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Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov reaction): application to the synthesis of *N*-polyheterocycles and related alkaloids

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1. Introduction

The Diels–Alder (DA) reaction, with its rich synthetic diversity, is recognized as a powerful reaction in the synthetic strategies of natural and unnatural polycarbocycles and polyheterocycles.[1] From the memorable publication by Diels and Alder[2] to our days '*diene synthesis*' is used as a standard method employed frequently for the formation of six-membered ring systems with excellent regio-, diastereo-, and enantio-selective controls. Because the use of DA reactions covers compounds of academic, industrial or medicinal interest, research work in this area has been discussed in several reviews and monographs from time to time.[3–10] The DA reaction methodology contains two basic variants of reaction, which can be classified as carbo-DA reaction (CDA) and hetero-DA reaction (HDA), which could be also subdivided as like oxa-DA reaction (HDA of carbonyl compounds) and imino (aza)-DA reaction (HDA of imines) (Fig. 1).

This latter variant is becoming a mainstay of heterocycles and natural product synthesis.[11–14] To complete the proposed classification, it is well to bear in mind that the imines can react in these reactions as either dienophiles or azadienes. The [4+2] cycloaddition reaction of *N*-aryl imines (Schiff's bases) with nucleophilic olefins is one of the most convenient methods of quinoline preparation, which is usually catalyzed by Lewis acids. $BF_3 \cdot OEt_2$ has been mainly used for this purpose since the pioneering works of Povarov.[15–19] Acid-mediated cycloaddition between the C=C–N=C azadiene moieties of *N*-aryl imines and dienophiles also has become an established route to various tetrahydroquinolines and consequently, quinolines, the major class of heterocycles. Thus, this interaction between *N*-aryl imines and electron-rich dienophiles should be named the Povarov reaction.[20]

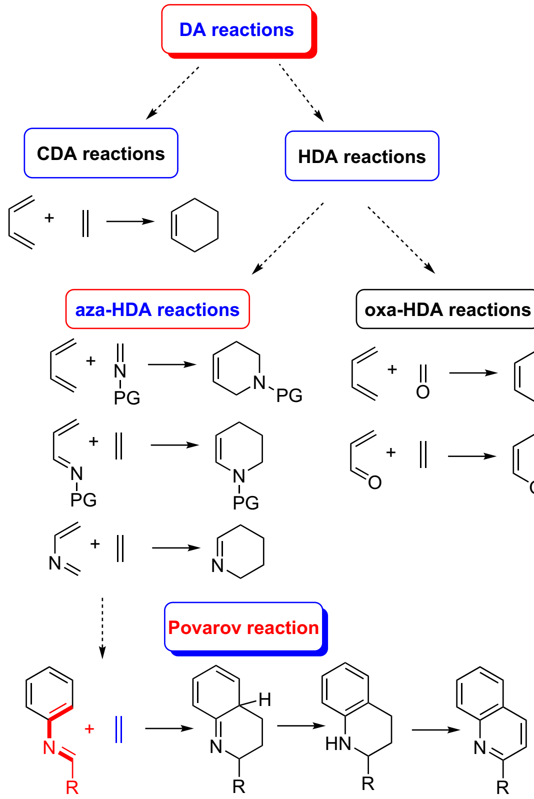


Figure 1.

The DA reaction can also take place intramolecularly when a molecule contains both the diene and dienophile moieties, which are connected by a chain at position C-1 of the diene (type 1 intramolecular DA reaction) or at position C-2 of the diene (type 2 intramolecular DA reaction).[21] As a result of these interactions, fused bicyclic adducts and bridged bicyclic compounds are obtained (Fig. 2). The type 2 intramolecular acyl imino DA reaction was utilized as an entry to a class of complex compounds that possess both a bridgehead alkene and bridgehead lactam unit.[21c]

Nowadays, these types of DA reactions are valuable tools in contemporary organic synthesis, generating heterocyclic rings where the size of the second ring depends on chain broadening. Indeed, multi-component inter- and intramolecular Povarov reactions have gained popularity in both diversity-oriented synthesis (DOS) and target-oriented synthesis (TOS). This review is devoted to the development of the Povarov reaction and focuses on new efficient approaches based on this process to construct simple substituted (tetrahydro)quinolines and diverse *N*-polyheterocycles, including some alkaloids, which contain pyrroloquinoline or cyclopentaquinoline ring systems. The review covers the literature up to September 2008, but does not mean to be strictly comprehensive, although its goal is to highlight the improvements in the synthesis of quinoline derivatives via the Povarov reaction. Also included are various applications, specially, the multi-component coupling strategy, which allows a quick access to these compounds, giving a special attention to environmentally friendly methodologies and to their synthetic potential in the structural diversification of new heterocyclic entities. However, to provide a good understanding of the quinoline derivatives preparation scope via the Povarov reaction, older reactions were included as well.

2. Construction of simple tetrahydroquinoline and/or quinoline ring systems via [4+2] cycloadditions between *N*-aryl aldimines and alicyclic dienophiles

Among the nitrogen heterocycles, quinolines and their derivatives represent an important class of organic molecules attracting the interest of both synthetic and medicinal chemists.

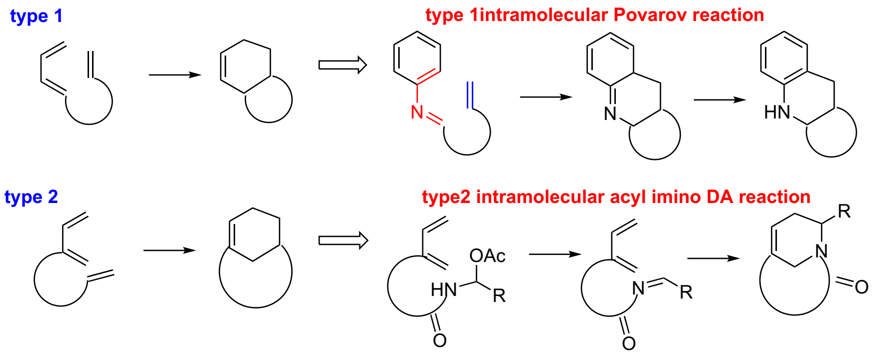


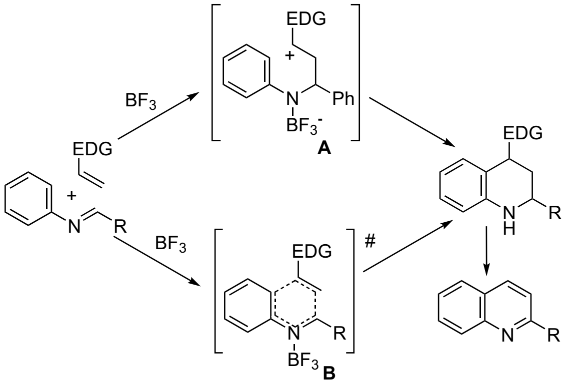
Figure 2.

Functionalized quinolines have found applications as pharmaceuticals and agrochemicals as well as useful synthetic blocks in the preparation of several alkaloids. Many syntheses of quinoline derivatives are known, but due to their importance, the development of new synthetic approaches remains an active research area.[22–24] In general, Schiff's bases are rather unreactive toward nucleophiles and acidic conditions. However, the most attractive strategy for these derivatives is the acid-promoted imino DA reaction between *N*-aryl aldimines (electron-poor azadienes) and electron-rich alkenes that has been a topic of continuing interest for 40 years. Among the electron-rich dienophiles, vinyl enol ethers, vinyl enamides, vinyl sulfide, cyclopentadiene, indene, alkynes, and enamines have been most used in this method. It seems that the emerging acid-catalyzed Povarov reaction and its multi-component version[25] can be useful tools for the generation of new quinoline derivatives with several degrees of structural diversity.[26]

The first works of Povarov[15,16] described reactions of ethyl vinyl ether **1a** or ethyl vinyl sulfide **1b** and *N*-aryl aldimine **2a** under acidic catalysis ($BF_3 \cdot OEt_2$) to obtain 2,4-substituted tetrahydroquinolines **3a**,**b**, which were converted into corresponding quinoline **4a**. Depending on the reaction conditions the tetrahydroquinolines or quinolines, formed by Lewis acid, become the main products of the Povarov reaction (Scheme 1). The intermediates, 4-ethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline **3a** and 4-ethylthio-2-phenyl-1,2,3,4-tetrahydroquinoline **3b**, were isolated and characterized (but the diastereoisomeric composition of these compounds was not studied). Povarov called them cycloadducts, classifying this reaction in term of Diels–Alder cycloaddition. Later, Povarov and co-workers discussed the scope of the reaction and some mechanistic aspects on this cycloaddition, indicating an important role of the Lewis acid catalyst, $BF_3 \cdot OEt_2$.[18,20]

Until now, the mechanism for this process has been debated: a stepwise mechanism via ionic intermediates (**A**) with the final step being an intramolecular electrophilic substitution of a carbenium ion was proposed as a more probable mechanism than a concerted one where a concerted asynchronous transition state (**B**) was suggested[13a,27] (Scheme 2).

From this works, alkenes **1a**,**b** and their analogues (Fig. 3) became the most popular dienophiles more to date in the cycloaddition of *N*-aryl aldimines to obtain 2,4-substituted tetrahydroquinolines.



Scheme 2.

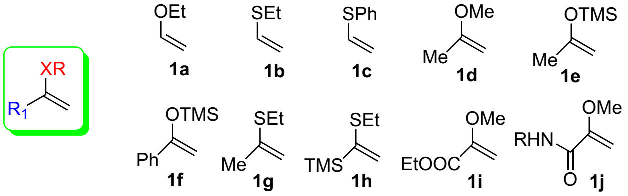
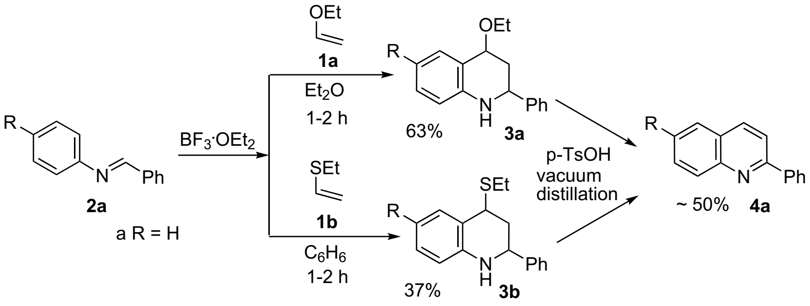


Figure 3.

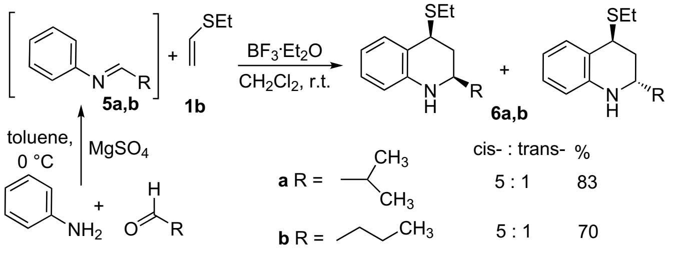
2.1. Vinyl enol ethers, vinyl sulfide, and silyl enol ethers as dienophiles

After Povarov's work, Joh and Hagihara reported the preparation of quinoline derivatives **3a**,**4** from the same reagents using dicobalt octacarbonyl as catalyst.[28] Kametani and his group undertook comprehensive investigations of this cycloaddition reaction between *N*-aryl aldimines and various vinyl ethers and applied the reaction to the synthesis of several natural products containing quinoline skeletons. Despite these reactions are afforded generally in low yield, the scientific interest of organic chemists was intensified. For example, it was found that the yield of the reaction between Schiff's base **2a** and ethyl vinyl sulfide **1b** was influenced by the amount of Lewis acid. Cycloadduct **3b** was afforded in favorable yield (90%) as a mixture of 1:1 diastereomers by the use of a catalytic amount (10 mol %) of $BF_3 \cdot OEt_2$[29] (Scheme 1). Not only aromatic Schiff's bases like *N*-benzylidenaniline **2a**, but also *N*-alkyl aldimines are also utilized as azadiene components. However, it is difficult to develop the addition reactions toward these aldimines, because they are easily hydrolyzed and polymerized under acidic conditions. Narasaka reported that Schiff's bases **5a**,**b** derived from various butanals can be employed and reacted with vinyl sulfide **1b** by the use of 1 mol equiv of $BF_3 \cdot OEt_2$. The synthesis of adducts **6a**,**b**, which were obtained in 70–83% yield, can be considered the first multi-component Povarov reaction[30] (Scheme 3).

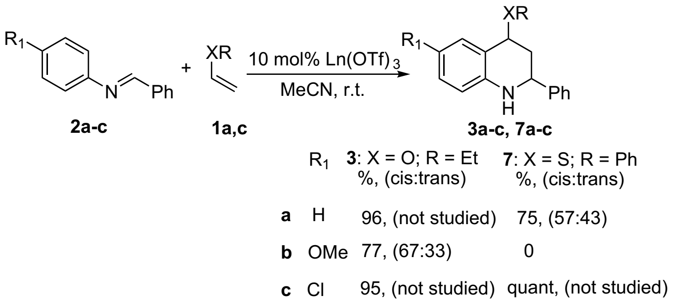
There has been a resurgence of real interest in this chemistry when Kobayashi and co-workers have shown that lanthanide triflates are excellent catalysts for imino DA reactions and a version of three-component condensations.[31,32] While stoichiometric amounts of Lewis acids are required in many cases, a small amount of the triflate effectively catalyzes the reactions between *N*-aryl aldimines **2a**–**c** and alkenes **1a**,**c** (Scheme 4).



Scheme 1.



Scheme 3.

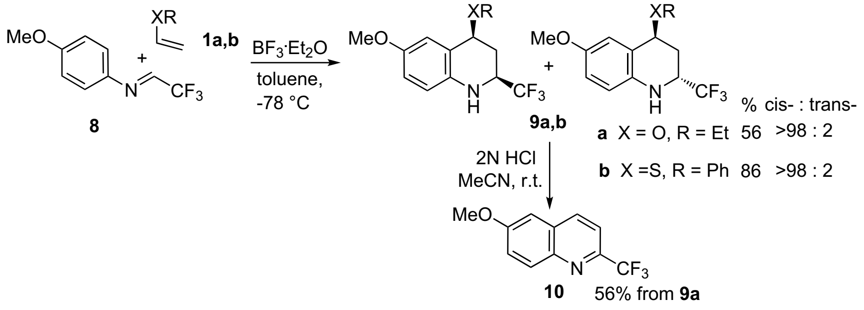


Scheme 4.

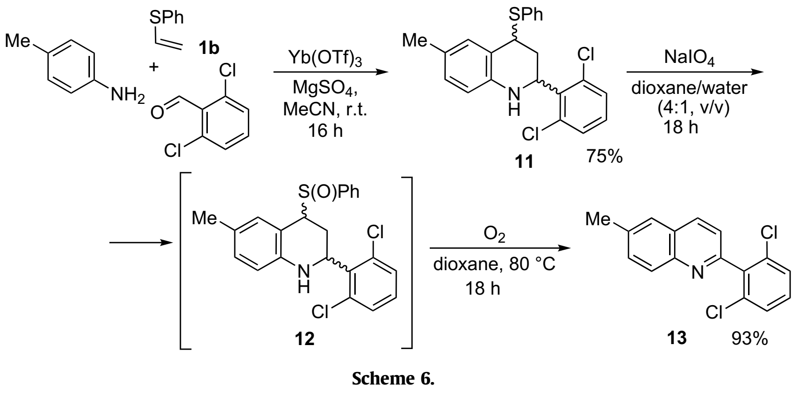
Nowadays several Lewis acids, Brønsted acids, and lanthanide triflates are known to catalyze these reactions. However, the first Lewis acid catalyst, BF$_3$·OEt$_2$ is still used successfully. To prepare substituted polyfunctionalized tetrahydroquinolines, different *N*-aryl imines and vinyl alkyl ethers (or vinyl ethyl sulfide) were used under conditions of Povarov (10 mol % BF$_3$·OEt$_2$). When the reactions between α-CF$_3$–*N*-arylaldimine **8** and vinyl ether **1a** or vinyl phenyl sulfide **1b** were performed in solvents such as CH$_2$Cl$_2$, Et$_2$O or THF, the yield of the cycloadducts was low. However, when toluene was used as solvent at −78 °C, the respective tetrahydroquinolines **9a**,**b** were obtained in good yield with good regio- and stereoselectivities.[32–35] The conversion of tetrahydroquinoline **9a** into fluorinated quinoline **10** was performed under acidic conditions (2 N HCl in MeCN) (Scheme 5).

The catalytic activity of samarium diiodide for the imino DA cycloaddition of *N*-aryl imine **2a** onto vinyl ether **1a** was also studied. This interaction gave mixtures of cycloadduct **3a** and of the corresponding quinoline **4** that could be separated by column chromatography, in both cases, products were obtained in low yield (20–25%)[36] (see, Scheme 1). It was found also that fluorinated alcohols (hexafluoroisopropanol—CF$_3$CH(CF$_3$)OH and trifluoroethanol—CF$_3$CH$_2$OH, which can act as Brønsted acid catalysts) promote Povarov reaction of *N*-benzylidenaniline **2a** and vinyl ether **1a** to afford the corresponding tetrahydroquinoline **3a** in good yields (71–92%) and in good stereoselective manner (cis/trans, 90:10) without Lewis acid under mild and neutral conditions.[37] These last observations can help to overcome the limitations in the synthesis of quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions. The general syntheses of these quinolines are less common[38] and often suffer from harsh reaction conditions, expensive reagents, or both. Moreover, the number of these commercially available reagents is exceedingly small, a fact that limits the preparation of quinolines substituted on the quinoline aryl moiety. It seems that the multi-component acid-catalyzed imino DA cycloaddition can be a useful tool for the generation of quinoline derivatives with several degrees of structural diversity. Indeed, Pasau and co-workers were able to synthesize 2-(2,6-dichlorophenyl)-6-methyl-4-phenylthio-1,2,3,4-tetrahydroquinoline **11** from *p*-methylaniline, 2,6-dichlorobenzaldehyde, and vinyl phenyl sulfide **1b**.[39] This intermediate was oxidized and subsequently pyrolyzed (via a sulfoxide **12**) to provide the corresponding quinoline **13** (Scheme 6).

