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Synthesis of substituted 1,2,3,4-tetrahydroquinones by the Povarov reaction. New potentials of the classical reaction

V A Glushkov, A G Tolstikov

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Abstract. Reactions of aromatic Schiff bases with alkenes affording substituted 1,2,3,4-tetrahydroquinolines are reviewed. The synthetic potential and the mechanisms of reactions and the effect of catalysts and solvents on the stereochemistry of products are considered. The bibliography includes 189 references.

I. Introduction

Quinolines represent a practically important class of heterocyclic compounds of which many exhibit biological activity and serve as medicinal drugs. This class includes well-known antitumour alkaloids of the streptonigrine series,[1–3] *N*-methyl-D-aspartate antagonists,[4] γ-secretase inhibitors for treatment of Alzheimer's disease,[5] platelet aggregation inhibitors,[6] potential antiasthmatic agents, *i.e.*, lipoxygenase inhibitors,[7] fluoroquinolone antibiotics,[8] compounds with anti-AIDS activity.[9,10]

Among conventional methods of synthesis of substituted quinolines, mention should be made of the widely known Scraup, Döbner, Döbner – Miller, Combes, Conrad – Limpach – Knorr, Camps, Nimetowski, Pfitzinger and Friedlaender syntheses (descriptions of these methods can be found in several reviews[11–17]). The latest advances in the field of synthesis of quinolines were summarised in a review by Kouztetsov *et al.*[18]

In the middle of the 20th century, Povarov, Mikhailov and Grigos published a series of papers[19–25] in which they described an approach, new in principle for that time, to the synthesis of substituted quinolines consisting of the formal [4 + 2] cycloaddition of aromatic Schiff bases (anils) to activated (electron-enriched) alkenes (vinyl ethers, alkyl vinyl sulfides, *etc.*). The results of these studies were summarised in a review.[26] In the chemical literature, the proposed method of synthesis of substituted quinolines is known as the Povarov reaction (another name is the aza-Diels – Alder reaction).

This method came into active use with the synthesis of differently substituted 2-aryl(hetaryl)-1,2,3,4-tetrahydroquinolines, despite the relatively low yields of products.[27–38] In the early 1990s, new catalysts (triflates of rare-earth metals) were developed and new protocols of this reaction were elaborated (three-component synthesis, combinatorial synthesis on polymeric supports), which led to a substantial increase in the quinoline yields. As a result, this reaction had experienced the second birth. Despite a vast number of publications devoted to the use of the Povarov reaction in the synthesis of substituted quinolines, no summarising publications could be found on this subject, which stimulated us to write this review.

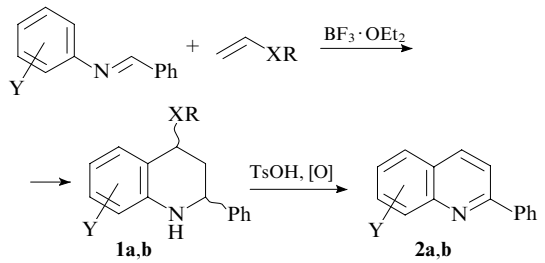
II. Reaction of aromatic Schiff bases with α,β-unsaturated ethers, alkyl vinyl sulfides and ketene dithioacetals

1. Synthetic potentials of the reaction

In the mid-1960s, Povarov and Grigos[19,20] showed that the condensation of ethyl vinyl ether with Schiff bases $YC_6H_4-N{=}CHPh$ (anils) in benzene in the presence of catalytic amounts (5 mol % – 10 mol %) of boron trifluoride etherate produces substituted 4-ethoxy-1,2,3,4-tetrahydroquinolines **1a** (X = O, R = Et) in moderate yields (up to 60%). Upon treatment of the reaction mixture with *p*-toluenesulfonic acid or oxidants [atmospheric oxygen[19] or $KMnO_4$ (Ref. 20)], quinolines **1a** eliminated ethanol to give the corresponding quinolines **2a** (yields up to 50%). In this case, ethyl vinyl ether acts as the C_2-synthon in the construction of the C(3)–C(4) fragment of the quinoline ring. Apart from vinyl ethers, this reaction was carried out with ethyl propenyl and ethyl isopropenyl ethers. Vinyl sulfides react similarly.[21]

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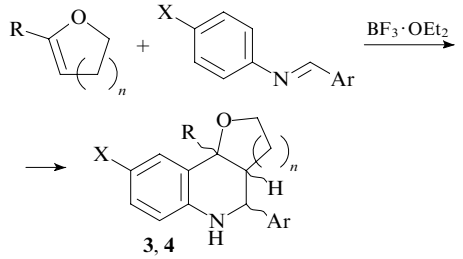


a: X = O; R = Et, Pr^i, Bu; Y = 6-Br, 6-I, 8-CO_2H;
b: X = S; R = Et, Bu; Y = H, 8-Me, 8-CO_2H, 6-MeO, 6-EtO (positions of substituents in products are shown).

This reaction may involve different anils of aromatic aldehydes that contain substituents in both the aniline residue and the benzene ring of the aromatic aldehyde. By the example of a reaction of such anils with alkyl vinyl sulfides, it was shown that the highest quinoline yields were reached with anils of low basicity. Thus the condensation of ethyl vinyl sulfide with benzylidene-*p*-anisidine and benzylidene-*p*-phenetidine more basic than benzylideneaniline afforded 6-methoxy- and 6-ethoxy-2-phenylquinolines in low yields (6.6% and 34.7%, respectively).[26]

Anils of non-aromatic unsaturated aldehydes can also undergo the Povarov reaction. Adducts of vinyl ethers and alkyl vinyl sulfides with anils of citral and cinnamaldehyde could be synthesised.[25] Anils of aliphatic aldehydes (*e.g.*, acetaldehyde anil) reacted with alkyl vinyl ethers generated *in situ* (the three-component version of the Povarov reaction, see below), whereas anils of alkyl aryl ketones (acetophenone, propiophenone, *etc.*) did not undergo this reaction.[26]

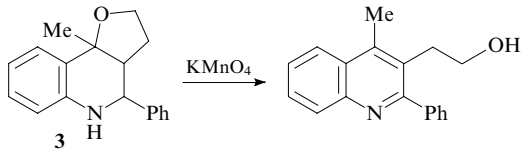
Cyclic vinyl ethers (particularly, dihydrosilvan (2-methyl-2,3-dihydrofuran) and 2,3-dihydropyran [19, 20, 22]) in their reactions with Schiff bases produced furo[3,2-*c*]quinolines **3** (yields 56% – 80%) and pyrano[3,2-*c*]quinolines **4** (yields 15% – 81%).



3: n = 1; R = Me; X = H, Cl, I, CO_2H, CO_2Me, OMe; Ar = Ph, 3-$NO_2C_6H_4$;
4: n = 2; R = X = H; Ar = Ph, 2-furyl, 2-thienyl.

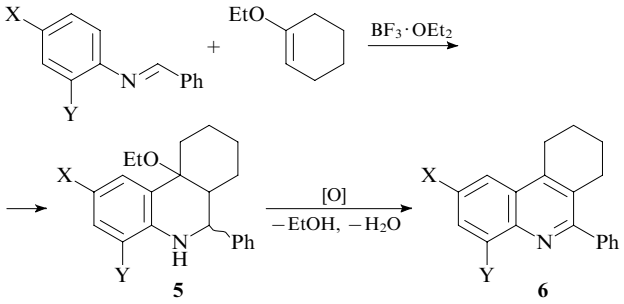
In contrast to compounds **1a**,**b**, the oxidation of compounds **3** and **4** does not produce the corresponding quinoline derivatives. Instead, the opening of the furan or pyran ring occurs.[26]

Thus oxidation of compound **3** with $KMnO_4$ led to the opening of the furan ring.[26]



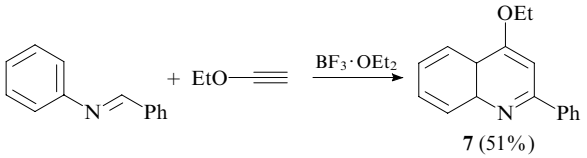
The above reactions furnished two (for compounds **1a**,**b**) or three (for compounds **3**, **4**) new asymmetric centres. However, in studies of Povarov *et al.*,[19–26] the stereochemistry of products was not specified (although in certain cases for compounds **3**, two diastereomers could be isolated in the ratio 1 : 1).†

The reaction of Schiff bases with 1-ethoxycyclohexene led to ethoxyoctahydrophenanthridines **5**. The isolation of compounds **5** was accompanied by spontaneous elimination of ethanol and aromatisation of the quinoline ring to afford 6-phenyltetrahydrophenanthridines **6**.[23]



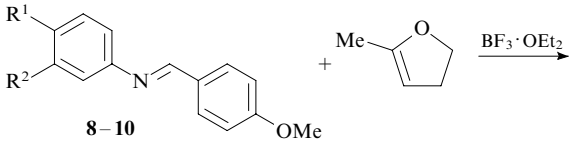
X = H, Br, CO_2H; Y = H, CO_2H.

In addition to vinyl ethers, the reaction with anils can also proceed with alkoxyacetylenes. Thus, condensation of ethoxyacetylene with benzylideneaniline yields 2-phenyl-4-ethoxyquinoline (**7**).[24]

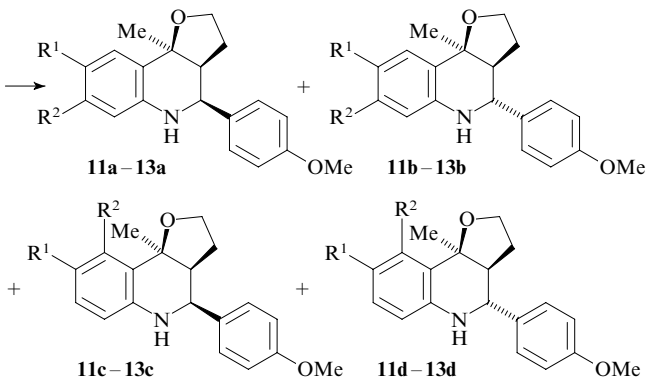


Povarov and Grigos [19–26] carried out most of their syntheses in benzene but also used diethyl ether, ethyl acetate and glacial acetic acid.[25] They used boron trifluoride etherate as the catalyst.

Further progress in the synthesis of tetrahydroquinolines fused with dihydrofuran and tetrahydropyran was associated with the studies of regioselectivity of the Povarov reaction.[28, 29] In the BF_3 -catalysed condensation of 5-methyl-2,3-dihydrofuran with anils **8** – **10**, four diastereomers were isolated in each case, where products **11a**,**b**; **12a**,**b** and **13a**,**b** substantially prevailed (> 10 : 1).

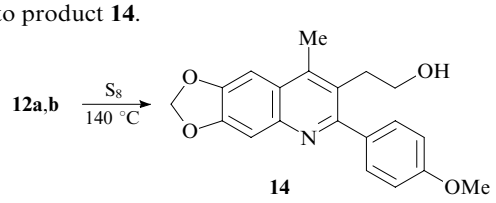


† Later, isomers of 9*b*-methyl-4-phenyl-2,3,3*a*,4,5,9*b*-hexahydrofuro-[3,2-*c*]quinoline were isolated using column chromatography and characterised by ^{1}H NMR.[27]

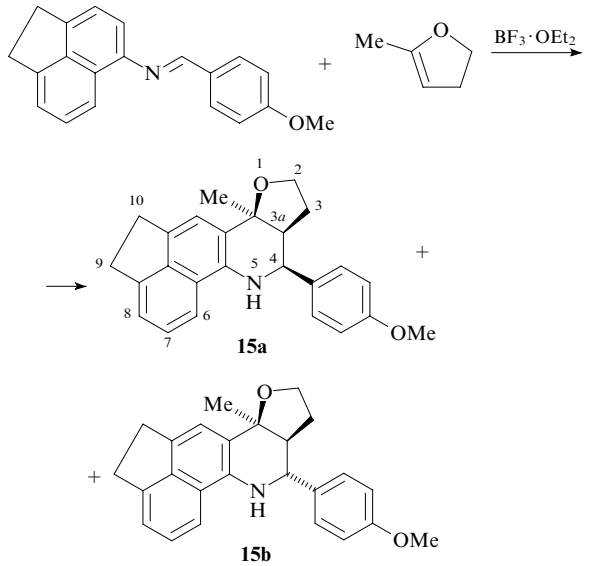


8, **11**: $R^1-R^2 = O(CH_2)_2O$; **9**, **12**: $R^1-R^2 = OCH_2O$;
10, **13**: $R^1-R^2 = (CH_2)_3$.

Heating of compounds **11**–**13** with sulfur led to their aromatisation accompanied by the furan ring scission. For example, under these conditions, isomers **12a** and **12b** were transformed into product **14**.

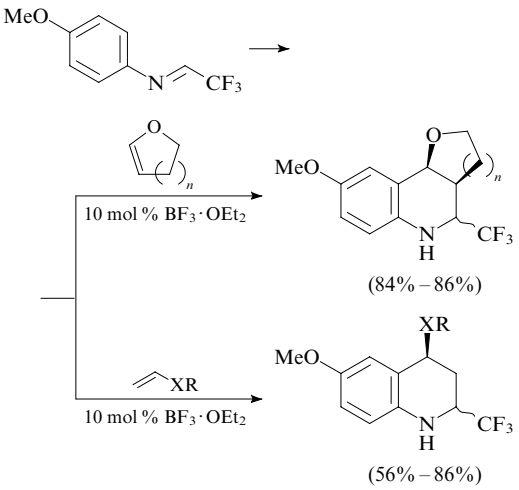


Synthesis of various polycyclic furo[3,2-*c*]quinolines, namely, cyclopenta[*g*]-, cyclopenta[*f*]-, benzo[*h*]- and indeno[1,7-*gh*]furo[3,2-*c*]quinolines was described [29] [particularly, *dl*-4-(*p*-methoxyphenyl)-11*b*-methyl-2,3,3*a*,4,5,9,10,11*b*-octahydroindeno[1,7-*gh*]furo[3,2-*c*]quinolines (**15a**,**b**)].



In the 1990s, interest was rekindled in the Povarov reaction, which led to the appearance of a vast number of publications in this field. For the most part, they were devoted to the search for new effective catalysts of this reaction. Besides $BF_3 \cdot OEt_2$ (Refs 19–41), the proposed catalysts for the Schiff base condensation with cyclic and acyclic vinyl ethers included other Lewis acids ($ZnCl_2$,[32] $AlCl_3$,[32] $EtAlCl_2$,[32] $SnCl_4$,[32] $TiCl_4$ both in the free state [32,42] and as complexes with chiral alcohols [43]); SmI_2;[44] $FeCl_3$ supported on K-10 montmorillonite clay;[45–47] a system $FeCl_3$–NaI,[48] chlorides MCl_3 [M = In,[49,50] Bi,[51] V,[52] Gd,[53] Sb (Ref 54)]; salts ($LiBF_4$,[55] lithium perchlorate [56]); Brønsted acids [triphenylphosphonium perchlorate,[57] CF_3CO_2H,[58–60] $KHSO_4$,[61] sulfamic acid,[62] phosphoric acid derivative of a chiral binaphthol (BINOL), *viz*., {1,1′-bi[3-(9-anthryl)]naphthyl-2-yl} phosphate,[63] acidic clay K-10,[64,65] cation exchange resins [66,67]; trimethylchlorosilane;[68] molecular iodine;[69,70] dicobalt hexacarbonyl;[71] lanthanide triflates both free [58,72–80] and polymer-supported [81] and their complexes with chiral ligands.[72,76] The range of solvents used in the Povarov reaction also increased. In addition to solvents proposed by Povarov *et al*., nitromethane,[32,38,73] tetrahydrofuran,[71,73] toluene,[32,39–41,63] dichloromethane [33,34,38,44–46,59,70,72,73] and dichloromethane–toluene mixture [43] were tested. Acetonitrile proved to be the solvent of choice.[47–49,53–55,57,58,60,67,68,70,74,79,82,83] Apparently, this is due to the fact that both the substrates and all the catalysts studied, particularly, molecular iodine and dysprosium triflate are easily soluble in acetonitrile. Trifluoroethanol and hexafluoroisopropyl alcohol also proved to be good solvents.[84–86] In CF_3CH_2OH, the Povarov reaction proceeded with good conversion and high yields.[85] A reaction in which liquid SO_2 simultaneously served as the solvent and the catalyst was described.[34] In some cases (*e.g*., in the catalysis with $InCl_3$ either added directly [51] or generated *in situ* from metallic indium and HCl and also in the catalysis with ion-exchange resins [66,75]), the synthesis could be conducted in water. Later, it was shown that the Povarov reaction easily proceeds in ionic liquids [77,87] and under controlled microwave radiation.[58] A solvent-free reaction was described.[88]

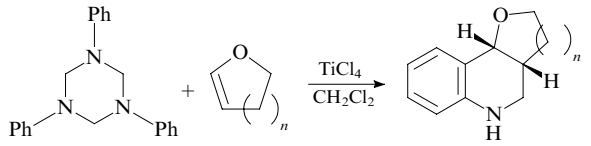
In addition to the quest for new catalysts for the Povarov reaction, attempts were undertaken to involve new substrates in this reaction (aimed at the synthesis of new biologically active tetrahydroquinoline derivatives) and at the development of new approaches to its execution. Particularly, biologically active fluoroalkyl derivatives of tetrahydroquinoline were obtained recently starting from (*E*)-α-trifluoromethyl-*N*-arylaldimines.[39,40]



X = O: R = Et, Bu; X = S: R = Ph; *n* = 1, 2.

