Pergamon

Tetrahedron, Vol. 52, No. 48, pp. 15031-15070, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00911-8

TETRAHEDRON REPORT NUMBER 410

Recent Progress in the Synthesis of 1,2,3,4-Tetrahydroquinolines

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Contents

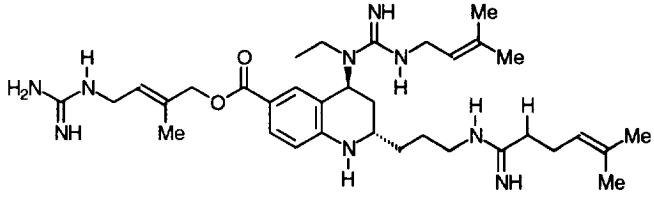
1. Introduction

1a. Scope of this Review

Rapid recent developments in the chemistry of 1,2,3,4-tetrahydroquinolines has prompted us to review and classify all their major synthetic methods currently in use. We restrict this report to 1,2,3,4-tetrahydroquinolines in which the C-2, C-3, and C-4 atoms are all sp^3 hybridized. 2-Oxo-, 4-oxo-, and 2,4-dioxo-1,2,3,4-tetrahydroquinolines (classified as such by Chemical Abstracts) and related compounds with one or more sp^2 carbon atoms form a large group of quinoline derivatives with their own properties and quite distinct synthetic methods: they are considered here only if they are used in the synthesis of "saturated" tetrahydroquinolines. This review is intended to cover the literature of the last ten years, 1986-95.

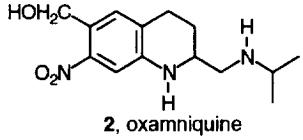
1b. Tetrahydroquinolines as Natural and Pharmaceutical Products

The greatest interest in 1,2,3,4-tetrahydroquinolines is due to their biological activities. Several of these compounds are naturally occuring. 2-Methyl-1,2,3,4-tetrahydroquinoline is present in human brain. Discohabdin C, a polycyclic system based on tetrahdyroquinoline, is a marine alkaloid.[2-7] Dynemycin, a natural antitumor antibiotic, has a complex structure built on the tetrahydroquinoline system.[8,9] The 2,4,6-trisubstituted tetrahydroquinoline **1**, isolated from Martinella iquitosensis, exhibits activity as a bradykinin antagonist and with α-adrenergic, histaminergic, and muscarinic receptors.[10]

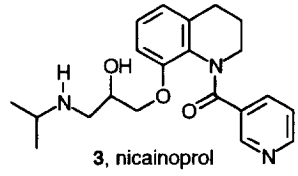


1

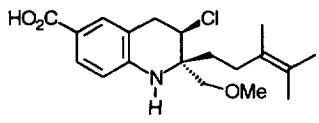
Many relatively simple synthetic of 1,2,3,4-tetrahydroquinolines are already used or have ben tested as potential drugs. Among them, oxamniquine (**2**), a schistosomicide,[11-16] nicainoprol (**3**), an antiarrhytmic drug,[17-21] and virantmycin (**4**), a novel antibiotic[22-24] are the best known. Tetrahydroquinoline L-689,560 (**5**) is one of the most potent NMDA antagonists yet found.[25-32]



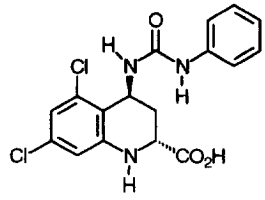
2, oxamniquine



3, nicainoprol



4, viratmycin



5, L-689,560

Hundreds of tetrahydroquinolines bearing various simple or complex substituents have interesting biochemial activity; some are potential pharmaceutical agents. Thus, a very simple derivative, 2-methyl-5-hydroxy-1,2,3,4-tetrahydroquinoline, exhibits analgestic activity one eighth as potent as morphine.[33] 1,2,3,4-Tetrahydroquinoline-4-carboxylic acid is used in tissue irrigating solutions.[34] Some tetrahydroquinolines are potent inhibitors of (H^++K^+) adenosine triphosphatase,[35] blood serum monoamine oxidase,[36] angiotensin I converting enzyme,[37] lipoxygenase,[38] lipid peroxidation,[39] bone resorption,[40] leukotriene synthesis[41,42] and bacterial dihydrofolate reductase.[43] Other tetrahydroquinolines are antagonists of vasopresin,[44] adrenergic α_2-receptor,[45] and calcium,[46] or agonists of dopamine D2.[47,48] Tetrahydroquinolines are potential antidepressants,[49] nervous system depressants,[50] potent antiulcer,[51,52] cardiovascular,[53] positive inotropic,[54] antithrombotic,[55,56] antiarrhytmic,[57] antiallergenic,[58] antitumor,[59] antirheumatic,[60] immunosuppressant,[61,62] anticonvulsant,[63] or antifertility[64] agents. Some tetrahydroquinolines are recognized as high affinity ligands at the glycine site of the NMDA receptor,[65] other as facilitators of noradrenergic transmissions,[66,67] or myofilament sensitizers without affecting cell Ca^{++} loading.[68] In this group are also promising drugs for the treatment of cerebral ischemia[69] and osteoporosis.[70]

