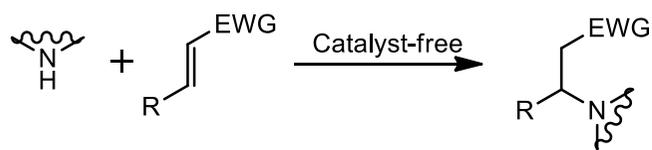
1.2 Aromatic aza-heterocyclic compounds.

1.2.1 Non-catalytic variant of nucleophilic conjugate addition.

As well as with (het)aromatic amines, aromatic azaheterocyclic compounds are able to react with Michael acceptors (α,β -unsaturated aldehydes, ketones, carboxylic acids, esters, nitrites, etc.) without additional chemical activation.

A number of papers describe the non-catalytic addition of substituted pyrazoles to α,β -unsaturated ketones [54], aldehydes [55, 56], mono- [57] and dicarboxylic acids [58], esters [57, 59] (Table 2).

Table 2.



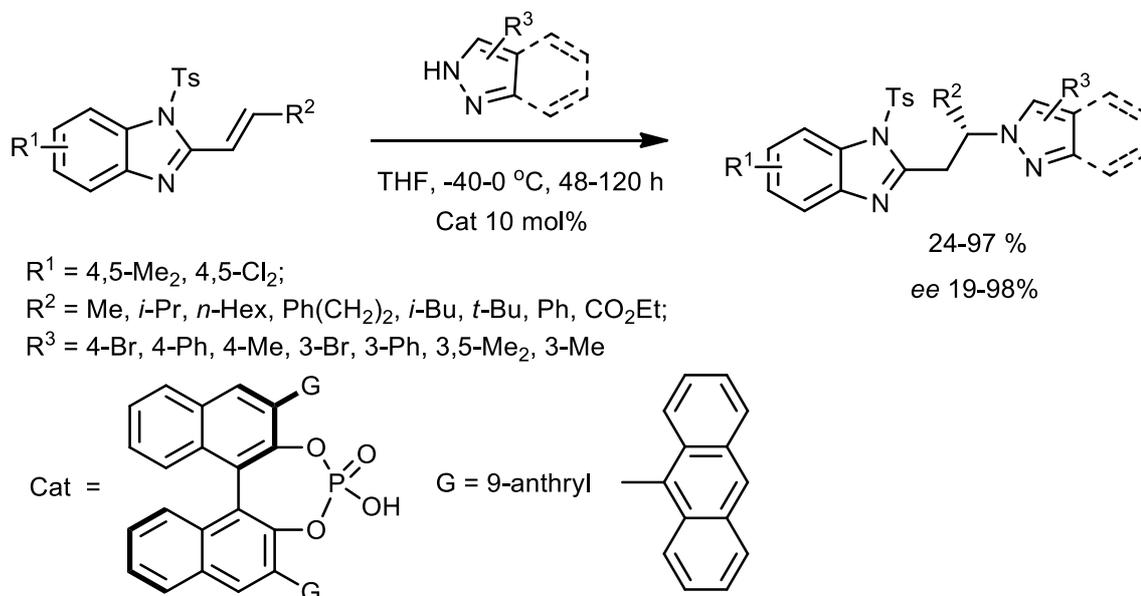
The Michael acceptor, A		Donor Michael, D	Reaction conditions			Product yield	Ref.
R	EWG		Solvent	T, °C	t, h	P , %	
H	C(O)Me	Pyrazole, 3-methylpyrazole, 3,5-dimethylpyrazole, imidazole, 1,2,4-triazole, 2 <i>H</i> -tetrazole	-	110	0.5-3	83-97	54
Me	C(O)H	3-Methylpyrazole, 5-methylpyrazole, 3,5-dimethylpyrazole	-	85-95	8-16	86-91	55
H	C(O)H	3,5-dimethylpyrazole	dioxane	40	24	76	56
Me	CO ₂ H	3-Methylpyrazole, 5-methylpyrazole,	-	85-90	3	73-77	57
Me	CO ₂ Et	3,5-dimethylpyrazole	-			11	
CO ₂ H	CO ₂ H	3-Methylpyrazole, 5-methylpyrazole, 3,5-dimethylpyrazole	-	110	2.5	65-96	58

The authors have found that the reaction of the nucleophilic addition of pyrazole and its derivatives to butenal proceeds more slowly than to acrolein [55]. Perhaps, due to the less pronounced electrophilic nature of the double bond due to the donor effect of the methyl group and the additional steric hindrance at the β -carbon atom. It has been noted that in the case of crotonic acid, an autocatalytic reaction takes place [57]. The authors of the article, having decided to test the hypothesis, add 5 mol% of the adduct to the initial reagents at the beginning of the reaction and observe an increase in the reaction rate several times as compared with the rate of the non-catalytic process. When using ethyl crotonate, the addition of pyrazoles proceeds not so smoothly, the yield of the target adduct is barely 11%.

1.2.2. Acid-base catalysis.

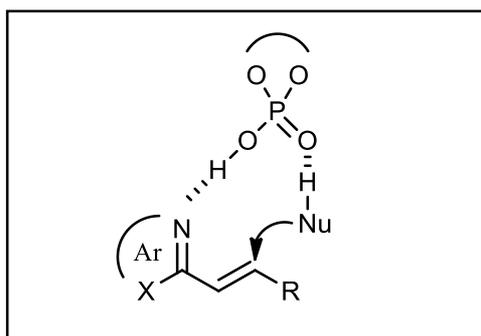
Enantioselective conjugate addition of pyrazoles and indazoles to alkenylbenzimidazoles easily proceeds in the presence of 10 mol% of chiral phosphoric acid [60] (Scheme 1.45).

Scheme 1.45



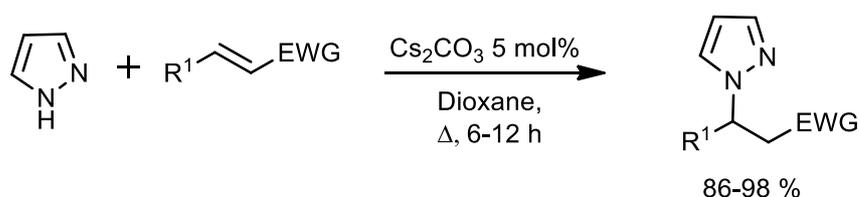
The authors suggest that the action of the phosphoric acid ester is the simultaneous activation of both the electrophilic center (due to the formation of the hydrogen bond with iminium nitrogen) and the nucleophilic center due to the acceptance of the pyrazole proton by the oxygen atom of the phosphate group (Figure 1).

Figure 1



Cesium carbonate has proven itself as a catalyst for the nucleophilic addition of pyrazole to chalcones, methyl acrylate and nitrostyrene [61] (Scheme 1.46).

Scheme 1.46

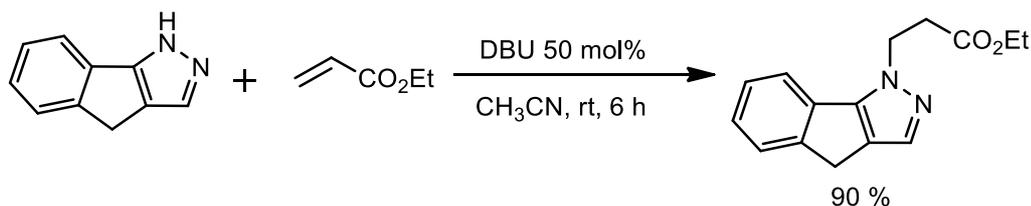


R1 = H, 4-ClC₆H₄, 4-BrC₆H₄, 4-MeC₆H₄, 4-MeOC₆H₄, 4-CF₃C₆H₄,
4-O₂NC₆H₄, 2-ClC₆H₄, 3-O₂NC₆H₄;
EWG = C(O)Ar, CO₂Me, NO₂;
Ar = H, 4-MeOC₆H₄, 4-MeC₆H₄, 4-ClC₆H₄, 4-O₂NC₆H₄

The Brønsted base makes it possible to obtain aza-Michael adducts in high yields. In the absence of a catalyst, only traces of the target adduct are observed [61].

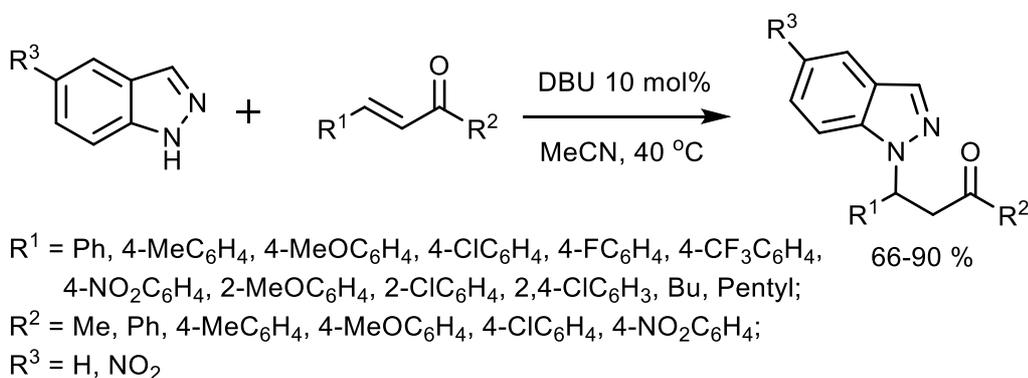
It is proposed to use DBU (1,8-diazabicyclo[5,4,0]-undec-7-ene) to catalyze the reaction of nucleophilic addition of polycyclic pyrazoles to ethyl acrylate [62] (Scheme 1.47).

Scheme 1.47



The effective addition of indazoles to β -substituted enones can also readily proceed in the presence of catalytic amounts of DBU, giving aza-adducts in high yields [63] (Scheme 1.48).

Scheme 1.48

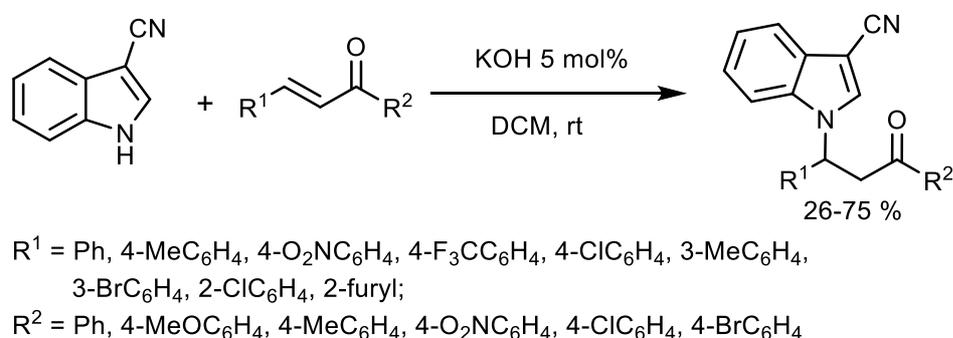


When choosing the optimal reaction conditions, the authors have used alkali metal carbonates, but only traces of aza-adducts are observed. The use of cesium carbonate only results to the high yield of the reaction product. When proceeding to organic bases, the authors have found that 10 mol% of DBU is sufficient for regioselective addition of indazoles to enones. It is not surprising that the authors have given the preference to the organic base, thus developing a regioselective method of attaching indazoles to a wide range of unsaturated ketones. The authors have also managed to involve in the reaction an electron-deficient heterocycle, such as 5-nitroindazole, to obtain the target adduct in high yield (87%).

The same group of authors, having decided to extend a number of nucleophiles, has tried to involve indole in the reaction, using the same conditions. But the attempt

turns out unsuccessful. Probably, the reason is the lower NH acidity of the indole (pKa = 16.97) compared to indazole (pKa = 13.86), that makes the former less nucleophilic in the selected basic conditions. To increase the NH acidity of the indole, the authors have introduced an electron-withdrawing group in the C3 position. The presence of cyano group significantly increases the indole acidity. Screening of organic (DMAP, TMG, DBU) and inorganic (sodium, potassium, cesium, lithium, sodium hydroxide) bases is carried out. As a result, the optimal reaction conditions have been selected: 5 mol% of KOH in dichloromethane at room temperature [64] (Scheme 1.49).

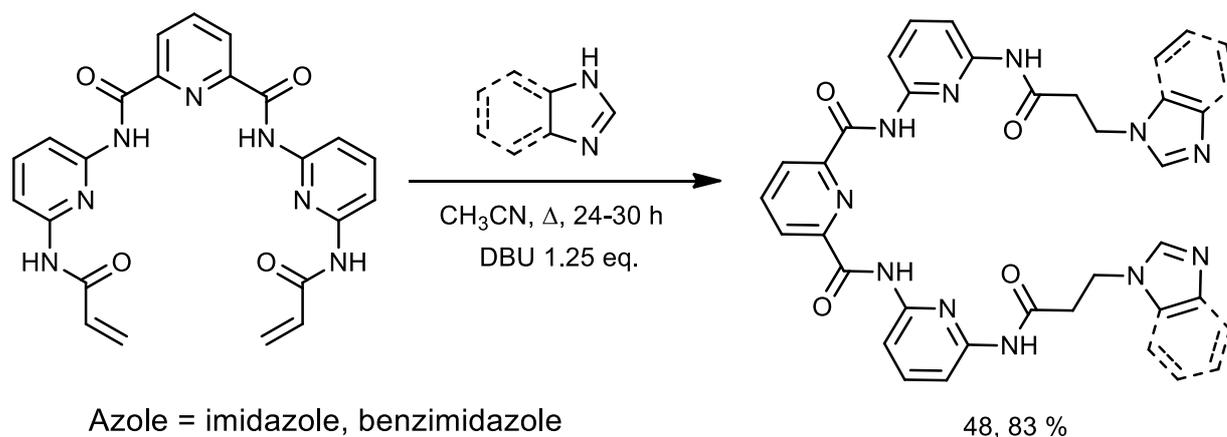
Scheme 1.49



The authors succeed to involve a wide range of chalcones in the reaction, obtaining β -aminoketones with moderate yields.

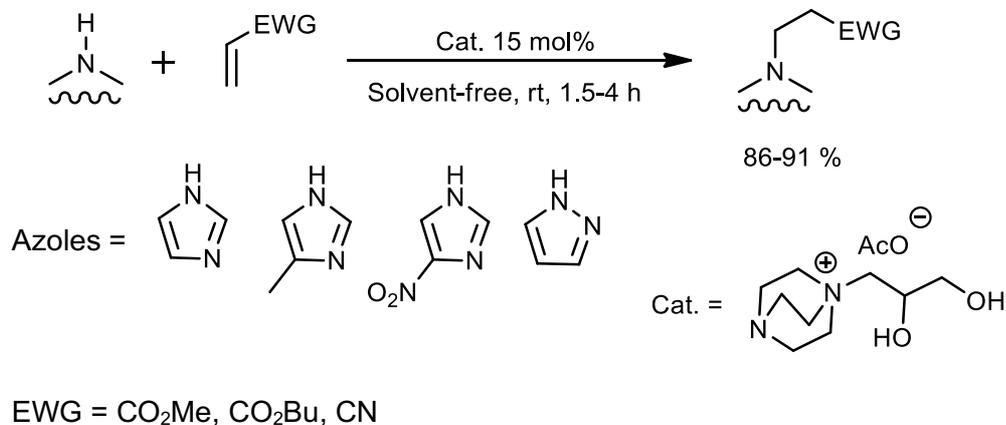
The use of an organic base as a catalyst for conjugate addition allows the (benz)imidazole to be involved in the reaction. Imidazole is able to react with 1,4-addition in the presence of DBU [65]. The authors use substituted acrylamide as the Michael acceptor, obtaining new aminocarbonyl imidazole (benzimidazole) derivatives with good yields (Scheme 1.50).

Scheme 1.50



Ionic liquids based on DABCO (1,4-diazabicyclo[2.2.2]octane) have found their application in the catalysis of the reaction of conjugate addition of azoles and their derivatives to activated alkenes [66] (Scheme 1.51).

Scheme 1.51

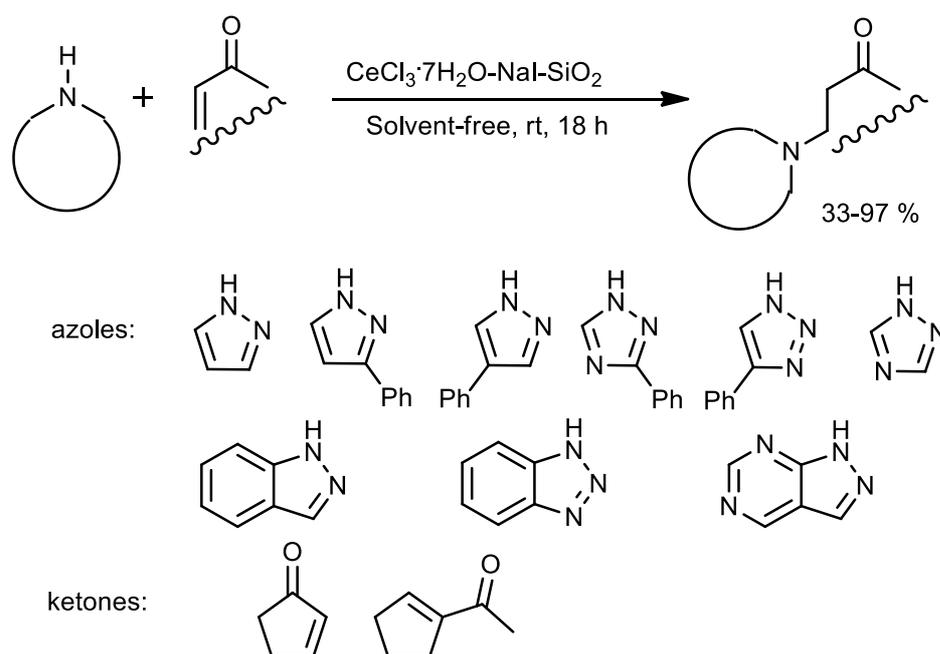


The mechanism of double activation proposed by the authors is based on increasing the electrophilicity of the double bond by activating the carbonyl group with hydroxyl protons of the catalyst and increasing the nucleophilicity of the secondary amino group by accepting the proton by a more basic tertiary nitrogen atom. The advantages of this catalyst are its stability, possibility of regeneration and reuse.