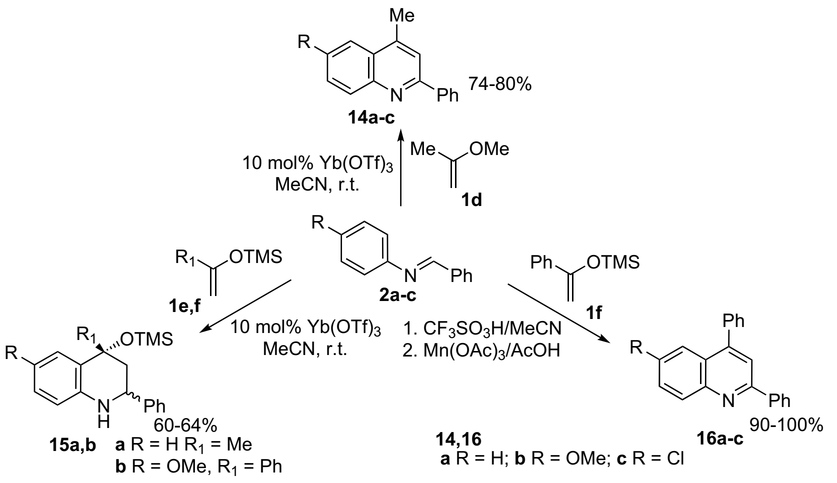
This new approach to 2-substituted quinolines was exemplified by liquid-phase production of a 25-membered library and was extended to solid-phase chemistry, starting from (L)-4-nitrophenylalanine on Wang resin for the generation of a 16-membered library.



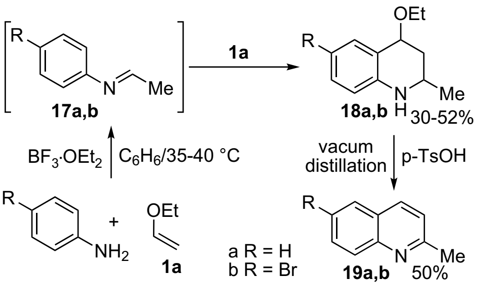
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

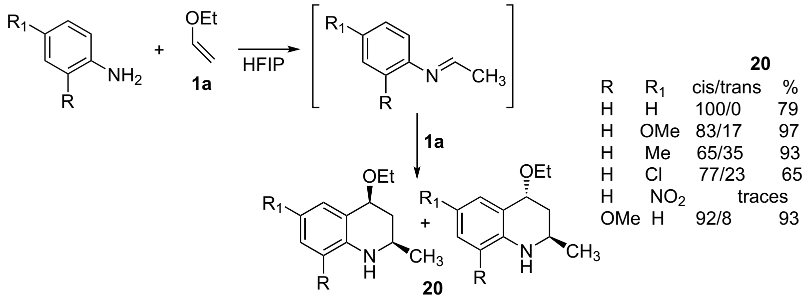
Kobayashi's protocol for the generation of substituted quinoline derivatives from *N*-aryl aldimines **2a**–**c** works well also with 2-methoxypropene **1d** and the trimethylsilyl ethers of acetone or acetophenone **1e**,**f**.[40] When these imines and dienophile **1d** were added successively to a solution of the ytterbium(III) triflate in MeCN at room temperature, 4-methyl-2-phenylquinolines **14a**–**c** were formed in good yields. Interestingly, when silyl ethers **1e**,**f** were used as a dienophiles in the cycloaddition of the same aldimines, 4-trimethylsilyloxy substituted 2-phenyltetrahydroquinilines **15a**,**b** were obtained in 60–64% yield as a mixture of two stereoisomers, in spite of the labile substituent (Scheme 7).

However, it was demonstrated that the activity of bismuth(III) chloride (2 mol % in MeCN, room temperature) was much higher that that of Yb(OTf)$_3$ for the preparation of tetrahydroquinoline **15a**.[41] This catalyst works too in the preparation of tetrahydroquinolines **3a**–**c**.[42] Moreover, when Brønsted acid catalysts were used in this synthesis, a strong effect of CF_3SO_3H (10 mol %) was found on cycloaddition reaction of silyl enol ether **1f** and corresponding aldimines **2a**–**c** to form tetrahydroquinolines like **15a**, those subsequent Mn(OAc)$_3$ mediated oxidation in situ furnished 2,4-diphenylquinoline derivatives **16a**–**c** in good to excellent yields.[43] Formation of 4,4-disubstituted tetrahydroquinolines like **15** via cycloaddition of *N*-aryl aldimines and other vinyl sulfides **1g**,**h** in the presence of $BF_3 \cdot OEt_2$ (10 mol %) was reported.[30]

Substituted quinoline 4-carboxylic esters or amides have been synthesized in a one-pot procedure from similar *N*-aryl aldimines and ethyl-2-methoxypropenoate **1i** or *N*-substituted 2-methoxypropenamide **1j**.[44] The choice of the catalyst (0.5 equiv $InCl_3$) and the microwave activation (150 W, 3 min) were crucial in obtaining satisfactory yields (40–57%) and in determining the reactivity of the formal imino DA reaction. It is worth to note that 'common' dienophiles **1a** and **1d** did not work in this procedure.

In 1964, Povarov and Mikhailov published a modification of the procedure in which *N*-alkyl aldimines **17a**,**b** were formed in situ from substituted anilines and ethyl vinyl ether **1a** and subsequently underwent an imino DA reaction with a second molecule of alkene **1a** to afford the corresponding 2-methyl-4-ethoxytetrahydroquinolines **18a**,**b**, which were converted into quinaldine derivatives **19a**,**b** (Scheme 8).[19] This reaction (that could be called by the modern term domino reaction) was performed in benzene and was promoted by $BF_3 \cdot OEt_2$.

This simple protocol was reinvestigated and improved using hexafluoroisopropanol (HFIP) (a very expensive reaction medium) as a solvent with the high hydrogen bond donor ability.[45] So, a range of tetrahydroquinolines **23** were prepared in good to excellent yields through a domino reaction performed in HFIP, starting from substituted anilines and enol ether **1a** and in the absence of Lewis acid catalysis (Scheme 9). It was demonstrated that the cis/trans ratio of tetrahydroquinolines **20** does not show a strong



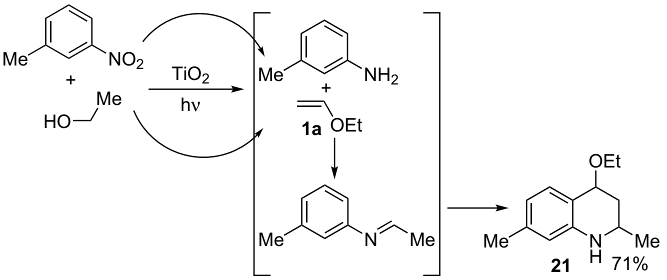
R	R1	cis/trans	%
H	H	100/0	79
H	OMe	83/17	97
H	Me	65/35	93
H	Cl	77/23	65
H	NO2	traces	
OMe	H	92/8	93

Scheme 9.

dependence on the electronic properties of the substituents in the aniline ring, however, the efficiency of the nucleophilic addition step in the cycloaddition reaction strongly depends on the electronic properties of the substituents of anilines.

Recently, CAN-catalyzed reaction between various anilines and vinyl ethers in MeCN was described as a convenient and efficient access to 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines, which could be dehydrogenated by Pd–C (toluene, reflux) to provide synthetically important 2-methylquinoline derivatives.[46]

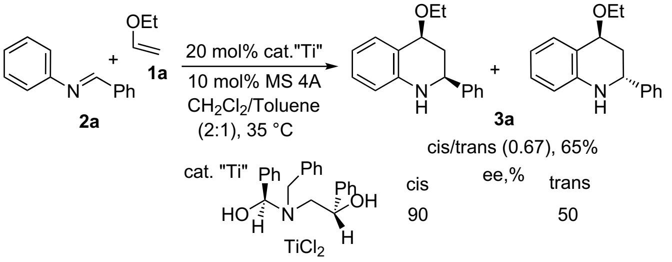
Similarly 4-ethoxytetrahydroquinoline **21** was formed in a one-pot reaction from a heterogeneous solution of 3-nitrotoluene, ethanol, and TiO_2 upon irradiation by UV light (λ=350 nm). This interesting conversion includes the formation of the corresponding aniline, ethyl vinyl ether **1a**, and *N*-ethylidene-*p*-methylaniline[47] (Scheme 10).



Scheme 10.

The enantioselective cycloaddition of electron-rich dienophiles to electron-poor azadienes with chiral Lewis acids as catalysts is still a relatively unexplored field,[10,15] probably because most chiral Lewis acids would be trapped by the basic nitrogen atoms to block the catalytic cycle. The first example of catalytic asymmetric imino DA reactions using a chiral lanthanide Lewis acid was described by Kobayashi and Ishitani.[48] It was discovered that cycloaddition of achiral *N*-aryl imines **22** with achiral enol ether **1a** in the presence of a catalytic amount of the chiral ytterbium Lewis acid, which was prepared from $Yb(OTf)_3$, (*R*)-(+)-BINOL, DBU, and an additive (2,6-di-*tert*-butylpyridine-DTBP) afforded the corresponding tetrahydroquinolines **23** in high yields with high diastereo- and enantioselectivities (Scheme 11). This was the first example of imino DA reactions using a catalytic amount of a chiral source. Ten years ago, Akiyama and co-workers utilized chiral Brønsted acid catalyst in this cycloaddition reaction with more success. They demonstrated that a phosphoric acid bearing 9-anthryl group on the 3,3′-position (*R*)-(+)-BINOL turned out to be highly effective in this process[49] (Scheme 11). Such chiral Brønsted acid catalysts will increase in popularity as green catalyst, which are free of metals, and assist the generation of valuable chiral cycloadducts.

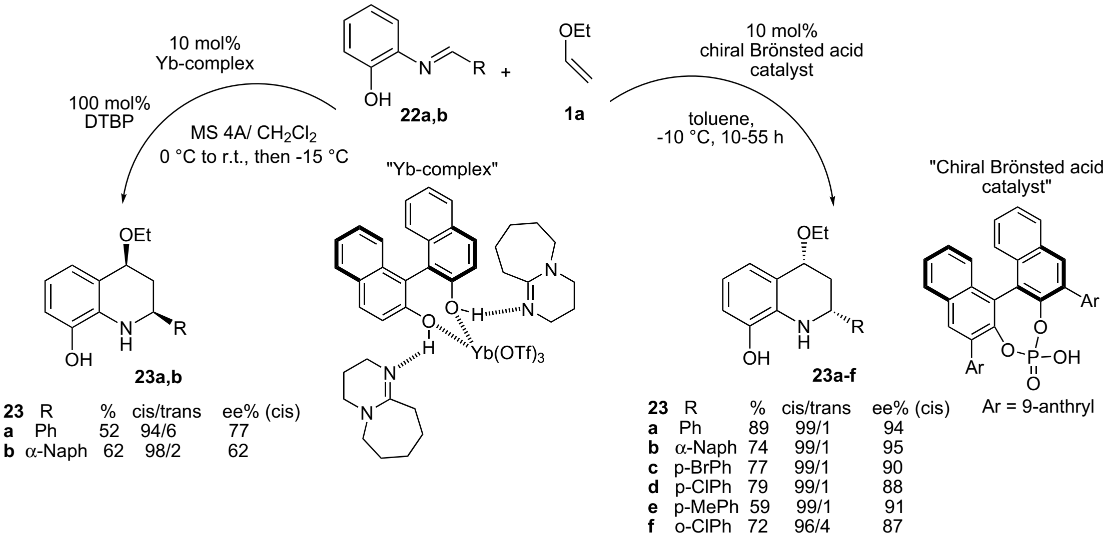
Other asymmetric cycloaddition process with achiral *N*-benzylidenaniline **2a** and ethyl vinyl ether **1a** using a chiral Lewis acid catalyst to give asymmetric tetrahydroquinoline **3a** was reported by Varghese and co-workers.[50] They demonstrated that new complex formed between titanium di(disopropoxide)chloride and (*R*,*R*)-3-aza-3-benzyl-1,5-dihydroxy-1,5-diphenylpentane (ABDDP–$TiCl_2$) promoted imino Diels–Alder reaction with moderate yields and high enantioselectivity (Scheme 12).



Scheme 12.

General syntheses of quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions are less common and often suffer from harsh reaction conditions, expensive reagents, or both. Moreover, the number of these commercially available reagents is exceedingly small and limits the preparation of substituted quinolines on the quinoline aryl moiety. From the examples mentioned above, it can be seen that one of the most attractive strategies for these derivatives is the acid-promoted imino DA reaction between *N*-aryl aldimines and vinyl enol ethers or vinyl sulfides.

Other quinoline derivatives can be constructed using electron-rich dienophiles and cationic 2-azabutadienes (iminium species, **25**) that are generated in situ by condensation of anilines with



23	R	%	cis/trans	ee% (cis)
a	Ph	52	94/6	77
b	α-Naph	62	98/2	62

23	R	%	cis/trans	ee% (cis)
a	Ph	89	99/1	94
b	α-Naph	74	99/1	95
c	p-BrPh	77	99/1	90
d	p-ClPh	79	99/1	88
e	p-MePh	59	99/1	91
f	o-ClPh	72	96/4	87

Scheme 11.

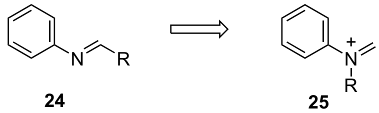
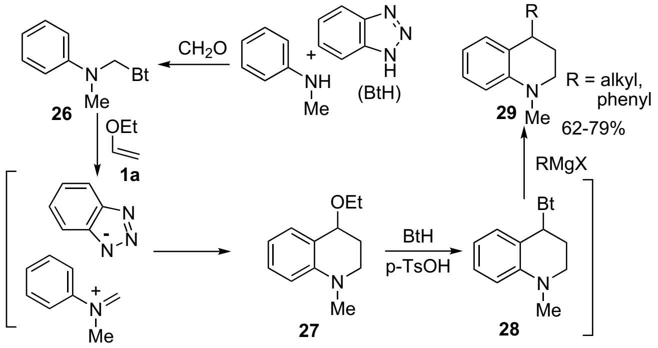


Figure 4.



Scheme 13.

carbonyl compounds under acidic condition or by heterolytic cleavage of α-heterosubstituted anilines and considerably more active and selective than neutral counterparts **24**[51–53] (Fig. 4). There has been a resurgence of interest in its chemistry when Katritzky demonstrated that benzotrizoles reacted with electron-rich alkenes to give formally the same products as those of the Povarov reaction.[54]

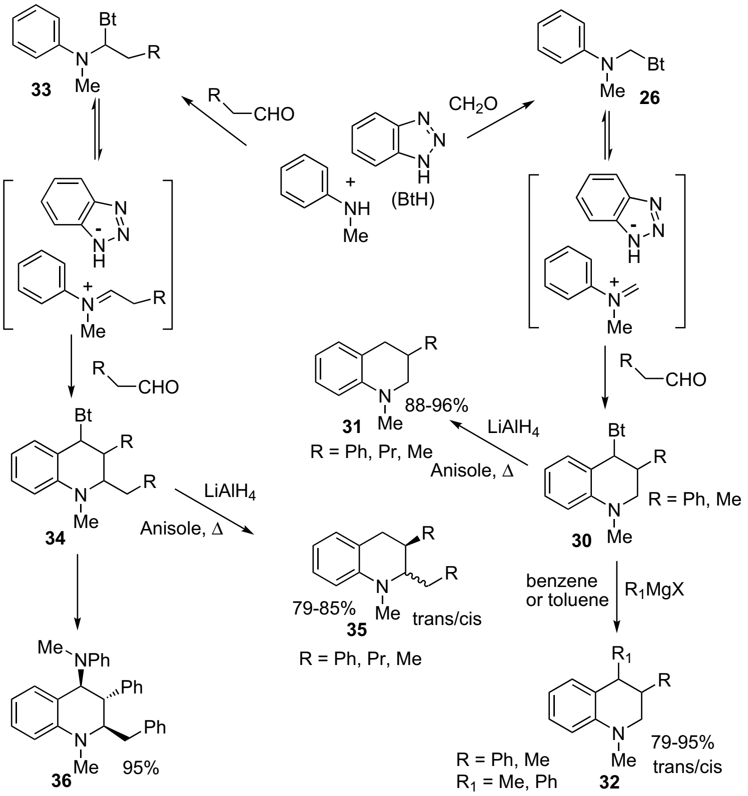
Therefore, benzotriazole-based intermediates like cationic 2-azabutadienes **25** have became as efficient reagents for synthesis of 1,4-disubstituted 1,2,3,4-tetrahydroquinolines. *N*-Methylaniline derivative **26** reacts with ethyl vinyl ether **1a** to form intermediate **27** that can be converted into another intermediate **28**, more stable. The latter reacts with Grignard reagents to yield 4-substituted *N*-methyl-1,2,3,4-tetrahydroquinolines[55,56] (Scheme 13).

Intermediate **27** was prepared in good yield (87%) from the one-pot condensation reaction of *N*-methylaniline with commercial formaldehyde solution and vinyl ether **1a** in the presence of $Dy(OTf)_3$ (1 mol %) at room temperature.[57]

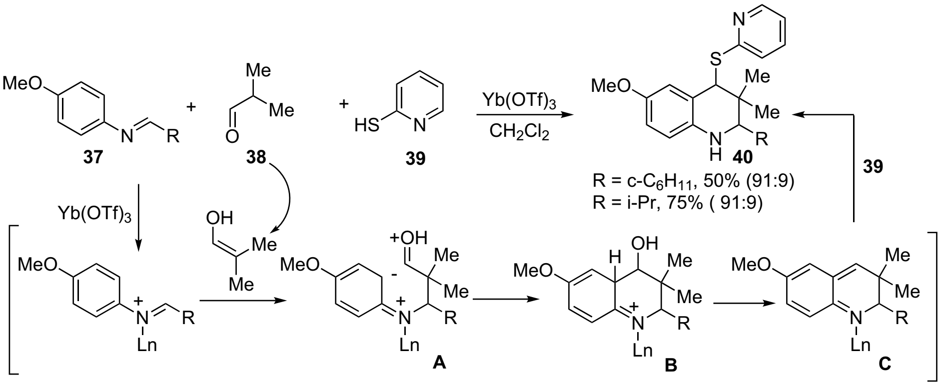
Employing of any enolizable aldehydes instead, alkene **1a** in Katrizky's scheme expands dramatically the scope of these reagents and provides considerable potential for the introduction of substituents into the C-2, C-3, and C-4 positions of the tetrahydroquinoline ring.[58,59] Thus, tetrahydroquinolines **30** and **34**, obtained from *N*-methylaniline derivatives **26** and **33** gave diverse quinoline products **31**,**32** and **35**,**36** (Scheme 14).