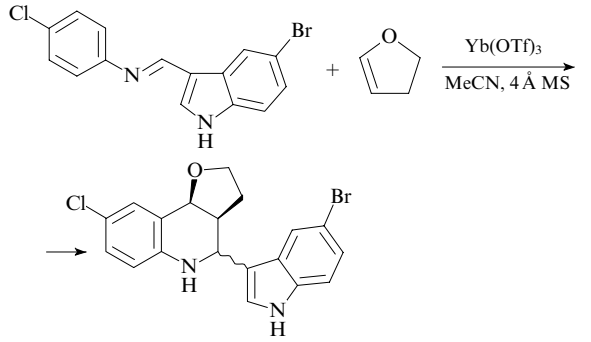
The reactions were regio- and stereoselective to yield preferentially *cis*-isomers. The use of 10 mol % $BF_3 \cdot OEt_2$ necessitated the use of low temperatures (−78 °C, toluene). Substitution of $Yb(OTf)_3$ for $BF_3 \cdot OEt_2$ neither increased the yield nor enhanced the stereoselectivity but made it possible to carry out these reactions at room temperature.

To synthesise tetrahydroquinolines with free position 2, Kametani *et al*.[33] used 1,3,5-triphenylperhydro-1,3,5-triazine (formaldehyde anil trimer) as the Schiff base.



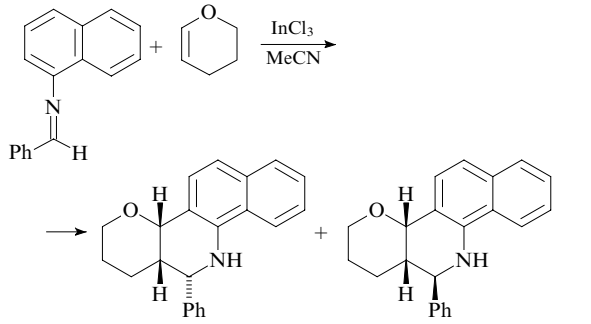
n = 1, 2.

Tetrahydroquinolines with heterocyclic substituents at C(2) were synthesised from hetarylcarbaldehyde anils.[33, 89] Thus a new antibacterial agent, 2-(1*H*-indol-3-yl)furo[3,2-*c*]-tetrahydroquinoline, was synthesised.[89]

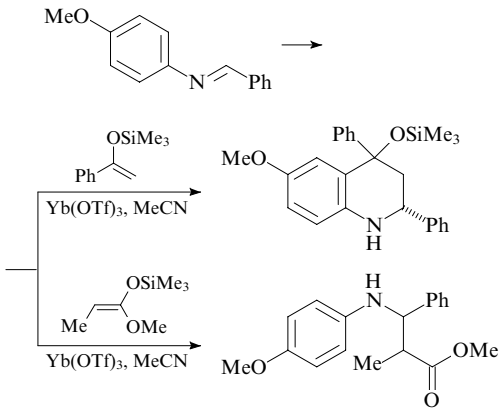


4 Å MS are 4 Å molecular sieves.

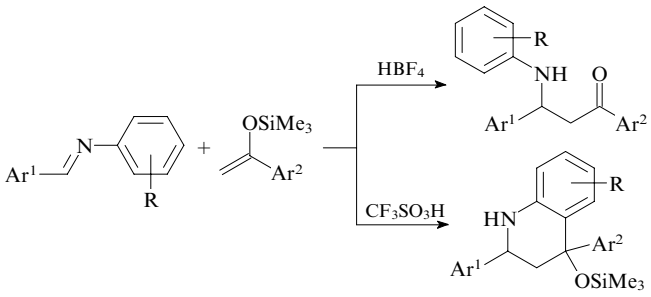
The reaction of 2,3-dihydropyran with 1-benzylideneaminonaphthalene furnished pyranobenzoquinoline derivative.[49]



In addition to vinyl ethers and alkyl vinyl sulfides, silyl ethers of enols may also serve as the substrates of the Povarov reaction.[74, 76, 90] However, the reaction did not always result in cyclisation (*e.g.*, see Refs 74, 76, 91); its direction substantially depended on the nature of the catalyst and the dienophile.

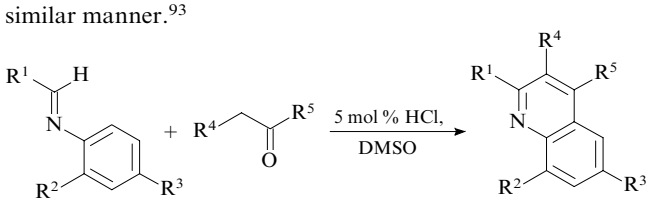


For example, the reaction of aldimines $Ar^1CH{=}NAr^2$ with silyl ethers of enols mediated by different Brønsted acids (HBF_4, CF_3CO_2H, HPF_6, CF_3SO_3H, *etc.*) was studied.[92] It was shown that cyclisation occurred only in the presence of CF_3SO_3H as the catalyst.



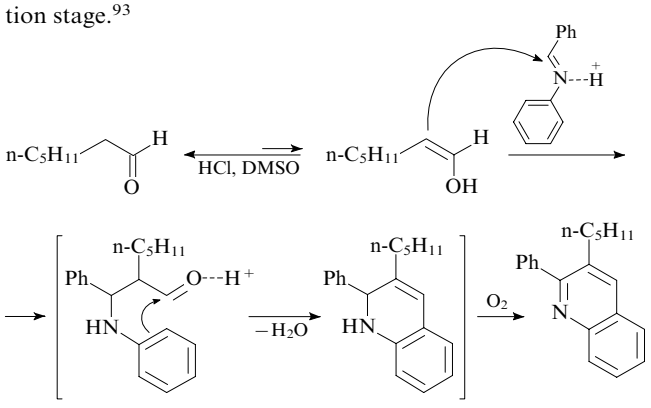
Ar^1 = Ph, C_6H_4Me-*o*, $C_6H_4NO_2$-*p*; Ar^2 = Ph, C_6H_4Me-*p*, C_6H_4OMe-*p*; R = H, Me-*p*, OMe-*p*, OMe-*o*, Cl-*p* (from hereon, the positions of substituents in the starting compound are shown).

Enolisable carbonyl compounds reacted with anils in a similar manner.[93]



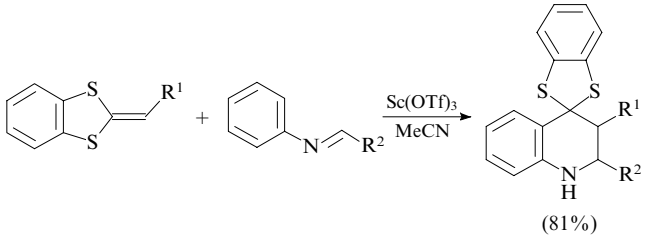
R^1 = Ph, 2-furyl; R^2 = H, OMe; R^3 = H, Cl, OMe; R^4 = H, Pr^n, n-C_5H_{11}; R^5 = H, Ph, CO_2Me.

The reaction mechanism includes a stage of aldehyde enolisation followed by the enol attack on the electrophilic C atom of the iminium ion. The original Schiff base or atmospheric oxygen may serve as the oxidant in the aromatisation stage.[93]



Being related to the Povarov reaction, this reaction represents a classical method of the Scraup synthesis of quinoline structures (these reactions will not be considered below).

Along with alkyl vinyl sulfides, the Povarov reaction can also proceed with ketene dithioacetals.[78]

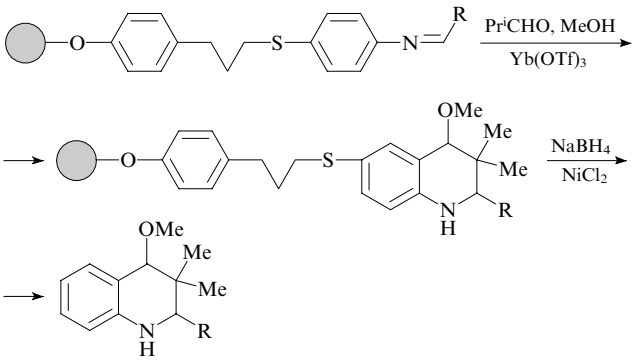


(81%)

R^1 = H, Ph, CH_2Ph, Pr^i; R^2 = 4-$MeO_2CC_6H_4$, Bu^i, Ph, Pr^i.

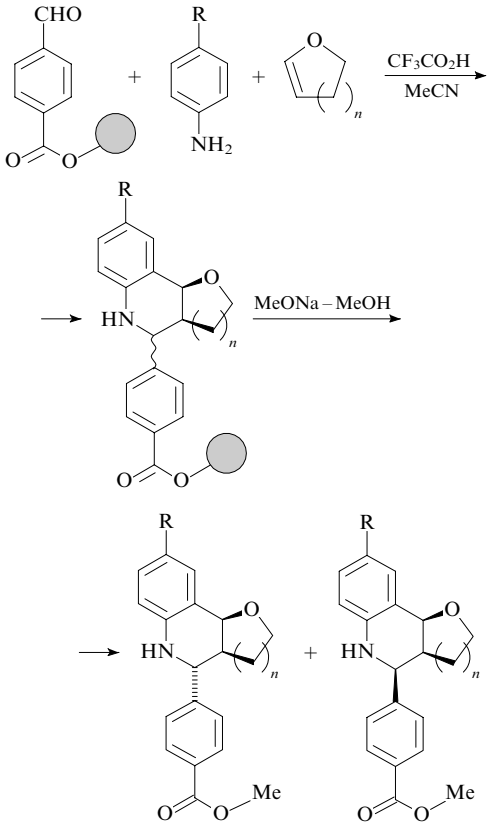
The use of 1,3-dithiolane and 1,3-dithiane derivatives instead of 1,4-benzodithiafulvene reduced the yields of the corresponding products to 38% and 35%.

Among the new approaches to performing the Povarov reaction, attention should be drawn to the use of immobilised substrates. Thus in the synthesis of various tetrahydroquinolines, poly(ethylene glycol)-immobilised Schiff bases were used.[94]



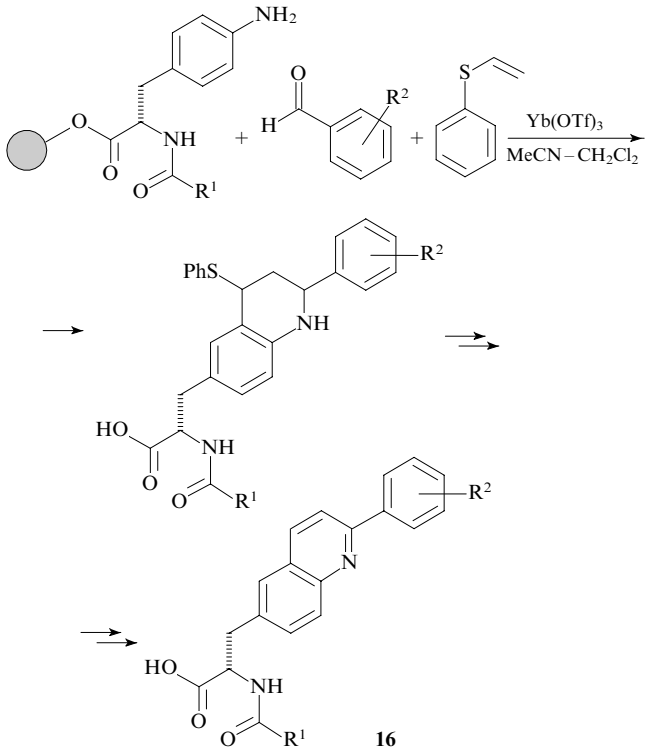
R = Ph, 4-FC$_6$H$_4$, 2-furyl, CO$_2$Et, Pr^i; ● — poly(ethylene glycol).

Immobilised aldehydes were also employed.[95,96]



R = H, F, Cl, Me, OMe; n = 1, 2.

This method was used in the production of non-natural hetarylamino acids of type **16**.[97]



16

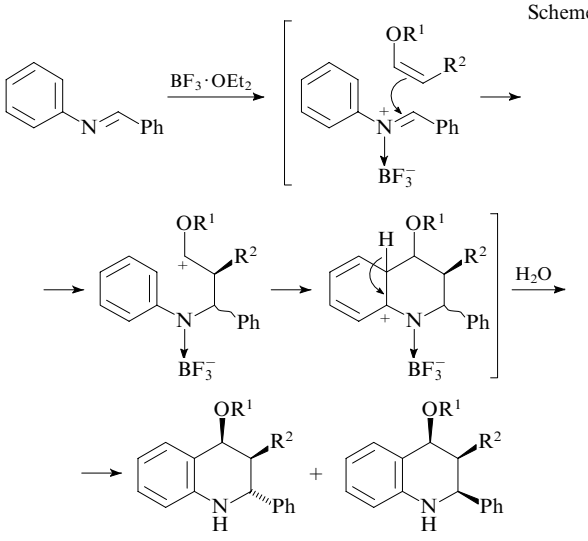
R^1 = 2-Me-6-ClC$_6$H$_3$, 2-Cl-4-MeSO$_2$C$_6$H$_3$, 2,6-F$_2$C$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$;
R^2 = 2-NO$_2$, 2-CF$_3$, 2-F-6-Cl, 2-OMe.

As is seen from the above Scheme, in this reaction, phenyl vinyl sulfide acts as a building block for the construction of the quinoline core [C(3) – C(4) fragment] of compound **16**.

2. Reaction mechanism

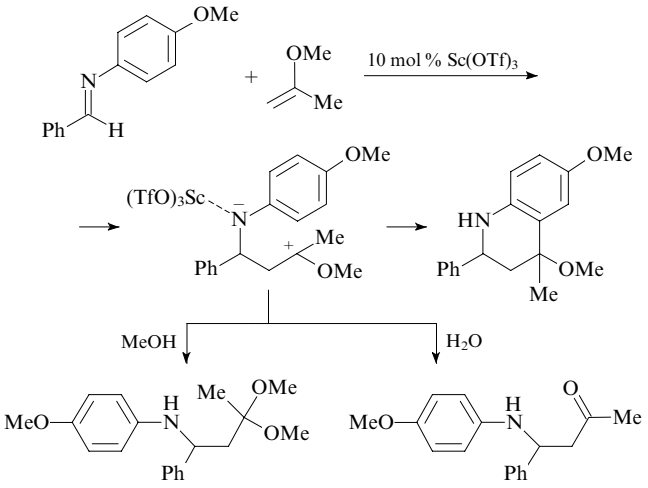
Povarov *et al.*[19–26] assumed that the reactions of aromatic Schiff bases with activated alkenes proceed as conjugated [4 + 2] cycloaddition. However, more recent numerous experimental studies (see *e.g.*, Refs 33, 38, 41, 73, 82 and 86), gave evidence in favour of the stepwise mechanism of the coupling of aromatic Schiff bases with activated alkenes catalysed by the Lewis or Brønsted acids (Scheme 1).