1.2.3. Nucleophilic addition of azoles to electron-deficient olefins catalyzed by salts of transition metals

Nucleophilic addition of five-membered aromatic aza-heterocycles to unsaturated ketones is readily achievable in the presence of a catalyst based on cerium chloride [67] (Scheme 1.52).

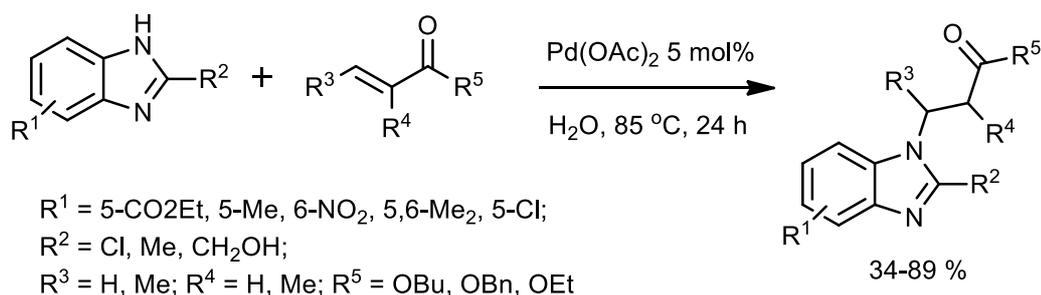
Scheme 1.52



Catalytic action has the whole system, namely a mixture of salts applied to silica gel. The authors note that the reaction is regioselective: there are no products of attack by the carbon nucleophilic center. The reaction proceeds without solvent and at ambient temperature, leading to the desired adducts in moderate to excellent yields.

An ecological method for the synthesis of benzimidazole derivatives is proposed in [68]. It is shown for the first time that palladium acetate effectively catalyses the addition of benzimidazole derivatives to unsaturated esters in an aqueous medium at room temperature (Scheme 1.53).

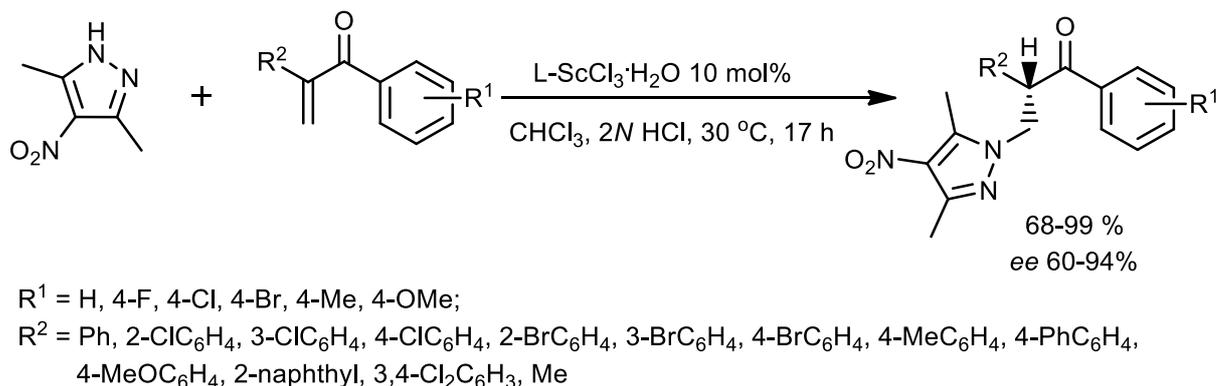
Scheme 1.53



It is interesting that the nucleophilic addition of benzimidazole and its derivatives to acrylates proceeds efficiently and without a catalyst, due to the solvent. The authors suggest that in this case water catalyzes the reaction by activating the carbonyl group by forming a hydrogen bond. Palladium ions, acting as a Lewis acid, activate the double bond of the electrophile, facilitating a nucleophilic attack on the β -carbon atom. But the authors have still encountered difficulties. When a methyl substituent is introduced into the α - or β -position with the carbonyl group, the yield of the product either decreases substantially or the reaction does not proceed at all. The authors have found that the presence of acceptor substituents in the structure of benzimidazole. Nitro-, ethoxycarbonyl groups reduce the nucleophilicity of the Michael donor. As a result, the yield of products decreases as well. The introduction of the phenyl, chloromethyl or thiol substituent at the C2 position of the five-membered ring does not lead to the target adducts at all.

But the authors from China are no longer confused by the presence of a substituent, moreover, such bulky as phenyl or naphthyl at α -atom of carbon. Perhaps, due to the fact that Michael acceptors are used more active ketones, and maybe due to more efficient catalyst based on scandium salts. Nonetheless, an enantioselective method for the synthesis of nitropyrazole derivatives based on the reaction of 4-nitropyrazoles and α -substituted vinyl ketones has been proposed in [69] (Scheme 1.54).

Scheme 1.54

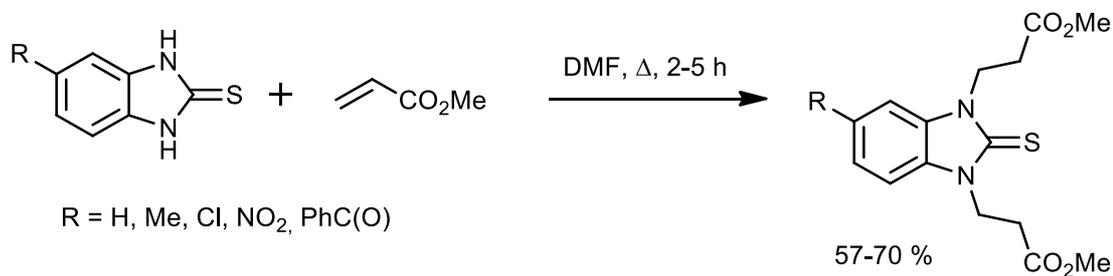


1.3. Other weak nucleophiles.

In this chapter, the examples of the involvement of such weak nucleophiles as acyclic and cyclic amides (lactams), imides, hydrazides, purine bases will be presented in the aza-Michael reaction.

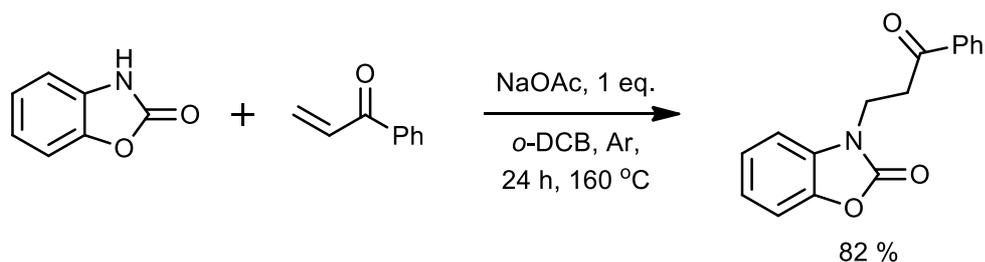
A non-catalytic variant of the addition of 5-substituted-benzo(dihydro)imidazolethions to methyl acrylate is described in [70]. The reaction proceeds in boiling DMF, where the nucleophile is predominantly in the thione form, leading to the desired adducts with moderate yields. The use of (six- or eleven-fold) excess of methyl acrylate does not lead to any noticeable increase in the yield of the reaction product (Scheme 1.55).

Scheme 1.55



Synthesis of β -amino ketones containing the oxazolidinone fragment is proposed [71] (Scheme 1.56).

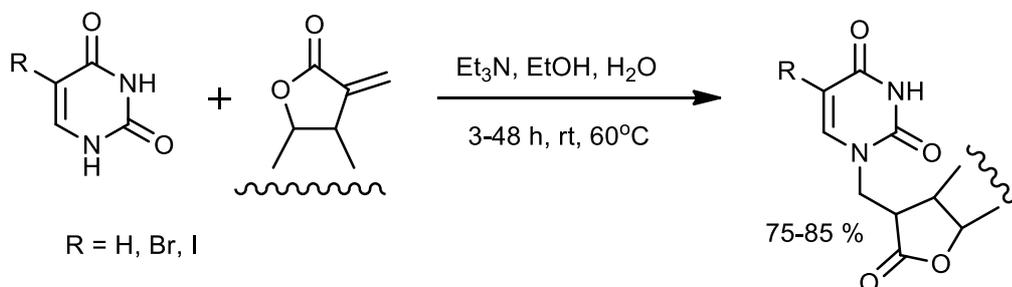
Scheme 1.56



The authors use an equimolar amount of sodium acetate as the Brønsted base to activate the nucleophile in an inert atmosphere and in a dichlorobenzene medium.

The addition of uracil and its derivatives to isolantolactone proceeds readily in aqueous ethanol in the presence of triethylamine [72] (Scheme 1.57).

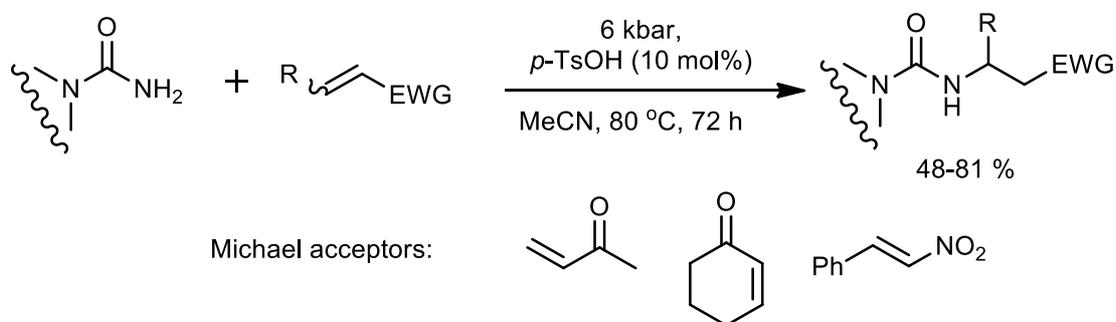
Scheme 1.57



The authors note that the reaction carries out chemoselectively, the formation of other reaction products, even in trace amounts, is not observed.

The use of high pressure in combination with a Brønsted acid (*n*-toluenesulfonic acid) for the addition of *N*-carbamoylacytisine (a natural alkaloid) to Michael acceptors (cyclic/acyclic ketones, nitrostyrene) is suggested [73] (Scheme 1.58).

Scheme 1.58



The authors note that this is the first case of an addition reaction involving carbamoylcytosine under hyperbaric conditions.

1.4 Conclusion

The analysis of published data has shown that the development of new efficient methods for the synthesis of β -aminocarbonyl compounds containing an aza-aromatic moiety attracts a great attention of organic chemists. Sometimes, the addition of arylamines to Michael acceptors occurs under non-catalytic conditions. In these cases the presence of a strong EWG and/or terminal double bond is required. When olefins bearing an internal double bond are used as electrophiles, the additional chemical (transition metals, Lewis/Brønsted bases or acids, organocatalysis) or physical (ultrasound, microwave irradiation, high temperatures) activation is necessary. The presence of sterically hindered substituents in Michael donor or acceptor significantly limits the use of many of the above-described catalytic systems. Thus, the development of new methods for the synthesis of β -aminocarbonyl based on the reaction of conjugate addition of low-reactivity amines to internal Michael acceptors is an actual problem of modern organic synthesis.

CHAPTER 2. AROMATIC AMINES IN AZA-MICHAEL REACTION

(the discussion of the results)

2.1. Double physico-chemical activation of aza-Michael reaction

Analysis of the literature shows that aromatic amines as weak nucleophiles are sufficiently inert with respect to Michael acceptors (especially with an internal bond C=C). Obviously, it should be performed one of two conditions for the successful involvement of the aromatic amines in the conjugated nucleophilic addition reaction. The first one is due to the presence of the initial substrate of the active electrophilic center in the molecule, which is achieved by introducing a strong electron-withdrawing group to the double bond. The second is based on the use of powerful promoters (or catalysts) that provide additional chemical or physical activation of the reaction centers of the reagents. Indeed, in the literature there are rare examples of a non-catalytic variant of aza-Michael reaction with arylamines. If this reaction occurs, then, as a rule, only with Michael acceptors containing a terminal double bond. The addition of aromatic amines to α β - or even more to β,β -disubstituted electron-deficient alkenes proceeds slowly and exclusively under catalytic conditions [8, 15, 16].

The low reactivity of the donor or Michael acceptor can be caused either by the weak amine nucleophilicity, or by the steric hindrance of the electrophilic substrate center or the nucleophilic amine center. In the thesis, we have tried to find a solution to both problems. The first part of the work is devoted to the development of an effective method to involve primary and secondary aromatic amines in the aza-Michael reaction. Moreover, both terminal and β -mono- and α,β - or β,β -disubstituted acrylic acid derivatives are used as substrates. In the second part of the thesis, the results of the conjugated nucleophilic addition of 1-aminoadamantane-nucleophile having a sterically hindered nucleophilic center are discussed in the reaction.

It is well known that the nucleophilicity of aromatic amines strongly depends on the solvent nature, substantially increasing in water. Thus, according to the data [74], the reactivity of aniline in water is two times higher than in acetonitrile, and becomes comparable with the benzylamine nucleophilicity.

It is also known that the conjugated addition of amines to electron-deficient alkenes preferably takes place in protic solvents. According to the polarity of solvents proposed by Reichardt, the top lines are occupied by such strongly polar solvents as water and fluorine-containing alcohols - 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) (see $E_T(30)$ Table 3, entries 8, 10) [75]. The empirical polarity parameters of these solvents are fairly close: $E_T(30)$ HFIP is 1.09 times larger than the similar parameter for TFE. However, there are significant differences in their proton-donor and proton acceptor capacity, that is, in the propensity to form a hydrogen bond: α and β for HFIP are more than similar parameters for TFE in 1.3 and 1.4 times, respectively (Table 3, entries 8-10). In addition, highly polar proton solvents have a positive effect on the nucleophilicity of aromatic amines that are weaker nucleophiles than aliphatic ones, which protic solvents are sufficiently acidic and protonate the aliphatic nitrogen atom [74, 76-78].

Thus, the authors [76] successfully have carried out the addition of aromatic amines to the enoates using HFIP, TFE or water as a solvent. Any additional promoters or catalysts have not been required. However, it should be noted that a number of Michael acceptors has been limited to highly reactive electron-deficient alkenes containing a terminal double bond.

Thus, the problem of involving weak nucleophiles (aromatic amines) in aza-Michael reaction *a priori* could be solved by using fluorinated alcohols as solvents.

The second problem - to overcome the steric factors hampering the reaction course, is effectively solved by the use of high pressure [79-81]. Back in 1986, the scientific tandem of D'Angelo and Maddaluno proposed the use of hyperbaric conditions for conjugated addition of primary aliphatic amines to crotonates [82].

The reactions at high pressure are particularly effective when spatially hindered and/or thermally unstable reagents are used. In most cases, this approach has really allowed to solve problems related, first of all, to the spatial features of the structure of the reagents.

The use of high pressure is based on the theory of the activated complex: in this case the so-called activation volume ΔV^\ddagger is taken into account. In the first approximation, this value can be considered as the difference between the volumes of the initial and transition states:

$$\Delta V^\ddagger = V^\ddagger - V_0$$

The mathematical expression connecting the reaction rate and the pressure applied to the system is the Evans-Polanyi equation.

$$\left(\frac{d \ln k}{d P} \right)_T = - \frac{\Delta V^\ddagger}{RT}$$

This equation shows that the reaction rate constant depends on the function ΔV^\ddagger and is directly proportional to the negative activation volume difference. In other words, then ΔV^\ddagger (in absolute value) is higher, the reaction course is more preferable under hyperbaric conditions.

$$\ln k = - \frac{\Delta V^\ddagger}{RT} \cdot P$$

Consequently, the use of high pressure is reasonable only if the reaction is characterized by negative values of ΔV^\ddagger . These processes are exactly the reactions of conjugated nucleophilic addition.

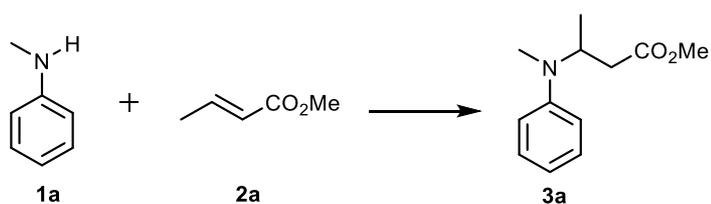
In the literature, there are cases of using high pressure as a promoter of the conjugated addition reaction, which makes it possible to involve such nucleophiles as aliphatic amines, imidazole, carbamates, and azides in this reaction [83, 84]. Known examples of the use of Michael arylamines and acceptors containing alkyl or aryl substituents at the β -carbon atom provide for the indispensable catalyst use.

2.1.1. The addition of primary and secondary arylamines to acrylic acid derivatives

As a model reaction with both a weak nucleophile and an electron-deficient alkene having a sterically hindered electrophilic center, the reaction of *N*-methylaniline with methyl crotonate was employed. First of all, we studied the effect of the solvent on the reaction rate that was determined by the conversion of the initial amine (Table 3). The reaction was carried out with 1 mmol of amine and 2 mmol of enoate in a corresponding solvent (0.5-1.5 ml) at room temperature.