New three-component reactions involving an imine (which can also be generated in situ), an α-branched and enolizable aldehyde, and a nucleophile to give a variety of differently substituted tetrahydroquinolines were described by Annunziata and co-workers.[60] For example, condensations between aldimines **37**, 2-methylpropal **38**, and 2-pyridylthiol **39** in the presence of $Yb(OTf)_3$ lead to the formation of substituted tetrahydroquinolines **40** (Scheme 15). Authors proposed that the enol form of aldehyde **38** should react with the aldimines activated by catalyst to afford adduct **B**, possibly via intermediate **A**. Adduct **B** could lose a molecule of water giving the reactive intermediate **C**, which reacts with a present nucleophile **39** to give the formation of the tetrahydroquinoline ring **40**.

The PEG-supported aldimine **41** was also subjected to similar condensations of aldehyde **38** and different nucleophiles (MeOH or 2-pyridylthiol) that allow obtaining PEG-supported tetrahydroquinolines **42**,**43** those reductive desulfurization reaction gives



Scheme 14.



Scheme 15.

released tetrahydroquinoline **44** in good yields from the starting aldimine[61] (Scheme 16).

Recently, Shimizu and co-workers reported an efficient and simple one-pot method for the synthesis of 2-carboethoxyquinoline derivatives **47** by the three-component coupling reaction of an arylamine, ethyl glyoxylate **45**, and an aliphatic aldehyde **46** in the presence of $Yb(OTf)_3$ (Scheme 17).

The mechanism for the formation of quinaldates **47** from obtained aldimines in situ was believed to be via a cyclization of intermediate **A** to give intermediate **B** that suffers a dehydration reaction to afford dihydroquinaldate **C**, which is dehydrogenated to yield final quinoline product[62] (Scheme 17).

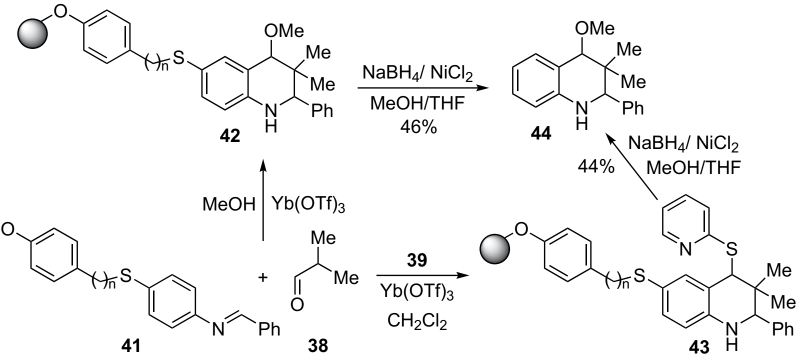
More recently, a variety of substituted quinolines **49** were synthesized from aldimines **48** and heptanal in the presence of catalytic amount of HCl under aerobic conditions, in which only water is a byproduct[63] (Scheme 18).

It is noteworthy that this simple and practical procedure permits quinoline preparation in a large scale. Related quinolines can be prepared via a molecular iodine- or $[IrCl_2H(cod)]_2$-catalyzed one-pot domino reaction of aldimines and enolizable aldehydes.[64]

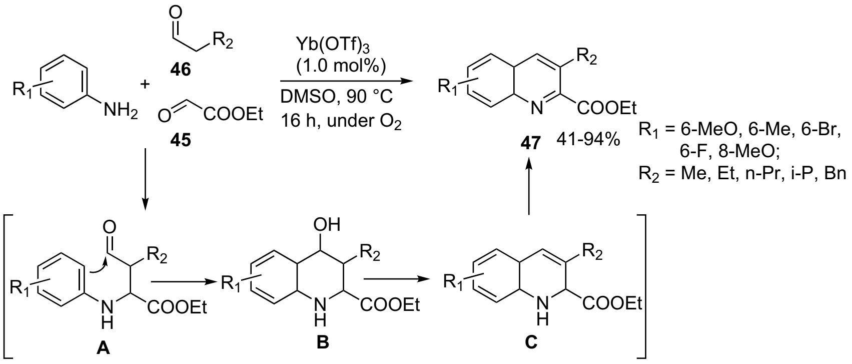
2.2. Vinyl enamides, enamines as dienophiles

The use of these alicyclic dienophiles (Fig. 5) helps to build straightforward amido(amino) substituted tetrahydroquinolines that are interesting models in bio-pharmacological studies.

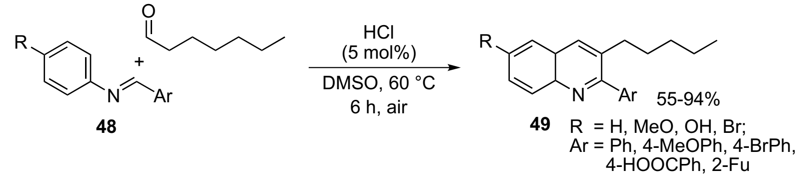
For example, *trans*-4-amido-2-carboxy-5,7-dichlorotetrahydroquinolines were synthesized and tested for in vitro antagonist activity as the glycine site on the *N*-methyl-D-aspartate (NMDA) receptor as selective glycine antagonists.[65,66] As an effective route to this system, cycloaddition between *N*-arylimino esters and various enamides was realized. Imine **51**, generated in situ, smoothly



Scheme 16.



Scheme 17.



Scheme 18.

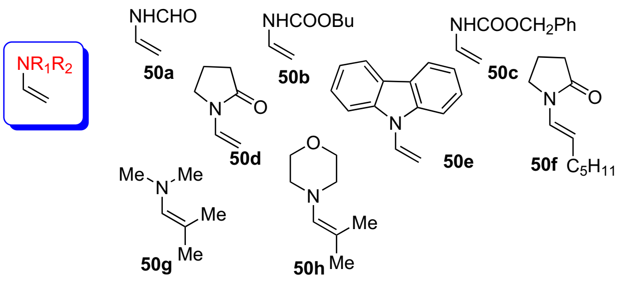
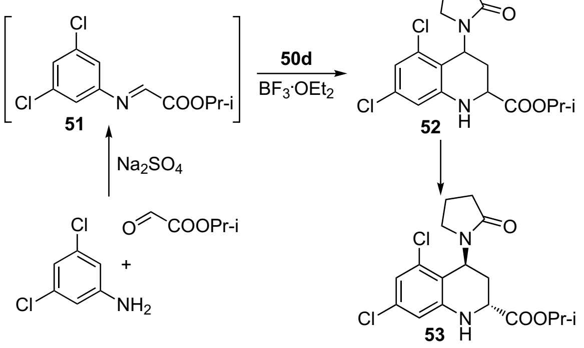


Figure 5.

reacted with *N*-vinyl-2-pyrrolidinone **50d** to give a 1:1 mixture of isomeric (cis/trans) tetrahydroquinolines **52**. Epimerization with methoxide resulted in enrichment (20:1) of the trans-isomer **53**, which could be isolated in its pure form, needed in bio-pharmacological studies (Scheme 19).



Scheme 19.

Using other esters based on 3-chloro-5-iodoaniline **54** and benzyloxy *N*-vinylcarbamate **50c** as the enamide gave substituted tetrahydroquinolines **55** as a mixture of stereo- and regioisomers (10:1 trans to cis, and 1:1 5-iodo to 7-iodo). Epimerization provide the trans regioisomeric mixture, which was separated by exhaustive crystallization and chromatography to yield 5-iodo **56** and 7-iodo **57** derivatives[66] (Scheme 20).

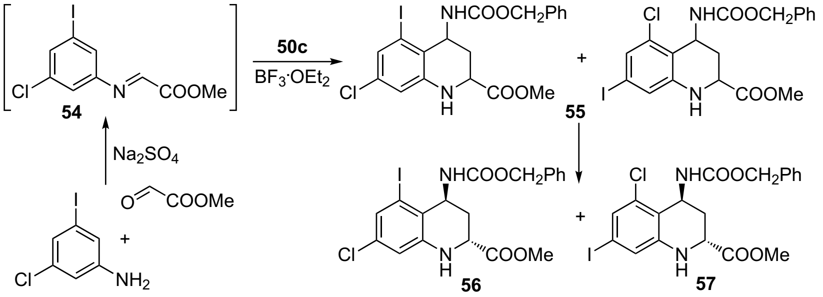
$BF_3\cdot OEt_2$-catalyzed [4+2] cycloaddition reaction of α-CF_3–*N*-arylaldimine **7** with nucleophilic olefins **50b,d** afforded CF_3-substituted tetrahydroquinoline derivatives with potential antiparasitic activity.[34]

Similar reaction of aldimine **58a** with alicyclic *E*-enamide **50f** proceeded smoothly at room temperature (MeCN, 20 mol % $InCl_3$) and gave a mixture of two diastereoisomers, in the ratio 2:1 and 67% combined yield[67] (Scheme 21). The diastereoisomers were separated by flash chromatography and proton NMR analysis confirmed the major product was *exo*-adduct **59**, with the stereochemistry of the enamide preserved, relative stereochemistry 2*S**3*R**4*S**, whereas the minor isomer was *endo*-adduct **60**, with the stereochemistry (2*S**3*S**4*S**) of the enamide reversed, which could be formed by a non-concerted process.

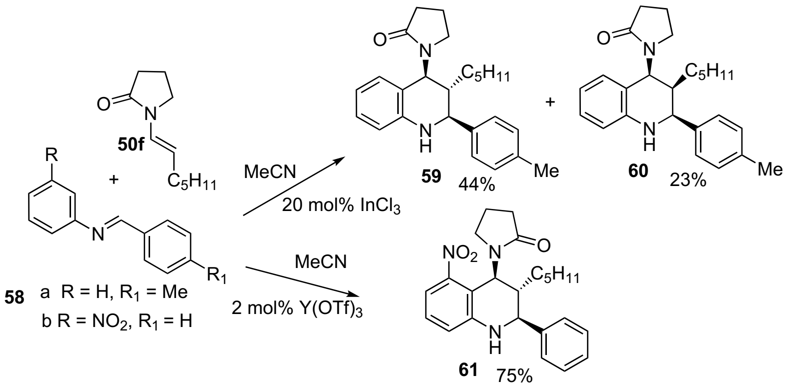
Typically, Povarov cycloaddition reactions of imines from aromatic amines and aromatic aldehydes are made with the *para*-substituted aniline component; the symmetry of this component guaranties the correct regiochemistry of substituted tetrahydroquinolines. To date no data is available on the regioselectivity of the cycloaddition reaction when 3-substituted aldimines are employed. Now, Stevenson and co-workers have demonstrated that reaction using enamide **50f** as an alkene component with 3-nitro substituted imine **58b** is completely regioselective and gave only 5-nitro substituted tetrahydroquinoline **61** (Scheme 21). Moreover, the reaction also became completely *exo*-selective with the stereochemistry of the *E*-enamide preserved in the tetrahydroquinoline product.[68]

In one of Kiselyov's work dedicated to the solid support synthesis of tetrahydroquinolines via a three-component condensation it was reported the successful preparation of 50-membered library between *N*-vinyl amide **50d**, anilines, and 4-carboxybenzaldehyde that was immobilized on acid sensitive methoxy benzaldehyde resin as the solid-supported component of imino DA cycloaddition. This procedure provided new tetrahydroquinolines in high yield (60–87%) and good purity (>80%).[69] However, these interesting studies have not been continued.

N-Vinyl amides **50a–e** and *N*-alkyl-*N*-phenyl-1*H*-benzotriazole-1-methanamines, the condensation products of aniline with formaldehyde (or higher aldehydes), type **26** were successfully employed in Katrizky's methodology to obtain 4-*N*-(dialkylamino)-1-alkyl-2-phenyl-1,2,3,4-tetrahydroquinolines in high yield.[70] Attention is drawn to the exclusive formation of only cis-diastereoisomer **64**,

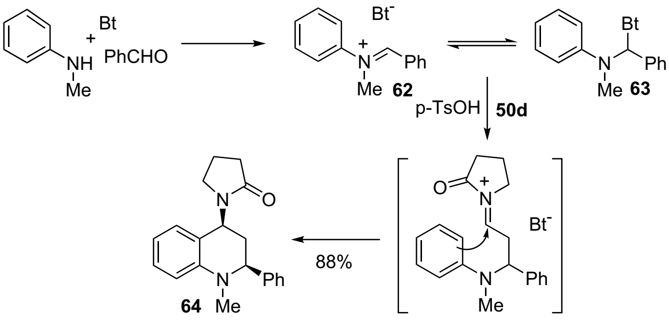


Scheme 20.



Scheme 21.

obtained from the reaction mixture of **62** and **63** (are easily available from the condensation between benzotriazole, *N*-methylaniline, and benzaldehyde) with *N*-vinyl amide **50d** (Scheme 22).

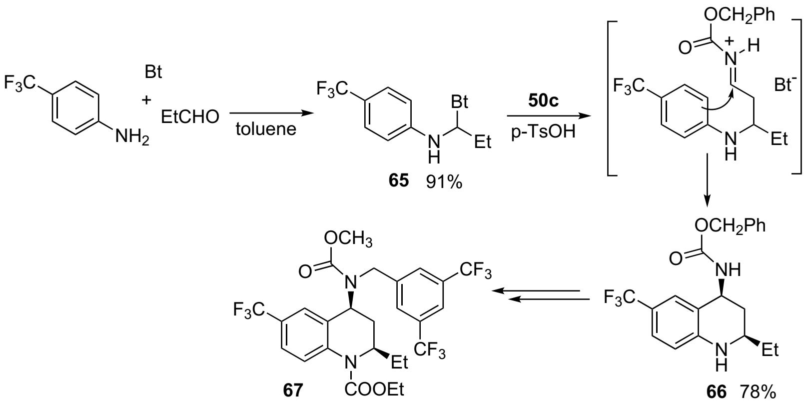


Scheme 22.

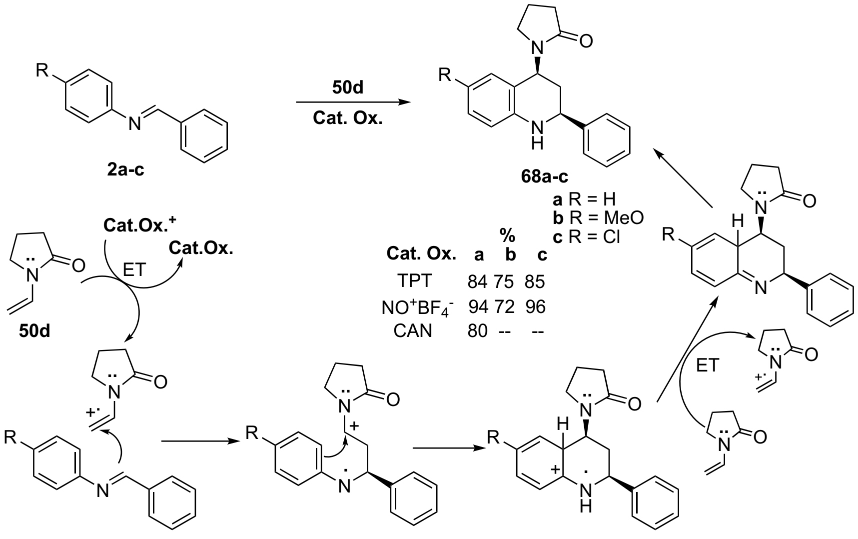
This exclusive formation of this diastereoisomer and the procedural simplicity became a decisive factor in selecting a practical synthesis of Torcetrapib (CP-529,414, **67**), an inhibitor of cholesteryl ester transfer protein that is currently being developed for the treatment of atherosclerosis and coronary heart disease.[71] Therefore, stirring 4-trifluoromethylaniline with *n*-propanal and benzotriazole in toluene followed by addition of *n*-heptane resulted in a Katrizky's adduct **65**, crystallizing from the reaction mixture in 91%. A key reaction of the synthesis of this drug candidate consists in the addition of *N*-vinyl amide **50c** to a toluene solution of **65** and in the presence of 1 mol % toluenesulfonic acid, which gave luckily only *cis*-2,4-disubstituted tetrahydroquinoline **66** in 78% yield[72] (Scheme 23).

The origin of the high cis stereoselectivity in the cyclization was rationalized by high-level quantum chemistry calculations. It was demonstrated that the selectivity is kinetically controlled, originated from both the ground-state conformational preference and the lower activation energy of the cis cyclization. An effective approach to the synthesis of a wide variety of C-2 nitro or aminophenyl substituted quinolines was reported using diverse intermediates 4-(2-oxopyrrolidinyl-1)-1,2,3,4-tetrahydroquinolines that were prepared by a three-component imino DA condensation between diverse anilines, 3-nitrobenzaldehyde, and enamide **50d** in the presence of 20 mol % $BiCl_3$. These intermediates were transformed into quinoline derivatives by their simple fusion with elemental sulfur. However, this aromatization process occurs with loss of the pyrrolidinone fragment.[73–75] Moreover, the straightforward synthesis of new carboxylic acids with hexahydrooxaisoindolo[2,1-*a*]quinoline core from the 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment via the intramolecular DA reaction was published.[76]

From the list of examples above, it can be noted that the acid-mediated imino DA reactions have a stepwise mechanism via ionic intermediates or via a concerted mechanism. Recent investigations on photochemically promoted imino DA cycloadditions could amplify the existent methods of new substituted tetrahydroquinolines' preparation. For example, irradiation at $\lambda \geq 345$ nm of CH_2Cl_2 solution of *N*-aryl aldimines **2a**–**c** with enamide **50d** and a catalytic amount of 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) at room temperature afforded corresponding *cis*-tetrahydroquinolines **68a**–**c** in high yields[77] (Scheme 24).



Scheme 23.



	%		
Cat. Ox.	a	b	c
TPT	84	75	85
NO$^+$BF$_4^-$	94	72	96
CAN	80	--	--

Scheme 24.

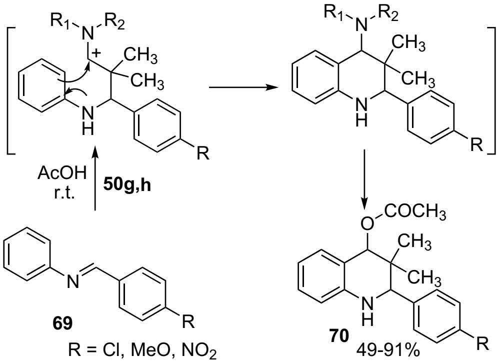
Since no reaction took place between *N*-aryl aldimines and **50d** in the absence of TPT under the same condition for prolonged irradiation, this cycloaddition might be rationalized as a TPT-catalyzed non-synchronous cation radical Diels–Alder reaction. Nitrosonium tetrafluoroborate initiated imino DA reactions between the same components to yield cis-adducts **68a**–**c**, an irradiation process was not even needed[78] (Scheme 24).