Scheme 1

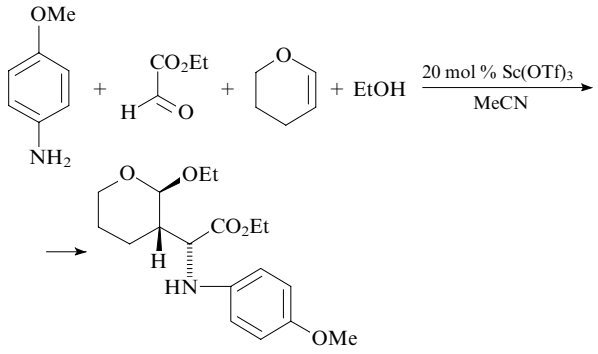


To prove that the Povarov reaction did follow this route, the ionic intermediates were 'captured' by nucleophiles, *e.g.*, methanol, introduced into the reaction medium (Scheme 2). The capture products were isolated and identified.[98]

Scheme 2

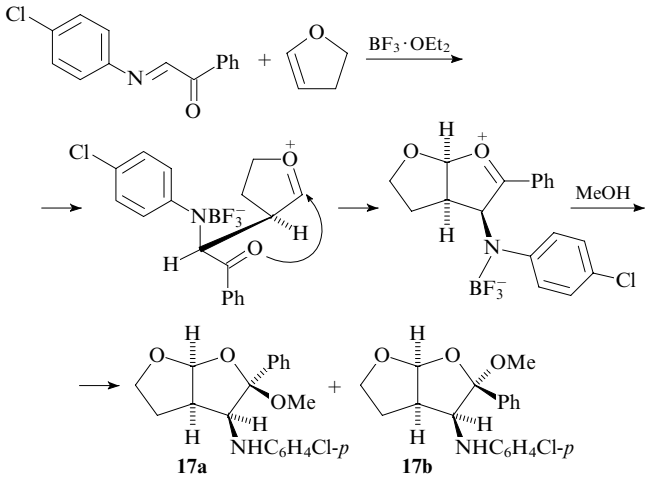


The capture by a nucleophile can also be the final stage in a multicomponent 'domino' condensation; in this case, no cyclisation was observed (one of the two diastereomers formed is shown).[42, 80]

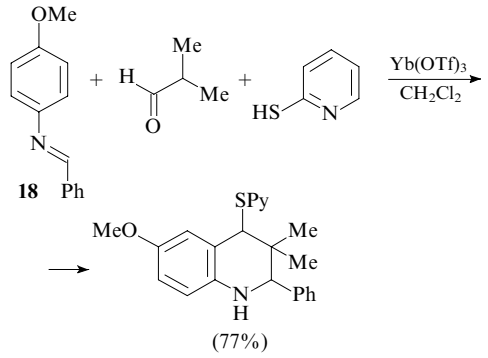


In addition to the Povarov reaction product (furo[3,2-*c*]-tetrahydroquinoline), the reaction of arylglyoxal anil with 2,3-dihydrofuran also produced substituted furo[2,3-*b*]furans **17a,b** (Scheme 3).[38] The structure of compound **17a** was confirmed by the X-ray diffraction analysis.

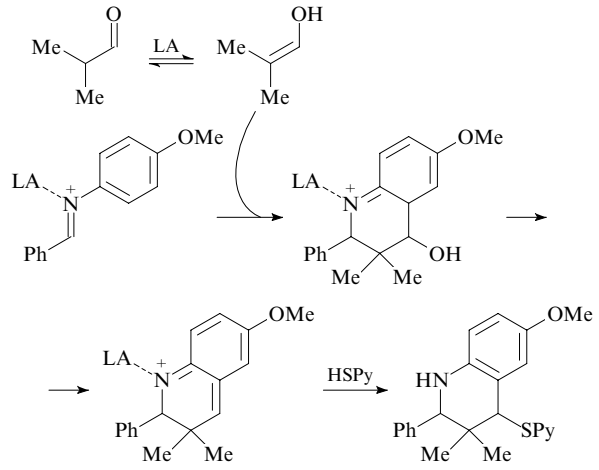
Scheme 3



The capture of a carbocation was the final stage in a peculiar three-component condensation of anil **18**, isobutyraldehyde and 2-mercaptopyridine.[73, 98]

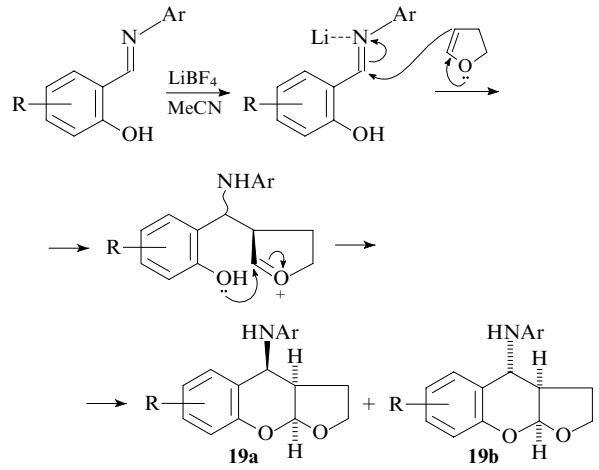


The reaction follows the route shown:



For salicylaldehyde anils, the cyclisation follows another route (Scheme 4).[55, 61]

Scheme 4

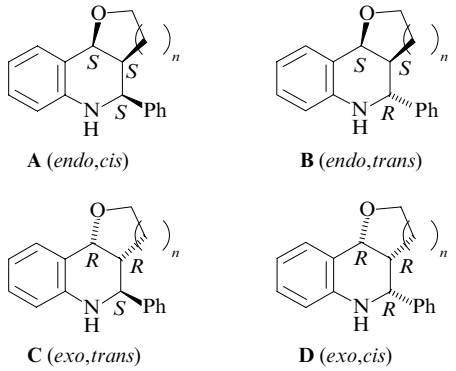


R = H, OMe, OEt; Ar = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$.

For the $LiBF_4$ as the catalyst, the ratio of diastereomers **19a** : **19b** was 100 : 0.[55] Stereochemistry of annulation of the tetrahydrofuran ring was determined using the nuclear Overhauser effect. For $KHSO_4$ as the catalyst, a mixture of isomers was obtained, which preferentially contained isomer **19b**.[61]

3. Stereochemical features of the reaction

In condensation of Schiff bases with dihydrofuran or dihydropyran derivatives, three asymmetric centres are formed in a single stage; however, insofar as in most cases, the annulation of a dihydrofuran or dihydrofuran ring proceeds in the *cis*-fashion, only four diastereomers are formed.

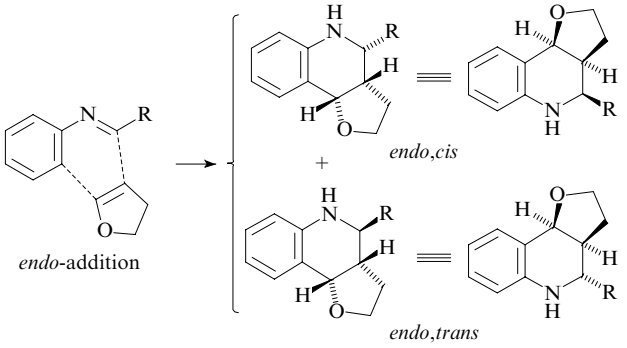


A (*endo*,*cis*) **B** (*endo*,*trans*)

C (*exo*,*trans*) **D** (*exo*,*cis*)

n = 1, 2.

Historically it happened that in the papers devoted to this issue the diastereomers shown in the upper row were referred to as the *endo* isomers.[46, 69, 79] Such a classification becomes clear once the *endo*-addition is presented as follows:



endo-addition

endo,*cis*

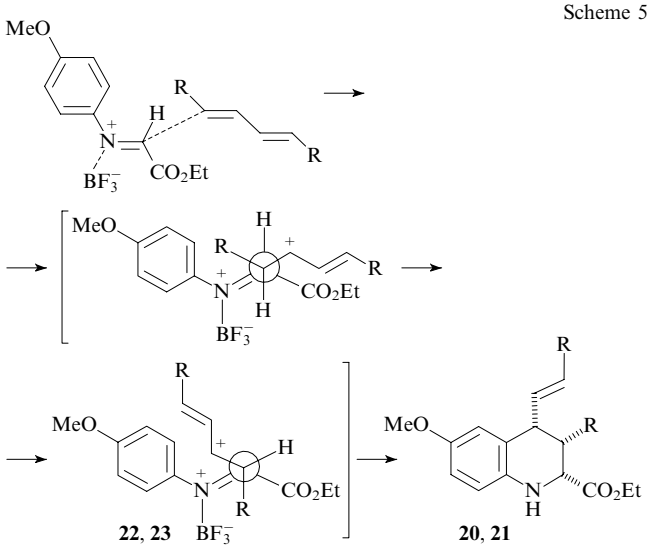
endo,*trans*

In this review, we will also stick to this classification, although, in our opinion, the concept of *endo*- and *exo*-addition is of little use in our case, being dependent on the point from which one looks at the molecule. In other words, rotated by 180° in the plane of the page, the reaction molecules may be considered as a case of *exo*-addition.‡

In each particular case, the ratio of diastereomers formed (*endo*,*cis* and *endo*,*trans*) is determined by the types of the catalyst and solvent; most often, *trans*-isomers slightly predominate (see, *e.g.*, Refs 47, 51–54, 66, 69), which was caused by steric effects of substituents in the transition state, although the opposite case is also observed.[38, 41, 48, 72]

The observed preferential formation of diastereomers **20**§ and **21** was explained[41] by the antiperiplanar arrangement of the ethoxycarbonyl group and the $RCH{=}CH{-}\overset{+}{C}H{-}CHR$ substituent in transition states **22** and **23** (Scheme 5).

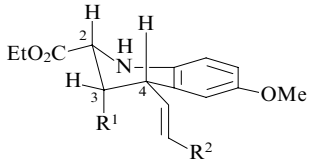
Scheme 5



22, **23** **20**, **21**

R = Me (**20**, **22**), $OSiMe_2Bu^t$ (**21**, **23**).

Stereochemistry of products **20** and **21** was unambiguously established by the ^1H NMR spectroscopy. The spin–spin coupling constants of the protons 2-H and 3-H pointed to small dihedral angles between these protons, which suggests the formation of the following *cis* structure:

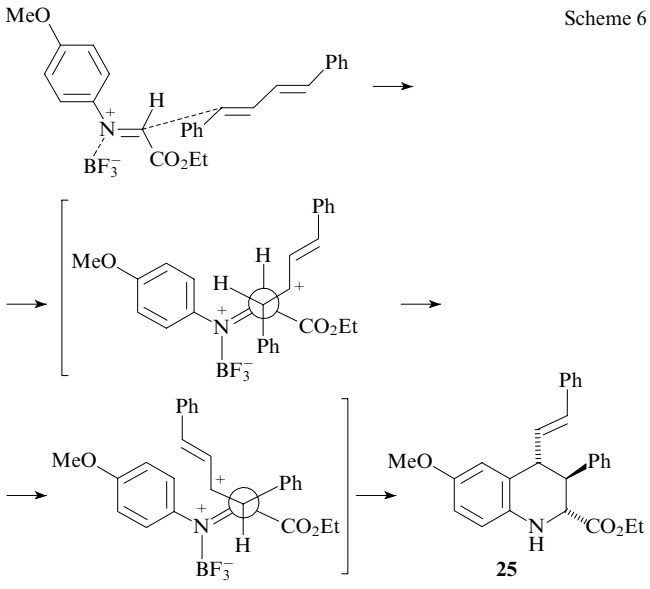


20: $J(2\text{-}H_a\text{–}3\text{-}H_e)$ = 3.0 Hz; $J(3\text{-}H_e\text{–}4\text{-}H_a)$ = 4.8 Hz;
21: $J(2\text{-}H_a\text{–}3\text{-}H_e)$ = 4.2 Hz; $J(3\text{-}H_e\text{–}4\text{-}H_a)$ = 3.9 Hz.

The stereochemistry of compound **20** was confirmed by the X-ray diffraction analysis.[41]

The addition of 1,4-diphenylbuta-1,3-diene to the Schiff base *p*-$MeOC_6H_4N{=}C(CO_2Et)H$ (**24**) followed a somewhat different route.[41] In this case, the product formed **25** had the 2,3-*trans*-2,4-*cis* stereochemistry. This stereochemistry was explained[41] by the nucleophilic attack of the diene to the imine face that bears the ethoxycarbonyl group, which was rather unexpected, because this face is sterically the most hindered (Scheme 6). Nonetheless, the stereochemistry

Scheme 6



25

‡ In the literature, the opposite description of *endo*–*exo*-isomerism can be found.[39, 40] Moreover, very often [77, 87, 99] a compound with a substituent at the C(2) of tetrahydroquinoline, oriented in the same direction as the annulated heterocycle is called the *endo*-isomer and its enantiomer with respect to C(2) atom is called the *exo*-isomer. In the present review, these classifications are not used.

§ Reactions of Schiff bases with dienes are considered in the next Section; however, it seems reasonable to consider the results obtained in Ref. 41 here.

of product **25** was confirmed by both ^{1}H NMR [J(2-H – 3-H) = 8.7 Hz, J(3-H – 4-H) = 8.7 Hz] and X-ray diffraction analysis.

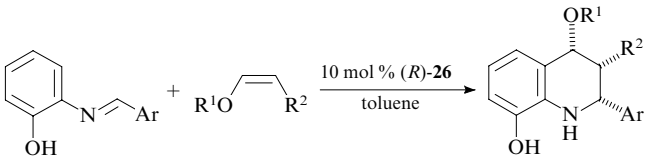
In all other cases, the stereochemistry of cyclisation products was determined in a similar way from ^{1}H NMR spectra wih recourse, if necessary, to the nuclear Overhauser effect [77] and double resonance.

The aforementioned studies [41] were analysed so thoroughly in order to demonstrate that the stereochemical outcome of the Povarov reaction may strongly depend on the substrate structure. Insofar as the quantum chemical calculations of the stepwise ionic mechanism of this reaction were carried out in only one study [31] (in contrast to calculations of the concerted mechanism),¶ the consideration of such schemes of transition states is speculative in many aspects, despite the seemingly logical explanation [38, 41, 82] of stereochemical results.

In some publications (see, *e.g.*, Refs 38, 69, 70), the effect of solvent on the stereoselectivity of cyclisation was studied. It was noted that in non-polar solvents the *cis* : *trans* isomer ratio with respect to positions 2 and 4 increases. A decrease in the temperature and the addition of 4 Å molecular sieves also favoured the increase in stereoselectivity.[43]

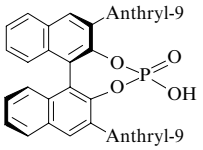
Insofar as three asymmetrical centres are formed in a single stage of the Povarov reaction, the possibility of controlling the stereochemistry of this reaction by using chiral catalysts seems attractive. The studies on this issue, started by Kobayashi [72] back in 1996, are continued today. Kobayashi used a Yb(OTf)$_3$ complex with (*R*)-(+)-BINOL, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2,6-di-*tert*-butylpyridine as the chiral inductor.[72] The reaction of ethyl vinyl ether or dihydrofuran with anils synthesised from derivatives of salicylaldehyde and 1-naphthylamine demonstrated high stereoselectivity of cyclisation [*endo*-addition, *cis* : *trans* isomer ratio varying from 99 : 1 to 94 : 6 (for ethyl vinyl ether) and from 93 : 7 to 91 : 9 (for dihydrofuran)].[72] For butyl vinyl ether, the *cis* : *trans* ratio was 66 : 34.

When the Povarov reaction was carried out in the presence of 10 mol % of catalyst (*R*)-**26**, the *cis* : *trans* ratio was 99 : 1 (Ref. 63). As is seen from the reaction scheme, this is *exo*-addition.



R^1 = Et, R^2 = H; R^1 – R^2 = $(CH_2)_2$, $(CH_2)_3$.

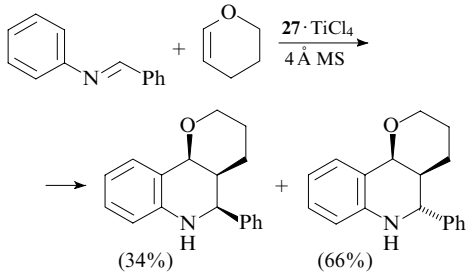
(*R*)-**26**:



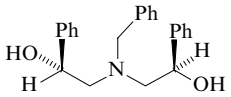
Presumably, the reaction proceeds *via* a nine-membered transition state in which oxygen atoms of the P(O)OH group form hydrogen bonds with the OH group and the nitrogen atom of the imine, respectively.

The *trans*-isomer dominated in a reaction catalysed by a TiCl$_4$ complex with a chiral diol BnN(CH$_2$CHPhOH)$_2$ (**27**).[43]

¶ For quantum chemical calculations of the classical Diels – Alder reaction, see, for example, Refs 100 and 101.



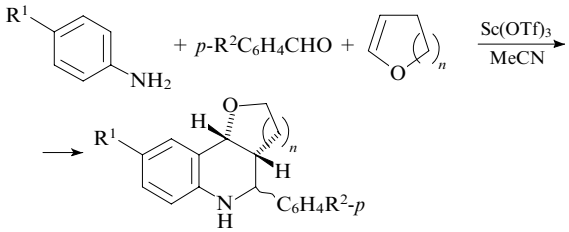
27:



Sometimes, but not necessarily, the diastereomers with respect to C(2) of the tetrahydroquinoline ring can be separated by column chromatography on silica gel.[40, 47, 52, 57]

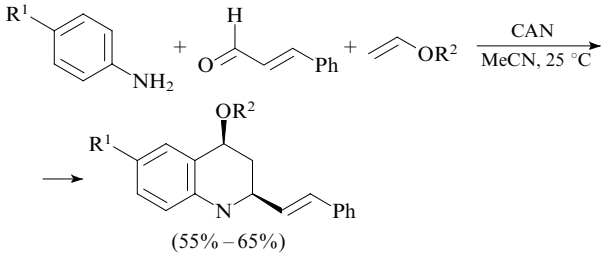
4. Three-component version of the reaction

Nowadays, multicomponent reactions have received wide acceptance [98, 102 – 104] due to the their simple protocol and the high processability index, although the product yields are sometimes low. The literature of recent years contains many examples of the three-component Povarov reaction (see, *e.g.*, Refs 53, 54, 82, 98, 99 and 105), particularly, those involving cyclic vinyl ethers.[54]



R^1, R^2 = H, Me, Cl, OMe; n = 1, 2.