As expected, no reaction occurred in aprotic solvents (DCM, THF, MeCN), the initial reagents were isolated (Table 3, entries 1-3). Attempts to use isopropyl alcohol, methanol and ethanol were also unsuccessful (Table 3, entries 4-6). Whereas, it is evident that the amine conversion depend on pKa and the proton-donor capacity of the solvent α (the increase of the *i*-PrOH – EtOH - MeOH series increases the conversion in the same one from 0 to 12%), although the degree of conversion is low. It made us use more acidic and more polar solvents. When the reaction was carried out in trichloroethanol (TCE) or trifluoroethanol (TFE), the conversion of the initial ester was 40% and 55%, respectively (Table 3, entries 7-8).

Table 3.



No	Solvent	$E_T(30)^a$	pK_a^b	α^a	β^a	P (kbar)	Time (h)	Conversion (%) ^c
1	CH ₂ Cl ₂	40.7		0.10	0.00	10	24	0
2	THF	37.4		0.00	0.58	10	24	0
3	MeCN	45.6		0.23	0.37	10	24	0
4	<i>i</i> -PrOH	48.4	16.5	0.53	0.68	10	24	0
5 ^d	EtOH	51.8	15.9	0.75	0.62	10	24	9
6	MeOH	55.4	15.5	1.00	0.54	10	24	12
7	TCE	54.1	12.2	0.92	0.20	10	24	40
8	TFE	59.8	12.5	1.36	0.23	10	24	55
9	H ₂ O	63.1	15.7	1.54	0.37	5	24	0
10	HFIP	65.3	9.3	1.86	0.16	5	24	73
11	HFIP					10	24	90
12 ^e	HFIP					14	17	100
13 ^f	HFIP/DCM					10	24	20
14	HFIP					0.5	24	8
15 ^g	HFIP					1·10 ⁻³	17	18

^aPhysico-chemical values (at atmospheric pressure) are given [85-87]. ^bValues in H₂O. ^cConversion is calculated from the ¹H NMR spectrum; only the aza-adduct is obtained. ^dThe reaction is carried out with ethyl crotonate. ^eThe yield of the product is 81%. ^fHFIP/DCM = 1 : 1 (V/V). ^gThe reaction is carried out at the temperature of 58°C.

Unfortunately, the initial reagents were insoluble in water, as with increasing pressure, the freezing temperature of the solvent increases. As known, at room temperature water freezes at 5-6 kbar, so we could not use a higher pressure. One of the limitations of using high pressure is the lack of the possibility of stirring the reaction mass, hence, considering the low solubility of the reagents in the water; it certainly influenced the result of the experiment, (Table 3, entry 9).

HFIP gave excellent results under pressure: 73% at 5 kbar and 90% at 10 kbar (Table 3, entries 10-11). It should also be noted that we attempted to use HFIP also as a co-solvent, but in this case, the conversion was only 20%. (Table 3, entry 13). Full conversion was attained at 14 kbar after 17 h, and the target adduct was obtained in 81% yield (Table 3, entry 12).

When searching for the optimal reaction conditions, we also varied the amine ratio: Michael acceptor. It was found that for the optimal time (~ 17 hours) full amine conversion was achieved with a double excess of ester, that made it possible to obtain mixtures containing only unreacted enoate and solvent along with the adduct. In this case, due to the absence of any additional promoter or catalyst, the pure product was recovered by simple removal of the volatiles (methyl crotonate bp - 120°C) and the solvent (HFIP bp - 58°C), which can be also be reused.

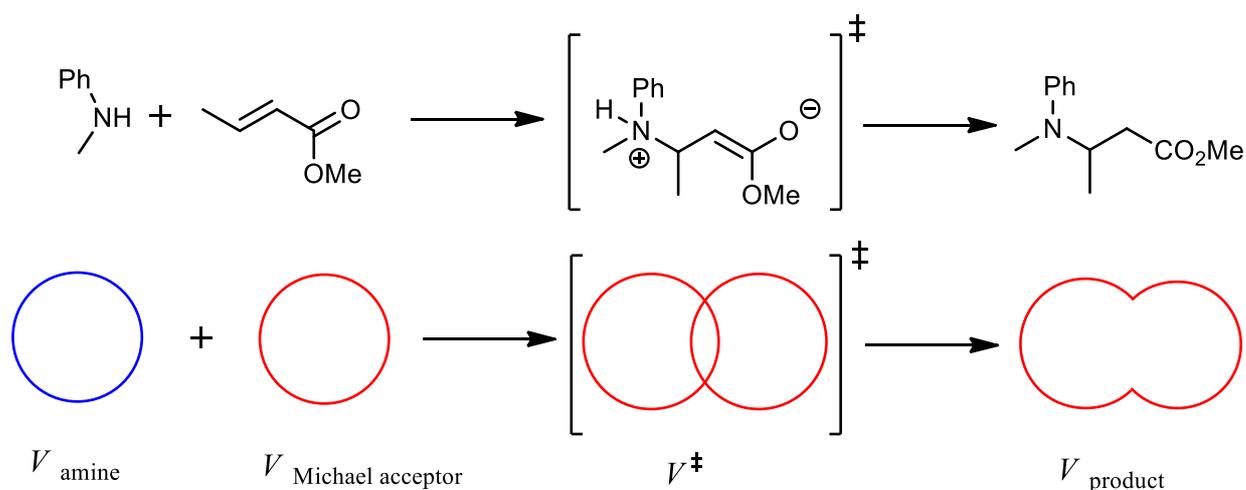
Highlighting the outstanding effect of HFIP under hyperbaric conditions, we decided to conduct two experiments: the first was at 0.5 kbar at room temperature; the second - at boiling at atmospheric pressure. It was found that conversions in both cases were sufficiently low: 8% at elevated pressure and 18% with prolonged boiling (Table 3, entries 14-15). These experiments underscored the key role of HFIP and high pressure combination. It is very important to note that, in contrast to regular alcohols (ethanol, isopropanol, trifluoroethanol), no transesterification of the enoate or amino ester in the case of HFIP.

The solvent effect is based on the activation of the Michael acceptor due to the formation of a hydrogen bond between the oxygen atom of the carbonyl group and the

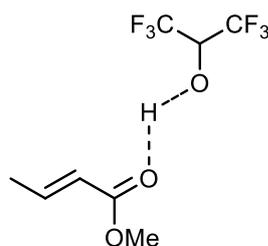
hydroxyl proton of the alcohol. Thereby, the electrophilic nature of the β -carbon atom increases and the nucleophilic attack by the amine facilitates. It is known highly polar solvents contribute to the stabilization of the zwitterion transition state (Scheme 2.1).

Further, we decided to apply the found optimized conditions (HFIP, $P \geq 10$ kbar, room temperature, 17h) to a series of anilines Michael acceptors (esters and nitriles) bearing substituents in the α or β positions (Scheme 2.1.).

Scheme 2.1.



High pressure effect

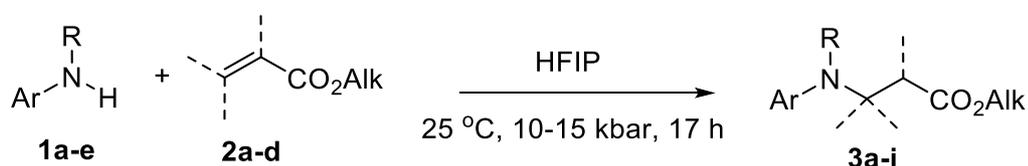


Solvent effect

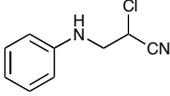
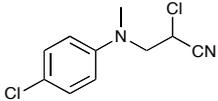
If unsubstituted aniline **1c** is added to crotonate **2a** (Table 4, entry 3) quantitatively, then its 4-chloro-substituted analogue **1d**, being less nucleophilic, reacts sluggishly, giving adduct **3d** only with a yield of 53% (Table 4, entry 4). Such a branched amine as 2,6-xylylidine(2,6-dimethylaniline) behaves well with

methylcrotonate, i.e. the yield of the adduct in this case reaches 73% (Table 4, entry 5). The reaction of 4,4,4-trifluorocrotonate ethyl **2b** with aniline proceeds moderately, leading to adduct **3f** with 45% yield (Table 4, entry 6). As already noted in the review, one of the acute problems of organic synthesis was nucleophilic conjugate addition to β,β -disubstituted Michael acceptors for a long time, although attempts to find ways to prepare β -aminocarbonyl compounds with a quaternary azacarbon center have been made repeatedly. In the chosen optimal conditions, we could involve β,β -dimethyl acrylate **2c**, which quite actively adds aniline, that gives an adduct with a quaternary azacarbon center (Table 4, entry 7).

Table 4.



No	Pressure, kbar	Reaction product	Yield, % ^a
1	14		81
2	14		90
3	10		100
4	14		53
5	10		73
6 ^b	15		45
7	10		54

5		3n	86
6		3o	83

The reaction of *N*-methylaniline **1a** and *N*-cyclohexylaniline **1f** with unsubstituted acrylonitrile **2e** proceeds easily, giving Michael adducts in quantitative yield (Table 5, entries 1-2). Crotonitrile **2f** also proves to be an excellent Michael acceptor in the reaction with *N*-methylaniline with target product **3l** in high yield (81%) (Table 5, entry 3). Finally, α -chloroacrylonitrile **2g** selectively reacts with primary and secondary anilines and gives exclusively mono-adducts **3m-o** in good yield (Table 5, entries 4-6).

One of the advantages of the proposed method is the ease of isolation of the target reaction product: when the conversion reached values close to quantitative, the target adduct was isolated purely after distillation of the light boiling solvent and excess of enoate or acrylonitrile in vacuum and often did not need further purification. At the same time, most of the known methods for the preparation of β -aminoenoates and β -aminonitriles require hydrolysis or extraction with organic solvents, that leads to yield reduction and waste increase [90].

Thus, we have shown that the conjugated addition of primary and secondary anilines to Michael acceptors, where one or both of the reagents contain a sterically hindered reaction center, easily proceeds with HFIP and high pressure combination. It allows to involve even sterically hindered electrophiles in the reaction, for example, β,β -dimethyl acrylates.

2.2. Conjugate addition of functionally-substituted anilines to activated alkenes. The effect of the solvent

The use of fluorinated alcohols as a solvent today has become a popular trend. Is there an alternative? Can a compound having similar pKa and proton-donor activity just as successfully promote the addition of weak nucleophiles to electron-deficient alkenes?

2.2.1. Conjugate addition to terminal alkenes

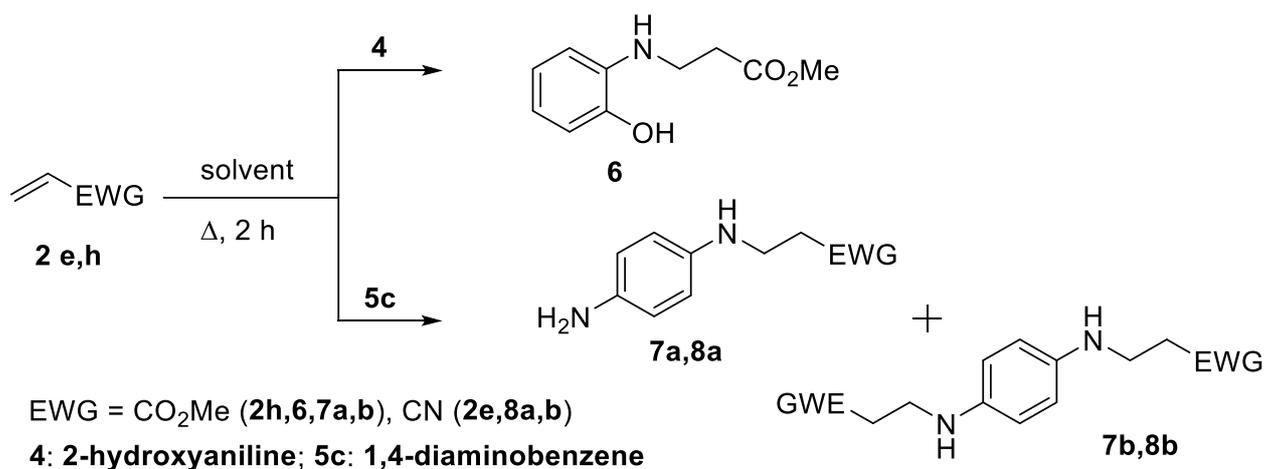
Trying to answer these questions, we have studied the reactions of 2-hydroxyaniline and 1,4-diaminobenzene with terminal electron-deficient alkenes (methyl acrylate **2h** and acrylonitrile **2e**) in both fluorinated and non-fluoro-containing solvents at atmospheric pressure. It is found that methyl acrylate **2h** reacts with 2-hydroxyaniline **4** slowly enough, the conversion is 20-40% (Table 6, entries 1-4). At the same time, the solvent polarity increase favored an increase in the conversion of the initial ester.

The reactions with 1,4-diaminobenzene **5c** proceed much faster: in the case of esters, the conversion is close to quantitative and weakly dependent on the solvent used. It should be noted that in the reaction with 1,4-diaminobenzene, mono- and bis-adducts are obtained in various ratios (Table 6, entries 5-8).

Unlike the ester of acrylic acid, the nature of the solvent has a significant effect on the addition of *para*-phenylenediamine to acrylonitrile. The best results have been obtained in methanol, while in hexafluoroisopropanol the conversion hardly reached 17%.

The complex nature effect of the solvent on the addition efficiency of substituted anilines to acrylic acid derivatives can be explained by the high electrophilicity of the olefinic carbon of acrylate or acrylonitrile compared to its β -methyl-substituted analogue.

Table 6.



No	Acceptor	Amine	Products	Solvent (Conversion, %) ^a
1	2h	4	6	MeOH (20)
2				TFE (30)
3				HFIP (40)
4				THF (0)
5	2h	5c	7a + 7b	MeOH (70)
6				TFE (90)
7				HFIP (95)
8				THF (0)
9	2e	5c	8a + 8b	MeOH (70)
10				TFE (40)
11				HFIP (17)
12				THF (0)

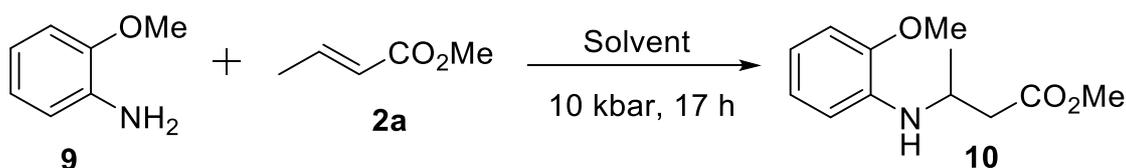
^a Conversion of the acceptor is calculated on the basis of the ¹H NMR spectrum with toluene as an internal standard

2.2.2. Nucleophilic addition to methyl crotonate

In an effort to understand the role of the solvent in the aza-Michael reaction with weak nucleophiles, we decided to study the effect of using protic solvents and

additives instead in the conjugate addition of anilines. Because phenol and HFIP have close pKa values (10.0 for PhOH vs. 9.3 for HFIP), we assumed that they should have similar influence on the reaction course. To test this hypothesis, we treated methyl crotonate **2a** with 2-anisidine **9** under different conditions. The reaction was conducted in protic solvents (MeOH and HFIP) at room temperature and under hyperbaric conditions (10 kbar) with/without phenol. It is worth noting that when a methyl crotonate is reacted with arylamines, the high pressure is a prerequisite condition, otherwise the reaction does not occur, or the conversion does not exceed 20%. As expected, the more acidic fluorinated alcohol favors the conjugate addition of anisidine (45%), while no reaction occurs when methanol was used (Table 7, entries 1-2). It is interesting, the addition of even one equivalent of the phenol promoted this process, and the ester conversion is already up to 19%, (Table 7, entry 3).

Table 7.



No	Solvent	Additive	Conversion, % ^a
1	HFIP	-	45
2	MeOH	-	0
3	MeOH	PhOH (1equi.)	19
4	MeOH	PhOH (3equi.)	84

^a The ester conversion **2a** is calculated from the ¹H NMR spectrum of the reaction mixture with toluene as an internal standard.

So, the use of another proton donor such as phenol instead of HFIP increases the reaction efficiency under the similar reaction conditions (84% vs 45%). To confirm the ability of phenol to activate the Michael acceptor, we recorded IR spectra of initial ester **2a** in the presence of both HFIP and phenol. The low-frequency shift ν (C=O) for 15 cm⁻¹ in these two cases corresponds to formation of hydrogen bond between

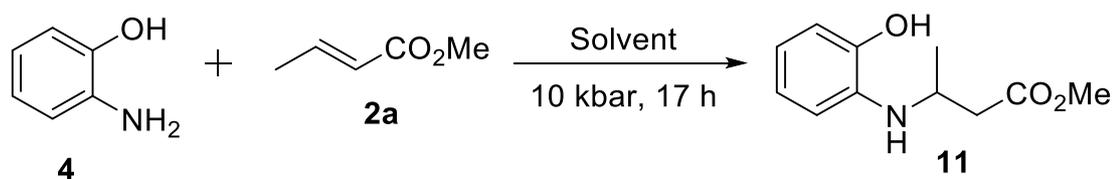
carbonyl oxygen atom and hydroxyl proton HFIP or PhOH (the work was carried out jointly with Ph.D. N. N. Chipanina).

It was interesting to see how the anilines containing an additional proton-donating group (-NH₂, -OH) behave in reactions with Michael acceptors. Is it necessary to use phenol (or another good proton donor) as a co-solvent in this case? In other words, if an additional functional group is already present in the aniline molecule, for example, the same hydroxy group, would it be necessary to use HFIP as a solvent for the conjugated nucleophilic addition in this case? To answer this question, we decided to study the reactions of methyl crotonate **2a** with anilines containing amino, hydroxy and sulfhydil groups.

First, we studied the 2-hydroxyaniline **4** with methyl crotonate **2a** under optimal conditions (room temperature, pressure 10 kbar) (Table 8).