An alternative cation radical initiator is cerium ammonium nitrate (CAN), which has recently emerged as a powerful one-electron oxidant and an inexpensive, non-toxic catalyst for realizing a wide array of transformations of synthetic importance. Therefore, cycloaddition of *N*-arylaldimine **2a** with **50d** in the presence of 10 mol % CAN in CH$_3$CN at room temperature produced the corresponding cis-adduct **68a**.[79] The later adduct have been synthesized in high yield (93%) from a three-component condensation between aniline, benzaldehyde, and enamide **50d** in water using 5 mol % CAN as catalyst[80] (Scheme 24). Imino DA reaction of *N*-aryl aldimines with *N*-vinylcarbazole (enamide **50e**) occurred to give a mixture of cis- and trans-isomers. The steric block of the carbazole ring promotes the formation of the trans-isomer.[77,78]

DA cycloaddition reactions of the enamines as the dienophiles are well documented; however, chemical information about imino DA reaction of *N*-aryl aldimines with enamines represents only one example. In 1978, Japanese researchers reported that enamines **50g**,**h** reacted with *N*-aryl aldimines **69** in acetic acid to provide cycloadducts, tetrahydroquinoline derivatives **70**. Mechanistically, this acid-catalyzed reaction was described as the initial Michael-type addition of enamines to the promoted *N*-aryl aldimines followed by intramolecular electrophilic aromatic substitution at the *ortho* position of the activated *N*-aryl ring to give **70** after deprotonation[81] (Scheme 25).

2.3. Alkene and alkyne derivatives as dienophiles

The first utilization of simple olefins as dienophiles in the Povarov reaction to construct substituted tetrahydroquinolines was described by Kametani and co-workers in 1984.[82] To obtain 2,4-diaryl-3-methyl-tetrahydroquinolines **72**,**73** from Schiff base **2a**, *o*-methylisoeugenol **71a** and isosafrol **71b** were used in [4+2] cycloaddition reaction that was catalyzed by BF$_3$·OEt$_2$ (Scheme 26). Twenty years later, French team researchers made a similar reaction between isoeugenol **71c** and aldimine **74** in the presence of the complex Et$_3$N–AlCl$_3$ in MeCN to give tetrahydroquinoline **75**[83] (Scheme 26). The obtained substituted tetrahydroquinolines possess a cis-(2e,4e)-form.

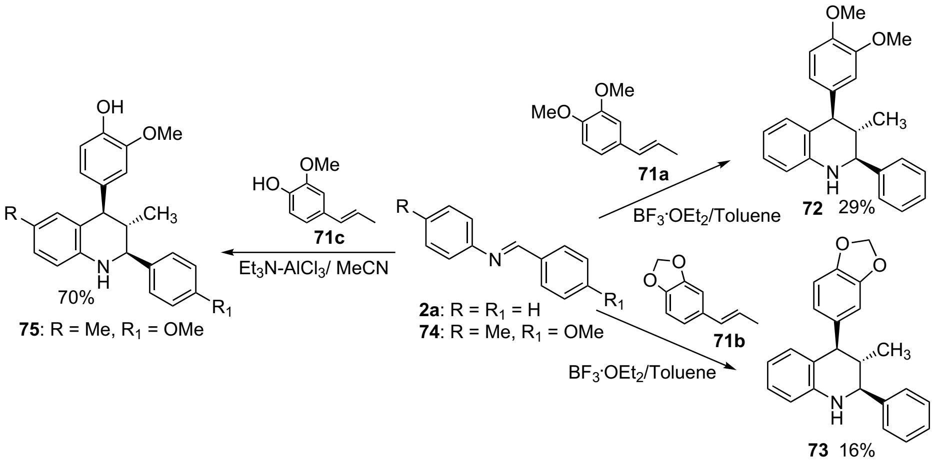


Scheme 25.

Recently, a study on three-component condensation between *trans*-anethole (and essential oil of star anise), anilines, and benzaldehyde, which resulted in a simple preparation of new 4-anisyl-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolines, and their direct preparation from essential anise oil (or from the seeds) under supercritical fluid conditions (scCO$_2$) was described.[84a] Similar diaryl substituted tetrahydroquinolines were easily prepared via a one-pot mode using BF$_3$·OEt$_2$ and PEG-400.[84b]

Other olefins that can be used in the imino DA reaction are styrene **76a**, α-styrene **76b**, and their derivatives **76c**–**e** (Fig. 6).

Utilization of α-styrene derivatives **76b**–**f** as active dienophiles in the Povarov reaction can afford new 2,4-diaryl 4-methyl-tetrahydroquinolines, while use of **76c**,**d** can provide analogous 2,4-diaryl 3-methyl-tetrahydroquinolines. It is curious that cycloaddition reactions catalyzed by Lewis or Brønsted acids were not reported. However, photoinduced electron transfer (PET)-catalyzed or non-PET-catalyzed imino Diels–Alder cycloaddition reactions between *N*-aldimines **77** and styrene or α-styrene derivatives were described as an efficient method of tetrahydroquinoline synthesis.[85,86] Thus, cycloaddition of **77** with α-methylstyrenes **76b**–**f** was efficiently catalyzed by tris(4-bromophenyl)aminium hexachloroantimonate (Ar$_3$N$^+$·SbCl$_6^-$) producing a mixture of *syn*- and *anti*-2,4-diaryl 4-methyl-tetrahydroquinoline products **78** in excellent yields[86] (Scheme 27).



Scheme 26.

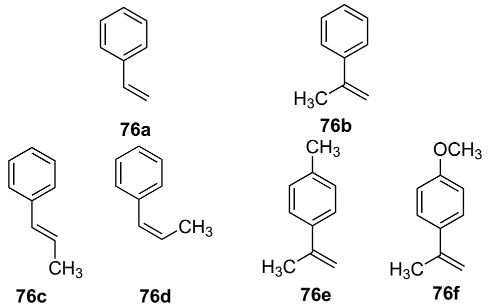
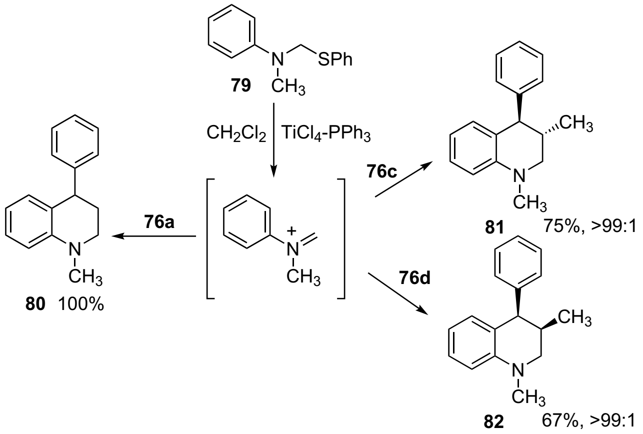


Figure 6.

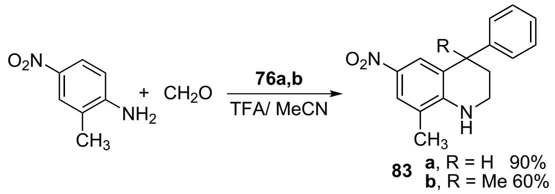
Column chromatographic purification (silica gel, hexane–acetone 40:1 to 20:1) of this mixture gave the pure products *syn*-**78** and *anti*-**78**. This cycloaddition was controlled by the oxidation potentials of the imine and the dienophiles.

Styrene derivatives shown in Figure 5 were also successfully employed in cationic cycloadditions[53,87] such as imino DA reaction and in Katrizky's methodology using *N*-(α-aminoalkyl)-benzotriazoles[88,89] to obtain new tetrahydroquinoline derivatives. For example, reaction of thiomethylamine **79** and styrene **76a** in the presence of a 2:1 mixture of $TiCl_4$ and triphenylphophine as Lewis acid gave 1-methyl-4-phenyl-tetrahydroquinoline **80** in quantitative yields. Accomplishing a similar reaction of amine **79** with (*E*)- and (*Z*)-methylstyrene **76c** and **76d**, authors demonstrated that the reaction of **76c** exclusively gave *trans*-3-methyl-4-phenyl-tetrahydroquinoline **81** while the reaction of **76d** produced the diastereoisomerically pure *cis*-tetrahydroquinoline **82**[53] (Scheme 28). Analogous results were obtained using **25** as starting material.[88,89]

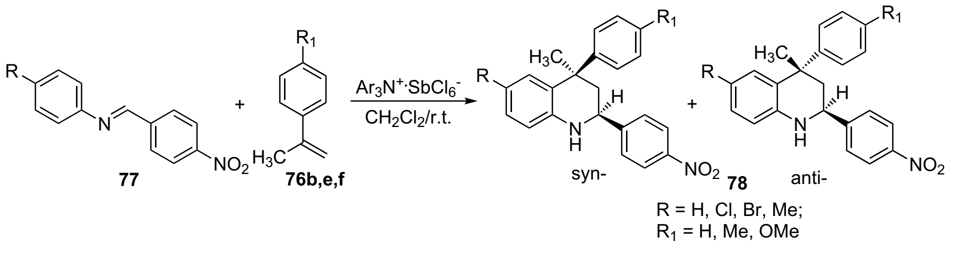


Scheme 28.

Using Grieco's method of a one-pot tetrahydroquinoline synthesis,[90] Mellor and co-workers accomplished the condensation between the 2-methyl-4-nitroaniline and formaldehyde (37% formalin solution) with **76a**,**b** in MeCN containing trifluoroacetic acid (TFA) to give the substituted tetrahydroquinolines **83**[87] (Scheme 29).

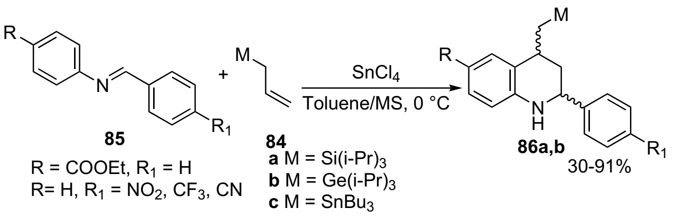


Scheme 29.



Scheme 27.

Akiyama and co-workers published a $SnCl_4$-catalyzed synthesis of tetrahydroquinolines **86** from *N*-aryl aldimines **85** via [4+2] cycloaddition where allylsilane **84a** acts as a new dienophile. Allylgermane **84b** did not work efficiently in this cycloaddition, and allylstannane **84c** did not afford cycloadducts at all[91a] (Scheme 30). Aldimines bearing electron withdrawing group gave cycloadducts **86** in good yields, being the cis-isomers, the major products.



Scheme 30.

Similar tetrahydroquinolines were obtained in good yields by using $GaCl_3$-catalyzed reaction of **84a** and *N*-aldimines in CH_2Cl_2.[91b]

Recently, $FeCl_3$-catalyzed imino DA reaction of similar imines with methylenecyclopropanes to provide a facile route for the synthesis of tetrahydroquinolines with a spirocyclopropyl ring was reported.[92]

Finally, terminal alkynes such as phenylacetylene **87a** or ethoxyacetylene **87b** and their derivatives (Fig. 7) were used little in quinolines preparation.

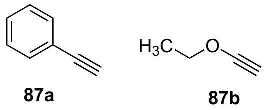
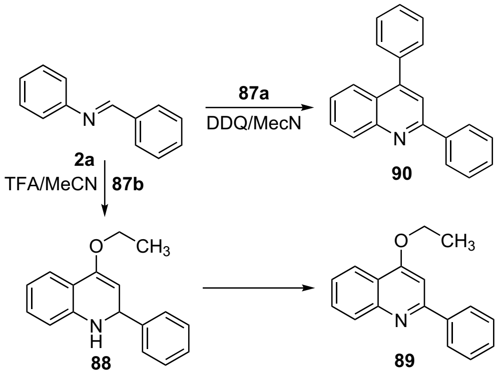


Figure 7.

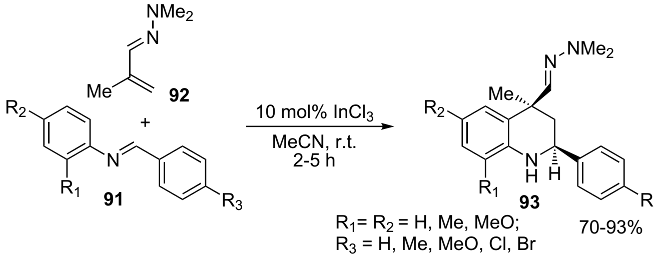
Baudelle and co-workers mentioned that expected cycloadduct **88** was obtained from reaction of **2a** with alkyne **87b**, but was slowly oxidized to the fully aromatic quinoline **89**.[93] The same Schiff base reacts with **87a** to give 2,4-diphenylquinoline in the presence of DDQ in poor 30% yield[94] (Scheme 31).



Scheme 31.

Synthesis of 2,4-disubstituted quinolines was achieved in one-pot reactions from anilines, benzaldehydes, and terminal alkynes in THF using CuCl (30 mol %) as catalyst.[95] This synthesis was also achieved on the surface of montrillonite clay impregnated with CuI (30 mol %) under microwave irradiation and solvent-free conditions.[96] New 2,3-disubstituted quinolines bearing an ester group at the 3-position were obtained via $Sc(OTf)_3$-catalyzed three-component coupling reaction of anilines, benzaldehydes, and ethyl propiolate at reflux in EtOH.[97]

To finish the discussion on [4+2] cycloadditions between *N*-aryl aldimines and alicyclic dienophiles, it is noteworthy that the synthetic potential of this reaction is not confined to using the simple above-listed alicyclic dienophiles. For example, recently the first imino DA reaction involving an α,β-unsaturated hydrozone as dienophile was reported by Menéndez and co-workers.[98] They described the reaction between *N*-aldimines **91** and methacrolein dimethylhydrazone **92** in the presence of 10 mol % $InCl_3$ that afforded in good to excellent yields biologically and synthetically relevant 1,2,3,4-tetrahydroquinolines **93** bearing a hydrozone function at C-4. It is noteworthy that the generation of tetrahydroquinoline ring occurs with complete control of the stereocenter at C-4 (Scheme 32).



Scheme 32.

This transformation can be considered a new type of vinylogous Povarov reaction, and offers the generation of C-4 functionalized 1,2,3,4-tetrahydroquinolines containing a quaternary stereocenter.

3. Intramolecular Povarov reaction

The type 1 intramolecular Povarov reaction (Fig. 2) and its multi-component version have gained popularity in both diversity-oriented synthesis and target-oriented synthesis. This intramolecular implementation of the imino Diels–Alder reaction has the added advantages including better control over the formation of stereoisomers and the creation of an additional ring.[99] To accomplish the type 1 intramolecular Povarov reaction, all one need to do is to have functionalized anilines and appropriated aldehyde–olefin tethers. These aldehydes can be classified in two groups: (i) ω-unsaturated aldehydes such as *R*-citronellal **94b** and *O*-(*N*,*S*)-alquenyl *ortho*-formylheteroarenes (for example, *O*-alkenylsalicylaldehyde **94f** or *o*-(*N*-alkenylamino)benzaldehyde **94h**) or (ii) *N*-alquenyl(alquinyl) *ortho*-heteroaldehydes **95** like an *N*-(4-methyl-3-pentenyl)pyrrolidine carboxaldehyde **95a** (Fig. 8). This conventional structural classification could help to perceive the synthetic power of this reaction in the generation of novel molecular diversity.

3.1. Octahydroacridine derivatives

Octahydroacridine (OHA) derivatives are an important class of heterocyclic compounds with interesting pharmacological activity. Although several syntheses of the octahydroacridine skeleton have been reported, the intramolecular imino DA reaction of *N*-arylamines with ω-unsaturated aldehydes tethered to the 2-azadiene system to obtain this skeleton seems to be more easy and convenient access to OHAs with a variety of substituents on the ring. Reports of Laschat and co-workers on the synthesis of OHA derivatives[100,101] in this elegant manner have started to investigate this intramolecular imino DA reaction. Laschat's work have demonstrated that treatment of *N*-aryl imines **96a–d** prepared from aldehydes **94a,b** and anilines, in CH_2Cl_2 with catalytic amounts of $SnCl_4$ for several hours at −78 °C followed by basic hydrolysis

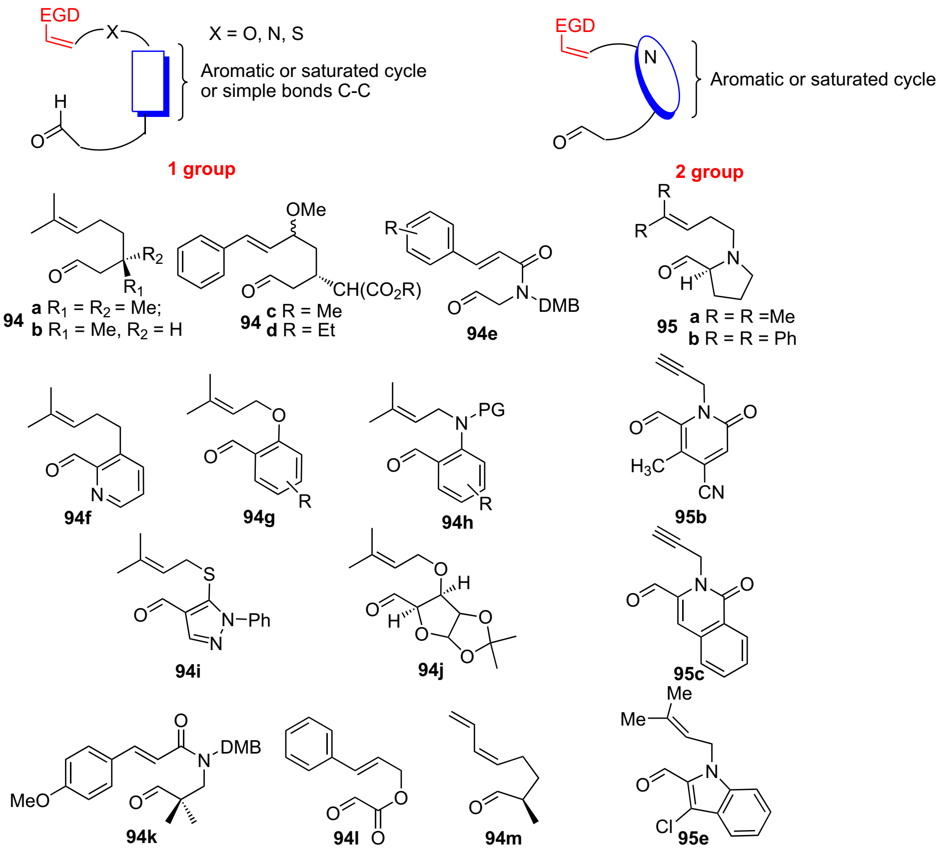
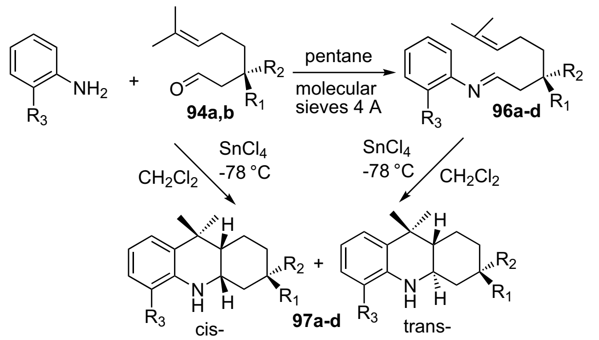


Figure 8.

resulted in the formation of OHAs **95a–d** in high yields and this cyclization also can be carried out as a one-pot reaction by successive addition of the Lewis acid and the aldehydes to a precooled solution (−78 °C) of the anilines (Scheme 33).