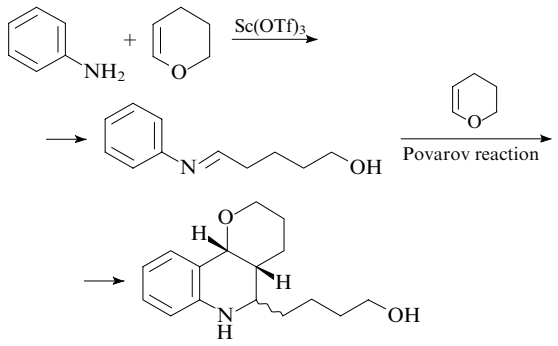
The use of acyclic vinyl ethers led to the formation of exclusively *cis*-isomers.[105]



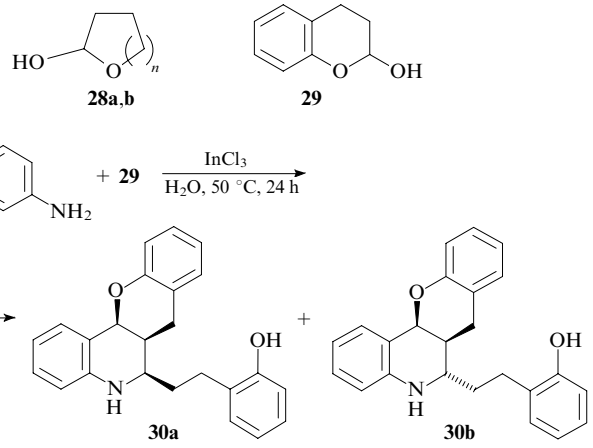
R^1 = H, Cl, Me; R^2 = Et, Pr^n, Bu^n; CAN is cerium ammonium nitrate.

The three-component version of the reaction was used most often provided the unstable Schiff bases derived from aniline and aliphatic aldehydes served as 2-azadienes. The *in situ* formation of *N*-arylaldimine and its 'domino' reaction with a dienophile made it possible to carry out the Povarov reaction in a single step.[79]

In some cases, dihydrofuran and dihydropyran may play a dual role, namely, of dienophiles and of masked ω-hydroxyaldehydes. In this case, the reaction involved two stages: first, dihydropyran (dihydrofuran) as the hydroxy aldehyde took part in the formation of a Schiff base and then, as a dienophile, underwent the Povarov reaction (see, *e.g.*, Refs 64, 69 and 82).

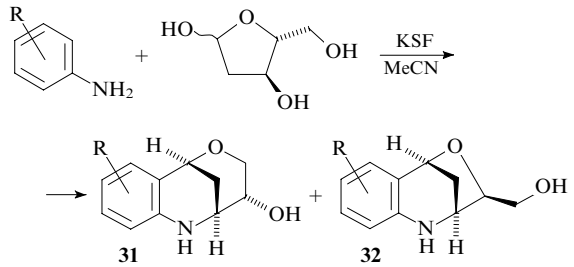


In place of dihydrofuran and dihydropyran, hemiacetals **28a**,**b** or hemiacetal **29** can be used.[103]



The ratio of isomers **30a** : **30b** was 24 : 76, the total yield of the products was 49%.

The same role was played by carbohydrate derivatives [103, 106] (a reaction with 2-deoxyribose is shown [106]).

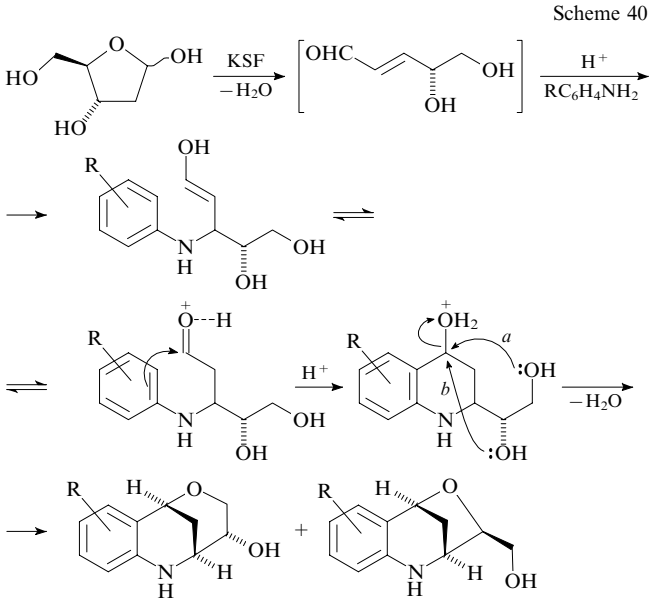


R = H, *p*(*m*,*o*)-Cl, *p*(*m*,*o*)-Me, *p*-Cl; KSF is montmorillonite KSF.

The reaction proceeds on the surface of montmorillonite KSF under mild conditions at ambient temperature. The yields of products were 70% – 86%. The structures of adducts **31** and **32** were established based on the ^{1}H NMR spectra [106] and the structure of adduct **31** was confirmed by X-ray diffraction analysis.[103]

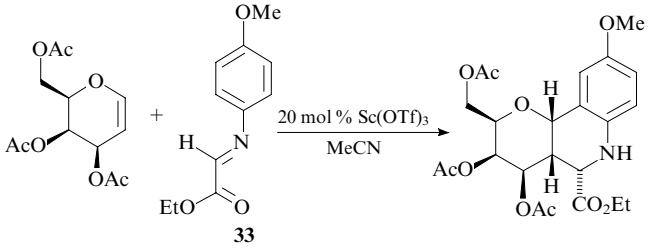
Different *ortho*-, *meta*-, *para*-substituted and 2,4-disubstituted anilines served as substrates of this reaction. No reaction was observed with 2,6-dichloro- and 2,6-dimethyl-anilines. This suggested that one *ortho* position in the aniline molecule should remain unsubstituted. The following reaction mechanism was proposed [106] (Scheme 7):

Scheme 40



Earlier, catalysis of this reaction by $InCl_3$ has been documented.[103]

Recently, the first case of using triacetylglucal in the Povarov reaction has been described.[80] Anil **33** derived from ethyl glyoxylate and *p*-methoxyaniline served as the Schiff base; this surpasses the anils of aromatic aldehydes in reactivity.



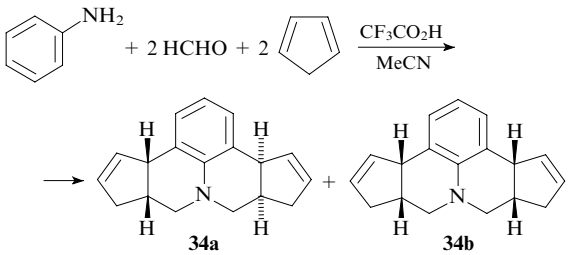
This method of annulation of tetrahydroquinoline with carbohydrate derivatives is of undoubtful interest from the synthetic viewpoint.[80]

In certain 'domino' reactions, aromatic amines were generated *in situ* by the reduction of the corresponding nitro compounds [107] or aromatic azides.[48]

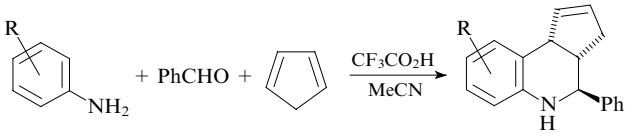
III. Reactions of anils with cyclopentadiene, indene and other alkenes

1. Synthetic potentials of the reaction

In 1988, Grieco and Bahsas [108] published the results of studies of reactions of cyclapentadiene with heterodienophiles where cyclopentadiene did not play its usual role of a classical diene, but paradoxically behaved as a dienophile.



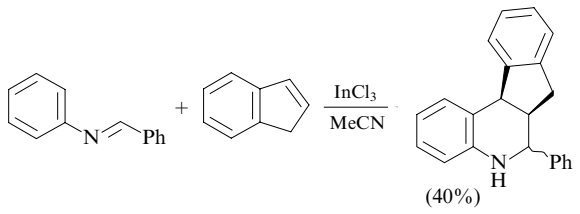
The ratio of diastereomers **34a** : **34b** was 3.7 : 1, the total yield of the products was 98%. The reaction with 1 equiv. of cyclopentadiene afforded tetrahydroquinolines annulated with the cyclopentene ring.[108]



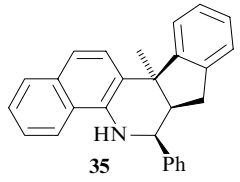
R = *o*-Cl, *o*-CO_2H, *p*-CO_2H, *p*-NO_2.

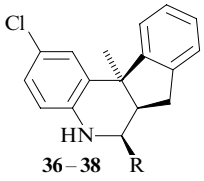
In some later studies, this transformation was named the 'Grieco reaction',[109] although, in essence, this is the Povarov reaction as applied to cyclopentadiene.

The reaction ofindene with aromatic Schiff bases resembles that of cyclopentadiene.[35, 37, 49, 56, 81] Thus benzylideneaniline reacted with indene in the presence of 20 mol % $InCl_3$ to form indeno[2,1-*c*]quinoline.[49]

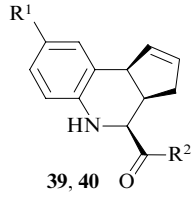


The indene ring adds strictly in the regioselective fashion,[35, 37, 56, 81] which is associated with the indene attack on the C(2) atom of the intermediately formed immonium ion (the resulting benzyl carbocation was more stable). Indene as a substituent with enhanced steric requirements enhances the reaction steroselectivity. Thus the addition of methylindene to Schiff bases derived from 1-aminonaphthalene and benzaldehyde, from *p*-chloroaniline and naphthalene-1-carbaldehyde, furfural or cyclohexanecarbaldehyde in the presence of polymer-supported scandium triflate afforded adducts **35**–**38**, respectively, as the only regio- and stereoisomers.[81] The condensation of cyclopentadiene with imino glyoxylates and α-keto imines proceeded smoothly (see Refs 35, 41, 81, 110–112) to afford adducts **39** and **40**, respectively.



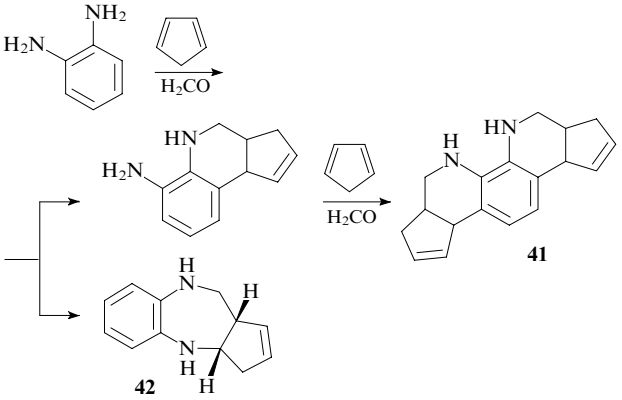


R = α-naphthyl (**36**), 2-furyl (**37**), cyclo-C_6H_{11} (**38**).



39: R^1 = H, R^2 = OEt (81%);[111]
40: R^1 = Cl, NO_2; R^2 = Ph (87%–88%).[112]

o-Phenylenediamine reacts with formaldehyde and cyclopentadiene to give a mixture of amines **41** and **42** (stereochemistry of compound **41** is unknown).[36]



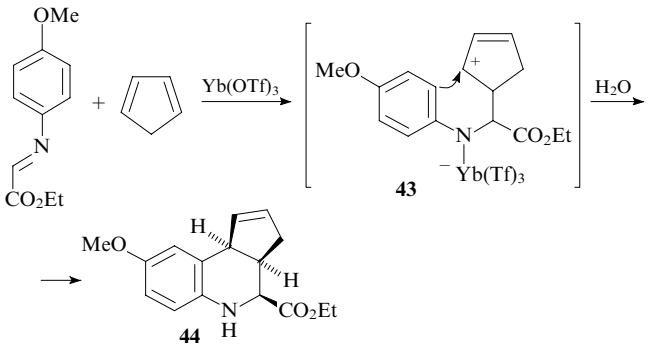
As in reactions of Schiff bases with vinyl ethers, the condensation of aromatic Schiff bases with cyclopentadiene proceeds in the presence of catalysts, namely, Lewis and Brønsted acids. However, in this case, it is not recommended to use too active Lewis acids such as BBr_3, $AlCl_3$, $SnCl_4$, $EtAlCl_2$, $TiCl_4$, $BF_3 \cdot OEt_2$,† as the catalysts, because they cause resinification and polymerisation of cyclopentadiene (as a rule, the latter is taken in the 2–5-fold excess with respect to the imine).[114] Several publications reported low degrees of conversion when this reaction was catalysed with classical Lewis acids.[112]

The catalysts used most often in the reaction of aromatic Schiff bases with cyclopentadiene and indene include $InCl_3$ in acetonitrile,[49] $AlCl_3 \cdot Et_3N$ adduct in CH_2Cl_2,[110, 113] triflates of copper and lanthanides in MeCN (Refs 72, 90, 111, 112, 114 and 115) including polymer-supported modifications,[81] SmI_2 in CH_2Cl_2,[44] lithium perchlorate in diethyl ether,[56] triphenylphosphonium perchlorate,[57] $BF_3 \cdot OEt_2$ in acetonitrile,[116] and certain Brønsted acids (CF_3CO_2H in MeCN,[109] formic acid,[117] sulfamic acid,[62] urea nitrate[118]). Some types of clays, *e.g.*, bentonite and montmorillonite, were also used.[119] In the reaction of cyclopentadiene with benzylideneaniline, dicyanoketene acetal was used,[84] but the product yield was only 17%.

2. Reaction mechanism and stereochemistry

Several publications were devoted to the mechanism of the reaction of aromatic Schiff bases with cyclopentadiene.[41, 110, 111, 114] The asynchronic ionic nature of the condensation catalysed by Lewis or Brønsted acids was disclosed,which was similar to the mechanisms of the reactions of anils with ethyl vinyl ether, dihydrofuran and dihydropyran. The reaction starts with the imine activation by a Lewis acid and proceeds *via* zwitterionic complex **43** (Scheme 8).

Scheme 8

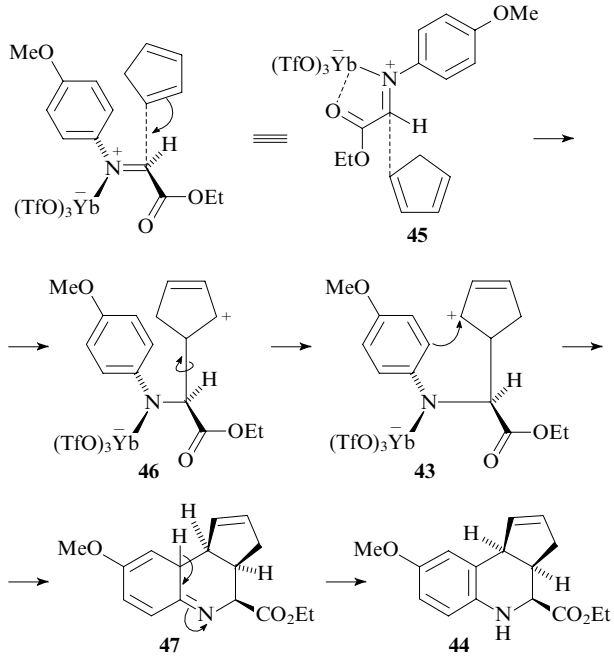


† It should be noted that the last three catalysts should be used at −78 °C.[37]

The preferential formation of *endo*,*cis*-product **44** was confirmed by ^{1}H NMR data.