In contrast with unsubstituted aniline, which adds to methyl crotonate almost quantitatively in HFIP, for 2-hydroxyaniline **4** (ten times less acidic than HFIP), the best solvent was methanol: the conversion of methyl crotonate in this case was 25%, whereas in HFIP it was not exceeded 10%.

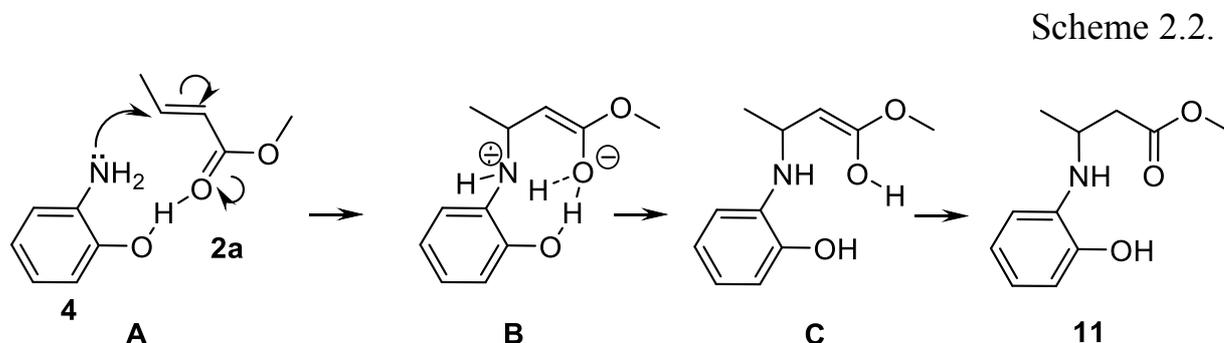
Table 8.



No	Solvent	Conversion, % ^a
1	HFIP	10
2	MeOH	25

^aConversion of ester **2a** is calculated on the basis of the ¹H NMR spectrum with toluene as an internal standard.

Quantum-chemical calculations showed that 2-hydroxyaniline **4** plays a role of promoter and weak nucleophile (the work was carried out jointly with Dr. E. Kondrashov) (Scheme 2.2).



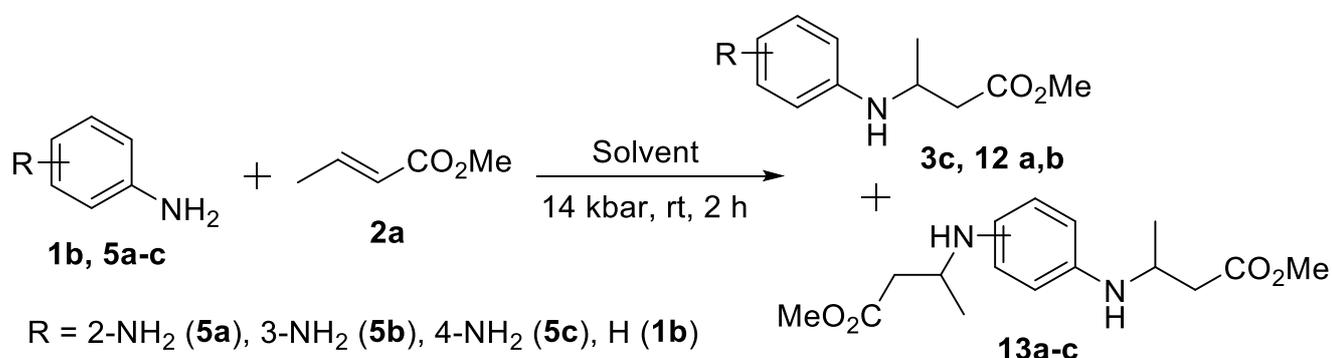
Thus, in accordance with the DFT calculations in the gas phase (B3LYP/6-311+G**) the complex **A** contains a strong intermolecular H-bond between the hydroxyl proton of aminophenol and the carbonyl oxygen atom (the distance $\text{OH}\cdots\text{O}=\text{C}$ is 1.823 Å, $E_{\text{obp}} = 7.2$ kcal/mol). Hence, we can conclude that the proton of the hydroxyl group of aminophenol participates in the activation of the carbonyl group, favoring further nucleophilic attack on the double bond. Zwitter-ion transition state **B**, as a result of the nucleophilic attack of the amino group on the β -carbon atom of the multiple bond, contains a rather strong intramolecular H-bond $\text{ArOH}\cdots\text{O}=\text{C}$ ($d_{\text{H}\cdots\text{O}} = 1.667$ Å). The activation energy barrier for the addition of amine to the double bond is 29.7 kcal/mol for 2-hydroxyaniline **4**, while for 2-anisidine **9** it increases up to 32.1 kcal/mol because of the hydroxyl group, able to activate the carbonyl function of Michael acceptor.

Based on the results obtained, we decided to test the reaction of methyl crotonate **2a** with anilines **5a-c** bearing a second amino group. The reactions were conducted both in fluorinated alcohol hexafluoroisopropanol and in methanol at room temperature and under hyperbaric conditions. It should be emphasized that, as the results discussed in Chapter 2.1, the high pressure is the necessary condition for the reaction to occur. Thus, when a mixture of methyl crotonate **2a** was refluxed 1,2-

diaminobenzene **5a** in methanol for 17 hours under atmospheric pressure, only starting materials were recovered.

To our surprise, the introduction of the second amino group to the *ortho*-position fundamentally changes the dependence of the reaction result on the solvent nature. As in monosubstituted anilines, the protic solvents favor the initial reagents: in THF no reaction occurred. However, in contrast to the mono-substituted anilines, the best results were obtained in methanol, whereas in HFIP the conversion reached only 10%. Similar patterns were observed in *para*- and *meta*-substituted diaminobenzenes (Table 9, entries 1-8).

Table 9.



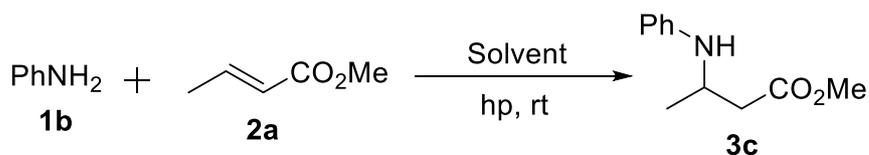
No	Aniline	Solvent	Conversion, % ^a	Product 12 (yield %)	Product 13 (yield %)
1	5a	MeOH	90	12a (65)	13a (10)
2	5a	HFIP	20		
3	5b	MeOH	60	12b (10)	13b (25)
4	5b	HFIP	25		
5	5c	MeOH	95	–	13c (72)
6	5c	HFIP	10		
7	1b	MeOH	12		
8	1b	HFIP	100	3c	–

^a The ester conversion is calculated from the ¹H NMR spectrum of the reaction mixture with toluene as an internal standard. ^b After 24 h.

The results obtained led us to the conclusion that the acidity of the amino group of diaminobenzene is enough to activate the Michael acceptor. But it is worth to add that we introduce a substituent with a positive mesomeric effect that, in turn, increases the arylamine nucleophilicity. Becoming more basic, they do not require additional substrate activation, and highly polar proton solvents have a deactivating effect on them. To confirm this conclusion, we performed an experiment with excess of aniline **1b** (Table 10).

Indeed, when methyl crotonate **2a** with 4-fold excess of aniline **1b** (instead of 0.5 equivalents as we used previously - see Chapter 2.1.1) in methanol (instead of HFIP), a high conversion of ester was observed (Table 10, entry 7).

Table 10.



No	Solvent	Aniline (equiv.)	Conditions	Conversion, % ^a
1	HFIP	0.5	14 kbar, 17 h	100
2	HFIP	0.5	10 kbar, 24 h	90
3	MeOH	0.5	10 kbar, 24 h	12
4	THF	5.0	10 kbar, 17 h	0
5	HFIP	5.0	10 kbar, 17 h	20
6	MeOH	5.0	10 kbar, 17 h	30
7	MeOH	4.0	14 kbar, 17 h	84

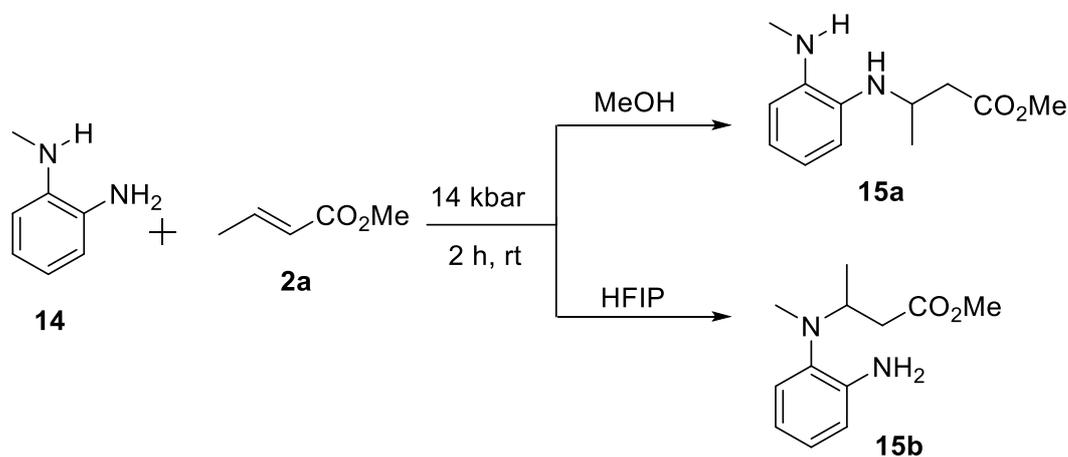
^a The ester conversion is calculated from the ¹H NMR spectrum of the reaction mixture with toluene as an internal standard.

Thus, it is shown for the first time that the conjugate nucleophilic addition of aromatic amines should be considered as an autopromotion process where functionally substituted anilines act simultaneously as a nucleophile and a catalyst (promoter). It is shown that unlike unsubstituted anilines, arylamines containing OH or NH₂ groups are good H-bond donors and do not require the use of expensive fluorinated alcohols as solvents, and the reactions proceed excellently in methanol.

2.2.3. Conjugate addition of *N*-methylaminoaniline to methyl crotonate

Further, we attempted to study the solvent nature effect on the selectivity of the conjugate aniline addition, containing a secondary amino group, to ester **2a**. It has been unexpectedly found that the reaction chemoselectivity depends on the solvent nature: the addition occurs with primary amino group in methanol, while the secondary is more active in HFIP (Table 11).

Table 11.



No	Solvent	Conversion, % ^a	Product (Yield, %)
1	MeOH	52	15a (45)
2	HFIP	68	15b (59)

^a The ester conversion **2a** is calculated from the ¹H NMR spectrum

of the reaction mixture with toluene as an internal standard.

How can these results be explained? *A priori*, secondary amino group is more basic than primary one (pKa of aniline is 4.6 vs 4.8 for N-methylaniline in water). Therefore, in HFIP, the nucleophilic attack must be carried out by the amino group NH₂, since the amino group NHMe, as the more basic, will be solvated by alcohol molecules. On the contrary, in less acidic methanol, the nucleophilic attack should be carried out by the secondary amino group, as more reactive. IR spectroscopy experiment of the starting diamine with different proton donors (HFIP, TFE, PhOH) was conducted to search an answer. Thus, the IR spectrum of the starting diamine in a CCl₄ contains three absorption bands: the primary amino group $\nu^{\text{as}}(\text{NH}_2)$ 3430 cm⁻¹, $\nu^{\text{s}}(\text{NH}_2)$ 3342 cm⁻¹ and the secondary amino group 3375 cm⁻¹. The addition of equimolar quantities of HFIP does not afford any changes. When an excess of alcohol was added, we observed an absorption band shift of the primary amino group to the low frequency region by 40-45 cm⁻¹ (3302 and 3383 cm⁻¹), while the position of the secondary amino group band are particularly conserved. The same trend of changes was observed in phenol and TFE. Thus, preliminary results confirm that more acidic solvents favor the attack by the secondary amino group due to the solvation of the NH₂ group.

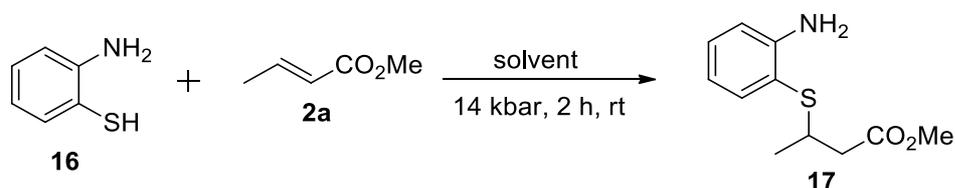
2.2.4. Conjugate addition of aminothiophenol to methyl crotonate

The replacement of the hydroxyl- or amino group in hydroxyl- or amino aniline by a more "acidic" sulfhydryl one would seem to have been even more conducive to the conjugate nucleophilic addition. Indeed, we have shown that 2-aminothiophenol **16** readily reacts with methyl crotonate **2a** under optimal conditions. However, the addition chemoselectivity is changed. The nucleophilicity of the sulfhydryl group is much higher than that of the amino group. Therefore, it is entirely expected that

crotonate reacts with 2-aminothiophenol, giving only thia-adduct **17**. The resulting ester is the only product of the reaction and its formation does not depend on the nature of the solvent (Table 12).

The starting thiol is an excellent nucleophile, and thia-Michael reaction is completely insensitive to the solvent nature change. It proceeds equally easily both in proton and in aprotic solvents. Moreover, thiols are much less basic than amines, so thia-adduct is selectively formed both in fluorinated and in usual alcohols.

Table 12.



No	Solvent	Conversion, % ^a
1	HFIP	90
2	MeOH	90 (85) ^b
3	THF	90

^a The ester conversion **2a** is calculated from the ¹H NMR spectrum of the reaction mixture with toluene as an internal standard.

^bPreparative output.

2.3. The obtaining of adamantyl aziridines initiated by the aza-Michael reaction

In the previous sections (2.1 and 2.2), the results to search a new efficient method for the synthesis of β -amino acid derivatives containing an arylamine fragment based on the conjugate nucleophilic addition of aromatic amines to enoates have been considered. Another equally difficult problem is the search of conditions to involve not only weak nucleophiles in the aza-Michael reaction, but also amines having a sterically hindered nitrogen atom. As an example of a sterically hindered amine, we chose adamantylamine. The adamantane moiety is a known pharmacophore. And it is

believed that the biological activity of adamantane derivatives is due to the presence of this particular tricyclic skeleton in the molecule. For example, memantine and tromantadine (Figure 2) have antiviral and antidiabetic activity, and has also been successfully used in the treatment of Parkinson's and Alzheimer's diseases [91-93].

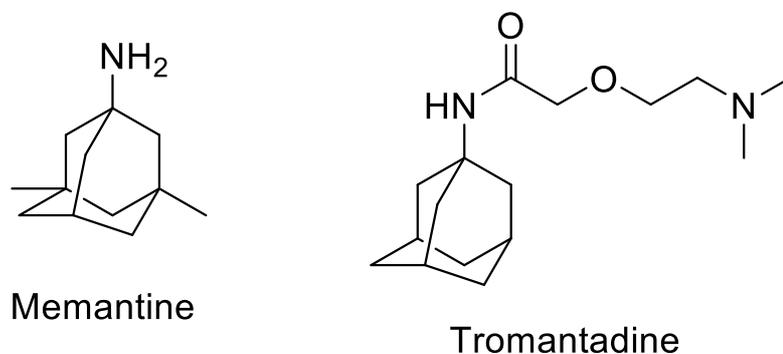
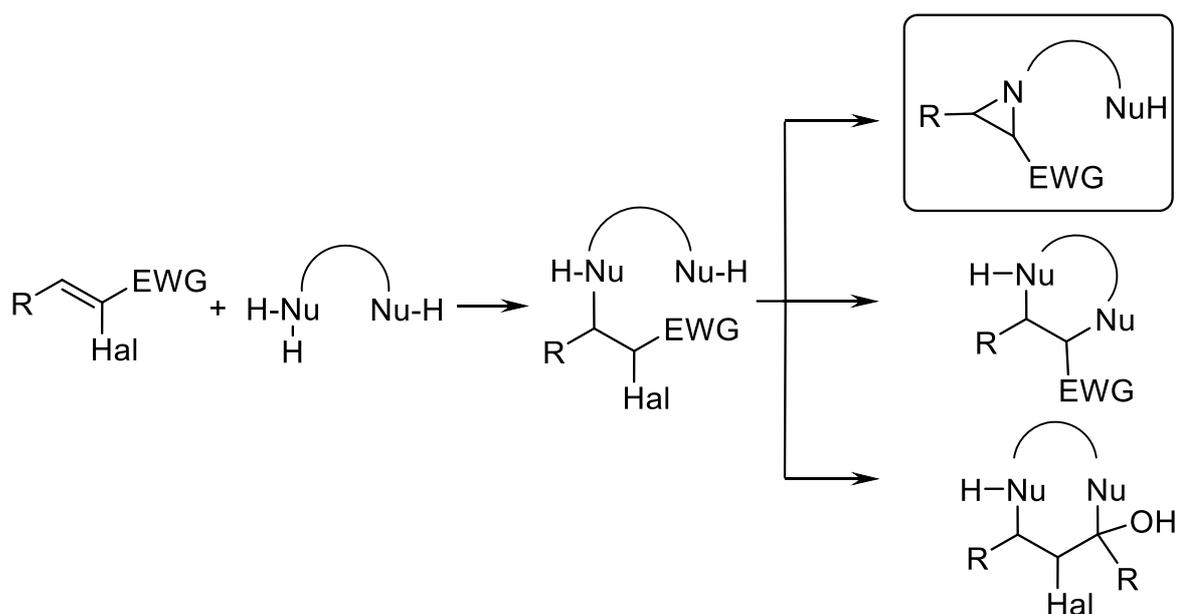


Figure 2. Aminoadamantane derivatives with biological activity

As already noted in Chapter 1, often the aza-Michael reaction initiates a cascade of transformations, resulting in the formation of various complex molecules, including heterocyclic ones. The aza-MIRC (aza-Michael Initiated Ring Closure) acronym is used to denote this type transformations (Scheme 2.3).