97a : $R_1 = R_2 = R_3$ = Me, 91%, 1:99 (cis:trans), from **96a**
97b : $R_1 = R_2$ = Me, R_3 = H, 86%, 1:99 (cis:trans), from **96b**
97c : R_1= Me, R_2 = H, R_3 = Me, 84%, 42:56 (cis:trans), from **94b**
97d : R_1= Me, $R_2 = R_3$ = H, 84%, 31:67 (cis:trans), from **94b**

Scheme 33.

The formation of OHAs **97** can be catalyzed by a broad range of Lewis or Brønsted acids. The acid catalysts differ mainly in their reactivity. Strong Lewis acids like $TiCl_4$, $BF_3·OEt_2$, $EtAlCl_2$, $FeCl_3$, Et_2AlCl, and CF_3COOH gave complete conversion of aldimines **96** within 20 h at −78 °C, while $ZnCl_2$, *p*-TsOH, or PPA required room temperature. However, the type of the Lewis acid plays only a minor role in determination of the cis/trans ratio. These were Laschat's work conclusions.

In recent years, the acid-catalyzed intramolecular multi-component imino DA reactions between substituted anilines and *R*-(+)-citronellal **94b**[102] have been reported as the most atom-economic procedure to furnish new OHAs **98**: solid-phase synthesis of these derivatives has been described using $Yb(OTf)_3$,[103] a one-pot procedure for the efficient preparation of OHAs by $BiCl_3$,[104] $TiCl_3$ or TFE,[105] molecular sieves,[106] and ionic liquids,[107] green and efficient methods for the synthesis of OHAs in the presence of a solid-supported catalyst ($SiO_2/ZnCl_2$) or selenonium ionic liquid salts under MW irradiation[108,109] have been developed (Table 1).

Among these investigations of the OHA synthesis, the results of Kiselyov and co-workers[103] and Lenardão and co-workers[108] are noteworthy. Solid support reaction between aniline resin **99** and *R*-(+)-citronellal **94b** provided single trans-diastereoisomer **101** in excellent yield after the cleavage of cycloadduct resin **100** with TFA[103] (Scheme 34).

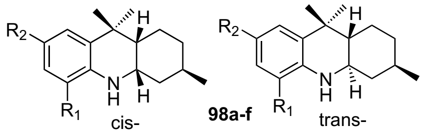
Lenardão and co-workers applied their eco-friendly protocol for the synthesis of OHAs from crude citronella oil, avoiding the necessity for separation of citronellal.[108]

Beifuss and co-workers reported in 1996 that the domino process between aniline or *N*-methylanilines **102a**,**b** and mixture of ω-unsaturated aldehydes **94c**,**d** exclusively gave the trans-annulated diastereoisomeric OHAs **103a**,**b** and **104a**,**b** with five stereogenic centers.[110] Compounds **103** and **104** differ only with respect to the arrangement of the methoxy group at C-1 and could be isolated. Best yields were observed when the cyclocondensations were performed with $BF_3·Et_2O$ (0.3 equiv) as the Lewis acid in dichloromethane (Scheme 35).

3.2. Tetrahydrochromano[4,3-*b*]quinoline derivatives

To afford the biologically important tetrahydrochromanoquinolines **106**, a one-pot reaction of substituted anilines with *O*-prenylsalicylaldehyde **94g** is used following the work of Kiselyov and Jones[111] (Scheme 36).

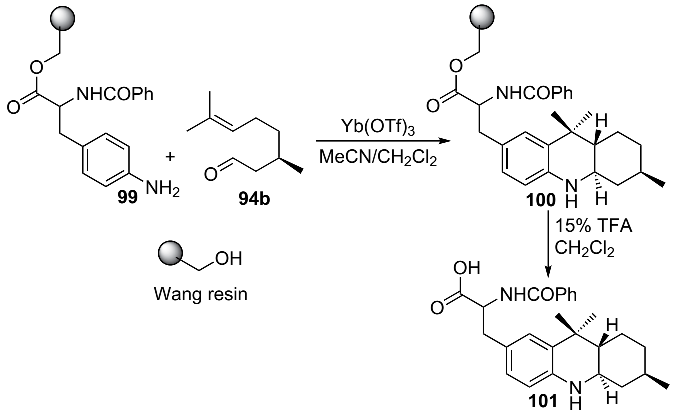
Table 1



a $R_1 = R_2 = H$; **b** $R_1 = H$, $R_2 = Me$
c $R_1 = H$, $R_2 = OMe$; **d** $R_1 = H$, $R_2 = Cl$
e $R_1 = Me$, $R_2 = H$; **f** R_1 = 1-naphthyl, $R_2 = H$

Compound	$BiCl_3$ (5 mol %), MeCN, 0 °C, 10–15 min[104]		$TiCl_3$ (10 mol %), MeCN, rt, 3 h[105]		TFE, rt, 3 h[105]		$SiO_2/ZnCl_2$ (10%), MW (280 W), 3 min[108]	
	Yield (%)	Ratio cis/trans	Yield (%)	Ratio cis/trans	Yield (%)	Ratio cis/trans	Yield (%)	Ratio cis/trans
98a	98	0:100	69	20:80	82	49:51	78	1:1
98b	97	4:94	72	39:61	89	48:52	87	1.8:1
98c	93	5:95	66	42:58	95	49:51	nt[a]	
98d	97	5:95	68	33:67	95	45:55	85	1:1
98e	96	3:97	67	30:70	85	45:55	83	1:1
98f	95	5:95	68	16:84	86	42:58	nt	

[a] Not tested.



Scheme 34.

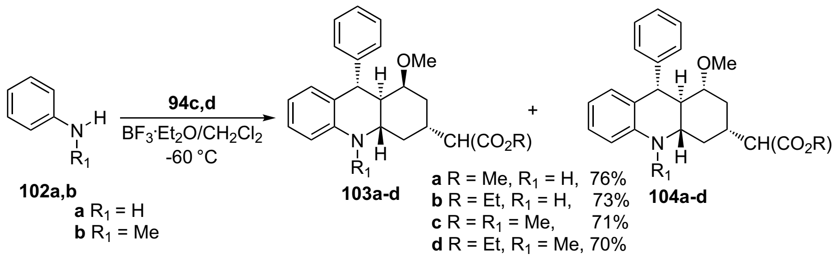
This approach is based on the TFA or $Yb(OTf)_3$-catalyzed intramolecular [4+2] cycloaddition of the intermediate aromatic *N*-aldimines **105**. In lieu these catalysts, other efficient catalysts such as sulfamic acid (50 mol %),[112] $InCl_3$ (20 mol %),[113] $BiCl_3$ (5 mol %),[114] $LiClO_4$ (5 M in Et_2O),[115] and $Ph_3P{\cdot}HClO_4$ (20 mol %)[116] have been utilized in the tetrahydrochromanoquinoline construction (Table 2).

These reported results are difficult to compare because different anilines and *O*-prenylsalicylaldehydes were used in these intramolecular [4+2] cycloaddition reactions. However, something of the general procedure for these cycloadditions can be mentioned: the target products are isolated as 1:1 mixture of the cis/trans diastereomers **106**, and none of the catalysts under study has any effect on the selectivity of the ring fusion, MeCN is found to be the optimal solvent for the reaction when Lewis acids are used, moreover, the use of substituted *O*-prenylsalicylaldehydes in this intramolecular reaction has been not explored.

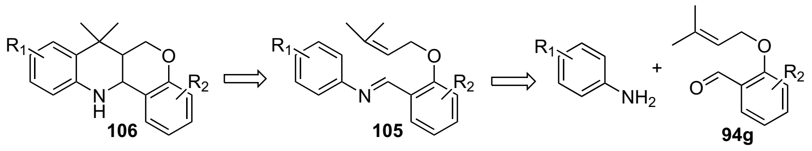
A series of such polysubstituted tetrahydrochromano[4,3-*b*]quinolines have been prepared by the solid-support reaction of immobilized anilines **107** with *O*-prenylsalicylaldehyde **94g** in the presence of catalytic amounts of TFA (1 mol %) or $Yb(OTf)_3$ (15 mol %) in MeCN. The final polyheterocycles **108** were isolated as 1:1 mixtures of diastereomers, whose ratio did not depend on the nature of the catalyst or the solvents tested. However, this diastereomeric mixture was separated using preparative HPLC[117] (Scheme 37, Table 3).

From the results given in Table 3, it can be seen that the Lewis acid catalyst $Yb(OTf)_3$ is vastly superior to the Brønsted acid catalyst TFA in this case.

Condensation of the cinnamyl salicylaldehyde ethers with substituted anilines and treatment with TFA (10 equiv) in MeCN at

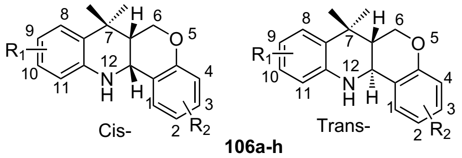


Scheme 35.



Scheme 36.

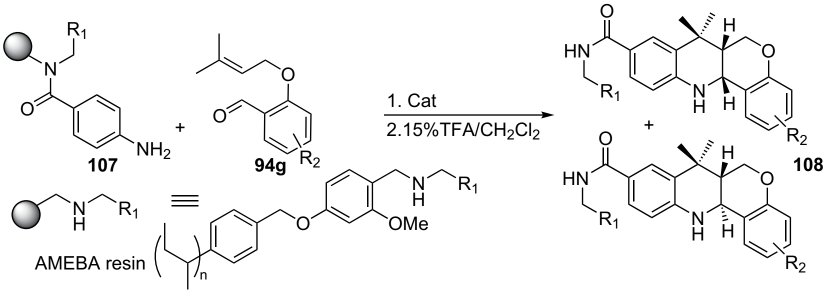
Table 2



106a-h

Compound **106**	R_1	R_2	Overall yields (%) of **106**; cis/trans isomers 1:1					
			TFA (1 mol %), MeCN[111]	NH_2SO_3H (50 mol %), MeOH[112]	$InCl_3$ (20 mol %), MeCN[113]	$BiCl_3$ (5 mol %), MeCN[114]	$LiClO_4$ (5 M in Et_2O)[115]	$Ph_3P\cdot HClO_4$ (20 mol %), MeCN[116]
a	H	H	68	91	98	83	85	94
b	9-Me	H	nt[a]	nt	nt	86	87	87
c	9-MeO	H	nt	92	96	nt	83	87
d	9-HOOC	H	78	nt	91	nt	nt	87
e	9-Br	H	nt	nt	93	nt	nt	88
f	11-Me	H	nt	nt	92	nt	85	87
g	9-CN	H	nt	nt	87	nt	nt	82
h	10,11-C_4H_4–	H	nt	nt	88	72	nt	84

[a] Not tested.



Scheme 37.

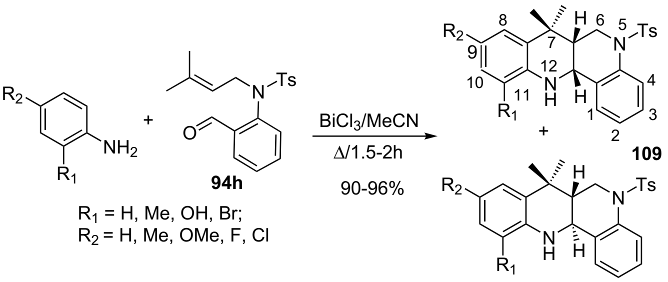
Table 3

Comp. **108**	R_1	R_2	Overall yields (%) of **108**; cis/trans isomers 1:1	
			TFA (1 mol %), MeCN	$Yb(OTf)_3$ (5 mol %), CH_2Cl_2
a	Me_2CH	H	68	93
b	Me_2CH	2-MeO	61	91
c	Me_2CH	2-Br	69	94
d	Ph	H	78	96
e	Ph	2-MeO	73	93
f	Ph	2-Br	75	94
g	2-FC_6H_4	H	88	92
h	2-FC_6H_4	2-MeO	81	94
i	2-FC_6H_4	2-Br	77	95

55 °C for 30 min afforded the corresponding 7-phenyl-tetrahydrochromano[4,3-*b*]quinolines, analogues of cycloadducts **106** and **108**, in good yields (70–86%). The major products isolated as single isomers after chromatographic or crystallographic purification possess the thermodynamically favored all-trans configuration.[118]

3.3. Hexahydrodibenzo[*b*,*h*][1,6]naphthyridine derivatives

Nitrogen analogues of the cited OHAs, hexahydrodibenzo[*b*,*h*][1,6]naphthyridines **109** are a novel class of nitrogen heterocyclic compounds that can be assembled by using $BiCl_3$-catalyzed [4+2] cycloaddition reactions of anilines with the *N*-prenyl derivative of 2-aminobenzaldehyde **94h**. The products were isolated again as mixtures of cis/trans diastereoisomers in a 1:1 ratio, in excellent yields[119] (Scheme 38).



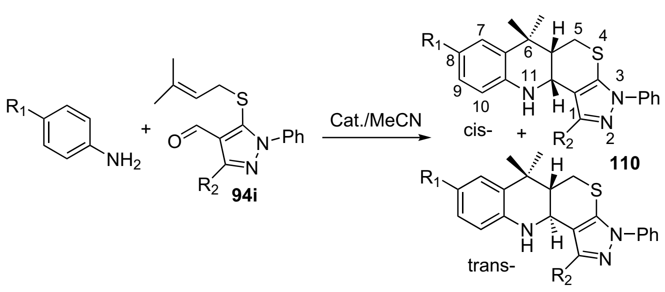
Scheme 38.

The preparation of the main precursor **94h** was achieved from methyl anthranilate by a four-step synthetic route based on N-tosylation, N-prenylation reactions and reduction (COOMe) and oxidation (CH_2OH) reactions.[119]

3.4. Hexahydropyrazolo[4′,3′:5,6]thiopyrano[4,3-*b*]quinoline derivatives

The structure of these derivatives can be considered as a formal union of the thiopyranoquinoline and thiopyranopyrazole rings.

Thiopyranoquinolines and thiopyranopyrazoles are reported as interleukin-1 inhibitors, diverse thiopyranopyrazoles are also known as a COX-2 selective inhibitors[120,121] that justify synthetic research on the pyrazolothiopyrano[4,3-*b*]quinolines. Their preparation based on the intramolecular imino DA reaction of *N*-aldimines derived from aromatic amines and *S*-prenyl derivative of *N*-phenylpyrazole aldehydes **94i** was studied by two scientific groups from India. A rapid synthesis of derivatives **110** was achieved in MeCN with $BiCl_3$ (5 mol %)[122] or $InCl_3$ (20 mol %) [123] (Scheme 39).

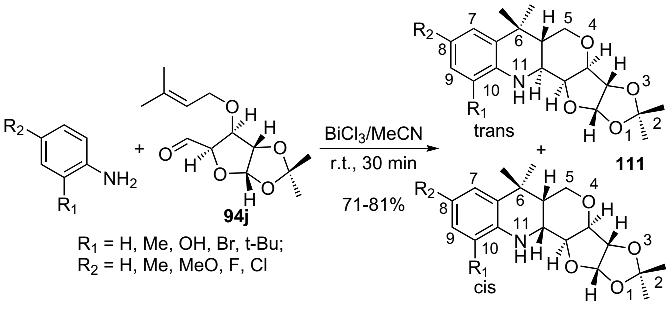


Scheme 39.

The first method needed more severe conditions, but produced a single cis-isomer exclusively, whereas the second method gave cis-cycloadducts **110** as the major products with trans-isomers being formed in minor amounts in overall yields of 88–96% (Table 4).

3.5. Furo[2′,3′:5,6]pyrano[4,3-*b*]quinoline derivatives

Fused *N*,*O*-polyheterocycles, such as furanopyrans or pyranoquinolines, being constituents of bioactive compounds, are also perspective targets for synthetic organic chemists. The synthesis of these heterocycles can be achieved by the [4+2] cycloaddition reactions of anilines with the *O*-prenyl derivative of the sugar derived aldehyde **94j**. Their simple interaction under $BiCl_3$ (10 mol %) catalysis conditions resulted in a new, efficient, and stereoselective synthesis of furo[2′,3′:5,6]pyrano[4,3-*b*]quinolines **111**. These final products were formed with extremely high trans selectivity in good yields[124] (Scheme 40). The preparation of main carbohydrate precursor **94j** was achieved from D-glucose.[125]



Scheme 40.

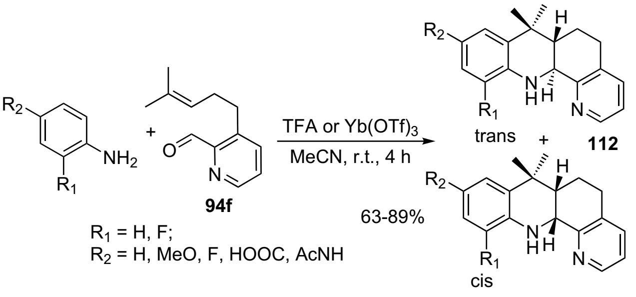
3.6. Hexahydrobenzo[*b*]phenanthroline derivatives

Phenanthrolines and their benzoanalogues are important heterocyclic compounds that have many useful applications. A convenient, new route to hexahydrobenzo[*b*]phenanthroline derivatives **112** consists in the interaction between substituted anilines and the C-3-alquenyl derivative of 2-pyridine carboxaldehyde **94f** catalyzed by both TFA (5 mol %) and $Yb(OTf)_3$ (1 mol %) in MeCN. The final cycloadducts were obtained as a 1:1 mixture of diastereomers in good yields (63–89%)[126] (Scheme 41).