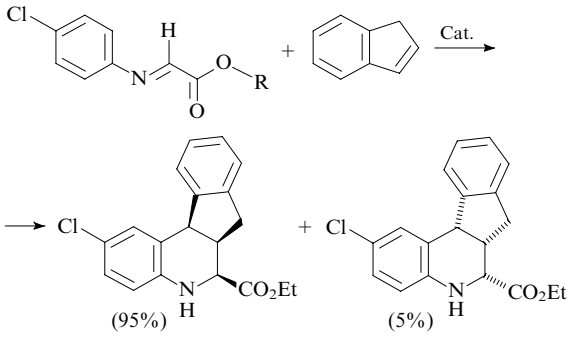
Stereochemistry of the target product is predetermined by the manner in which cyclopentadiene approaches the imine. In other words, the stereochemistry of the molecule is established in the very first stage and depends on the way in which the addition of cyclopentadiene to the imine occurs.[111] Scheme 9 shows the stereochemical peculiarities of this reaction. A nucleophile approaches the sterically less hindered face of the activated complex, by orienting itself away from the ethoxycarbonyl group with respect to the C=N bond (complex **45**). Such an orientation favours the formation of a C–C bond. Rotation of the cyclopentene substituent about the C–C bond in intermediate **46** leads to intermediate **43**, which is followed by the electrophilic attack of the allylic cation on C(2) atom of the aromatic ring to afford intermediate **47**. Aromatisation of the latter upon hydrolysis leads to target compound **44** with three asymmetric centres.[111]

Scheme 9



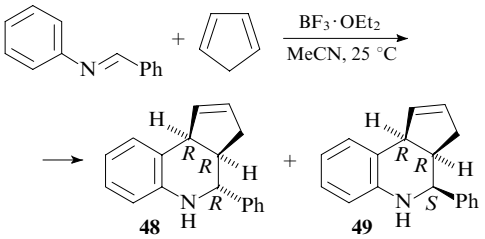
The proposed scheme is valid only if the starting imine has the *E*-stereochemistry, *i.e.*, is completely in the *s-trans*-configuration. Otherwise, the stereochemistry of the cyclopentene ring annulation is the opposite. As a rule, imines exist in the *E*-configuration; moreover, this configuration is reinforced due to the Lewis acid coordination to the carbonyl oxygen (complex **45**).

One of early studies[37] devoted to streochemistry of the addition of cyclopentadiene and indene to chiral imines derived from *p*-chloroaniline and bornyl, menthyl or 8-phenylmenthyl glyoxylate considered the asymmetric induction of the condensation reaction. The highest stereoselectivity (the ratio of diastereomers 96 : 4) was reached in the reaction of indene with (–)-8-phenylmenthyl glyoxylate anil.



R = (–)-menthyl, (–)-8-phenylmenthyl;
Cat. = $BF_3 \cdot Et_2O$, $TiCl_4$, $SnCl_4$, $EtAlCl_2$.

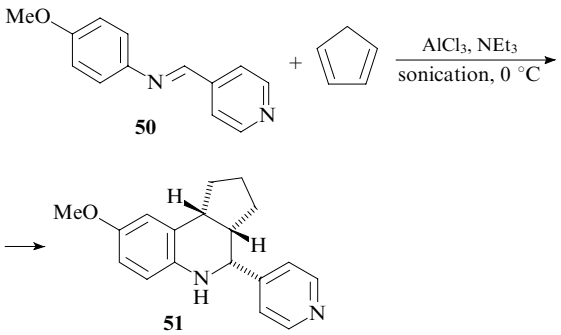
As regards the annulated ring orientation (*endo*–*exo*-selectivity), this primarily depends on the catalyst nature. For example, according to our data, the $BF_3 \cdot OEt_2$-catalysed reaction of benzylideneaniline with cyclopentadiene in acetonitrile produced a mixture of *endo*-(2*R*,3*R*,4*R*)-**48** and *endo*-(2*S*,3*R*,4*R*)-**49** isomers in the 3 : 2 ratio.



The absolute configuration of *endo*-(2*R*,3*R*,4*R*)-**49** was determined by X-ray diffraction analysis (unpublished results).

Catalysis with bentonite favoured the predominant formation of *endo*,*cis*-isomer **49**, its structure being confirmed by ^{1}H NMR.[120] The high stereoselectivity of the formation of *endo*,*cis*-isomer **49** (the ratio *cis* : *trans* = 98 : 2) was also observed in the reaction catalysed by a chiral complex of ytterbium triflate with (*R*)-(+)-BINOL.[72] A similar result was obtained in the condensation of cyclopentadiene with imines derived from substituted anilines and aryl glyoxylates.[121] On the whole, the preferential formation of *endo*-isomers was observed.

Schiff base **50** synthesised from *p*-anisidine and pyridine-4-carbaldehyde in the reaction with cyclopentadiene catalysed by a system $AlCl_3$–Et_3N afforded *exo*-isomer **51**; its structure was confirmed by X-ray diffraction analysis.[114]

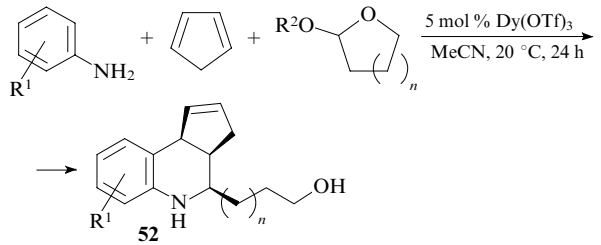


Sonication increased the yield of compound **51**.

3. Three-component and combinatorial syntheses

The three-component version of the reaction of anils with alkenes is very popular due to the simplicity and practical feasibility of this process.[57, 62, 109, 116, 120]

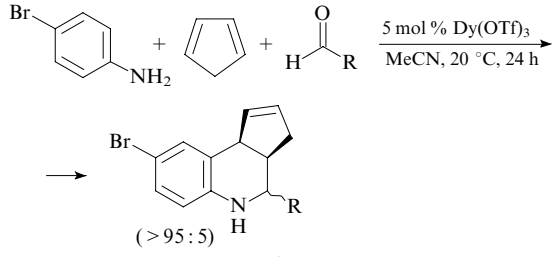
Thus the reaction of substituted anilines, cyclopentadiene and masked aldehydes, namely, 2-ethoxytetrahydrofuran or 2-methoxytetrahydropyran, afforded *endo*,*cis*-isomers **52** with diastereoselectivity >95%.[79]



R^1 = H, *p*-Cl, *o*-Cl, *p*-Br, *p*-Ph, *p*-CO_2Me, *p*-CF_3;
R^2 = Et (*n* = 1), Me (*n* = 2).

Typically, anilines with electron-donating groups, such as *o*-aminophenol and *p*-anisidine, did not undergo this reaction, and 2,3-dihydropyran reacted with a small yield (18%).

Even aliphatic easily enolisable aldehydes could be the substrates of this reaction.[79] To minimise the aldol condensation of aldehydes and the competitive self-coupling of transient *N*-arylamine according to the Döbner–Miller type mechanism, the aliphatic aldehyde was introduced dropwise over a long period. This allowed maintaining of a low concentration of free aldehyde in the reaction mixture.[79] The use of a mild catalyst, $Dy(OTf)_3$ increased the yield of the target products to 58%–92%; the diastereomeric purity of the compounds formed reached 95%. It should be noted that the addition of a chiral aldehyde, namely, (*R*)-glyceraldehyde acetonide, led to the total loss of diastereoselectivity.[79]

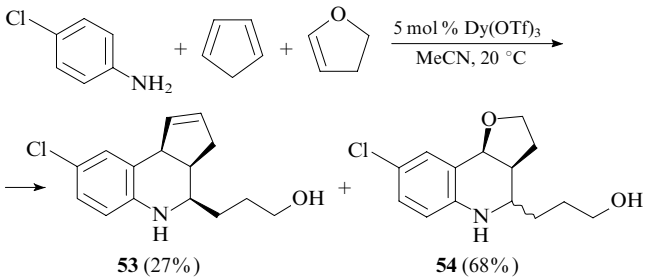


R = Et, Pr^i, Pr^n, Bn, CH_2CH_2Ph,



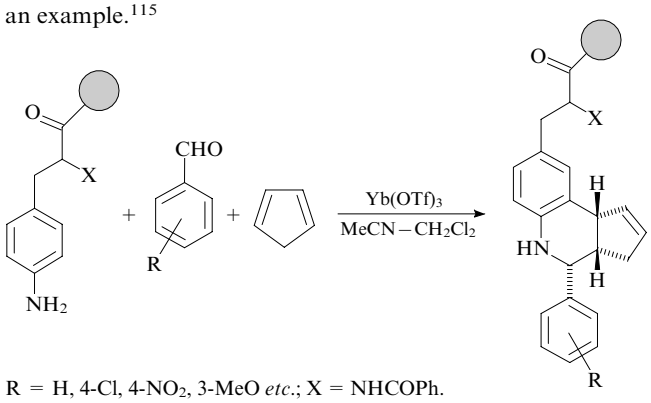
.

Upon the introduction of a mixture of dienophiles, namely, dihydrofuran and cyclopentadiene, into the reaction with *p*-chloraniline, competition between these dienophiles was observed.[79] The yields of products **53** and **54** were 27% and 68% when all three substances were added simultaneously;



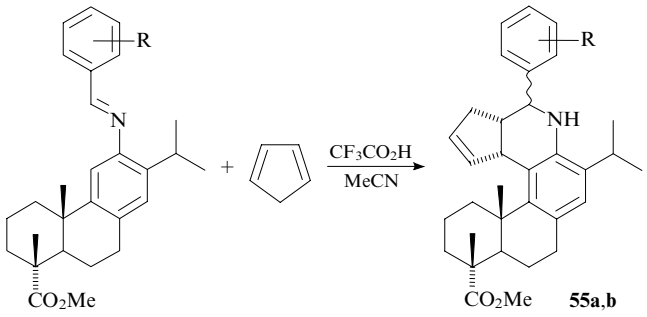
however, the gradual addition of dihydrofuran into the reaction mixture containing *p*-chloroaniline and cyclopentadiene afforded only one product **53** in 45% yield.[79]

Using the methods of combinatorial chemistry, Kiselyov and Armstrong [109, 115] collected libraries of substituted tetrahydroquinolines. They used three-component condensation of a polymer-supported aniline, various aldehydes and dienes. The aldehydes were represented by benzaldehyde and its derivatives, α-naphthaldehyde, furfural; the alkenes included cyclopentadiene, indene, aryl-substituted ethylenes. The best results were obtained for cyclopentadiene as the alkene. As the catalyst, either trifluoroacetic acid [109] or ytterbium triflate [115] were used. The reaction of immobilised 4-aminophenylalanine with benzaldehyde derivatives and cyclopentadiene is shown as an example.[115]



R = H, 4-Cl, 4-NO_2, 3-MeO *etc.*; X = NHCOPh.

The stereochemistry of the cyclopentene ring annulation depends on the nature of the aromatic compound used. Thus, being sterically overcrowded, Schiff bases derived from methyl 12-aminodehydroabietate produced *exo*-isomers **55a**,**b** in a ratio *R*:*S* = 3:2. The structure of the products was established by ^{1}H and ^{13}C NMR spectroscopy.[116]

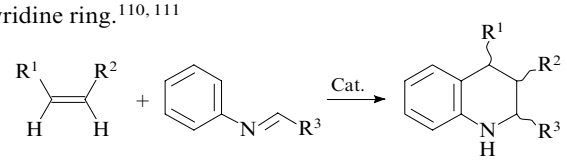


R = H, 3-NO_2, 4-CF_3.

The effect of the catalyst on the yield of condensation products was studied.[115] As the catalysts, 1% and 3% trifluoroacetic acid, 1% $BF_3 \cdot OEt_2$, 1% $TiCl_4$, 5% $InCl_3$, 0.1% $Yb(OTf)_3$, *etc*. were assayed. The use of $Yb(OTf)_3$ produced the highest yields.

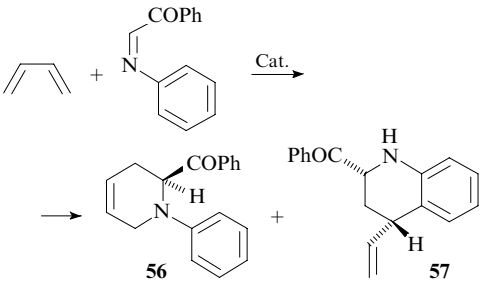
Apart from cyclopentadiene and indene, other substituted alkenes were recently introduced into the Povarov reaction, particularly, styrene [83] and its α-methyl [36, 121–123] and β-methyl derivatives,[36, 124, 125] 1-methoxybuta-1,3-diene,[41] 1-acetoxybuta-1,3-diene,[110, 111] 1-trimethylsiloxybuta-1,3-diene,[110, 111] 1-(*tert*-butyldimethylsiloxy)buta-1,3-diene,[41] 1,4-bis(*tert*-butyldimethylsiloxy)buta-1,3-diene,[41] hexa-2,4-diene,[41] 1-phenylcyclohexa-1,3-diene,[123] 1-methoxycyclohexa-1,3-diene (Refs 110, 111). A characteristic feature of the chemical behaviour of 1-methoxy-, 1-trimethylsiloxy-, 1-acetoxybuta-1,3-diene and analogous compounds is that they react with aromatic Schiff bases as alkenes rather than as vinyl ethers. In

contrast to the aforementioned substituted buta-1,3-dienes, the Danishefsky diene (1-methoxy-3-trimethylsiloxybuta-1,3-diene) does not undergo the Povarov reaction, but reacts with amines exclusively as a diene, which results in closure of the pyridine ring.[110, 111]

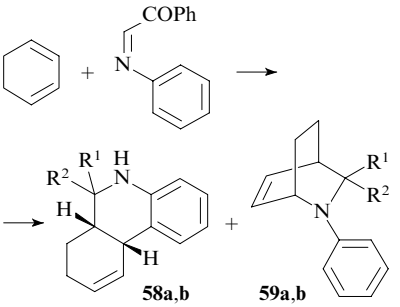


R^1 = Ar, CH=CH_2, CH=CHOMe, CH=$CHOSiMe_3$, CH=$CHOSiBu^t_3$, CH=CHOAc; R^2 = H, Me, $OSiMe_3$, $OSiBu^t_3$; R^3 = Ar, CO_2Et, COPh.

Buta-1,3-diene behaved in a dual manner in the reaction with a reactive amine synthesised from aniline and phenyl glyoxal, namely, as a diene and as a dienophile (the ratio of products **56** : **57** = 1 : 3);[112] 2,3-dimethylbuta-1,3-diene did not undergo this reaction.[111]



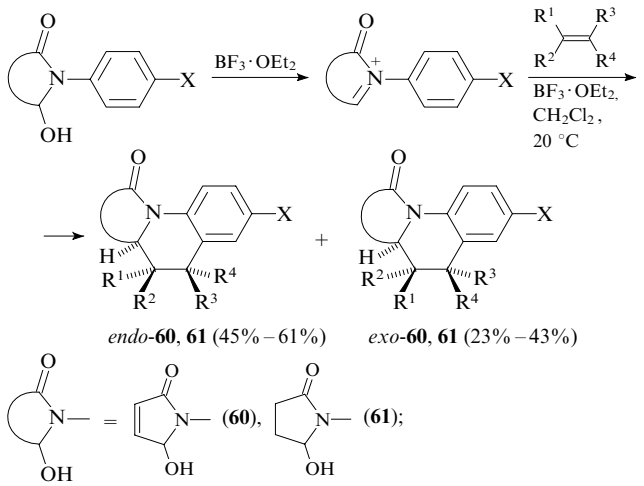
As regards cyclohexa-1,3-diene, in 2004 Whiting and co-workers[111] pointed out that copper(II) and ytterbium(II) triflates do not catalyse its reaction with aromatic Schiff bases. On the other hand, back in 1988 Prato and co-workers[112] described compound **58** as the rearrangement product of adduct **59** obtained in a $BF_3 \cdot OEt_2$-catalysed 'normal' Diels–Alder reaction. Apparently, boron trifluoride etherate is a more active catalyst of this reaction as compared with triflates.



a: R^1 = COPh, R^2 = H; **b**: R^1 = H, R^2 = COPh.