Scheme 2.3.



Such approach is more appropriate to use for the synthesis of functionally substituted aziridines (primarily, aziridine-carboxylates). Obviously, it was first necessary to find the optimal conditions for adamantylamine to add to Michael acceptors containing either a terminal or an internal double bond for the successful synthesis of target aziridines.

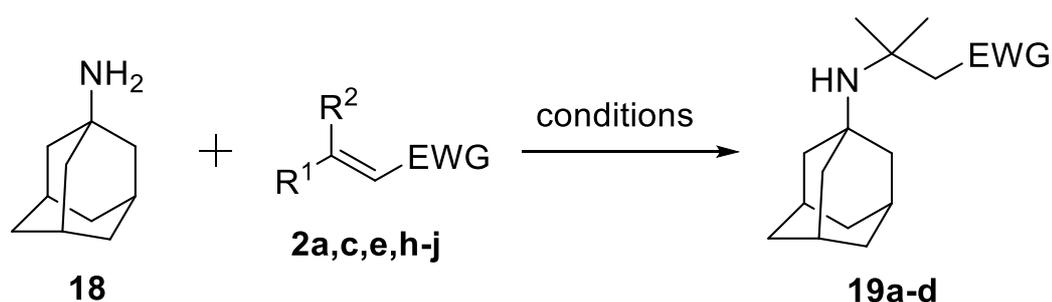
2.3.1. Conjugate addition of adamantylamine to activated alkenes

Studies have been initiated with the reaction of adamantylamine addition to terminal electron-deficient alkenes. As a highly basic amine ($pK_a = 10.5$ in water), adamantylamine **18** is added to methyl acrylate **2h**, giving the aza-Michael adduct **19a** in good yield (Table 13, entry 1). The reaction proceeds at atmospheric pressure after reflux in methanol for 12 hours. The use of fluorinated alcohols to activate the initial substrate is not required. Moreover, in the HFIP, the aza-Michael reaction is not due entirely to the complete deactivation of the nucleophile by the solvent.

Similar results were obtained with other Michael acceptors **2**. The nature of the activating acceptor group does not significantly affect the addition efficiency: in all cases, the reaction proceeds easily at room temperature, and the aza adducts **19b**, **c** were isolated in high yields (Table 13, entries 2,3).

Unlike methyl acrylate, its homologue methyl crotonate **2a** does not react at atmospheric pressure. In this case, hyperbaric conditions allow the adduct of adamantylamine **19d** to be obtained in a yield of 28%. Unfortunately, the presence of a second methyl group (dimethylcrotonate **2c**) or a phenyl substituent (4-phenylbutene-3-one-2 **2j**) with an electrophilic carbon atom significantly complicates the nucleophilic attack by such a cumbersome amine (Table 13, entries 6, 7).

Table 13.



№		Michael acceptor			Reaction conditions	Product, (Yield, %)
		R ¹	R ²	EWG		
1	2h	1	2h	CO ₂ Me	rt, 17 h	19a (79)
2	2e	2	2e	CN	rt, 17 h	19b (82)
3	2i	3	2i	SO ₂ Ph	rt, 17 h	19c (92)
4	2a	4	2a	CO ₂ Me	rfx, 17 h	0
5	2a	5	2a	CO ₂ Me	25°C, 10 kbar, 17 h	19d (28)
6	2c	Me	Me	CO ₂ Et	25°C, 10 kbar, 24 h	traces ^a
7	2j	Ph	H	C(O)Me	25°C, 10 kbar, 24 h	0

^aThe starting ester **2c** is isolated

Thus, we have shown that adamantylamine is readily added to Michael terminal acceptors, whereas their β -substituted analogs having an intrinsic double bond react with it only in nonclassical conditions (at high pressure). The obtained results open the prospects of successful assembly of three-membered aza-heterocycles (aziridines) upon introduction of adamantylamine into reaction with halogen-substituted unsaturated carbonyl compounds.

2.3.2. Adamantylamine with α -halogen-substituted Michael acceptors

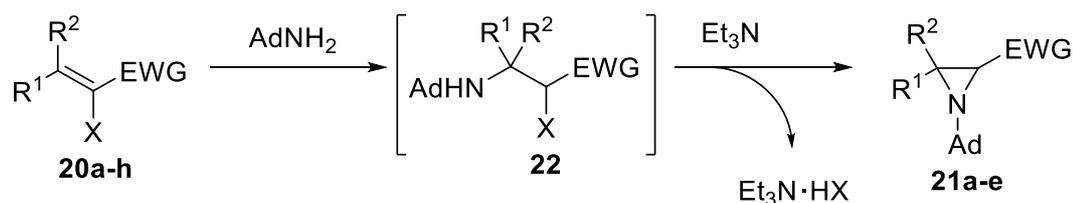
When the optimal conditions for the aza-Michael reaction with 1-adamantylamine were determined, we studied its interaction with α -halogen-substituted terminal alkenes. A bromine or chlorine atom in the sp^2 of carbon atom significantly increases the electrophilicity of the multiple bond, thereby facilitating a nucleophilic attack. In addition, the halide ion is a good leaving group that favors further nucleophilic substitution and aziridine ring closure.

Experiments with Michael terminal acceptors were run at atmospheric pressure. We observed that adamantylamine adds efficiently to α -halogen-substituted terminal alkenes. Subsequent intramolecular substitution of halogen (with an additional strong base - triethylamine - for hydrogen halide binding) made it possible to obtain aziridines in high yields. The reaction proceeds easily in protic solvents at room temperature.

In contrast to non-halogenated substrates **2**, the result of the reaction of their halogen derivatives **20** with adamantylamine depends on the nature of the activating group. Thus, if the reaction of methyl vinyl ketone **20c** and acrylic acid derivatives (ester **20a** and nitrile **20b**) is completed by the formation of target aziridines **21** in good yield, then the reaction of α -bromosulfone **20d** with adamantylamine stops at the aza-adduct formation stage **22**. All attempts to perform the subsequent displacement of bromine with other bases (DBU, DABCO) failed.

The reaction of adamantylamine with α -chlorocrotonate **20e** (at atmospheric pressure) gives the expected aziridine **21d** in good yield (Table 14, entry 5). The use of α -bromosubstituted crotonate **20f** as a substrate under the same conditions (MeOH, 25°C, 17h) turns out unsuccessful, probably, due to the weaker inductive effect of the bromine atom ($-I < +M$) and its larger size (Table 14, entry 7). Applying high pressure, we were able to obtain aziridine in the form of a single isomer.

Table 14.

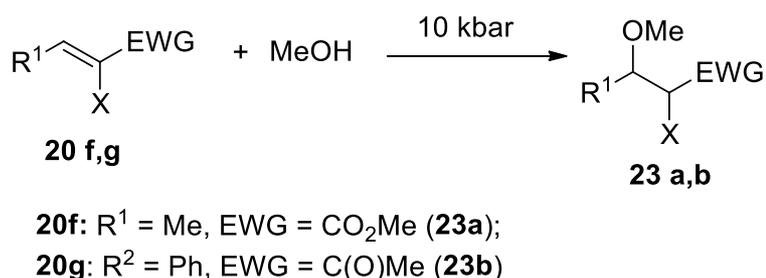


№	Michael acceptor	R ¹	R ²	X	EWG	Reaction conditions ^a	Product (yield,%) ^b
1	20a	H	H	Cl	CO ₂ Me	MeOH, Et ₃ N, 25°C	21a (67)
2	20b	H	H	Cl	CN	EtOH, Et ₃ N, 25°C	21b (58)
3	20c	H	H	Br	C(O)Me	MeOH, Et ₃ N, 25°C	21c (82)
4	20d	H	H	Br	SO ₂ Ph	EtOH, Et ₃ N, 25°C	22 (81)
5	20e	Me	H	Cl	CO ₂ Me	MeOH, Et ₃ N, 25°C	21d (67)
6	20f	Me	H	Br	CO ₂ Me	MeOH, Et ₃ N, 25°C, 6 kbar	21d (44) + 23a (32)
7	20f	Me	H	Br	CO ₂ Me	EtOH, Et ₃ N, 25°C	-
8	20g	Ph	H	Br	C(O)Me	MeOH, 25°C, 10 kbar	21e (39) + 23b (12)
9	20g	Ph	H	Br	C(O)Me	MeOH, Et ₃ N, Δ	-
10	20h	Me	Me	Br	CO ₂ Et	EtOH, 25°C, 10 kbar ^c	24 (38)

^a Reaction time 17 ч; ^b Preparative yield; ^c Reaction time 24 ч.

The moderate yield of aziridine **21d** (44%) can be explained by the competitive addition of methanol (used as a solvent) to the substrate, that led to the oxa-Michael adduct **23a** in 33% yield (Scheme 2.4). Attempts to avoid the side reaction by replacing methanol with another solvent (isopropanol, *tert*-butanol) remained unsuccessful due to the low solubility of the initial amine in these solvents.

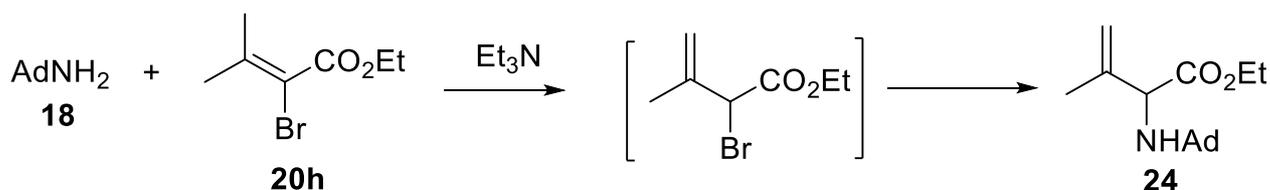
Scheme 2.4.



Pleasingly, 3-bromo-4-phenylbut-3-en-2-one **20g** absolutely inactive toward adamantylamine under classical conditions, gives, under high pressure aziridine **21e** in 39% yield (Table 14, entries 8,9). However, in this case, we also observed the formation of the oxa-adduct **23b** (Scheme 2.4).

Finally, we carried out the reaction of ethyl α -bromo- β,β -dimethyl acrylate **20h** with amino-adamantane in ethanol to avoid transesterification. To our surprise, only product **24** was isolated with a yield of 38% (Scheme 2.5). The formation of compound **24** can be explained by the initial double bond migration under base with subsequent substitution of the halogen atom by amine. Similar process proceeding in the presence of strong bases is described [94].

Scheme 2.5.



As is known, aziridines are distinguished by a relatively high barrier of pyramidal inversion of the nitrogen atom. Therefore, it was quite expected to obtain the target aziridines as a mixture of invertomers. But, owing to such a voluminous substitute as adamantyl, acting as a conformational anchor, inversion becomes practically impossible, and we have as a result only one isomer.

The ^1H NMR spectra of the obtained aziridines **21** exhibit the sharp, well-resolved signals of the aziridine ring. The data allowed us to determine the relative configuration of protons H^2 and H^3 rings. The 3J for *cis*-aziridine ring protons reach 6.2-6.6 Hz while these values are known to be in the 2.6-2.8 Hz range for *trans*-2,3-protons [95, 96]. Based on the values of the measured constants 3J and additional NMR experiments (NOESY), the geometry of the aziridines obtained has been determined (Figure. 3).

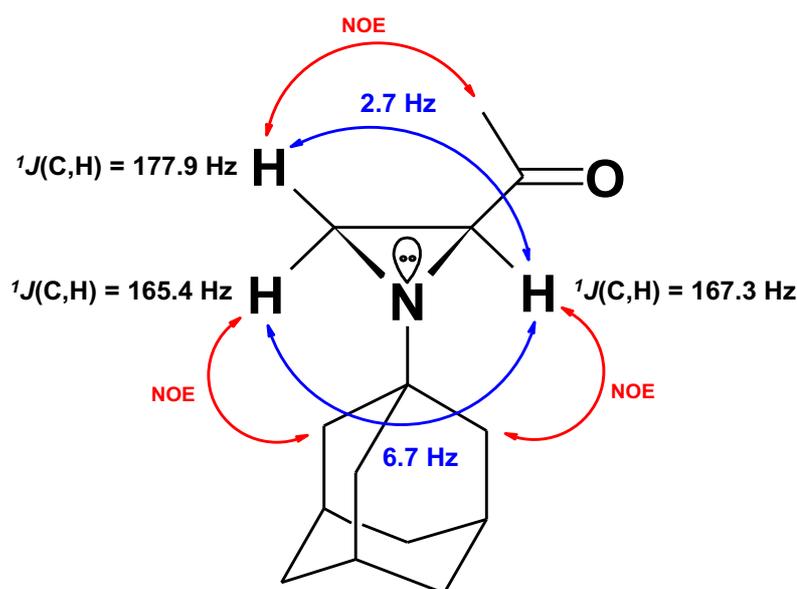
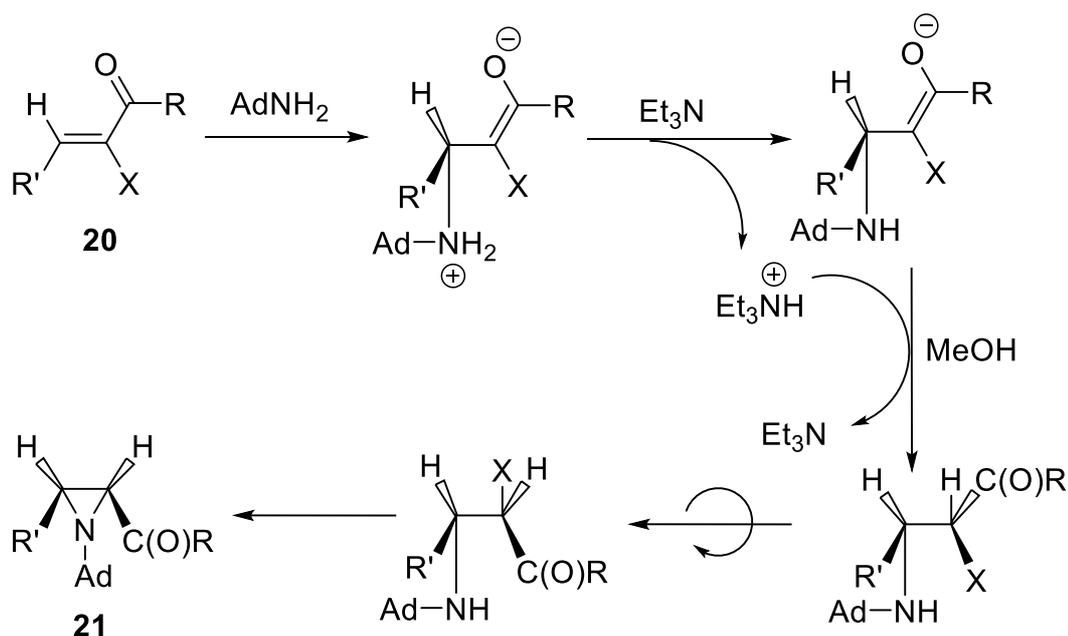


Fig. 3. The main correlations of NOESY for aziridine **21c**

Stereoselective formation of aziridines **21** suggests that the protonation of the intermediate enolate, being in the first stage of the reaction, occurs in an intermolecular fashion with the proton solvent molecules (methanol) or ammonium salt (Scheme 2.6).

Scheme 2.6.



Thus, we could involve the primary amine (adamantylamine) containing a sufficiently voluminous substituent in the reaction of the conjugate nucleophilic addition. The use of halogen derivatives **20** with the same nucleophile in the reaction allowed the selective one-reactor synthesis of adamantyl aziridines to be carried out. The combination of two important pharmacophore fragments in their molecules makes these compounds attractive for medical chemistry, and the method proposed is simple and effective. When sterically hindered β -substituted Michael acceptors are reacted, hyperbaric conditions help to occur the reaction efficiently.

CONCLUSIONS

1. The conjugate nucleophilic addition of primary and secondary arylamines to derivatives of acrylic and crotonic acids under classical and hyperbaric conditions has been studied. It was shown that the reaction of weak Michael donors and acceptors bearing a sterically hindered reaction center proceeds smoothly when strong proton-donor solvents (hexafluoroisopropanol, trifluoroethanol) and high pressure were used simultaneously.
2. Different β -amino acid derivatives bearing an arylamine fragment were prepared in good to excellent yield under proposed conditions. Sometimes the preparation of these derivatives is difficult or impossible under classical conditions. The generality of the method was shown on a wide series of Michael acceptors, including those bearing a low activated double bond.
3. It was shown that phenol can be used as a proton donor in aza-Michael addition of arylamines. It was found that in the presence of one to three equivalents of phenol the addition of aniline to the internal enoates occurs under high pressure without the use of fluorinated alcohols.
4. In contrast to unsubstituted aniline, its analogues bearing an additional hydroxy or amino group in benzene ring are good hydrogen bond donors. Their reaction with enoates proceeds under mild conditions in usual protic solvents and does not require the use of fluorinated alcohols.
5. A method of stereoselective assembly of functionally substituted aziridines bearing a pharmacophore adamantane fragment was developed. The successful preparation of aziridine carboxylates from sterically hindered esters occurs

under hyperbaric conditions only. The cascade of transformations is initiated by aza-Michael reaction (aza-MIRC methodology) of adamantylamine to α -halogenated Michael acceptors.