Table 4

Comp. **110**	R_1	R_2	Overall yields (%)	
			$BiCl_3$ (5 mol %), MeCN, reflux, 1 h, only cis-isomer [122]	$InCl_3$ (20 mol %), MeCN, rt, 15–30 min (cis/trans)[123]
a	H	Me	80	88 (86:14)
b	Me	Me	80	90 (91:9)
c	MeO	Me	nt[a]	92 (90:10)
d	EtO	Me	85	nt
e	Cl	Me	83	95 (87:13)
f	H	Ph	82	96 (94:6)
g	Me	Ph	nt	90 (90:10)
h	MeO	Ph	nt	87 (88:12)
i	EtO	Ph	78	nt
j	Cl	Ph	nt	92 (92:8)

[a] Not tested.



Scheme 41.

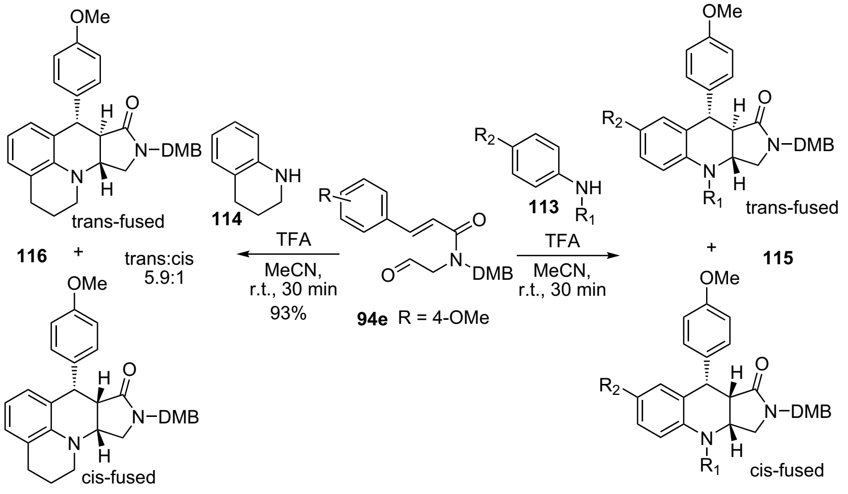
Aldehyde **94f** was prepared in a 31% overall yield by a three-step procedure starting from 3-methylpicolinic acid. Notably, the attempted reactions of the 2-pyridyl aldehydes derivatives with a single or no Me substituent at the double bond failed, presumably due to the insufficient electron density on the olefinic fragment.

3.7. Hexahydropyrrolo[3,4-*b*]quinolin-1-one derivatives

To construct an hexahydropyrrolo[3,4-*b*]quinolinone core, all one needs are appropriate aldehydes that can provide a pyrrole ring during an intramolecular imino DA reaction. This idea was recently exploited by Spaller and co-workers.[118,127] Thus, *N*-cinnamoyl-α-aminoaldehyde **94e** was synthesized in a four-step procedure from glycine methyl ester and 2,4-dimethoxybenzaldehyde (DMB), and allowed to react with secondary anilines like **113** in the presence of 3 equiv of TFA at room temperature for 30 min. To any case, two diastereomers **115** were obtained in good to excellent yields. Using 1,2,3,4-tetrahydroquinoline **114** as the aniline moiety in this cycloaddition reaction, polycyclic products **116** were obtained in a 5.9:1 ratio with an overall yield of 93% (Scheme 42, Table 5).

Moreover, the glycine unit **94e** was replaced with an aldehyde that possesses an additional methylene **94k** or the glyoxyl ester of cinnamate **94l** (Fig. 6). The subsequent imino DA reaction with *N*-methylaniline **113a** afforded a diastereomeric trans/cis mixture (2:1) of hexahydro-2*H*-benzo[*b*][1,6]naphthyridin-1-one **117** or a single trans isomer of tetrahydrofuro[3,4-*b*]quinolin-1-one **116**[127] (Scheme 43).

These imino DA transformations generate a diverse array of quinolinic structures with multiple stereogenic centers, many of which resemble lignan and arylnaphthalene-type natural products.



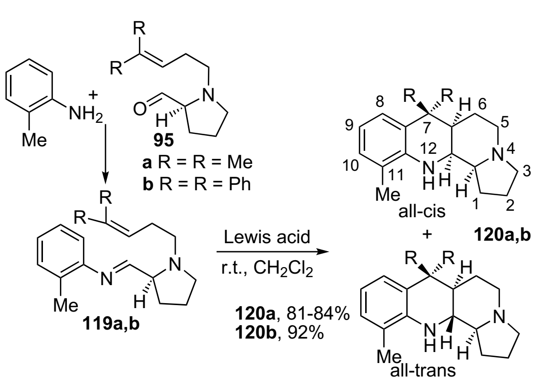
Scheme 42.

Table 5

Comp. **115**	R_1	R_2	Overall yields (%)	Ratio trans/cis
a	Me	H	96	7.0:1
b	Et	H	91	8.1:1
C	Allyl	H	98	4.2:1
d	*i*-Pr	H	89	2.4:1
e	Cyclohexyl	H	42	2.0:1
f	Ph	H	91	5.5:1
g	Me	F	95	4.3:1
h	Me	MeO	95	4.6:1

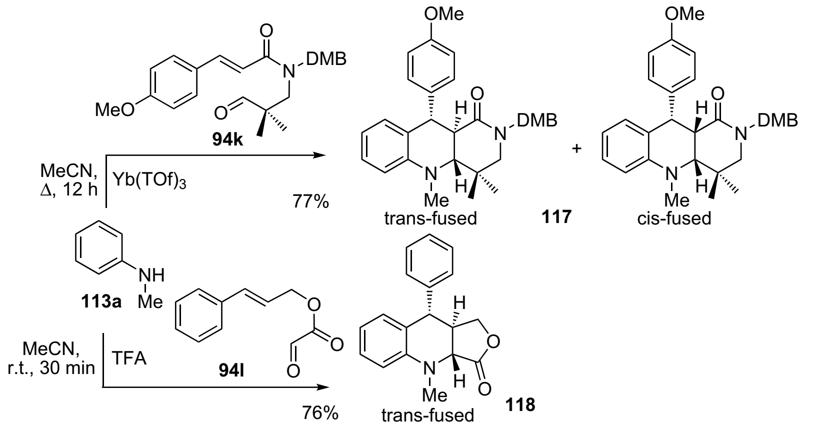
3.8. Indolizino[3,4-*b*]quinoline derivatives

The utilization of *N*-(4-methyl-3-pentenyl)pyrrolidine carboxyaldehyde **95a** or its 2,6-diphenyl analogue **95b** and *o*-toluidine in the intramolecular imino DA reaction provides a facile route to new indolizino[3,4-*b*]quinolines preparation. Laschat and co-workers demonstrated that this intramolecular Lewis-catalyzed cyclization of preformed prolinal-derived *N*-aryl imines **119a**,**b** could be converted into indolizino[3,4-*b*]quinoline derivatives **120a**,**b**, those diastereoisomeric ratio was completed by the suitable choice of the Lewis acid[128,129] (Scheme 44).



Scheme 44.

Authors found that best results concerning the cis/trans selectivity were obtained by using 1.3–2.5 equiv of the acidic catalyst and these imines **119a**,**b** displayed a remarkable Lewis acid-dependent reversal of the diastereoselectivity: whereas $SnCl_4$ or $BF_3 \cdot OEt_2$ yielded almost exclusively all-trans isomer **120a**, the ratio was completely reversed in favor of the all-cis isomer **120a**, when $EtAlCl_2$ or $MeAlCl_2$ was used. However, when aldimine **119b** was used in the similar intramolecular reaction conditions, no Lewis acid-induced reversal of the product ratio **120b** was observed (Table 6).



Scheme 43.

Table 6

Catalyst, Lewis acid	Indolizino[3,4-*b*]quinoline **120a**, ratio[a]		Indolizino[3,4-*b*]quinoline **120b**, ratio[a]	
	All-cis	All-trans	All-cis	All-trans
$BF_3 \cdot OEt_2$	2	98	1	99
$SnCl_4$	1	99	1	99
$EtAlCl_2$	99	1	2	98
$MeAlCl_2$	99	1	nt[b]	nt[b]

[a] Determined by capillary GC of the crude products.

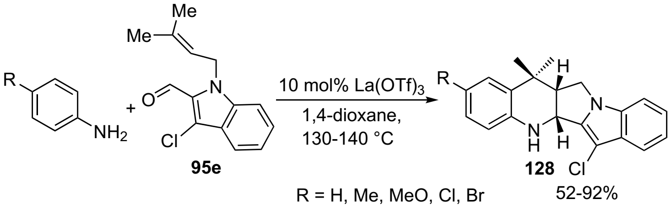
[b] Not tested.

These investigations on the preparation of the indolizino[3,4-*b*]quinoline skeleton resulted in the design of potential oligodentate artificial receptors, semi-rigid tweezers, compounds **124**,**125** or rigid concave systems, compounds **126**,**127**.[130–132] The synthesis of these receptor indolizino[3,4-*b*]quinoline molecules started with the biscondensation of aldehyde **95a** and appropriate diaminoarenes to form the corresponding bis-aldimines **121**–**123**, which underwent a Lewis acid-catalyzed intramolecular biscyclization to afford the corresponding compounds **124**–**127** in good yields (Scheme 45).

It is interesting to note that whereas the use of $EtAlCl_2$ led to the formation of the concave product **126**, the corresponding planar polycycle **127** was formed in the presence of $SnCl_4$. Both rigid molecules **126** and **127**, as well as tweezer **124** were characterized by X-ray crystal-structure analysis.

3.9. Benzo[5,6]pyrrolizino[1,2-*b*]quinoline derivatives

Structurally interesting and bioactive important indolopyrroloquinolines, e.g., tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]quinolines **128** were successfully assembled via a one-pot cycloaddition reaction using *N*-prenylated-2-formyl-3-chloroindole **95e**.[133a] These indole-annulated pyrroloquinolines were formed in moderate to good yields as single diastereomers having the cis-configuration. The intramolecular reaction was promoted by 10 mol % $La(OTf)_3$ in 1,4-dioxane at reflux temperature (Scheme 46).

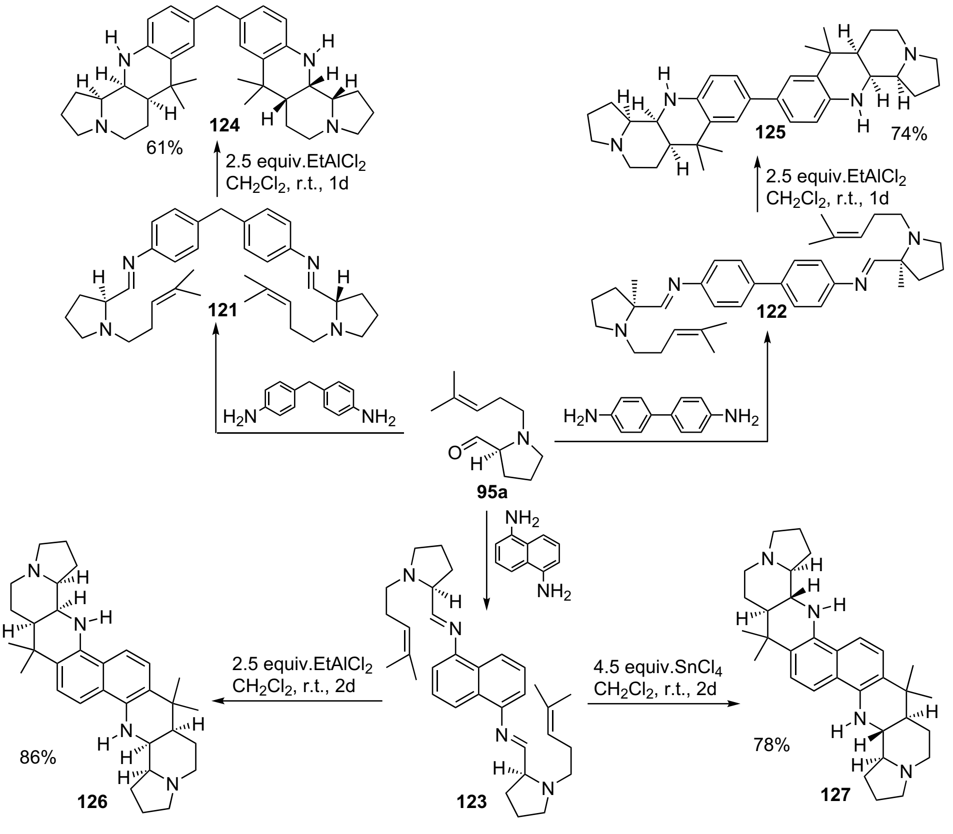


Scheme 46.

Related pyrrolo[2,3-*d*]pyrimidine tetrahydroquinoline derivatives were prepared in good yields using 20 mol % $InCl_3$ as catalyst and MeCN as solvent.[133b]

4. Intramolecular imino Diels–Alder approach to the synthesis of indolizino[1,2-*b*]quinolin-9(11*H*)-one alkaloids

The quinoline derivatives discussed above are closely related to several quinoline alkaloids. Despite the large number of the quinoline derivatives synthesis based on the intramolecular imino DA reaction, there have been only a few examples of the use of this reaction in total synthesis. However, the growing interest for the development of an intramolecular cycloaddition began to produce initial, but remarkable results, specifically in constructing pyrrolo[3,4-*b*]quinoline-based alkaloids. The most well-known example is camptothecin **129**, isolated from the stem wood of Chinese tree, *Camptotheca acuminate*,[134] from which was obtained



Scheme 45.

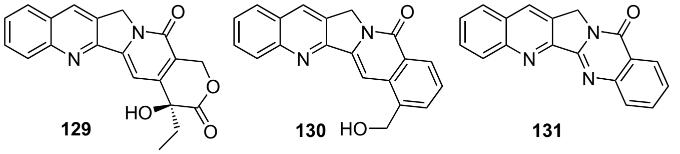


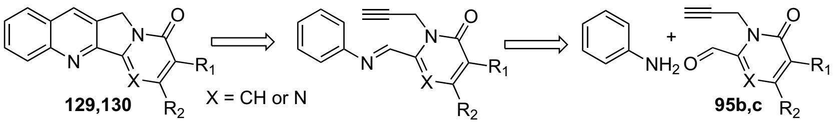
Figure 9.

(0.000006%) a rare alkaloid, named 22-hydroacuminatine **130**,[135] called ‘aromathecin’.[136] Another interesting pyrrolo[3,4-*b*]quinoline-based alkaloid is luotonin A **131**, first isolated in 1997 from the aerial parts of Chinese plant *Peganum nigellastrum Bunge*[137] (Fig. 9).

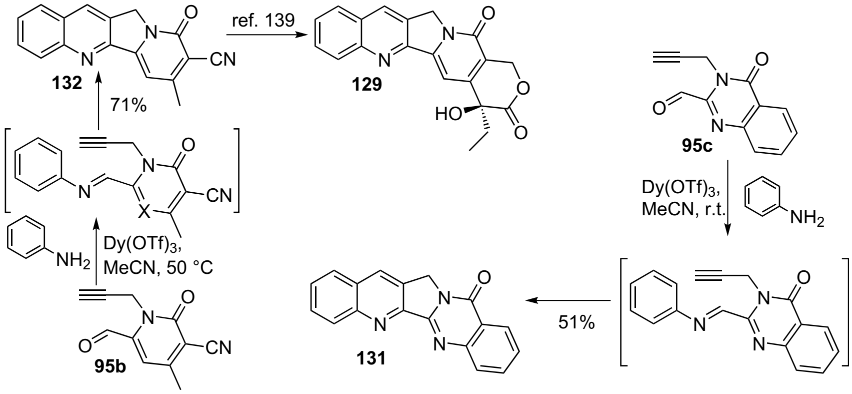
All three pyrrolo[3,4-*b*]quinoline derivatives are cytotoxic alkaloids, those synthetic and biomedical studies allowed to develop antineoplastic chemotherapeutic drugs (for example, irinotecan and topotecan). Thus, a flexible route that would open up a new way to synthesize analogues for investigation of structure–activity relationships is always needed. This new method based on the intermolecular imino Diels–Alder reaction of the aniline and heterocyclic aldehydes **95b,c** have been accomplished by Batey and Twin[138] (Scheme 47).

The construction of the camptothecin core requires an *N*-propargyl formyl-pyridone precursor **95b**, those preparation was achieved in three steps with an overall yield of 25% from commercially available pyruvic acid dimethylacetal, dimethylacetamide dimethylacetal, and cyanoacetamide. The key imino DA reaction between aldehyde **95b** and aniline in the presence of $Dy(OTf)_3$ (10 mol %) at 50 °C for 16 h afforded pyrrolo[3,4-*b*]quinoline derivative **132** in 71% yield. The preparation of this derivative constitutes a formal synthesis of camptothecin.[139] The synthesis of luotonin A using an analogous approach requires the use of another precursor, *N*-propargyl quinazolinone aldehyde **95c**, which was prepared in seven steps from commercially available isatoic anhydride and propargylamine. The final construction of luotonin A was made again, by using intramolecular imino DA reaction between aldehyde **95c** and aniline in the presence of $Dy(OTf)_3$ (10 mol %) at room temperature for 24 h. The synthetic efforts to construct these alkaloids are summarized in Scheme 48.

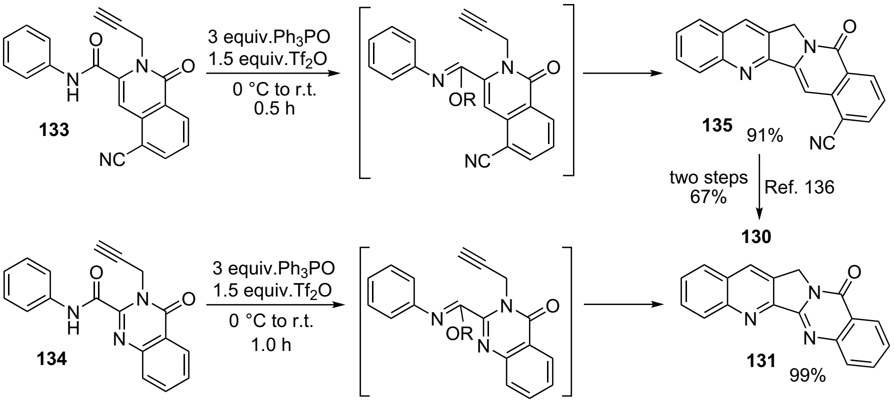
Small modifications in the tactics based on intramolecular imino DA condensation allowed obtaining cytotoxic aromathecin **130** and luotonin A **131**. These chemical modifications consisted into simple treatment of amide precursors **133**,**134** with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (prepared in situ from Ph_3PO and Tf_2O) at room temperature for 0.5–1.0 h, and improved overall yield of desired molecules that was recently reported by Yao and co-workers[140] (Scheme 49).