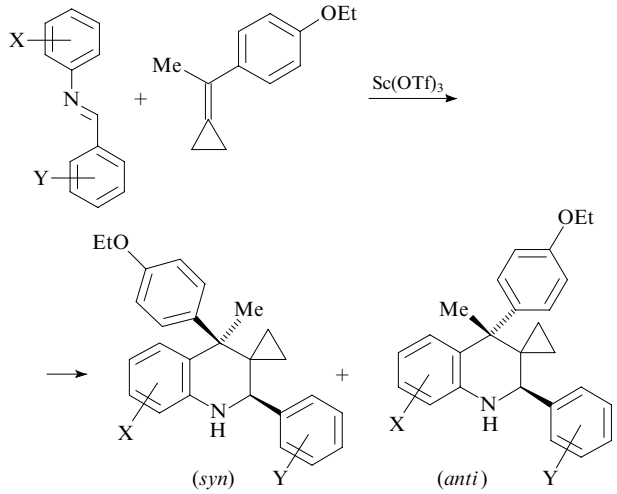
The reaction of anils with alkenes was catalysed by different compounds, namely, $BF_3 \cdot OEt_2$,[41, 124, 126–129] $Et_3N \cdot AlCl_3$,[125] CF_3CO_2H,[123] CF_3SO_3H and n-$C_8F_{17}SO_3H$,[127] Co(acac)$_3$,[111] Cu(OTf)$_2$,[111] Yb(OTf)$_3$,[111, 127] triflates of scandium, zirconium, tin, zinc,[127] clay montmorillonite KSF.[65] This reaction was also catalysed by 2,3-dichloro-5,6-dicyanobenzoquinone, tris(4-bromophenyl)amminium hexachloroantimonate,[122] and photochemically.[121]

The synthesis of pyrrolino- (**60**) and pyrrolidino[1,2-*a*]quinolin-1-ones (**61**) by the reaction of styrene, α-methylstyrene, anethole or indene with *N*-acyliminium cations generated *in situ* from 5-hydroxy-1-arylpyrrolin-2-ones or -pyrrolidin-2-ones was described.[126]

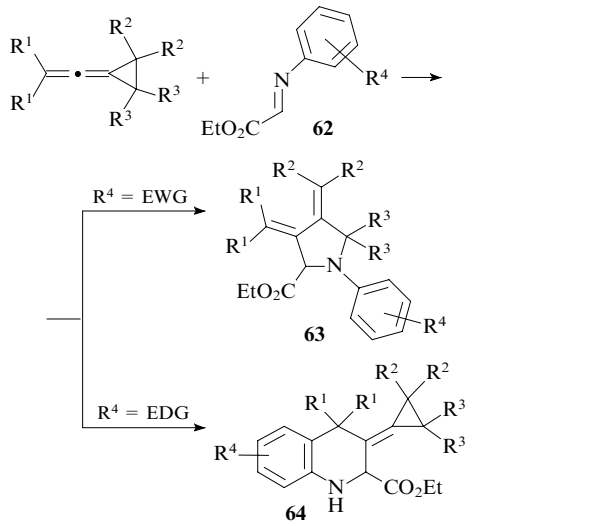


X = H, Me, OMe, Cl; R^1 = H, Me; R^2 = H, Bn; R^3 = Ph, Bn; R^4 = H, Me.

Reactions of anils with methylenecyclopropanes[65, 127] and vinylidenecyclopropanes[128, 129] were also described. The reactions were catalysed by boron trifluoride etherate or triflates of ytterbium, scandium, zirconium(IV), indium(III) and tin(II).[129]



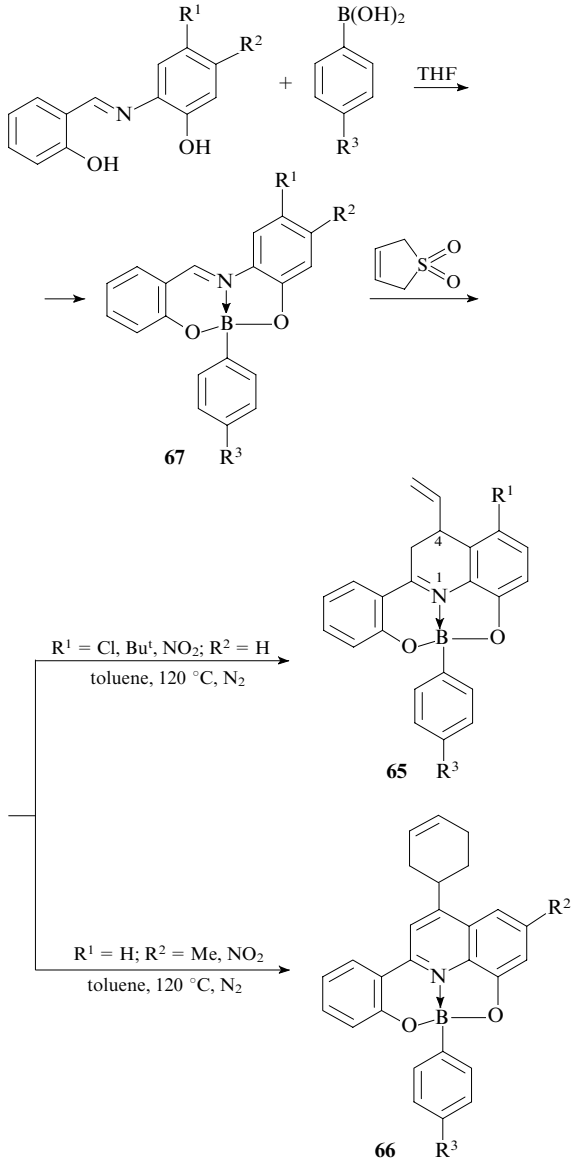
X = H, *m*-CF_3, *o*-MeO, *p*-EtO; Y = H, *p*-MeO, *p*-NO_2.



R^1 = Me, Ph; R^2 = Me, Ar; R^3 = H, Me; R^4 = H, *p*-F, *p*-Cl, *p*-Me, *p*-MeO, *m*-Me, *o*-CF_3.

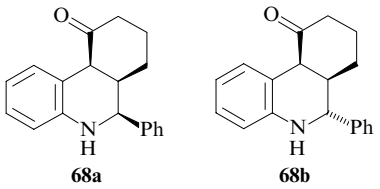
Depending on the structure of the parent vinylcyclopropane and the nature of substituent R^4 [electron-donating (EDG) or electron-withdrawing (EWG) groups] in the aromatic nucleus of imine **62**, the reaction may involve either the cyclopropylalkyl rearrangement step to afford pyrrole derivatives **63** or follow the mechanism of intramolecular alkylation to form quinoline derivatives **64**. For R^4 = *p*-Br, *p*-Cl or *o*-CF_3, the reaction produced substituted pyrroles; for R^4 = *m*-Me, *p*-Me, quinolines were formed.[129] Thus, electron-donating groups in the aromatic ring of the imine favour the Povarov reaction, whereas electron-withdrawing groups favour the cyclopropylalkyl rearrangement.[129]

Mexican chemists proposed an unconventional template method for the synthesis of boronates **65** and **66**.[130] Starting boronates **67** were heated in toluene with a six-fold excess of sulfolene in sealed tubes at 120 °C. Under these conditions, boronates **67** (R^2 = H) afforded 4-substituted 3,4-dihydroquinoline **65** with a *cis* Ar group at the B atom and a vinyl group in position 4. Boronates **67** with substituents (R^2 = Me, NO_2) in the aromatic rings afforded quinolines **66**.

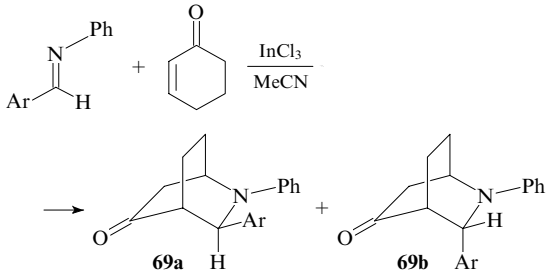


R^1 = H, Me, Bu^t, Cl, NO_2; R^2 = H, Me, NO_2; R^3 = H, CO_2Me.

As regards the introduction of cyclohexenone into the Povarov reaction, the available literature data are controversial. Certain authors (see, *e.g.*, Refs 56 and 68) reported that the Povarov reaction of cyclohexenone with imines catalysed by $LiClO_4$ in diethyl ether or by Me_3SiCl in MeCN affords tetrahydroquinolines **68a**,**b**, as follows from the NH group absorption band in the IR spectrum of compounds **68** at 3370 cm^{-1}.



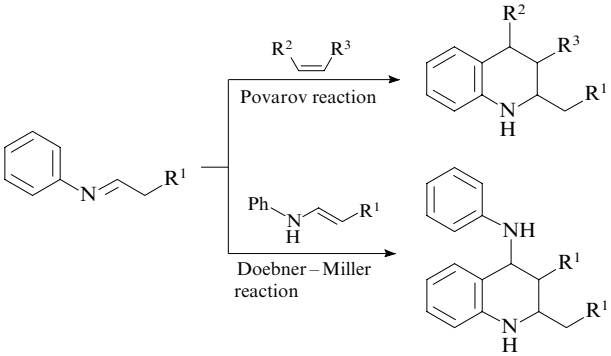
However, according to other data,[131] the $InCl_3$-catalysed reaction of imines with cyclohexenone led to compounds **69a**,**b** with the 2-azabicyclo[2.2.2]octane skeletone.



^{1}H NMR spectra of compounds **68** and **69** are very similar. At the same time, the IR spectroscopic data [131] for compounds **69** fit better the structure of **68**.

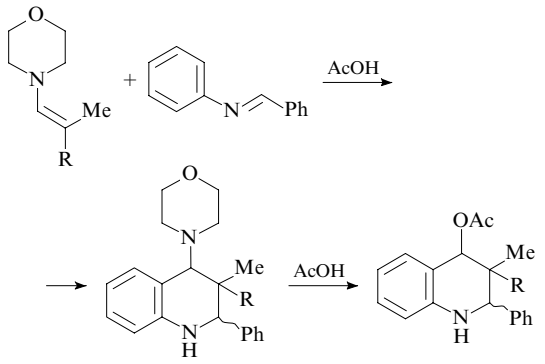
IV. Reactions of anils with enamines, enamides and dihydropyridines

The reaction of enamines with Schiff bases was known for quite a long time. The reactions of enamines with the corresponding tautomeric imines is traditionally considered as a stage of the Döbner – Miller quinoline synthesis and competes with the Povarov reaction.[79]

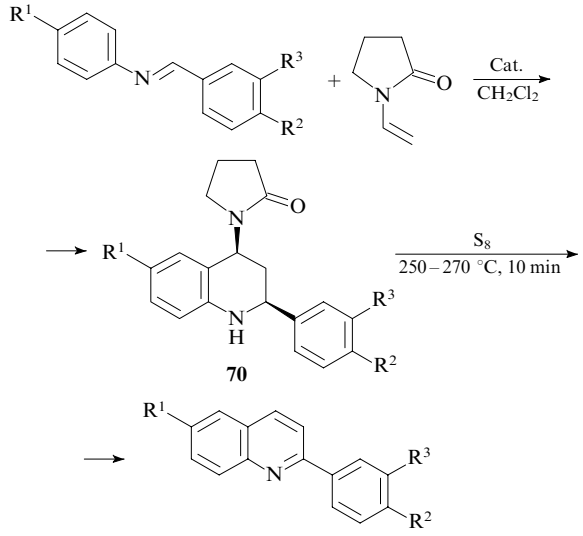


R^1, R^3 = Alk; R^2 = OAlk, SAlk, SAr.

The reaction of anil with classical enamines was observed to proceed with both retention [132] and elimination [133, 134] of the amine residue.



N-Vinyl-2-pyrrolidone reacted in a similar manner [135–143] (the predominantly formed diastereomer **70** is shown).

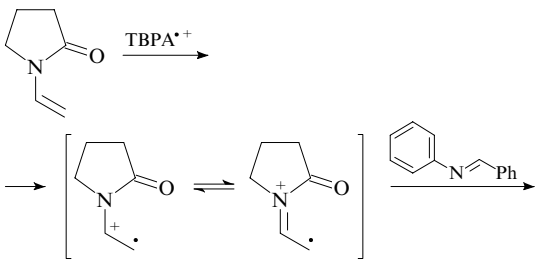


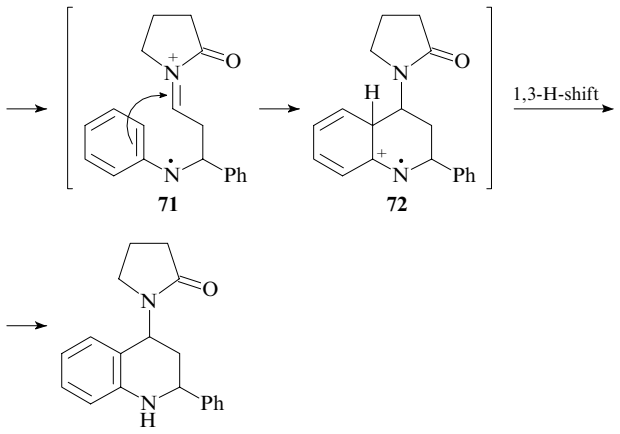
R^1 = H, Cl, Br, Me, OMe; R^2 = H, Cl, Br, Me, OMe, NO_2; R^3 = H; $R^2–R^3$ = OCH_2O.

Heating of compounds **70** with elemental sulfur led to aromatisation with elimination of pyrrolidone.[141]

Similar reactions were also observed for *N*-vinylazepan-2-one,[140] *N*-(hept-1-en-1-yl)pyrrolidone [144] and *N*-vinylcarbazole [137] $BF_3 \cdot OEt_2$ in CH_2Cl_2,[136, 143] $BiCl_3$ in MeCN,[141] $Y(OTf)_3$,[144] TsOH (see Ref. 142) and 2,4,6-triphenylpyrylium tetrafluoroborate [137] were proposed as the catalysts and promoters of this reaction. The reaction proceeded by a stepwise ionic mechanism. When radical cation salts [*e.g.*, tris(4-bromophenyl)amminium hexachloroantimonate, $TBPA^{\bullet+} \cdot SbCl_6^-$],[141] nitrosonium tetrafluoroborate ($NO^+ \cdot BF_4^-$) [138] or oxidants (cerium ammonium nitrate in MeCN) [139, 143] were used, the reactions proceed *via* radical cations **71** and **72** (Scheme 10). The reaction can be activated photochemically.[137]

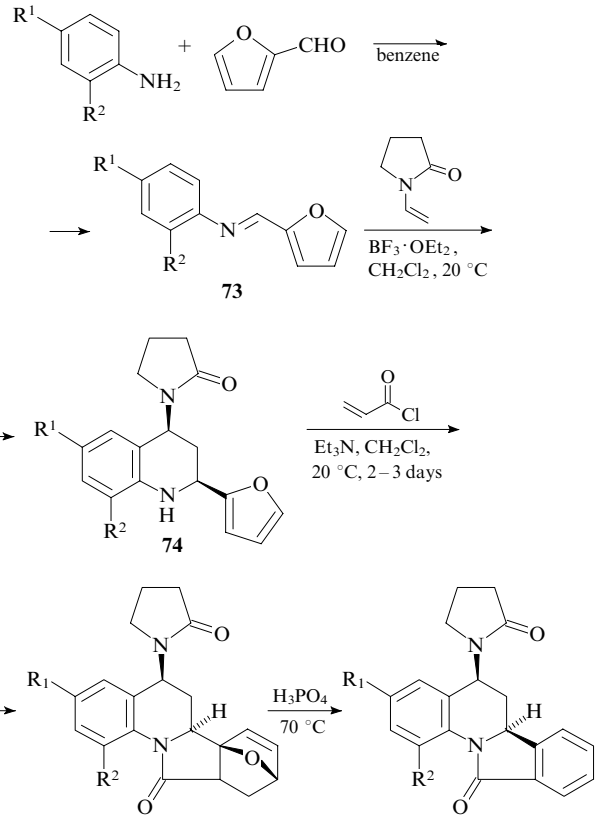
Scheme 10





In certain studies, the stereochemistry of these transformations established based on the ^1H, ^{13}C and ^2D NMR data was discussed.[137, 143, 144] The regioselectivity of cyclisation of *meta*-substituted anilines was studied.[144]

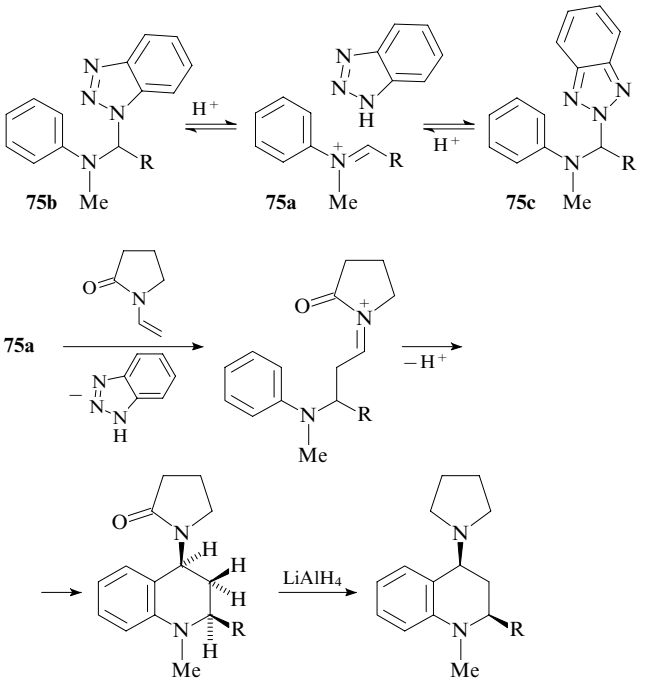
The use of furfural in the synthesis of Schiff bases and the subsequent reaction of anils formed **73** with *N*-vinyl-2-pyrrolidone afforded the corresponding 2,4-substituted tetrahydroquinolines **74**. The reaction of the latter with acryloyl chloride or maleic anhydride opened up a way to the isoindolo[2,1-*a*]-quinoline derivatives.[142]



R^1 = Me, OMe, Cl, Br, F; R^2 = H, Me, OMe.