Chapter 3. EXPERIMENTAL SECTION

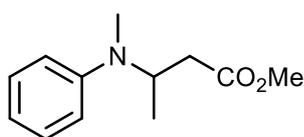
3.1. General methods

High-pressure reactions were performed in a piston-cylinder type apparatus U101 and U22(Unipress, Warsaw, Poland), designed for pressures up to 12 kbar and up to 15 kbar, respectively and a piston-cylinder type apparatus (Ollivaud/Lebas, France) for pressures from 12 to 14 kbar. ^1H , ^{13}C , ^{19}F and ^{15}N NMR spectra were recorded on a Bruker AVANCE 400 MHz (at 400, 100, 282 and 40 MHz, respectively) and Bruker AVANCE 300 MHz (at 300 and 75 MHz, respectively) spectrometers for solution in CDCl_3 . Chemical shifts (δ) in ppm are reported using residual chloroform (7.24 for ^1H and 77.2 for ^{13}C) as internal reference. The coupling constants (J) are given in Hertz. The concerted application of ^1H - ^1H 2D homonuclear experiments COSY and NOESY as well as ^1H - ^{13}C 2D heteronuclear experiments HSQC and HMBC were used for the distinction of the carbon and proton resonances in all cases. The IR spectra were measured with Bruker Vertex 70 FT-IR and portable Varian 3100 diamond ATR/FT-IR instruments. The GC/MS analyses were performed on a Hewlett-Packard HP 5971A instrument (EI, 70 eV). High-resolution mass data were recorded on a Micromass Q-TOF (Quadrupole time-of-flight) instrument with an electrospray source in the EI or ESI mode. The silica gel used for flash chromatography was 230-400 Mesh

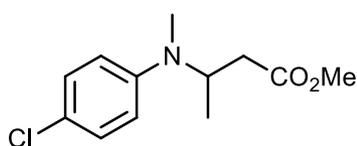
3.2. Starting materials

All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use. Haloderivatives **20 a,b** are commercial. 3-Bromobut-3-ene-2-one **20c** was prepared as reported previously [97]. Bromovinyl phenyl sulfone **20d** was prepared according to the known procedure [98].

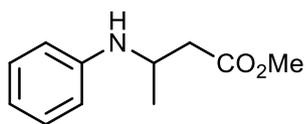
3.3. General Procedure for the reaction of Michael acceptors with anilines): The mixture of amine(1 mmol) and Michael acceptor (2 mmol) in HFIP (0.5-1.5 mL) was placed in a Teflon reactionvessel and kept under 0.5-15 kbar at room temperature overnight (17 h). After the pressure was released and the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (cyclohexane/AcOEt, from 90:10 to 60:40). The compounds **3a-q** were prepared according to this procedure. The spectral data of compounds **3c,d,f,i,j,l,n,p** coincide with published earlier [99-105].



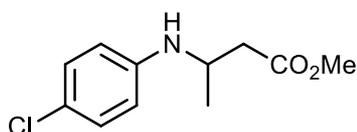
3-(Methyl(phenyl)amino)butanoate 3a: brown oil, 230 mg, 81% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 1.22 (d, $J = 6.6$ Hz, 3H), 2.46 (dd, $J = 14.4, 7.2$ Hz, 1H), 2.66 (dd, $J = 14.4, 7.2$ Hz, 1H), 2.75 (s, 3H), 3.63 (s, 3H), 4.48 (m, 1H), 6.73-6.93 (m, 3H), 7.21-7.30 (m, 2H); ^{13}C NMR(CDCl_3 , 75 MHz): δ 17.2, 30.2, 39.0, 51.6, 51.9, 114.2, 117.5, 129.1, 150.0, 172.2; IR (neat) ν (cm^{-1}): 1730 (C=O). HRMS (ES+) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ 208.1338; found 208.1332.



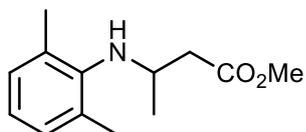
Methyl 3-((4-chlorophenyl)(methyl)amino)butanoate 3b: brown oil, 217 mg, 90% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 1.18 (d, $J = 6.9$ Hz, 3H), 2.43 (dd, $J = 14.7, 6.9$ Hz, 1H), 2.62 (dd, $J = 14.7, 7.8$ Hz, 1H), 2.69 (s, 3H), 3.61 (s, 3H), 4.39 (m, 1H), 6.77 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 9.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 17.2, 30.4, 39.0, 51.8, 52.2, 115.3, 122.2, 128.9, 148.7, 172.2; IR (neat) ν (cm^{-1}): 810 (C Cl), 1732 (C=O); (ES+) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{17}\text{ClNO}_2$ 242.0949; found 242.0948.



Methyl 3-(phenylamino)butanoate 3c[99]: brown oil, 192 mg, quantitative yield; ^1H NMR(CDCl_3 , 300 MHz): δ 1.29 (d, $J = 9.6$ Hz, 3H), 2.44 (dd, $J = 22.5, 10.5$ Hz, 1H), 2.68 (dd, $J = 22.5, 7.8$ Hz, 1H), 3.70 (s, 4H, CH_3), 3.89-4.07 (m, 1H), 6.60-6.80 (m, 3H), 7.15-7.27 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.7, 40.8, 46.0, 51.6, 113.6, 117.7, 129.4, 146.8, 172.3; IR (neat) ν (cm^{-1}): 1726 (C=O), 3387(NH).

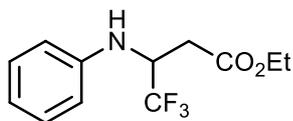


Methyl 3-((4-chlorophenyl)amino)butanoate 3d [100]: brown oil, 121 mg, 53% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 1.25 (d, $J = 6.3$ Hz, 3H), 2.43 (dd, $J = 15.0, 6.6$, Hz, 1H), 2.60 (dd, $J = 15.0, 5.1$ Hz, 1H), 3.67 (s, 3H), 3.50-3.75 (mask, 1H), 3.88 (m, 1H), 6.53 (d, $J = 9.0$ Hz, 2H), 7.10 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.5, 40.6, 46.2, 51.7, 114.7, 122.2, 129.2, 145.5, 172.2; IR (neat) ν (cm^{-1}): 815 (C-Cl), 1725 (C=O), 3390 (NH).

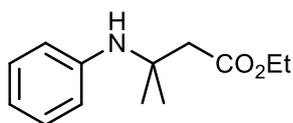


Methyl 3-((2,6-dimethylphenyl)amino)butanoate 3e: brown oil, 161 mg, 73% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 1.18 (d, $J = 6.6$ Hz, 3H), 2.27 (s, 6H), 2.44 (dd, $J = 15.0, 6.6$ Hz, 1H), 2.51 (dd, $J = 15.0, 6.0$ Hz, 1H), 3.22 (br.s, 1H), 3.65 (s, 3H), 4.48 (m, 1H), 6.75-6.84 (m, 1H), 6.95-7.00 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.0, 21.2, 42.1, 49.8, 51.7, 121.9, 129.1, 129.7, 144.3, 172.6; IR (neat) ν (cm^{-1}): 1731

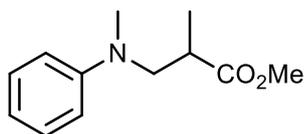
(C=O), 3378 (NH); HRMS (ES+) m/z [M + H]⁺ calcd for C₁₃H₂₀NO₂ 222.1494; found 222.1489.



Ethyl 4,4,4-trifluoro-3-(phenylamino)butanoate 3f [101]: brown oil, 118 mg, 45% yield; ¹H NMR (CDCl₃, 300 MHz): δ 1.20 (t, J = 7.2 Hz, 3H), 2.62 (dd, J = 15.6, 8.7 Hz, 1H), 2.84 (dd, J = 15.6, 4.5 Hz, 1H), 3.90 (br.s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.40-4.60 (m, 1H), 6.70-6.85 (m, 3H), 7.17-7.25 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1, 35.2, 53.5 (q, $2J_{CF}$ = 30.2 Hz), 61.5, 125.7 (q, J = 282 Hz), 114.1, 119.6, 129.5, 145.9, 169.6; ¹⁹F NMR (CDCl₃, 300 MHz): -76.10 (d, J = 7.2 Hz); IR (neat) ν (cm⁻¹): 1117 (CF), 1728 (C=O), 3391 (NH).

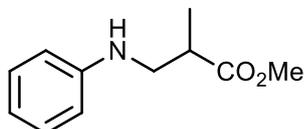


Ethyl 3-methyl-3-(phenylamino)butanoate 3g: brown oil, 119 mg, 54% yield; ¹H NMR (CDCl₃, 300 MHz): δ 1.24 (m, 4H, NH), 1.40 (s, 6H), 2.56 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 6.80-6.85 (m, 3H), 7.10-7.25 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.4, 28.7, 45.4, 53.5, 60.5, 119.6, 119.9, 129.0, 146.3, 171.9; IR (neat) ν (cm⁻¹): 1722(C=O), 3395 (NH); HRMS (ES+) m/z [M+H]⁺ calcd for C₁₃H₂₀NO₂ 222.1494; found 222.1492.

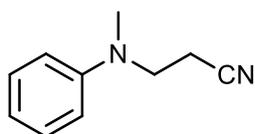


Methyl 2-methyl-3-(methyl(phenyl)amino)propanoate 3h: brown oil, 83 mg, 40% yield; ¹H NMR (CDCl₃, 300 MHz): δ 1.21 (d, J = 6.0 Hz, 3H), 2.89-3.01 (m, 4H, CH), 3.35 (dd, J = 14.7, 6.6 Hz, 1H), 3.72 (dd, J = 14.7, 7.8 Hz, 1H), 3.66 (s, 3H), 6.70-6.77 (m, 3H), 7.23-7.30 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 15.2, 38.4, 39.2, 51.8,

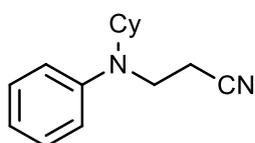
56.4, 112.3, 116.6, 129.3, 149.0, 172.1; IR (neat) ν (cm^{-1}): 1732 (C=O); HRMS (ES+) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ 208.1338; found 208.1341.



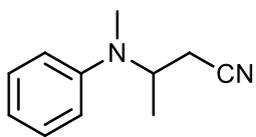
Methyl 2-methyl-3-(phenylamino)propanoate 3i [102]: brown oil, 17 mg, 9% yield; ¹H NMR(CDCl_3 , 300 MHz): δ 1.24 (d, J = 6.0 Hz, 3H), 2.74-2.85 (m, 1H), 3.23 (dd, J = 13.2, 5.7 Hz, 1H), 3.42 (dd, J = 13.2, 8.1 Hz, 1H), 3.70 (s, 3H), 3.98 (br.s, 1H), 6.60-6.75 (m, 3H), 7.14-7.21(m, 2H); ¹³C NMR (CDCl_3 , 75 MHz): δ 15.2, 39.3, 47.0, 52.0, 113.0, 117.7, 129.4, 147.9, 176.0; IR (neat) ν (cm^{-1}): 1724 (C=O), 3408 (NH).



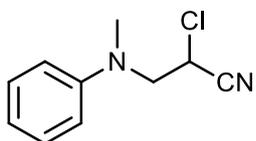
3-(Methyl(phenyl)amino)propanenitrile 3j [103]: brown oil, 160 mg, quantitative yield; ¹H NMR(CDCl_3 , 300 MHz): δ 2.57 (t, J = 6.9 Hz, 2H), 3.03 (s, 3H), 3.72 (t, J = 6.9 Hz, 2H), 6.70-6.85(m, 3H), 7.25-7.33 (m, 2H); ¹³C NMR (CDCl_3 , 75 MHz): δ 15.3, 38.7, 49.0, 112.7, 117.8, 118.6, 129.6, 147.7; IR (neat) ν (cm^{-1}): ν 2247 (C \equiv N).



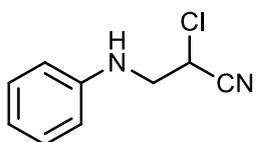
3-(Cyclohexyl(phenyl)amino)propanenitrile 3k: brown oil, 225 mg, 99% yield; ¹H NMR (CDCl_3 , 300 MHz): δ 1.10-2.00 (m, 10H), 2.54 (t, J = 6.9 Hz, 2H), 3.48-3.68 (m, 3H), 6.75-6.85(m, 3H), 7.23-7.33 (m, 2H); ¹³C NMR (CDCl_3 , 75 MHz): δ 17.6, 25.8, 26.1, 31.0, 58.8, 41.1, 114.7, 118.4, 118.5, 129.5, 147.3; IR (neat) ν (cm^{-1}): 2247 (C \equiv N); HRMS (ES+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2$ 229.1705; found 229.1709.



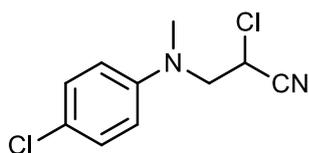
3-(Methyl(phenyl)amino)butanenitrile 3l: [104]: brown oil, 141 mg, 81% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 1.40 (d, $J = 6.6$ Hz, 3H), 2.49 (dd, $J = 16.8, 7.2$ Hz, 1H), 2.57 (dd, $J = 16.8, 6.0$ Hz, 1H), 2.80 (s, 3H), 4.30 (m, 1H), 6.75-6.87 (m, 3H), 7.25-7.35 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 17.3, 21.9, 30.5, 51.7, 114.4, 118.3, 118.5, 129.4, 149.3; IR (neat) ν (cm^{-1}): 2248 ($\text{C}\equiv\text{N}$).



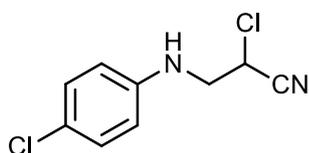
2-Chloro-3-(methyl(phenyl)amino)propanenitrile 3m: brown oil, 126 mg, 65% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 3.18 (s, 3H), 3.92-4.00 (m, 2H), 4.62 (t, $J = 6.9$ Hz, 1H), 6.70-6.95 (m, 3H), 7.30-7.40 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 39.2, 39.8, 57.8, 112.2, 116.8, 118.3, 129.7, 147.0; IR (neat) ν (cm^{-1}): 2247 ($\text{C}\equiv\text{N}$); HRMS (EI+) m/z $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{ClN}_2$ 194.06108; found 194.05992.



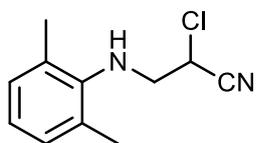
2-Chloro-3-(phenylamino)propanenitrile 3n: [105]. brown oil, 155 mg, 86% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 3.64-3.86 (m, 2H), 4.30 (br.s, 1H), 4.57 (t, $J = 6.6$ Hz, 1H), 6.60-6.90 (m, 3H), 7.21-7.30 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 41.1, 48.6, 113.3, 116.4, 119.4, 129.7, 145.2; IR (neat) ν (cm^{-1}): 2249 ($\text{C}\equiv\text{N}$), 3407 (NH).



2-Chloro-3-((4-chlorophenyl)(methyl)amino)propanenitrile 3o: brown oil, 190 mg, 83% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 3.11 (s, 3H), 3.85-3.95 (m, 2H), 4.57 (dd, $J = 7.5, 6.9$ Hz, 1H), 6.64 (d, $J = 9.0$ Hz, 2H), 7.22 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 39.1, 39.9, 57.9, 113.5, 116.6, 123.4, 129.5, 145.8; IR (neat) ν (cm^{-1}): 809 (C-Cl), 2247 ($\text{C}\equiv\text{N}$); HRMS(EI+) m/z $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{Cl}_2\text{N}_2$ 228.02210; found 228.02156



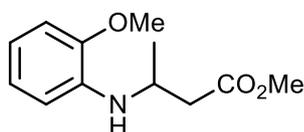
2-Chloro-3-((4-chlorophenyl)amino)propanenitrile 3p [105]: brown oil, 157 mg, 73% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 3.60-3.83 (m, 2H), 4.33 (br.s, 1H), 4.55 (dd, $J = 6.9, 6.6$ Hz, 1H), 6.58 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 41.1, 48.5, 114.4, 116.3, 123.9, 129.5, 143.9; IR (neat) ν (cm^{-1}): 802 (C-Cl), 2247 ($\text{C}\equiv\text{N}$), 3424 (NH).



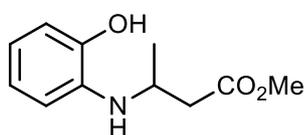
2-Chloro-3-((2,6-dimethylphenyl)amino)propanenitrile 3q: brown oil, 125 mg, 60% yield; ^1H NMR (CDCl_3 , 300 MHz): δ 2.36 (s, 6H), 3.46-3.72 (m, 3H), 4.44 (dd, $J = 6.0, 5.7$ Hz, 1H), 6.90-7.10 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 18.6, 42.5, 52.2, 116.4, 123.4, 129.3, 130.1, 142.5; IR (neat) ν (cm^{-1}): 2254 ($\text{C}\equiv\text{N}$), 3402 (NH); HRMS (EI+) m/z $[\text{M}]^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{ClN}_2$ 208.07673; found 208.07716.

3.4. General Procedure for the reaction of methyl crotonate with substituted anilines:

The mixture of functionally substituted aniline (1 mmol) and Michael acceptor (2 mmol) in corresponding solvent (0.5-1.5 mL) was placed in a Teflon reaction vessel and stand under 10-14 kbar at room temperature for 2-17 h. After that the pressure was released and the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (Silica gel, eluent Pentane/Diethyl ether, from 90:10 to 50:50). The spectral data of compounds **10**, **17** coincide with published earlier [106-107].