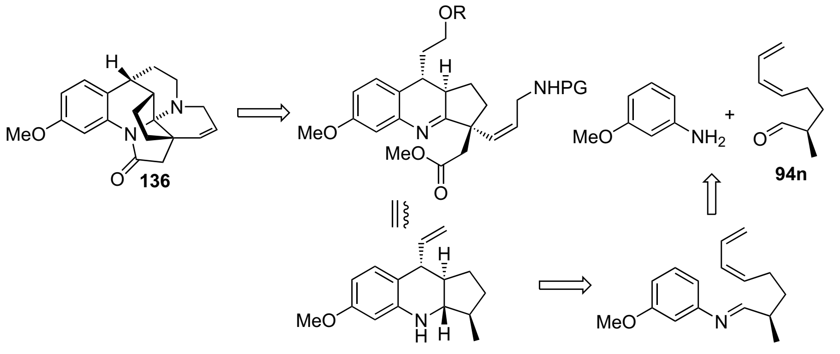
Scheme 47.



Scheme 48.



Scheme 49.

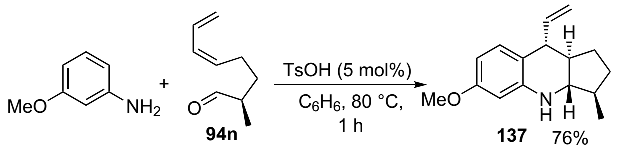


Scheme 50.

Amide precursors **133** and **134** were prepared from commercial available 2,6-dicyanotoluene and anthranilamide via five or four steps, respectively. The cascade annulation of **133** gave the known intermediate **135**, whose conversion to aromathecin **130** was previously carried out by Cushman and co-workers using a two-step DIBAL-H reduction procedure.[136] This highly efficient cascade reaction triggered by bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate was successfully applied in the total synthesis of camptothecin.[141]

These syntheses underline the power of inverse-electron demand imino DA reactions for alkaloid preparation, particularly when are conducted in an intramolecular fashion.[142] Recently, new analogues of isomeric ellipticine derivatives fused with biologically important pyrroloindole or chromene ring were synthesized by utilizing this reaction in a single step.[143]

Alkaloid isoschizogaline **136**, isolated from the leaves of *Schizozygia coffaeoides*, a plant used in Kenyan traditional medicine for treatment of skin diseases[144] is also an attractive target for synthesis. In 2003, Magomedov described the results of a model study toward the construction of cyclopenta[*b*]quinoline core of this alkaloid by an intramolecular formal imino DA reaction[145] (Scheme 50).



Scheme 51.

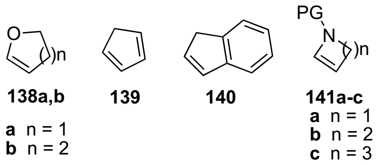


Figure 10.

After some experimentation, the optimized conditions for the intramolecular reaction between *m*-anisidine and dienyl aldehyde **94n** were found to involve refluxing the two components in benzene in the presence of *p*-TsOH (5 mol %) with azeotropic removal of water. The condensation of *m*-anisidine with aldehyde **94n** furnished cyclopenta[*b*]quinoline derivative **137**, containing four contiguous stereogenic centers, as the only diastereomers (Scheme 51).

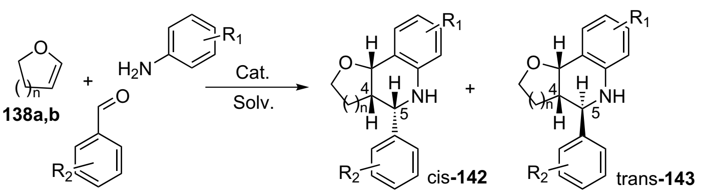
This diastereoselective reaction of aldehydes bearing α-stereocenters supports the projected synthesis of isoschizozygane alkaloids.[144] Although intramolecular reactions of aryl imines with unsaturated aldehydes to give cyclopentaquinoline ring system were reported previously,[146] this efficient assemblage of the cyclopenta[*b*]quinoline core of isoschizozygane alkaloids deserves further investigation.

5. [4+2] Cycloadditions between *N*-aryl aldimines and cyclic dienophiles

This part of the review deals with the [4+2] cycloadditions between *N*-aryl aldimines and cyclic dienophiles (Fig. 10), which offer different structural quinoline derivatives. Earlier numerous works on their interactions were discussed in several reviews,[13,14,23] an in-depth analysis on the interesting process of polycyclic quinolines construction will not be taken up. This part will focus on the generation of new polyfunctionalized quinoline derivatives, including pyrrolo[3,2-*c*]quinoline alkaloids.

5.1. Cyclic enol ethers and cyclopendadiene or indene derivatives as dienophiles

Cyclic enol ethers like 2,3-dihydrofuran **138a**[147] and 3,4-2*H*-dihydropyran **138b** are dienophiles more used in the imino DA reaction since the pioneering work of Povarov.[17] Utilization of these enol ethers in the cycloaddition process allows to construct corresponding diverse cis-fused furo[3,2-*c*]- and pyrano[3,2-*c*]quinoline derivatives **142** and **143**. Various Lewis acids[148] and protic acids are normally employed to catalyze such reactions, where are formed almost usually cis- and trans-isomers **142** and **143** (with respect to H-4a and H-5), which could be easily separated by column chromatography over silica gel (Scheme 52).



Scheme 52.

Although a considerable body of data on furo- or pyranoquinoline derivatives synthesis is accumulated, yet, there is the need to develop a new synthetic recipe for imino DA reaction using cheap and non-toxic, both catalyst and solvent, because the products containing furano and pyranoquinoline moieties are widely distributed in nature and with a wide range of biological activities. The reported results on Lewis acid-catalyzed cycloaddition process (Table 7) are difficult to compare because different anilines and benzaldehydes were used in these intermolecular [4+2] cycloaddition reactions with cyclic enol ethers **138a**,**b**.[42,149–155] However, something of the general procedure for these cycloadditions can be mentioned: the target products are isolated as a mixture of cis/trans diastereomers **142**,**143**, always obtaining a trans-isomer as the major product, and aprotic polar MeCN is found to be the optimal solvent for the reaction when Lewis acids are used, moreover, the use of diverse substituted benzaldehydes in this intermolecular reaction has been not explored. No observable substituent effect was noted both for the various anilines in terms of product yield.

Among the Lewis acids cited-above, zirconium tetrachloride ($ZrCl_4$) stands out as an inexpensive and potential green catalyst.[153,154] However, in general, unfortunately for many Lewis acids in a one-pot procedure, the presence of amines and water from the formation of imines can decompose or deactivate them. Moreover, some of them are not easily available or expensive, non-reusable, and toxic.

Recently, new protocols for the synthesis of **142**,**143** using another types of promoters were proposed.[112,156–166] Some of them are noteworthy. Molecular iodine can be used as inexpensive and readily available catalyst in the one-pot synthesis of furo- or pyranoquinolines that was demonstrated by Xia and Lu.[156] Use of TMSCl (20 mol %) as catalyst in this cycloaddition process allowed to obtain various furo- or pyranoquinolines with aliphatic, furyl or thienyl moieties in excellent yield.[157] A simple and efficient protocol for the synthesis of **142**,**143** in the presence of commercially available and cheap phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) under solvent-free conditions was described by Indian team.[159] This catalyst is an environmentally friendly solid acid and ease of handling, and allow cleaner cycloaddition reactions in comparison to conventional catalysts (Table 8).

Acid-catalyzed imino DA cycloadditions in water and under solvent-free conditions would have much to promise in the synthesis of heterocycles. First this process was developed using a polymer-supported π-acid (poly-DCKA-1) by Masaki and coworkers.[161] They reported that this catalyst works well in two- and three-component imino DA reactions to give pyrano[3,2-*c*]quinolines **144**,**145** at room temperature in water and under solvent-free conditions (Scheme 53, Table 9).

This catalyst is prepared by copolymerization of dicyanoketene acetals (DCKA) bearing a styrene functionality with ethyleneglycol dimethacrylate. Although the preparation of this catalyst is rather complicated for many organic laboratories, this protocol looks very attractive.

Chemical diversification of these fused furo- and pyranoquinoline derivatives is still underdeveloped, only 1-naphthylamines[149,151,159] and aminophenols[150,165] were used as amino-components in the three-component imino DA cycloaddition with cyclic enol ethers **138a**,**b** to give new respective furo- and pyranophenanthridine or hydroxy substituted furo- and pyranoquinoline derivatives. The later compounds were prepared under controlled microwave heating in the presence of a catalytic amount of TFA in MeCN.[165] Use of another participant, carbonyl component in this process, is too important for the structural diversification of this type of heterocycles searching new pharmaceutical agents. Study on novel antibacterial agents against methicillin-resistant *Staphylococcus aureus*, fused furo- and pyrano-2-(1*H*-indol-3-yl)quinolines, prepared via Yb(OTf)$_3$-catalyzed imino DA process,[167] proves this importance.

Moreover, when salicylaldehydes **146** are used instead of benzaldehydes, usually employed in this three-component reaction, functionalized cis-fused *N*-arylamino furano- and

Table 7

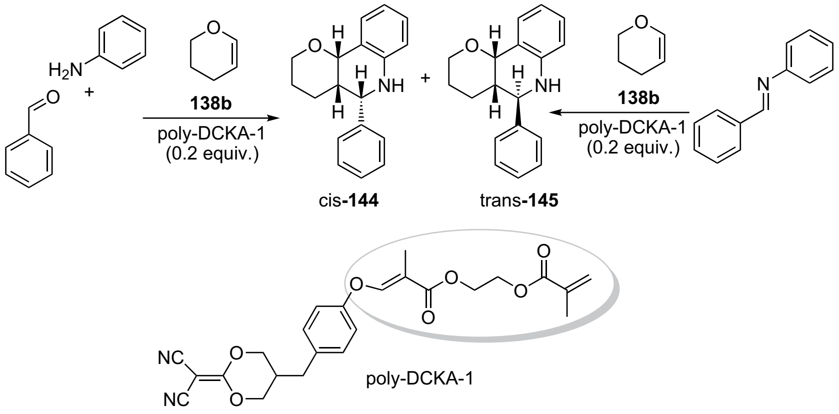
Entry	*n*	R_1	R_2	Overall yields (%) of **142**, **143** (ratio cis/trans isomers)[a]					
				$BiCl_3$ (10 mol %), MeCN[142]	$SbCl_3$ (10 mol %), MeCN[149]	$GdCl_3$ (20 mol %), MeCN[150]	$InCl_3$ (20 mol %), MeCN[151]	$ZrCl_4$ (10 mol %), CH_2Cl_2[153]	$CuBr_2$ (50 mol %), MeCN[155]
a	1	H	H	nt	92 (52:48)	88 (35:65)	nt[b]	95 (30:70)	68 (47:53)
b	1	H	4-Cl	nt	80 (43:57)	nt	nt	97 (33:77)	nt
c	2	H	H	95 (30:70)	90 (28:72)	86 (33:67)	80 (41:59)	82 (30:70)	76 (21:79)
d	2	H	4-Cl	nt	75 (31:69)	nt	nt	81 (25:75)	58 (38:62)
e	2	4-Cl	H	nt	80 (32:68)	75 (47:53)	50 (34:66)	nt	nt
f	2	4-Me	H	nt	nt	nt	70 (68:32)	72 (32:68)	52 (16:84)
g	2	4-OMe	H	nt	86 (28:72)	81 (23:77)	70 (58:42)	75 (28:72)	46 (37:63)

[a] The ratio is based on isolation by chromatography.
[b] Not tested.

Table 8

Entry	*n*	R_1	R_2	Overall yields (%) of **142**, **143** (ratio cis/trans isomers)[a]				
				I_2 (30 mol %), MeCN[156]	TMSCl (20 mol %), MeCN[157]	Fe^{3+}–K-10 clay MeCN[158]	PMA (1 mol %), solvent-free[159]	CAN (25 mol %), MeCN[160]
a	1	H	H	nt[b]	84 (21:79)	84 (18:82)	92 (12:88)	81 (20:80)
b	1	H	4-Cl	nt	82 (18:82)	85 (16:84)	89 (15:85)[c]	84 (25:75)
c	2	H	H	84 (23:77)	95 (13:87)	86 (13:87)	90 (10:90)	86 (20:80)
d	2	H	4-Cl	nt	82 (12:88)	91 (8:92)	87 (15:85)	91 (30:70)
e	2	4-Cl	H	81 (43:57)	nt	86 (15:85)	nt	89 (30:70)
f	2	4-Me	H	91 (16:84)	nt	89 (10:90)	83 (13:87)	86 (15:85)
g	2	4-OMe	H	95 (8:92)	83 (13:87)	85 (20:80)	85 (22:78)	nt

[a] The ratio is based on isolation by chromatography or from crude NMR spectral values.
[b] Not tested.
[c] R_2 is 4-F.



Scheme 53.

Table 9

Solvent	Overall yields (%) of **144**, **145** (ratio cis/trans isomers)	
	Two-component	Three-component
H_2O	71 (16:84)	73 (15:85)
—	66 (19:81)	61 (16:84)

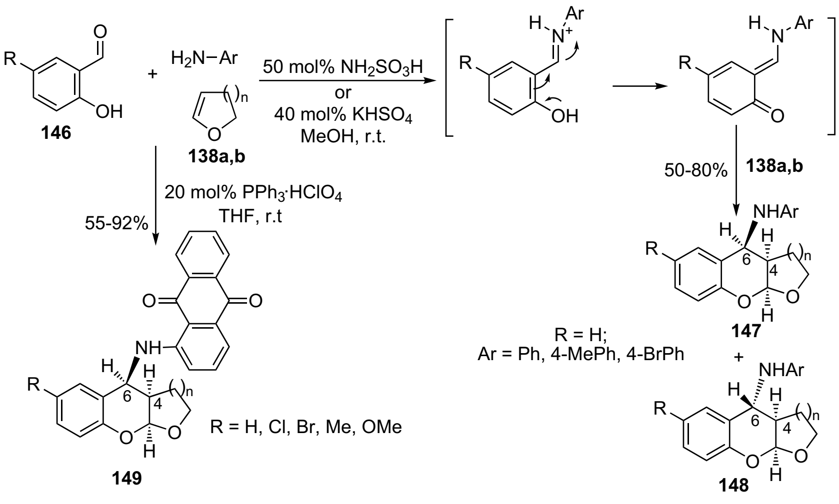
pyranobenzopyrans as a mixture of cis/trans diastereomers **147**,**148** (with respect to H-4 and H-6) or furano- and pyranobenzopyrans **149** with an aminoanthraquinone moiety can be successfully generated following Scheme 54. This cycloaddition is promoted by sulfamic acid,[168] potassium hydrogen sulfate,[169] triphenylphosphonium perchlorate (TPPP)[170] or molecular iodine.[171] TPPP catalyzes three-component reactions of 1-aminoanthraquinone and salicylaldehydes **146** with cyclic enol ethers **138a**,**b**, yielding the products as single diastereomers with cis-configuration.

From the work of Loh and co-workers[172] it is known that some Lewis acids are effective catalysts for various reactions in aqueous medium. Thus, treatment of anilines with cyclic enol ethers **138a**,**b** by $InCl_3$ in water[173] or $Dy(OTf)_3$ in MeCN[174] and in the absence of the benzaldehydes offered new hydroxyalkyl substituted furo-**150**,**151** and pyranoquinoline derivatives **152**,**153** (Scheme 55). The same domino process can be catalyzed by resin AG®50W-X2,[175] montmorillonite KSF,[176] TMSCl,[156] and $Sc(OTf)_3$ in ionic liquids.[177]

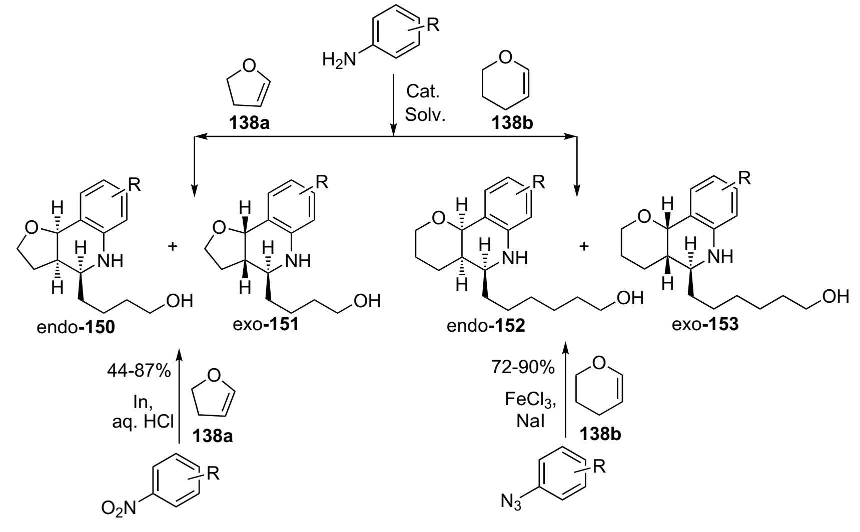
Moreover, these derivatives can be easily constructed via a domino reaction of nitroarenes with 2,3-dihydrofuran **138a** using an In/HCl system[178] or aryl azides with 3,4-dihydro-2*H*-pyran **138b** in the presence of $FeCl_3$–NaI.[179] In general, final products were obtained in moderate to high yields as a mixture of *endo*- and *exo*-isomers (cis/trans isomers, respectively), favoring the *endo*-diastereomer. This domino reaction may proceed via a facile opening of hydrated cyclic enol ethers to give alicyclic intermediate imine, which would react with cyclic enol ethers generating quinoline derivatives **150**–**153**.[173,174]

Cyclic alkenes like cyclopentadiene **139** and indene **140** are common dienophiles for the study on catalytic activity of some acids in the imino DA cycloaddition, and the results of its interaction with preformed *N*-aldimines (or *N*-aldimines formed in situ) were reported in many above-cited works (see, Refs. 33,34,36,42,48,53,69,88–90,152,153,161, and 168). This interaction, that affords cyclopenta[*c*]quinolines **154** and indeno[2,1-*c*]quinoline derivatives **155** (Scheme 56), needs also an acid catalysis.[180–185]

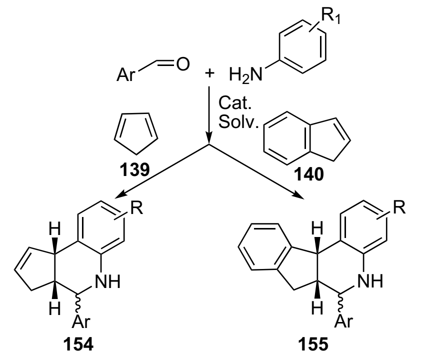
Interestingly, such obtained cyclopenta[*c*]quinolines or indeno[2,1-*c*]quinolines have not yet received wide acceptance as potential pharmacological scaffolds, useful in search of new pharmaceuticals.[186] Among these polycyclic quinoline systems, the indeno[2,1-*c*]quinolines are the most representative and interesting structures due to their antitumoral activity.[187] For instance, the 6-[[2(dimethylamino)ethyl]amino]-3-hydroxy-7*H*-indeno[2,1-*c*]quinolin-7-one, known as TAS-103, is the most



Scheme 54.