Katritzky *et al.*[145] described a reaction of *N*-vinyl-2-pyrrolidone with iminium cations **75a** (Scheme 11) that are generated from anil adducts with benzotriazole and exist in tautomeric forms **75b**,**c**.

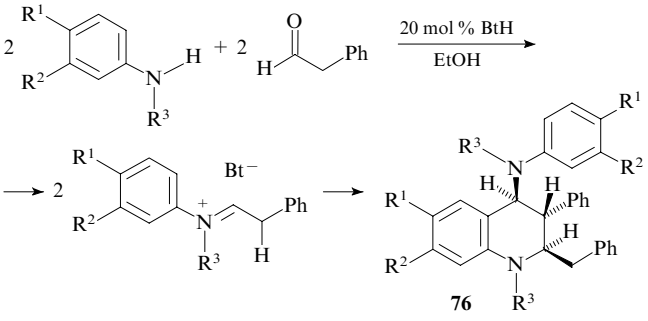
Scheme 11



R = Ph, Pr^i.

The exclusive formation of the *cis*-isomer was confirmed by the ^{1}H NMR data including those obtained using the nuclear Overhauser effect.

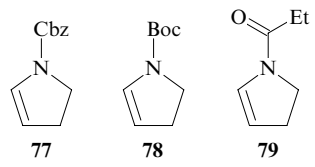
Chinese chemists [146] accomplished a stereoselective synthesis of substituted 1,2,3,4-tetrahydroquinolines **76** using the Döbner reaction promoted by benzotriazole (BtH) and catalysed by either SmI_2 or SmI_3. Based on the ^{1}H NMR data, it was shown that in all the cases 2,3-*trans*-2,4-*cis*-isomer was the main product; this was the only product for $R^1-R^2 = OCH_2O$ and $R^3 = H$ or for $R^1 = R^2 = H$ and $R^3 = Me$.



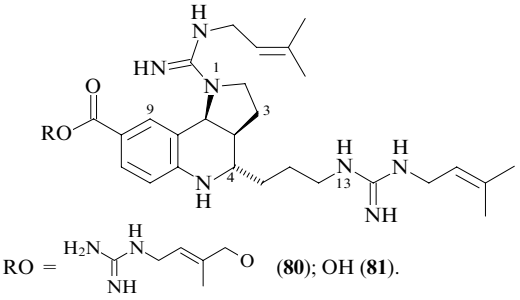
R^1 = H, Cl; R^2 = H, Me, OMe; $R^1-R^2 = OCH_2O$; R^3 = H, Me.

It another study,[147] the same authors used benzotriazole derivatives covalently immobilised on a polymeric carrier [the Merrifield resin, the Wang resin or monomethyl ether of poly(ethylene glycol)].

Enamides **77**–**79** allow direct transition to the pyrrolo[3,2-*c*]quinoline heterocyclic system, which lies in the core of structures of alkaloids martinelline (**80**) and martinellic acid (**81**),[148–155] found in *Martinella iquitosensis* that grows in Amazon area.



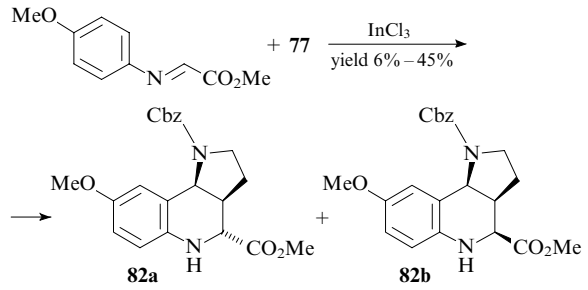
Cbz = C(O)OCH$_2$Ph, Boc = C(O)OBu^t.



RO = (**80**); OH (**81**).

These alkaloids are capable of binding to G-proteins present in many receptor systems including the bradykinine, histamine and muscarine receptors, and α-adrenergic receptors. Martinellines were the first discovered bradykinine B2 receptor antagonists of the non-protein type; they can be used as potential therapeutics for rhinitis and asthma.[149, 152]

Syntheses of martinellines by the Povarov reaction were accomplished by several research groups from Canada,[148, 149, 153] Ireland,[150, 151, 155] India [154] and China.[152] Here, a scheme of construction of the heterocyclic core of martinelline is shown.

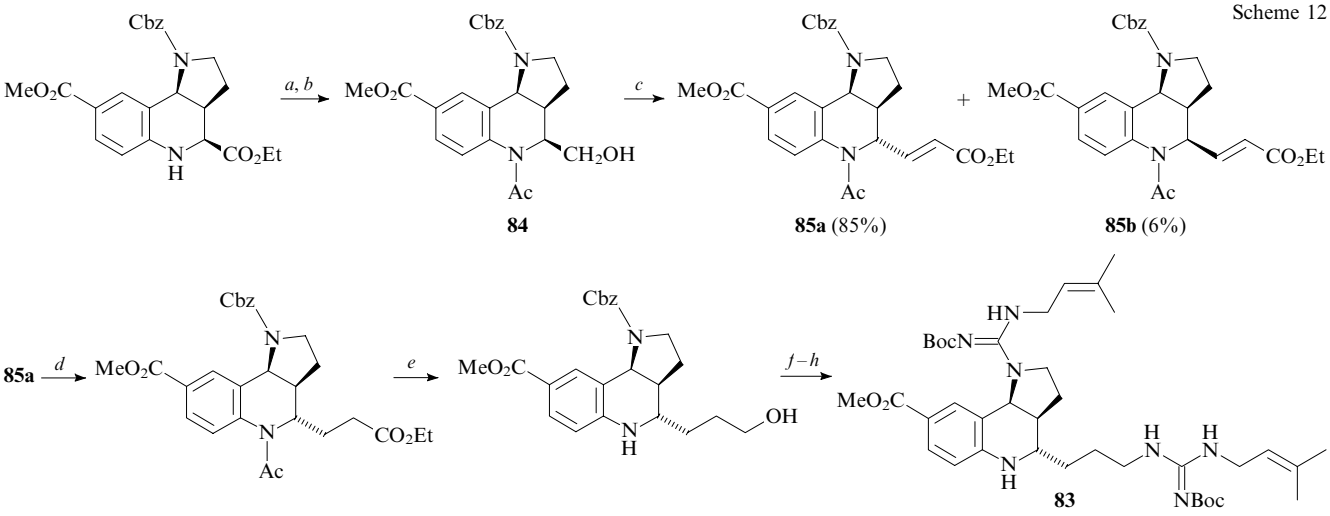


The ratio of isomers **82a** : **82b** can be regulated by choosing a proper catalyst. Thus in the $InCl_3$-catalysed reaction, the total yield of compounds **82a** and **82b** was ~50% (**82a** : **82b** ≈ 1 : 1),[150–152] the catalysts $Sc(OTf)_3$ (Ref. 152) or $Dy(OTf)_3$ (Ref. 149) in MeCN increased the yield of products to 72% (ratio **82a** : **82b** = 2 : 1). The majority of studies [148–155] on the martinelline synthesis were devoted to the quest for catalysts and reaction conditions that would result in the highest yields of *endo*,*trans*-isomer **82a**. As the catalysts, $InCl_3$,[150–152, 155] dysprosium(III)[149, 150, 153] and scandium(III)[152] triflates, montmorillonite KSF,[154] and protic acids (AcOH, CF_3CO_2H, *p*-TsOH, tartaric acid, citric acid [153]) were tested. The effect of solvent on the streochemistry of cyclisation was also considered. The best ratio **82a** : **82b** = 89 : 11 was obtained in THF in the catalysis with 5 mol % camphorsulfonic acid; in this case, the total yield reached 74%.[153]

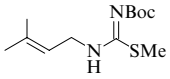
The isomer ratio (*trans* : *cis*) also depended on the nature of substituents in the aromatic ring of the parent substituted aniline.[148, 149, 154]

Scheme 12 illustrates the synthesis of methyl martinellate **83** (as a Boc-disubstituted derivative) by the Povarov reac-

Scheme 12



(*a*) $NaBH_4-LiCl$ (92%); (*b*) 1) $Bu^tMe_2SiCl-Et_3N$, 2) Ac_2O, 100 °C, 3) TsOH – MeOH (76%); (*c*) 1) the Swern oxidation, 2) $Ph_3P{=}CHCO_2Et$; (*d*) Pd/C, H_2 (87%); (*e*) $NaBH_4-LiCl$, MeOH – THF, 50 °C (82%); (*f*) 1) $(CF_3CO)_2O-4\text{-}Me_2NPy(DMAP)-Et_3N-CH_2Cl_2$, 2) $MsCl-Et_3N$, 3) NaN_3 – DMF; (*g*) 1) K_2CO_3 – MeOH, 25 °C (88%), 2) Pd/C, H_2, MeOH, HCl (87%);

(*h*) , $AgNO_3-Et_3N$, MeOH – MeCN (65%).

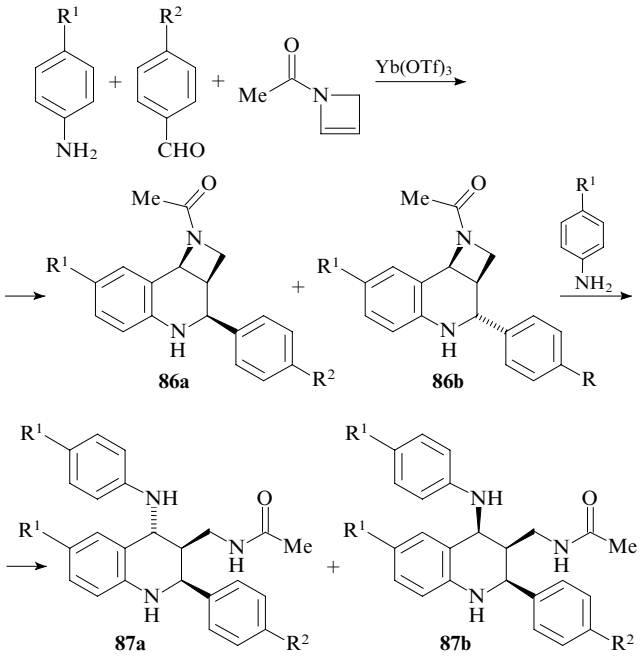
tion.[152] This synthetic scheme is remarkable in the selective reduction of a heterocycle-bound ester group by the $NaBH_4-LiCl$ system (stage *a*).

In the course of synthesis, it was found that in stage *c*, compound **84** is rearranged into thermodynamically more stable *trans*-isomer **85a**.‡ At the same time, the reversibility of the Povarov reaction in the presence of Lewis acids was noted,[155] which may change the composition of isomers formed in this reaction.

In view of the lack of stereoselectivity in the Povarov reaction,[151,153] the preferential formation of the *endo*,*cis*-isomer (while it is the *endo*,*trans*-isomer that is required) and the impossibility of exercising reliable control over the stereochemistry of the adducts formed, alternative approaches to the synthesis of martinelline derivatives were developed in recent years.[156–160] Insofar as the synthesis of martinelline was the subject of a recent review,[161] we will not dwell into this issue.

The three-component synthesis of substituted tetrahydroquinolines, which involved enamides and imines, was considered in several studies.[141–143,148,149,152] Three-component Povarov reaction of aldehydes, *N*-acetyl-2-azetidine and aromatic amines led to unstable products **86a**,**b**. If, from the very beginning, the reaction was carried out in the presence of two equivalents of aromatic amine $p\text{-}R^1C_6H_4NH_2$, the strained azetidine ring in compound **86a** opened to form diastereomers **87a**,**b** in an overall yield of 90% – 97%. The ratio of isomers **87a** : **87b** varied from 90 : 10 to 99 : 1 depending on the electronic properties of substituents R^1 and R^2 (Refs 162–164). For $R^1 = CO_2Me$ and $R^2 = OMe$, the ratio **87a** : **87b** was 72 : 28.[162]

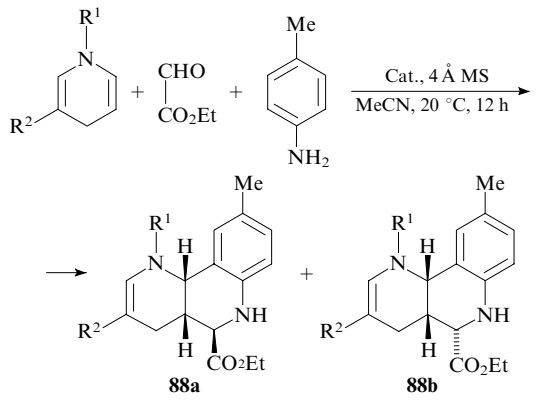
‡ The higher stability of *trans*-isomers was pointed out by other authors.[151]



R^1 = H, Me, OMe, CO_2Me; R^2 = H, NO_2, OMe.

Exposure of adducts **87a,b** at room temperature in the presence of AcOH in CH_2Cl_2 or 2,3-dichloro-5,6-dicyanoquinone in MeCN, and their refluxing with $Y(OTf)_3$ in MeCN led to aromatisation with elimination of the arylamine residue.[163]

Recently, a three-component Povarov reaction involving *p*-toluidine, ethyl glyoxylate and 1,4-dihydropyridines was described.[164]

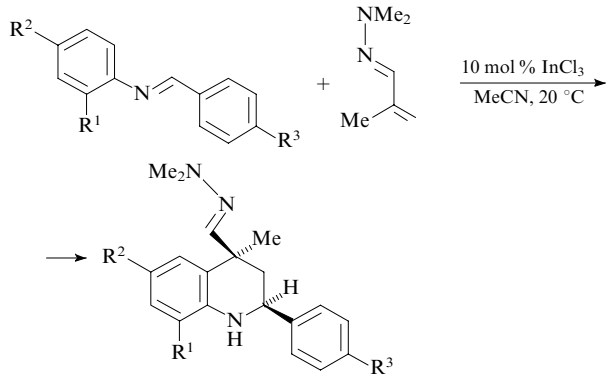


R^1 = Me, Bn; R^2 = CN, CO_2Me, $CONH_2$; Cat. = $InCl_3$, $Sc(OTf)_3$.

The overall yield of compounds **88a**,**b** was 65% – 86%. The ratio of isomers **88a** : **88b** varied from 2 : 1 to 1 : 2 depending on the nature of substituents R^1 and R^2.

Later, this reaction was carried out with 1,4-dihydropyridines immobilised on polymers.[165] The best results were obtained for the catalysis with metal triflates under the effect of microwave radiation (yields 74% – 89%).

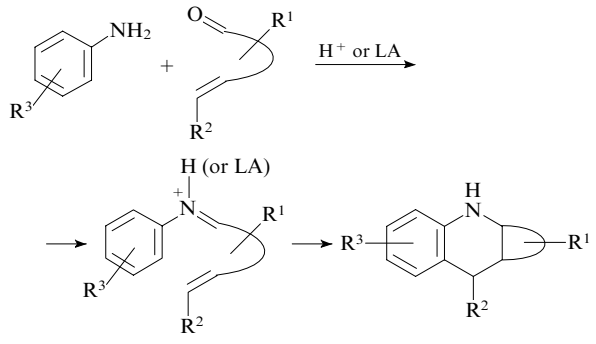
Finally, new dienophiles, α,β-unsaturated hydrazones, were introduced into the Povarov reaction.[166] Thus the reaction of Schiff bases with methacrolein dimethylhydrazone catalysed by $InCl_3$ in MeCN follows the scheme



R^1, R^2 = H, Me, OMe; R^3 = H, Cl, Br, Me, OMe.