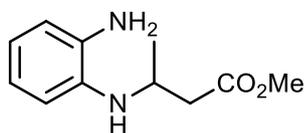


Methyl 3-((2-methoxyphenyl)amino)butanoate 10 [106]. oil, 66 mg, 30% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.31 (d, $J = 6.4$ Hz, 3H, CH_3CH), 2.40 (dd, $J = 14.9, 7.6$ Hz, 1H, CH_2), 2.73 (dd, $J = 14.8, 5.0$ Hz, 1H, CH_2), 3.69 (s, 3H, OMe), 3.84 (s, 3H, $\text{CH}_3\text{OC}(\text{O})$), 3.91-4.02 (m, 1H, CH), 4.29 (br.s, 1H, NH), 6.64-6.71 (m, 2H, Ar), 6.75-6.81 (m, 1H, Ar), 6.85-6.92 (m, 1H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.9 (CH_3C), 41.2 (CH_2), 45.7 (CH), 51.7 (CH_3O), 55.5 (CH_3O), 109.8, 110.6, 116.8, 121.4, 136.7, 147.1 (Ar), 172.4 (C=O).

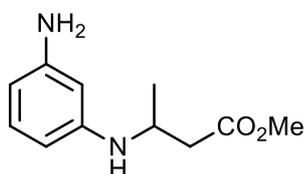


Methyl 3-((2-hydroxyphenyl)amino)butanoate 11: oil, 146 mg, 70% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.16 (d, $J = 6.0$ Hz, 3H, CH_3C), 2.37 (dd, $J = 15.0, 6.0$ Hz, 1H, CH_2), 2.55 (dd, $J = 15.0, 6.0$ Hz, 1H, CH_2), 3.61 (s, 3H, CH_3O), 3.68-3.80 (m, 1H, CH), 4.50 (br.s, 1H, OH), 6.53-6.78 (m, 4H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.7

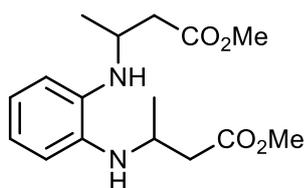
(CH₃C), 41.2 (CH₂), 47.3 (CH), 52.0 (CH₃O), 115.0, 116.1, 119.9, 121.0, 134.9, 146.1 (C_{Ar}), 173.3 (C=O). IR (cm⁻¹): ν 1711 (C=O), 3385 (NH). HRMS (ESI, m/z) calcd for C₁₁H₁₅NO₃ 209.1052; found 209.1045.



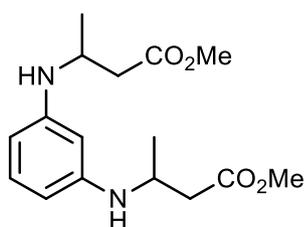
Methyl 3-((2-aminophenyl)amino)butanoate 12a: oil, 135 mg, 65% yield. ¹H NMR (CDCl₃, 300 MHz): δ 1.28 (d, J = 6.0 Hz, 3H, CH₃C), 2.46 (dd, J = 15.0, 6.0 Hz, 1H, CH₂), 2.66 (dd, J = 15.0, 6.0 Hz, 1H, CH₂), 3.39 (br. s, 3H, NH), 3.70 (s, 3H, CH₃O), 3.85-3.96 (m, 1H, CH), 6.68--6.78 (m, 4H, Ar), 7.21-7.30 (m, 2H, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 20.8 (CH₃C), 41.1 (CH₂), 46.2 (CH), 51.7 (CH₃O), 114.5, 116.9, 119.7, 120.4, 135.6, 135.7 (C_{Ar}), 172.6 (C=O). IR (cm⁻¹): ν 1723 (C=O), 3339 (NH). HRMS (ESI, m/z) calcd for C₁₁H₁₆N₂O₂ 208.1212; found 208.1222.



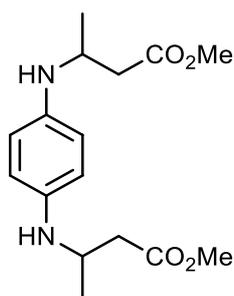
Methyl 3-((3-aminophenyl)amino)butanoate 12b: oil, 52 mg, 25% yield. ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (d, J = 6.0 Hz, 3H, CH₃C), 2.41 (dd, J = 15.0, 6.0 Hz, 1H, CH₂), 2.66 (dd, J = 15.0, 6.0 Hz, 1H, CH₂), 3.30 (br. s, 3H, NH), 3.68 (s, 3H, CH₃O), 3.83-3.96 (m, 1H, CH), 5.95--6.15 (m, 3H, Ar), 6.90-7.00 (m, 1H, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 20.8 (CH₃C), 40.9 (CH₂), 46.1 (CH), 51.8 (CH₃O), 100.4, 104.9, 105.4, 130.4, 147.7, 148.0 (C_{Ar}), 172.5 (C=O). IR (cm⁻¹): ν 1721 (C=O), 3359 (NH). HRMS (ESI, m/z) calcd for C₁₁H₁₆N₂O₂ 208.1212; found 208.1221.



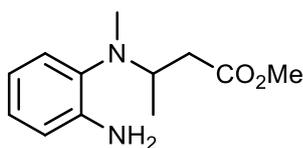
Dimethyl 3,3'-((1,2-phenylenebis(azanediyl))dibutanoate 13a: oil, 31 mg, 10% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.24-1.30 (m, 7H, CH_3C , NH), 2.38-2.50 (m, 2H, CH_2), 2.58-2.71 (m, 2H, CH_2), 3.60-3.90 (m, 9H, CH_3O , CH, NH), 6.65--6.75 (m, 4H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.9 (CH_3C), 41.3 (CH_2), 46.6 (CH), 51.7 (CH_3O), 115.5, 120.1, 136.6 (C_{Ar}), 172.7 ($\text{C}=\text{O}$). IR (cm^{-1}): ν 1727 ($\text{C}=\text{O}$), 3325 (NH). HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ 308.1736; found 308.1741.



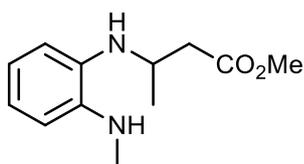
Dimethyl 3,3'-((1,3-phenylenebis(azanediyl))dibutanoate 13b: oil, 77 mg, 25% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.26 (d, $J = 6.0$ Hz, 6H, CH_3C), 1.55 (s, 1H, NH), 2.41 (dd, $J = 15.0, 6.0$ Hz, 2H, CH_2), 2.66 (dd, $J = 15.0, 6.0$ Hz, 2H, CH_2), 3.65 (s, 1H, NH), 3.68 (s, 6H, CH_3O), 3.84-3.96 (m, 2H, CH), 5.80-5.9- (m, 1H, Ar), 5.95-6.05 (m, 2H, Ar), 6.90-7.05 (m, 1H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.9 (CH_3C), 41.0 (CH_2), 46.1 (CH), 51.8 (CH_3O), 98.9, 103.9, 130.4, 148.1 (C_{Ar}), 172.2 ($\text{C}=\text{O}$). IR (cm^{-1}): ν 1724 ($\text{C}=\text{O}$), 3386 (NH). HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ 308.1736; found 308.1726.



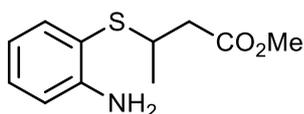
Dimethyl 3,3'-((1,4-phenylenebis(azanediyl))dibutanoate 13c: oil, 221 mg, 72% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.23 (d, $J = 6.0$ Hz, 6H, CH_3C), 2.38 (dd, $J = 15.0, 6.0$ Hz, 2H, CH_2), 2.61 (dd, $J = 15.0, 6.0$ Hz, 2H, CH_2), 3.30 (br.s, 2H, NH), 3.66 (s, 6H, CH_3O), 3.70-3.80 (m, 2H, CH), 6.56 (s, 4H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.9 (CH_3C), 40.9 (CH_2), 47.6 (CH), 51.7 (CH_3O), 116.3, 139.5 (C_{Ar}), 172.6 ($\text{C}=\text{O}$). IR (cm^{-1}): ν 1714 ($\text{C}=\text{O}$), 3361 (NH). HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ 308.1736; found 308.1727.



Methyl 3-((2-aminophenyl)(methyl)amino)butanoate 15a: dark brown oil, 130 mg, 59% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.10 (d, $J = 6.6$ Hz, 3H, CH_3C), 2.38 (dd, $J = 6.8, 15.0$ Hz, 1H, CH_2), 2.62 (s, 3H, NCH_3), 2.66 (dd, $J = 6.8, 14.9$ Hz, 1H, CH_2), 3.66 (s, 3H, CH_3O), 4.06 (br.s, 2H, NH_2), 3.67-3.75 (m, 1H, CH), 6.65-6.75 (m, 2H, Ar), 6.88-7.00 (m, 2H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 15.4, 33.7, 39.1, 51.7, 52.5, 115.4, 117.9, 122.9, 124.7, 138.0, 142.6, 173.1. IR (cm^{-1}): ν 1733 ($\text{C}=\text{O}$), 3353, 3449 (NH_2)



Methyl 3-((2-(methylamino)phenyl)amino)butanoate 15b: dark brown oil, 100 mg, 45% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.27 (d, $J = 6.4$ Hz, 3H, CH_3C), 2.46 (dd, $J = 6.3, 15.2$ Hz, 1H, CH_2), 2.65 (dd, $J = 6.3, 15.2$ Hz, 1H, CH_2), 2.86 (s, 3H, NMe), 3.50 (br.s, 2H, 2NH), 3.70 (s, 3H, CH_3O), 3.81-3.95 (m, 1H, CH), 6.65-6.95 (m, 4H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.8, 31.0, 41.2, 46.2, 51.7, 110.9, 114.8, 118.3, 120.6, 134.7, 140.1, 172.6. IR (cm^{-1}): ν 1732 (C=O), 3340 (NH).

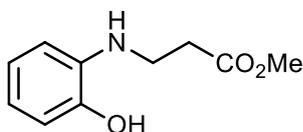


Methyl 3-((2-aminophenyl)thio)butanoate 17 [107]: oil, 202 mg, 90% yield. ^1H NMR (CDCl_3 , 300 MHz): δ 1.29 (d, $J = 9.0$ Hz, 3H, $\underline{\text{CH}_3\text{CH}}$), 2.46 (dd, $J = 15.0, 6.0$ Hz, 1H, CH_2), 2.60 (dd, $J = 15.0, 6.0$ Hz, 1H, CH_2), 3.38-3.57 (m, 1H, CH), 3.65 (s, 3H, CH_3O), 4.48 (br.s, 2H, NH_2), 6.60-6.67 (m, 2H, Ar), 7.10-7.23 (m, 1H, Ar), 7.30-7.45 (m, 1H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.1 ($\underline{\text{CH}_3\text{CH}}$), 39.1 (CH_2), 41.5 (CH), 51.7 (CH_3O), 114.9, 115.4, 118.1, 130.5, 137.7, 149.4 (Ar), 172.0 (C=O). IR (cm^{-1}): 1728 (C=O), 3361, 3462 (NH). HRMS (ESI, m/z) calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$ 225.0824; found 225.0820.

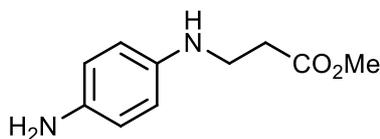
3.5 General procedure for the reaction of methyl acrylate and acrylonitrile with substituted anilines.

The mixture of functionally substituted aniline (1 mmol) and Michael acceptor (1 mmol) in corresponding solvent (1.0 mL) was heated in a sealed tube at 100°C for 2-4

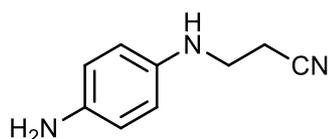
h. The crude product was purified by column chromatography (Silica gel, eluent Methanol/Chloroform, from 5:95 to 10:90).



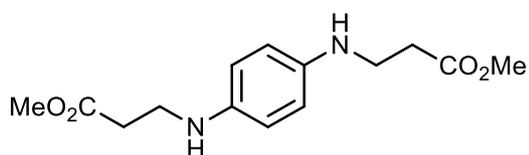
Methyl 3-((2-hydroxyphenyl)amino)propanoate 6: oil, 58 mg, 30% yield. ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 (t, $J = 6.4$ Hz, 2H, $\text{CH}_2\text{C}(\text{O})$), 3.44 (t, $J = 6.4$ Hz, 2H, CH_2N), 3.71 (s, 3H, CH_3), 5.10 (br.s, 1H, OH), 6.64-6.86 (m, 4H, Ar); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 34.1 ($\text{CH}_2\text{C}(\text{O})$), 40.4 (CH_2N), 52.0 (CH_3), 113.5, 114.8, 118.9, 121.4, 136.3, 144.9 (C_{Ar}), 173.4 ($\text{C}=\text{O}$); IR (cm^{-1}): ν 1732 ($\text{C}=\text{O}$), 3401 (OH); Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$: C 61.53; H 6.71; N 7.17. Found: C 61.38; H 6.84; N 7.07. MS (EI) m/z (relative intensity): m/z (%): 195 (22, M^+), 122 (100), 120 (24), 109 (15), 95 (21).



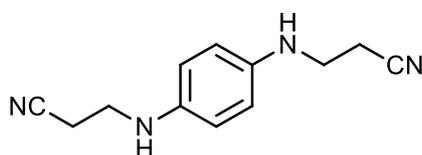
Methyl 3-((4-aminophenyl)amino)propanoate 7a: oil, 53 mg, 30% yield. ^1H NMR (CDCl_3 , 400 MHz): δ 2.58 (t, $J = 6.4$ Hz, 2H, $\text{CH}_2\text{C}(\text{O})$), 3.32-3.55 (m, 4H, CH_2N , NH_2), 3.68 (s, 3H, CH_3), 6.50-6.61 (m, 4H, Ar); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 33.9 ($\text{CH}_2\text{C}(\text{O})$), 40.8 (CH_2N), 51.7 (CH_3), 115.1, 116.9, 138.3, 140.6 (C_{Ar}), 173.0 ($\text{C}=\text{O}$); IR (cm^{-1}): ν 1732 ($\text{C}=\text{O}$), 3230, 3352, 3403 (NH); Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$: C 61.84; H 7.27; N 14.42. Found: C 62.02; H 7.27; N 14.30. MS (EI) m/z (relative intensity): m/z (%): 194 (49, M^+), 122 (13), 121 (100), 119 (17), 93 (21).



3-((4-Aminophenyl)amino)propanenitrile 8a: oil, 86 mg, 40% yield. ^1H NMR (CDCl_3 , 400 MHz): δ 2.52 (t, $J = 6.1$ Hz, 2H, CH_2CN), 3.30-3.60 (m 3H, CH_2N), 6.40-6.50 (m, 2H, Ar), 6.55-6.65 (m, 2H, Ar); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 18.1 (CH_2CN), 41.1 (CH_2N), 115.3, 116.8, 138.9, 139.0 (C_{Ar}), 118.6 (CN); IR (cm^{-1}): ν 2246 (CN), 3349 (NH); Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3$: C 67.06; H 6.88; N 26.07. Found: C 67.08; H 6.86; N 26.08. MS (EI) m/z (relative intensity): m/z (%): 161 (33, M^+), 121 (100), 94 (15), 93 (21), 60 (19).



Dimethyl 3,3'-((1,4-phenylenebis(azanediy))dipropoate 7b: oil, 168 mg, 60% yield. ^1H NMR (CDCl_3 , 400 MHz): δ 2.59 (t, $J = 6.4$ Hz, 4H, $\text{CH}_2\text{C}(\text{O})$), 3.38 (t, $J = 6.4$ Hz, 4H, CH_2N), 3.60-3.75 (m, 8H, CH_3 , NH), 6.56 (s, 4H, Ar); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 33.9 ($\text{CH}_2\text{C}(\text{O})$), 40.9 (CH_2N), 51.8 (CH_3), 115.4, 140.3 (C_{Ar}), 173.2 ($\text{C}=\text{O}$); IR (cm^{-1}): ν 1721 ($\text{C}=\text{O}$), 3385 (NH); Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_4$: C 59.99; H 7.19; N 9.99. Found: C 60.31; H 7.14; N 10.08. MS (EI) m/z (relative intensity): m/z (%): 280 (33, M^+), 207 (100), 133 (46), 119 (23), 66 (28).

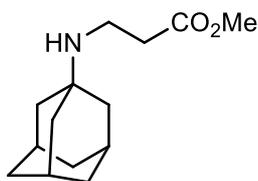


3,3'-((1,4-Phenylenebis(azanediy))dipropanenitrile 8b: oil, 86 mg, 40% yield. ^1H NMR (CDCl_3 , 400 MHz): δ 2.59 (t, $J = 6.3$ Hz, 4H, CH_2CN), 3.44 (t, $J = 6.3$ Hz, 4H, CH_2N), 3.60 (br.s, 2H, NH), 6.56 (s, 4H, Ar); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 18.4 (CH_2CN), 41.2 (CH_2N), 115.6, 139.4 (C_{Ar}), 118.5 (CN); IR (cm^{-1}): ν 2254 (CN), 3355

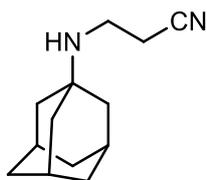
(NH); Anal. Calcd for C₁₂H₁₄N₄: C 67.27; H 6.59; N 26.15. Found: C 67.11; H 6.60; N 26.26.

3.6. General procedure for the reaction of adamantylamine with Michael acceptors

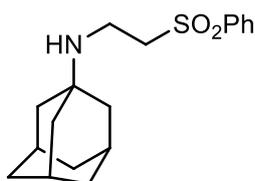
The mixture of 1-aminoadamantane **18** (151 mg, 1 mmol) and Michael acceptor (**2a,c,e,h-j**) (2 mmol) in solvent (2 mL) was stirred at room temperature for 17 h. The crude product was purified by column chromatography (Silica gel (**19a,b**) or Aluminium oxide (**19c**), eluent Pentane/Ether, from 90:10 to 50:50 (**19c**) or Methanol/Chloroform from 5:95 to 10:90 (**19a,b**)). The following compounds were prepared according to this procedure.