Scheme 55.

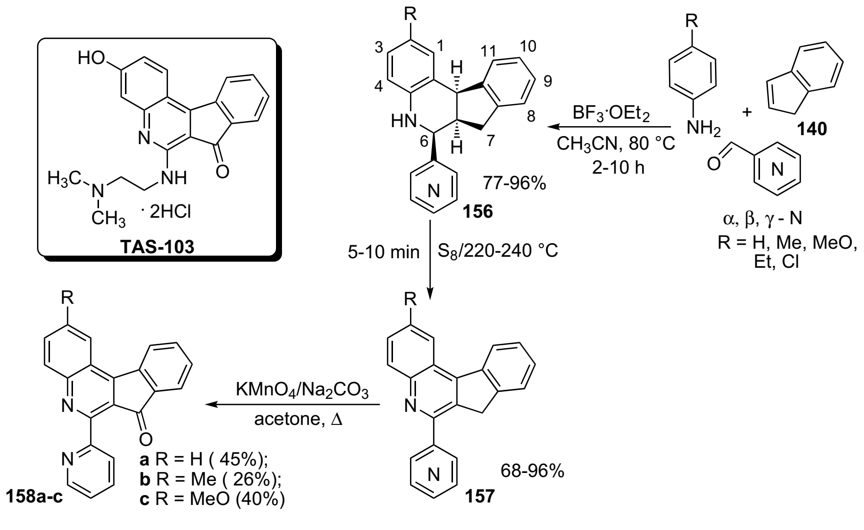


Scheme 56.

important compound of this family because its anti-cancer activity as a dual inhibitor of topoisomerases I and II is highly significant and it is used in clinical studies.[188] Imino DA methodology could be useful in the diversification process of 7*H*-indeno[2,1-*c*]quinolin-7-ones, because an efficient and general route for the synthesis of substituted indeno[2,1-*c*]quinoline derivatives **156**–**158** in a three-step synthesis was reported.[189] The target compounds are available from anilines, isomeric α-, β-, and γ-pyridinecarboxyaldehydes and indene **140** using a three-component imino DA cycloaddition as the key ring forming step. Subsequent treatment of obtained 5,6,6a,11b-tetrahydroindeno[2,1-*c*]quinolines **156** with powdered sulfur gives corresponding indeno[2,1-*c*]quinolines **157**, whose subsequent oxidation with potassium permanganate in acetone offers 7*H*-indeno[2,1-*c*]quinolin-7-ones **158** (Scheme 57).

5.2. Cyclic enamides as dienophiles. Construction of pyrrolo[3,2-*c*]quinoline alkaloids and related polycyclic quinolines

The isolation and identification of two alkaloids with potent bradykinin B antagonist, martinellic acid **159**, and martinelline **160** (Fig. 11), from the roots of Amazonian plant *Martinella iquitosensis*,[190] provided further inventive to synthetic methodology progress in cycloaddition chemistry. Containing central hexahydropyrrolo[3,2-*c*]quinoline core with multiple guanidine side chains, these alkaloids and their derivatives are still of



Scheme 57.

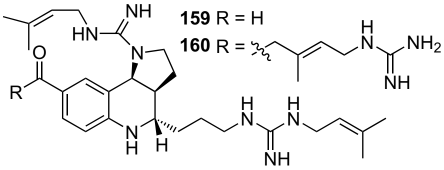


Figure 11.

pharmaceutical interest. Three research groups have accomplished the total synthesis of one or both of these alkaloids that was already reviewed.[191,192] It is noteworthy that intensive studies on the interaction between *N*-aldimines and endocyclic enamine derivatives **141** (Fig. 10) have greatly advanced to the development of total martinella alkaloids synthesis.

First finding on the use of cyclic enamides as dienophiles in the imino DA reaction to give central cis-fused hexahydropyrrolo[3,2-*c*]quinoline core were published in 1999 by Batey's group[193] and Stevenson's group.[194] Thus, cis-fused hexahydropyrrolo[3,2-*c*]quinolines **161**,**162** were constructed using Dy(OTf)$_3$- or InCl$_3$-catalyzed reaction of *N*-substituted 2-pyrrolines (type **141b**) and imines (Scheme 58).

However, this approach gave a 1:1 mixture of *endo*/*exo*-isomers and failed with aliphatic aldehydes making it difficult to introduce the required 4-(3′-aminopropyl) chain that was sending chemists in search of new approaches to construct key tricyclic triamine intermediate **166** with *exo*-orientation. Thus, reaction of aldimine **163** and *N*-Cbz 2-pyrroline using 12 mol% InCl$_3$ as catalyst afforded a 1.1:1 mixture of *exo*/*endo* isomers **164** and **165**, respectively, from which the desired *exo*-isomer **164** was separated by flash chromatography in 40% yield. This isomer was converted to intermediate **166** in six additional synthetic operations[67,195] (Scheme 59).

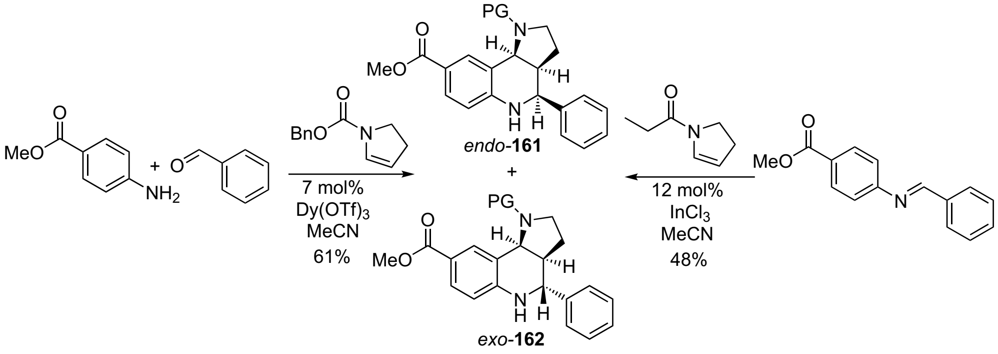
This key intermediate was also obtained via multi-linear steps starting with squaric-catalyzed imino DA reaction of 4-methoxycarbonylaniline, ethyl glyoxalate, and *N*-Cbz 2-pyrroline.[196] However, these approaches for construction of tricyclic triamine intermediate **166** with *exo*-orientation are not efficient and too long.

An elegant solution to this problem was given by Batey and co-workers when they noted that in absence of an aldehyde, 4-methoxycarbonylaniline coupled with 2 equiv of *N*-Cbz 2-pyrroline to provide *endo*/*exo*-isomers **167**,**168** those ratio could be considerably controlled by using Lewis acid (Dy(OTf)$_3$) or Brønsted acid (CSA, camphorsulfonic acid)[193,197] (Scheme 60).

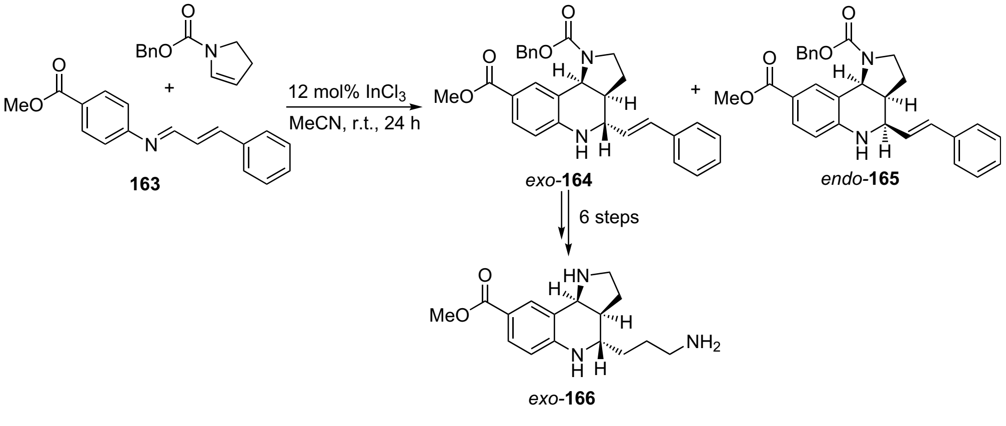
Curiously, these excellent results came from the failed three-component coupling of aniline, pentanal, and *N*-Cbz 2-pyrroline and led to the shorter total synthesis of martinellic acid and martinelline.[197] Moreover, this approach to the martinelline core can be used in combinatorial chemistry, making surrogate martinelline molecules.[198]

Recently, Yadav and co-workers reported that 4-methoxycarbonylaniline react with endocyclic enamides type **141b**,**c** on the surface of montmorillonite KSF clay under mild conditions to give the corresponding 3-aminopropylhexahydropyrrolo[3,2-*c*]quinoline **169** or 4-aminobutyloctahydrobenzo[*h*][1,6]naphthyridine **170** derivatives in excellent yields, but with moderate diastereoselectivity[199] (Scheme 61).

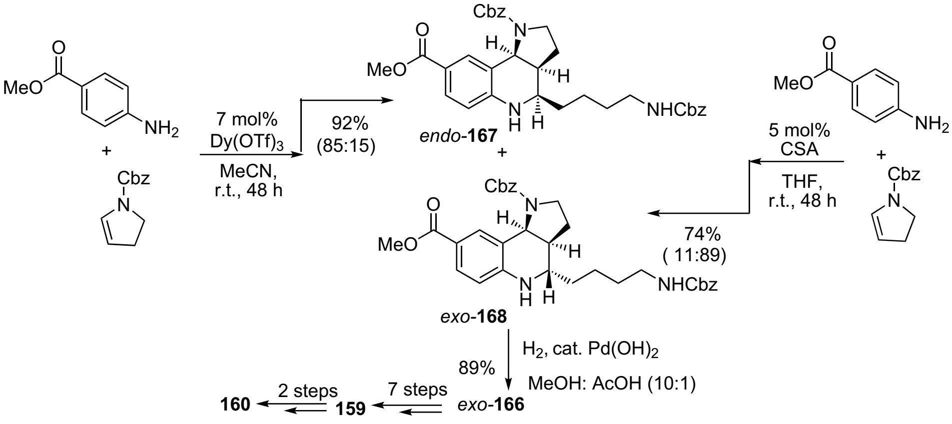
Another cyclic enamide, *N*-acetyl 2-azetine **141a**, is a special case of an enamide incorporating a highly strained reactive double bond, which reacts easily with various cyclic dienes.[200] This



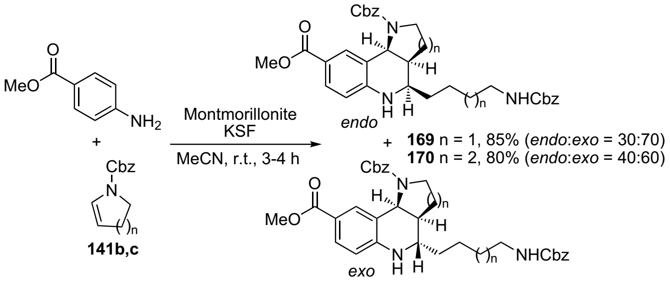
Scheme 58.



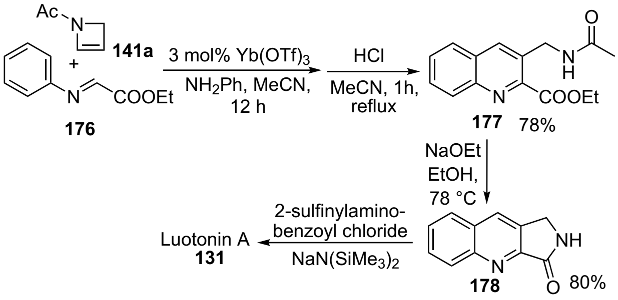
Scheme 59.



Scheme 60.



Scheme 61.



Scheme 63.

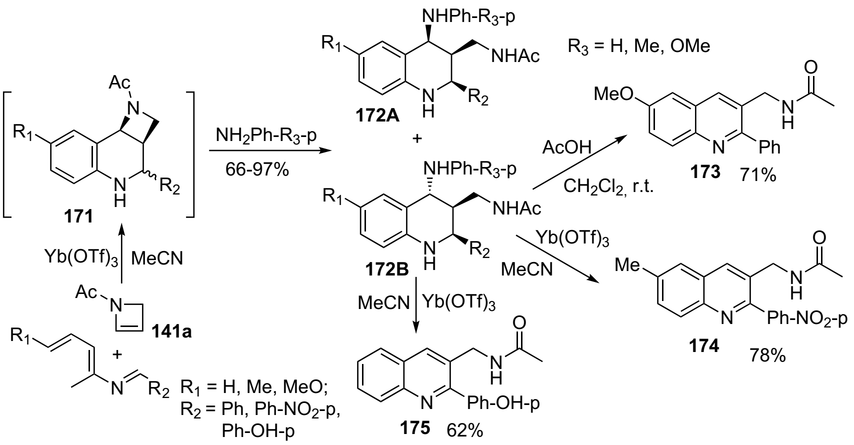
enamide undergoes also Yb(OTf)$_3$-catalyzed [4+2] cycloaddition with *N*-aldimines to initially give a 1:1 mixture of *exo*/*endo*-isomers of unstable cycloadduct **171** that reacted further with anilines to afford 2,3,4-trisubstituted tetrahydroquinolines **172** in good to excellent yield, predominantly as a single diastereoisomer **172B** with the two substituents at C-3 and C-4 trans-diaxial.[201,202] The later compounds could be converted into 2,3-disubstituted quinolines **173**–**175** through mild elimination or oxidation reactions (Scheme 62).

This cycloaddition chemistry was successfully extended to a 2-glyoxylate imine **176** to give 2,3-disubstituted quinoline **177** that was converted into tricyclic lactam **178**[203] (Scheme 63), a closer precursor to the antitumor alkaloid luotinin A **131**[204] (see, Fig. 9).

6. Conclusions

The major developments of both intra- and intermolecular imino DA reactions (Povarov reactions) of *N*-aryl imines and diverse electron-rich alkenes have been presented. Povarov reaction, a simple variant of venerable DA cycloadditions provides a direct route to different *N*-heterocycles in a single step from available precursors, Schiff's bases. In more recent developments, this reaction has served as a key step in the construction of complex polycyclic rings that make up the core of a number of important natural products.

Although a lot of effort has been devoted to the development of catalytic diastereoselective Povarov reactions of *N*-aldimines, only



Scheme 62.

a few successful enantioselective reactions have been published. Moreover, cycloaddition reactions of ketimines under Povarov reaction conditions have not been well studied. Thus, the invention of new efficient methods for the diastereo- and enantioselective synthesis of tetrahydroquinoline derivatives using three-component Povarov reactions is still in early development and remains a major objective for synthetic organic chemists.

Mechanistic insight into these reactions will be of outmost importance for further synthetic developments of bioactive quinoline production, while there does not appear to be one generic mechanism to adequately explain all reactions in this class.

However, the scope of this reaction is impressive. Products range from simple quinoline derivatives to the core of diverse antitumor alkaloids. Three-component imino DA reaction is a well-appreciated tool for the generation of moderate to large libraries of related *N*-heterocyclic compounds that are to be screened for pharmacological activity, taking into consideration that analysis of drugs in late development or on the market shows that 68% of them are heterocycles, where *N*-heterocyclic molecules have a strong preponderance. So, highly functionalized tetrahydroquinolines with well-defined stereochemistry, obtained easily via three-component Povarov reaction, would be reliable specific small molecules acting as modulators of protein–protein interactions that it is important for understanding protein function.

Truly general, efficient and easy-to-perform procedures for the Povarov reaction of used in situ simple imines or their surrogates are works in progress, and I hope this review helps to inspire further discoveries and innovations in the multi-component cycloaddition methodology for *N*-containing heterocycles preparation.

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Biographical sketch

Vladimir V. Kouznetsov was born and raised in Murmansk, Russia, in 1957. He studied Chemistry at the Russian Peoples Friendship University, Moscow where he received his Laurea M.Sc. (1981), Ph.D. (1986), and D.Sc. (1994) degrees in Chemistry, working with Professor Nikolai S. Prostakov and Associate Professor Ludmila A. Gayvoronskaya. He spent postdoctoral fellowship (1990–1992) with Professor José Barluenga and Professor Miguel Tomas at the University of Oviedo (Spain), working on synthetic approach to hetaryl substituted polyamines and tetraponerine alkaloids. He became Associate Professor in 1993 at the Russian Peoples Friendship University. In 1994 he moved to Colombia through a Colciencias' program of scientific mobilization. Very soon he became Professor Titular at the Industrial University of Santander (Bucaramanga, Colombia), where he founded the Laboratory of Organic Chemistry. Now he is director of the Laboratory of Organic and Biomolecular Chemistry. He was principal tutor of 19 graduated and 17 under graduated students, both in Russia and Colombia. He authored and co-authored over 130 papers, 5 patents, 3 books, and 1 book chapter. Actually, he is editorial board member of organic journals: *Letters in Organic Chemistry*, *Current Organic Synthesis* and *the Open Organic Chemistry Journal*. Kouznetsov's research interest focus on heterocyclic diversity-oriented, including natural product synthesis, interface between chemistry and biology.