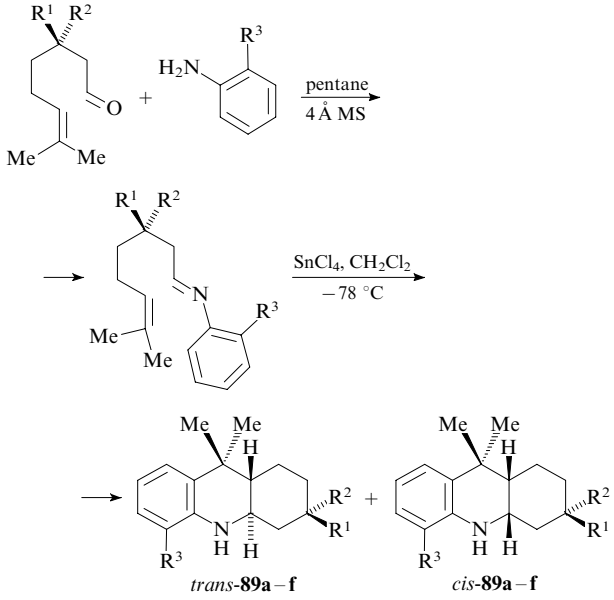
V. Intramolecular version of the Povarov reaction

A concept of building a quinoline system by condensation of 2-azadienes with alkenes was also implemented in its intramolecular version.[167 – 179]

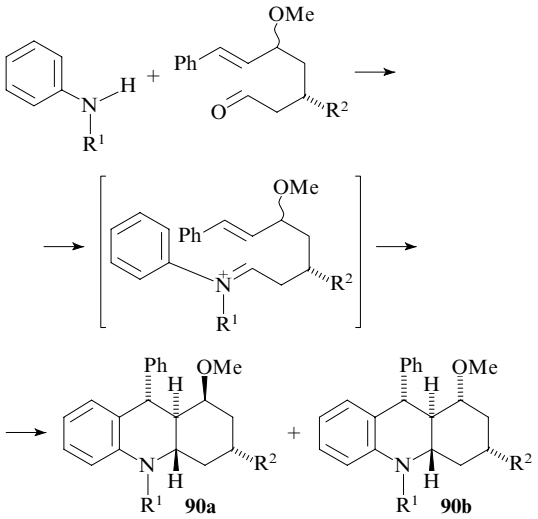


R^1, R^2 = Alk, Ar; R^3 = H, Hal, OMe *etc.*; LA is a Lewis acid.

It was assumed that the intramolecular version of the Povarov reaction would provide better stereocontrol. For example, the synthesis of octahydroacridines **89a** – **f** and **90a**,**b** was described.[167, 168]



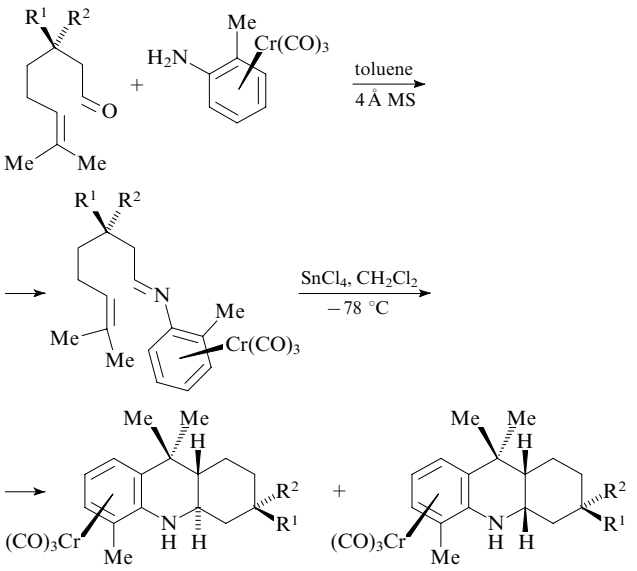
a: $R^1 = R^2 = R^3$ = Me; **b**: $R^1 = R^2$ = Me, R^3 = H;
c: $R^1 = R^3$ = Me, R^2 = H; **d**: R^1 = Me, $R^2 = R^3$ = H;
e: $R^1 = R^2$ = H, R^3 = Me; **f**: $R^1 = R^2 = R^3$ = H.



R^1 = H, Me; R^2 = $CH(CO_2Me)_2$, SPh.

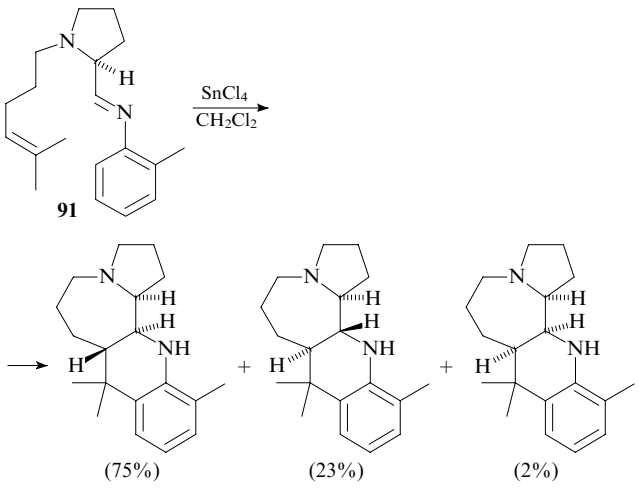
In the first reaction, Lewis acids ($EtAlCl_2$, $TiCl_4$, $FeCl_3$, $BF_3 \cdot OEt_2$, *etc.*), CF_3CO_2H, *p*-TsOH and polyphosphoric acid were used as the catalysts, CH_2Cl_2, toluene, pentane, THF and diethyl ether were used as the solvents. The *cis* : *trans* isomer ratio was shown to be independent of the catalyst type and primarily determined by the nature of substituents $R^1 - R^3$. For $R^1 = R^2$ = Me, the *trans*-isomer was preferentially formed (the ratio *trans* : *cis* = 99 : 1), for $R^1 = R^2$ = H the isomer ratio changed from 60 : 40 (for R^3 = H) to 36 : 64 (for R^3 = Me).

Chromium η^6-arene complexes were also involved into this reaction.[169]

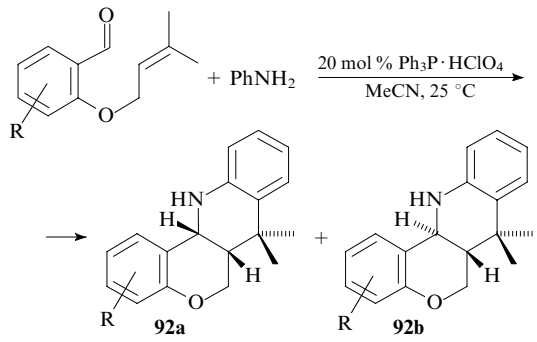


R^1, R^2 = H, Me.

Cyclisation of proline derivative **91** led to isomeric pyrrolo[1,2-*a*]azepino[3,4-*b*]quinolines.[170]

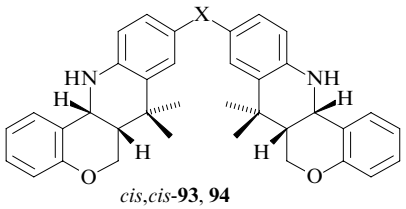


The synthesis of tetrahydrochromano[4,3-*b*]quinolines was conducted in a similar way. Sulfamic acid [62] and triphenylphosphonium perchlorate served as the catalysts.[171]



R = H, 3-MeO, 5-Cl.

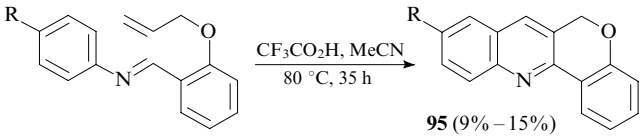
In the latter case, a mixture of *cis*- (**92a**) and *trans*-isomers (**92b**) in approximately equal amounts was formed in the overall yield of 82% – 92%. Isomers **92a**,**b** were separated by chromatography. If 4,4′-methylenedianiline or 4,4′-diaminodiphenyl ether were taken in place of aniline,[171, 172] bis-structures **93**, **94** were formed as mixtures of *cis*,*cis*-, *cis*,*trans*- and *trans*,*trans*-isomers, which were also separated by column chromatography (only *cis*,*cis*-isomer is shown).



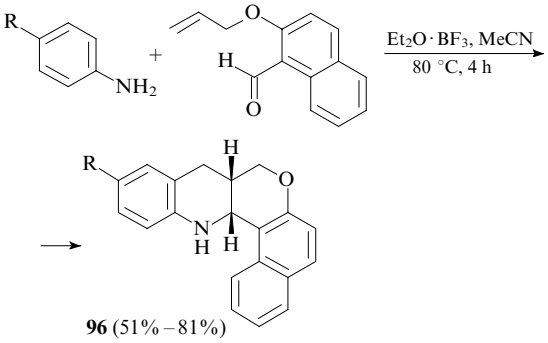
cis,*cis*-**93**, **94**

93: X = CH_2; **94**: X = O.

Recently, the synthesis of chromeno[4,3-*b*]quinolines **95** and their benzo analogues **96** in the reaction of *O*-allylsalicylaldehyde (or the corresponding allyl derivative of 2-hydroxy-1-naphthaldehyde) with anilines was described.[173]



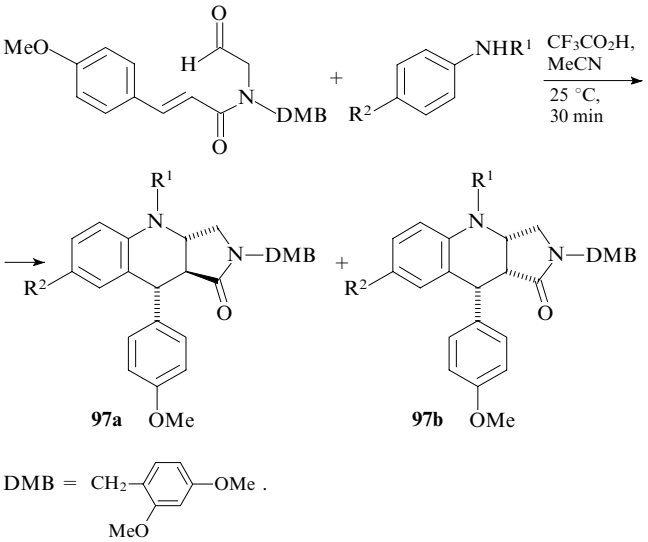
95 (9% – 15%)



96 (51% – 81%)

R = NO_2, CO_2H, CO_2Et, Me.

Substituted pyrrolo[3,4-*b*]quinolines **97** and **98** were synthesised in a similar way.[174, 175]

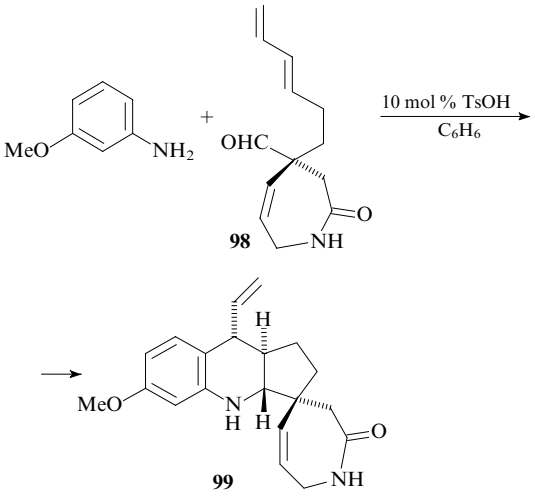


DMB = .

As in the synthesis of hexahydroacridines, in this case, too, the ratio of isomers formed *trans* : *cis* (**97a** : **97b**) was independent of the chosen catalyst type and varied from 2.4 : 1 to 8.1 : 1. The streochemistry of the products and the mechanism of this reaction were studied in detail. [174]

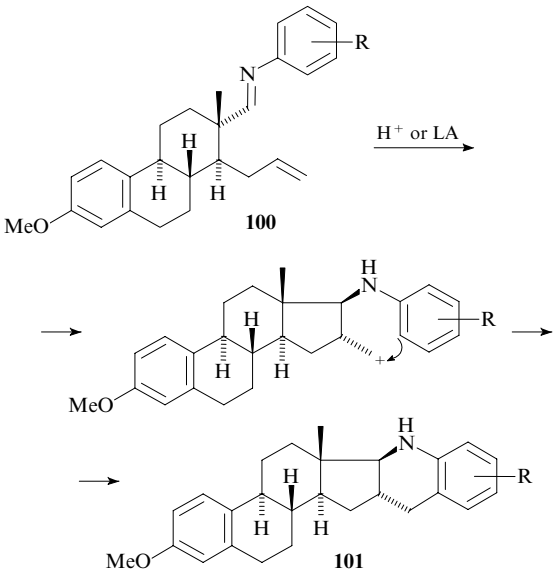
Acid-catalysed reaction of aromatic amines with unsaturated aldehyde **98** followed by intramolecular cyclisation was

proposed as a promising route to the synthesis of isoschizozygane alkaloids of type **99**.[176, 177]



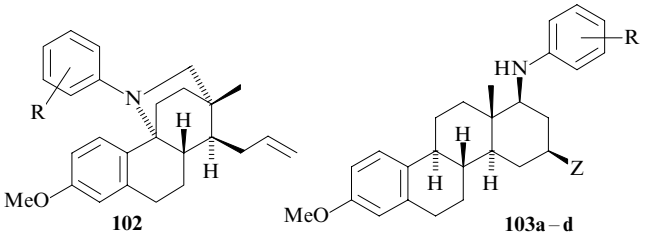
The reaction leads to the stereoselective formation of three asymmetric centres and is catalysed by CF_3COOH, BF_3, and also by zinc, scandium, and ytterbium triflates in CH_2Cl_2. The highest yield of compound **99** (76%) was reached in the catalysis with TsOH in benzene.

In 1999, Tietze described [178] the intramolecular cyclisation of arylamines **100**, *i.e.*, estrone derivatives, that led to tetrahydroquinolines **101** annulated to the steroid skeleton.



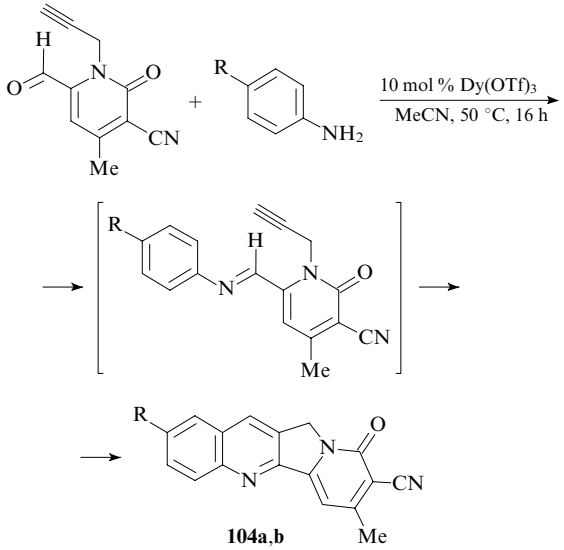
R = *p*(*m*,*o*)-Me; *p*(*m*,*o*)-OMe; *p*(*m*,*o*)-Br; *p*-NO_2; LA is the Lewis acid.

Compounds of the type **102** and the capture products of transient carbocations by nucleophiles, *i.e.*, compounds **103a–d**, were obtained in insignificant yields as by-products.

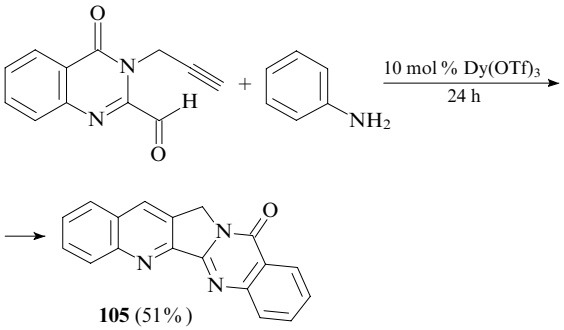


Z = F (**a**), Cl (**b**), Br (**c**), OTs (**d**).

Finally, the recently conducted synthesis of an analogue of alkaloids camptothecin (compounds **104a**,**b**) and luotonin A (**105**) by the intramolecular Povarov reaction should be mentioned.[179]



104a: R = H (71%); **104b**: R = OMe (64%).



Several related reactions were not discussed in our review, *e.g.*, the aforementioned Döbner–Miller synthesis of quinolines,[11–14] the Kozlov synthesis of phenanthridines [180–182] (coupling of Schiff bases with 1,3-dicarbonyl compounds), reactions of 1-azabuta-1,3-dienes with dienophiles,[183, 184] and dimerisation of *N*-phenylpyrrolidone under the action of strong bases.[185]

VI. Conclusion

The material presented above shows that the cyclisation of Schiff bases (anils) with activated alkenes, discovered by L S Povarov in the 1960s, has found a proper place among the synthetic methods of modern heterocyclic chemistry. The strategy developed by Povarov is successfully used today in the preparation of differently substituted 1,2,3,4-tetrahydroquinolines annulated with cyclopentene, cyclohexane, furan, pyran, chroman, pyrrole, azepine and other heterocycles and with their benzoannulated analogues, including natural and synthetic alkaloids. A special role is given to the methods of combinatorial chemistry and multicomponent reactions.

The high demand for the Povarov reaction is reflected in the regular appearance of new publications on its use in the synthesis of tetrahydroquinolines. Thus several publications devoted to the three-component synthesis of substituted tetra-

hydroquinolines (see Refs 186 – 189) appeared when this review was prepared for publication.

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