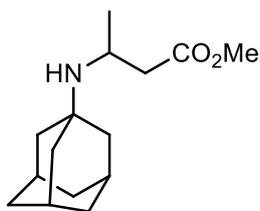
Methyl 3-(adamantan-1-ylamino)propionate 19a. Yellow oil (187 mg, 79%) ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (br.s, 1H, NH), 1.48-1.60 (m, 12H, Ad), 1.98-2.05 (m, 3H, Ad), 2.42 (t, *J* = 6.0 Hz, 2H, CH₂CO), 2.80 (t, *J* = 6.0 Hz, 2H, CH₂N), 3.61 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 29.6, 36.8, 42.7, 50.4 (Ad), 35.7 (CH₂CO), 36.0 (CH₂N), 51.5 (CH₃), 173.4 (C=O). IR (cm⁻¹): ν 1738 (C=O), 3317 (NH). HRMS (ESI, m/z) calcd for C₁₄H₂₃NO₂ 237.1729; found 237.1728.



3-(Adamantan-1-ylamino)propionitrile 19b. White solid (168 mg, 82%). m.p. = 48 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 1.00 (br.s, 1H, NH), 1.50-1.70 (m, 12H, Ad), 2.01 (br.s, 3H, Ad), 2.40 (t, $J = 6.8$ Hz, 2H, CH_2CN), 2.83 (t, $J = 6.8$ Hz, 2H, CH_2N); ^{13}C NMR (CDCl_3 , 100 MHz): δ 20.3 ($\underline{\text{C}}\text{H}_2\text{CN}$), 29.5, 36.6, 42.8, 50.7 (Ad), 36.8 (CH_2N), 119.0 (CN). IR (cm^{-1}): ν 2247 (CN), 3310 (NH). MS (EI) m/z (relative intensity): m/z (%): 204 (17, M^+), 164 (50), 147 (69), 135 (62), 106 (100), 79 (21). Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2$: C 76.42; H 9.87; N 13.71. Found: C 76.46; H 9.87; N 13.81.



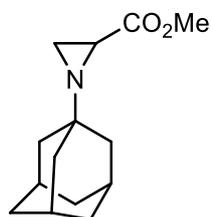
Adamantan-1-yl-(2-benzenesulfonylethyl)amine 19c. Colorless oil (294 mg, 92%). ^1H NMR (CDCl_3 , 400 MHz): δ 1.36 (br.s, 1H, NH), 1.50-1.68 (m, 12H, Ad), 1.98-2.05 (m, 3H, Ad), 2.87-3.00 (m, 2H, CH_2N), 3.12-3.37 (m, 2H, CH_2SO_2), 7.42-7.50 (m, 2H, Ar), 7.60-7.68 (m, 1H, Ar), 7.85-7.95 (m, 2H, Ar); ^{13}C NMR (CDCl_3 , 100 MHz): δ 29.6, 36.7, 42.6, 50.8 (Ad), 34.6 (CH_2N), 57.6 (CH_2SO_2), 128.1, 129.4, 133.8, 139.6 (Ph). IR (cm^{-1}): ν 1143, 1307 (SO_2), 3317 (NH). MS (EI) m/z (relative intensity): m/z (%): 319 (6, M^+), 263 (24), 262 (100), 177 (67), 135 (57), 120 (82), 93 (46), 77 (74). Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{S}$: C 67.68; H 7.89; N 4.38; S 10.04. Found: C 67.44; H 7.90; N 4.31, S 9.78.



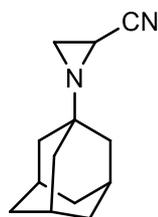
Methyl 3-(adamantan-1-ylamino)butanoate 19d: The mixture of aminoadamantane (151 mg, 1 mmol), and methyl crotonate (200 mg, 2 mmol) in methanol (1.0 mL) was placed in a Teflon reaction vessel and pressurized to 10 kbar at room temperature for 17 h. After that, the pressure was released and the mixture was concentrated *in vacuo*. The crude product **2d** was purified by column chromatography (Silica gel, eluent Ether). Colorless oil (70 mg, 28%). ¹H NMR (CDCl₃, 300 MHz): δ 0.97 (br.s, 1H, NH), 1.08 (d, *J* = 6.4 Hz, 3H, CH₃C), 1.50-1.63 (m, 12H, Ad), 1.98-2.03 (m, 3H, Ad), 2.26 (dd, *J* = 15.1, 6.1 Hz, 1H, CH₂), 2.36 (dd, *J* = 15.1, 6.4 Hz, 1H, CH₂), 3.24-3.35 (m, 1H, CH), 3.63 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ 25.0 (CH₃), 29.8, 36.8, 43.2, 51.2 (Ad), 43.2 (CH₂), 45.3 (CH), 51.5 (CH₃O), 173.0 (C=O). IR (cm⁻¹): ν 1732 (C=O), 3319 (NH). HRMS (ESI, *m/z*) calcd for C₁₅H₂₆NO₂ 252.1964; found 252.1962.

3.7. General procedure for the synthesis of aziridines (**21a-d**) and aza-adduct **22**:

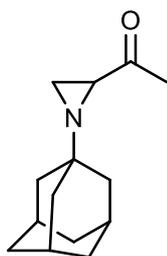
Under classical conditions. The mixture of 1-aminoadamantane **18** (151 mg, 1 mmol), Michael acceptor (**20a-e**) (2 mmol), and triethylamine (111 mg, 1.1 mmol) in the corresponding solvent (2 mL) was stirred at room temperature for 17 h. Then the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (Silica gel, chloroform/methanol 98/2 (for **22**); 9/1 (for **21a**), 95/5 (for **21c**), diethyl ether (for **21d**); or Al₂O₃, chloroform (for **21b**)). The following compounds were prepared according to this procedure. The spectral data of compound **21c** coincide with published earlier [108].



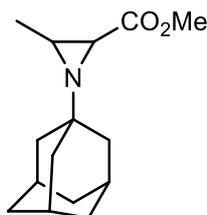
Methyl (1-adamantan-1-yl)aziridine-2-carboxylate 21a. Light yellow oil (158 mg, 67%). ^1H NMR (CDCl_3 , 400 MHz): δ 1.40-1.60 (m, 12H, Ad), 1.86 (dd, $J = 2.8, 1.3$ Hz, 1H, CH_2), 1.92 (dd, $J = 6.3, 1.3$ Hz, 1H, CH_2), 1.97-2.05 (m, 3H, Ad), 2.39 (dd, $J = 6.3, 2.8$ Hz, 1H, CH), 3.65 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 26.2 (CH_2), 28.9 (CH), 29.4, 36.6, 40.0, 53.5 (Ad), 52.2 (CH_3), 172.5 (C=O); ^{15}N NMR (CDCl_3 , 40 MHz): δ -332.4. IR (cm^{-1}): ν 1732 (C=O). MS (EI) m/z (relative intensity): m/z (%): 235 (7, M^+), 136 (12), 135 (100), 107 (15), 93 (23), 79 (28), 41 (21). Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2$: C 71.46; H 8.99; N 5.95. Found: C 71.49; H 8.94; N 5.97.



(1-Adamantan-1-yl)aziridine-2-carbonitrile 21b. White solid (119 mg, 58%), m.p. 48-49 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 1.40-1.69 (m, 12H, Ad), 1.95-2.05 (m, 2H, CH_2), 2.02-2.10 (m, 3H, Ad), 2.24-2.29 (m, 1H, CH); ^{13}C NMR (CDCl_3 , 100 MHz): δ 15.5 (CH_2), 26.4 (CH), 29.4, 36.5, 39.8, 53.8 (Ad), 119.9 (CN). IR (cm^{-1}): ν 2245 (CN). MS (EI) m/z (relative intensity): m/z (%): 319 (6, M^+), 263 (24), 262 (100), 177 (67), 135 (57), 120 (82), 93 (46), 77 (74). Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2$: C 77.18; H 8.97; N 13.85. Found: C 76.86; H 8.95; N 13.83.

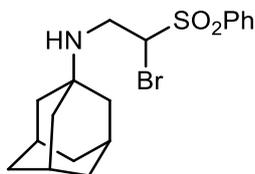


1-(1-Adamantan-1-yl-aziridin-2-yl)ethanone 21c. [108]. White solid (180 mg, 82%), m.p. 48-49 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 1.45-1.56 (m, 9H, Ad), 1.57-1.67 (m, 3H, Ad), 1.81 (dd, $J = 2.7, 1.3$ Hz, CH, CH_2), 1.96-2.00 (m, 1H, CH_2), 1.99 (s, 3H, CH_3), 2.00-2.07 (m, 3H, Ad), 2.41 (dd, $J = 6.7, 2.7$ Hz, 1H, CH); ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.8 (CH_3), 26.9 (CH_2), 29.5, 36.8, 40.3, 53.4 (Ad), 36.7 (CH), 209.4 (C=O); ^{15}N NMR (CDCl_3 , 40 MHz): δ -320.2. IR (cm^{-1}): ν 1700 (C=O). MS (EI) m/z (relative intensity): m/z (%): 219 (4, M^+), 178 (16), 135 (100), 93 (10), 79 (31), 67 (14), 41 (22). Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: C 76.67; H 9.65; N 6.39. Found: C 76.31; H 9.56; N 6.24.



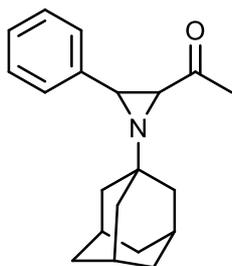
Methyl (1-adamantan-1-yl)-3-methylaziridine-2-carboxylate 21d. Colorless oil (167 mg, 67%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.18 (d, $J = 5.5$ Hz, 3H, CH_3CH), 1.37-1.70 (m, 13H, Ad), 1.97-2.10 (m, 3H, Ad), 2.18-2.26 (m, 1H, CHCH_3), 2.47 (d, $J = 6.6$ Hz, 1H, $\text{CHC}=\text{O}$), 3.68 (s, 3H, CH_3O); ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.5 (CH_3C), 29.4, 38.8, 40.1, 53.5 (Ad), 32.7 (CHCH_3), 34.3 ($\text{CHC}=\text{O}$), 52.0 (CH_3O)

171.5 (C=O). IR (cm⁻¹): ν 1748 (C=O). HRMS (ESI, m/z) calcd for C₁₅H₂₄NO₂ 250.1807; found 250.1806.

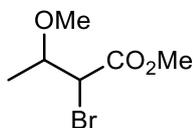


Adamantan-1-yl-(2-benzenesulfonyl-2-bromoethyl)amine 4: Yellow oil (324 mg, 81%). ¹H NMR (CDCl₃, 400 MHz): δ 1.30 (br. s, 1H, NH); 1.50-1.69 (m, 12H, Ad); 2.03 (br.s, 3H, Ad); 3.10 (dd, J = 13.3, 8.4 Hz, 1H, CH₂); 3.50 (dd, J = 13.3, 4.4 Hz, 1H, CH₂); 4.80 (dd, J = 8.4, 4.4 Hz, 1H, CH); 7.54-7.58 (m, 2H, C₆H₅); 7.65-7.70 (m, 1H, C₆H₅); 7.92-7.95 (m, 2H, C₆H₅); ¹³C NMR (CDCl₃, 100 MHz): δ 29.5, 36.5, 42.8, 50.9 (Ad); 42.4 (C-N); 66.7 (C-S); 129.1, 129.9, 134.6, 135.9 (C₆H₅). IR (cm⁻¹): ν 1150, 1310 (SO₂); 3325 (N-H). MS, (EI) m/z (relative intensity): m/z (%): 399 (1, M⁺ + 1); 297(1, M⁺ - 1); 342 (18); 340 (18); 164 (100); 135 (95). Calcd. for C₁₈H₂₄BrNO₂S: C 54.27; H 6.07; N 3.52; S 8.05. Found: C 54.44; H 6.21; N 3.55; S 7.94.

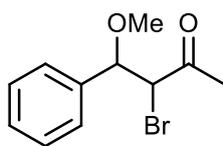
Under high pressure: The mixture of 1-aminoadamantane **18** (151 mg, 1 mmol), Michael acceptor (**20e-h**) (2 mmol), and triethylamine (111 mg, 1.1 mmol) in solvent (2 mL) was placed in a Teflon reaction vessel and pressurized to 10 kbar at room temperature for the corresponding time. After that, the pressure was released and the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (Silica gel, pentane/ether, 9/1 (for **23a**, **24**), 7:3 (**21e**, **23b**)). The following compounds were prepared according to this procedure.



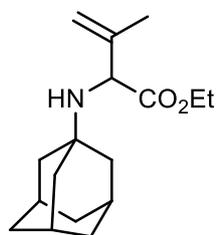
1-(1-Adamantan-1-yl)-3-phenylaziridin-2-yl)ethanone 21e: Colorless oil (115 mg, 39%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.50-1.70 (m, 12H, Ad), 1.56 (s, 3H, CH_3), 2.00-2.15 (m, 3H, Ad), 2.79 (d, $J = 6.4$ Hz, 1H, $\text{CHC}(\text{O})$), 3.38 (d, $J = 6.4$ Hz, 1H, CHPh), 7.15-7.27 (m, 3H, Ph), 7.34-7.38 (m, 2H, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 28.3 (CH_3), 29.5, 36.8, 40.4, 53.4 (Ad), 40.6 (CHPh), 44.6 ($\text{CHC}(\text{O})$), 127.4, 128.2, 128.3, 136.9 (Ph), 208.6 ($\text{C}=\text{O}$). IR (cm^{-1}): ν 1699 ($\text{C}=\text{O}$). HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{26}\text{NO}$ 296.2014; found 296.2010.



Methyl 2-bromo-3-methoxybutanoate 23a: Dark brown oil (68 mg, 32%). (53:47) Mixture of two diastereomers. *Major isomer:* ^1H NMR (CDCl_3 , 300 MHz): δ 1.26 (d, $J = 6.2$ Hz, 3H, CH_3), 3.34 (s, 3H, CH_3O), 3.60-3.75 (m, 1H, CHBr), 3.77 (s, 3H, $\text{CH}_3\text{OC}(\text{O})$), 4.32 (d, $J = 6.5$ Hz, 1H, CH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.4 (CH_3), 48.2 (CHBr), 53.0 (CH_3O), 57.4 ($\text{CH}_3\text{C}(\text{O})$), 77.3 (CHO), 168.8 ($\text{C}=\text{O}$). *Minor isomer:* ^1H NMR (CDCl_3 , 300 MHz): δ 1.33 (d, $J = 6.2$ Hz, 3H, CH_3), 3.10 (s, 3H, CH_3O), 3.60-3.75 (m, 1H, CHBr), 3.77 (s, 3H, $\text{CH}_3\text{OC}(\text{O})$), 4.18 (d, $J = 8.3$ Hz, 1H, CH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.7 (CH_3), 49.9 (CHBr), 53.1 (CH_3O), 57.5 ($\text{CH}_3\text{C}(\text{O})$), 77.5 (CHO), 169.5 ($\text{C}=\text{O}$). IR (cm^{-1}): ν 1743 ($\text{C}=\text{O}$). HRMS (ESI, m/z) calcd for $\text{C}_6\text{H}_{11}\text{BrO}_3$ 211.9892; found 211.9898.



3-Bromo-4-methoxy-4-phenylbutan-2-one 23b: Pale yellow oil (31 mg, 12%). (51:49) Mixture of two diastereomers. *Major isomer:* ^1H NMR (CDCl_3 , 300 MHz): δ 2.37 (s, 3H, $\text{CH}_3\text{C}(\text{O})$), 3.18 (s, 3H, CH_3O), 4.43 (d, $J = 7.6$ Hz, 1H, CH), 4.55 (d, $J = 7.6$ Hz, 1H, CHBr), 7.25-7.40 (m, 5H, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 28.6 ($\text{CH}_3\text{C}(\text{O})$), 57.3 (CH_3O), 57.7 (CHBr), 84.1 (CHO), 128.1, 128.9, 129.1, 137.3 (Ph), 201.1 (C=O). *Minor isomer:* ^1H NMR (CDCl_3 , 300 MHz): δ 2.15 (s, 3H, $\text{CH}_3\text{C}(\text{O})$), 3.26 (s, 3H, CH_3O), 4.23 (d, $J = 9.5$ Hz, 1H, CH), 4.52 (d, $J = 9.5$ Hz, 1H, CHBr), 7.25-7.40 (m, 5H, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 26.8 ($\text{CH}_3\text{C}(\text{O})$), 54.4 (CH_3O), 57.6 (CHBr), 82.7 (CHO), 127.9, 128.7, 129.1, 137.2 (Ph), 201.0 (C=O). IR (cm^{-1}): ν 1720 (C=O). HRMS (ESI, m/z) calcd for $\text{C}_{11}\text{H}_{14}\text{BrO}_2$ 258.0106; found 258.0106.



Ethyl (1-adamantan-1-ylamino)-3-methylbut-3-enoate 24: Colorless oil (105 mg, 38%). ^1H NMR (CDCl_3 , 300 MHz): δ 1.26 (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 1.47-1.70 (m, 12H, Ad), 1.77 (s, 3H, CH_3), 1.81 (s, 1H, NH), 2.00-2.05 (m, 3H, Ad), 3.90 (s, 1H, CH), 4.17 (q, $J = 7.2$ Hz, 2H, CH_2), 4.84-4.87 (m, 1H, $\text{CH}_2=$), 4.93-4.96 (m, 1H, $\text{CH}_2=$); ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.3 (CH_3CH_2), 20.0 (CH_3C), 29.8, 36.7, 43.1, 51.2 (Ad), 59.3 (CH), 61.1 (CH_2), 112.9 ($\text{CH}_2=$), 144.7 ($=\text{C}$), 175.2 (C=O). IR (cm^{-1}): ν 1736 (C=O), 3327 (NH). HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_2$ 278.2120; found 278.2114.

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