1c. Other Applications of Tetrahydroquinolines

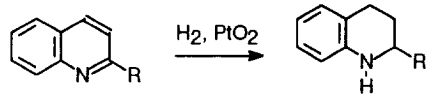
Besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides,[71-75] antioxidants,[76-79] and corrosion inhibitors.[80] 2,2,4-Trimethyl-8-hydroxy-1,2,3,4-tetrahydroquinoline is a specific reagent for photometric determination of iron(III) salts.[81] Tetrahydroquinolines are used as active components in various types of dyes: for hair,[82] for acrylic fibers,[83,84] for polyesters,[85,86] and for polyamides.[87,88] (2S)-2,6-Dimethyl-1,2,3,4-tetrahydroquinoline was used in synthesis of chiral polymethine dyes with interesting optical properties.[89]

Tetrahydroquinoline derivatives are also widely used in modern recording technologies: as charge-transporting agents for electrophotographic photoconductors,[90-96] as leuco dyes for thermal and pressure sensitive materials,[97-101] as antiirradiation filter dyes in photography,[102,103] in the preparation of optical information recording media,[104,105] as intermediates for photographic couplers,[106] as dyes for colored electrostatographic toners,[107] and as high sensitivity photosensitizers in photography.[108]

2. From Unsaturated to Saturated Heterocyclic Ring

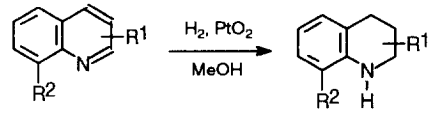
2a. Reduction of the Heterocyclic Ring in Quinolines

Despite the recent availability of many alternations (see below), when the appropriate quinolines are easily accessible, direct reduction of the heterocyclic ring can still be the best option for the preparation of tetrahydroquinolines. Hydrogenation over platinum is a common approach,[48, 109-112] which gives high yields of tetrahydroquinolines when there are electron-withdrawing substituents on the heterocyclic ring, as is illustrated by conversion of methyl quinoline-2-carboxylate[113] (**6a**) and quinoline-2-carbaldehyde[114] (**6b**) to tetrahydroquinolines **7a** and **7b**, respectively. Hydrogenation of quinaldinic acid over platinum dioxide in methanol proceeds well under very mild conditions, at room temperature and under atmospheric pressure.[115]

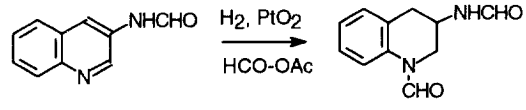


6a, R = CO_2Me **7a**, R = CO_2Me (92%)
6b, R = CHO **7b**, R = CH_2OH (95%)

Electron-donor groups at C-3 have practically no effect on the hydrogenation (conversion of **8a** to **9a**[35] and **10** to **11**[47]), whereas even a methyl group at C-4 retards the reaction dramatically (conversion of **8b** to **9b**[35]).

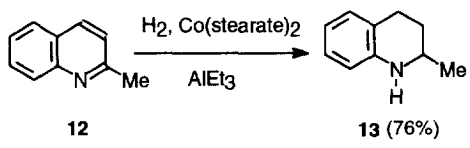


8a, R^1 = 3-Me, R^2 = CH_2OH **9a**, R^1 = 3-Me, R^2 = CH_2OH (90%)
8b, R^1 = 4-Me, R^2 = CH_2OH **9b**, R^1 = 4-Me, R^2 = CH_2OH (27%)

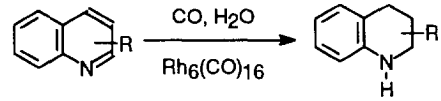


10 **11** (69%)

Other metal catalysts can also be used in the hydrogenation of quinolines to give tetrahydroquinolines. Thus, cobalt stearate in the presence of triethylaluminum converts 2-methylquinoline (**12**) into 2-methyl-1,2,3,4-tetrahydroquinoline (**13**) quite well.[116] The use of rhodium complexes as a catalyst and of a mixture of carbon monoxide and water as a hydrogenating agent were considered as a breakthroughs: for example, methylquinolines **12** and **14** were hydrogenated to tetrahydroquinolines **13** and **15** in high yields.[117,118]

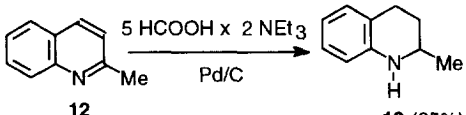


12 **13** (76%)

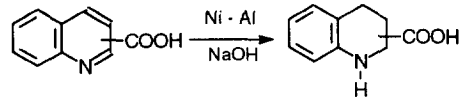


12, R = 2-Me **13**, R = 2-Me (95%)
14, R = 4-Me **15**, R = 4-Me (91%)

To avoid pressure reactors, hydrogen transfer can be utilized. Thus, quinoline **12** is reduced efficiently to tetrahydroquinoline **13** by mixing formic acid and triethylamine in the presence of a palladium catalyst.[119] Nickel-aluminum alloy is a convenient agent in the reduction of quinolinecarboxylic acids,[120] as shown by the conversion of **16a**, **16b**, and **16c** to **17a**, **17b**, and **17c**, respectively.

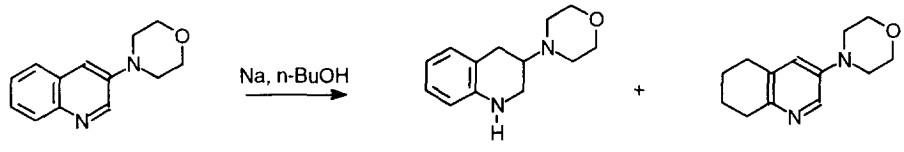


12 **13** (85%)



16a, 2-COOH **17a**, 2-COOH (97%)
16b, 3-COOH **17b**, 3-COOH (78%)
16c, 4-COOH **17c**, 4-COOH (87%)

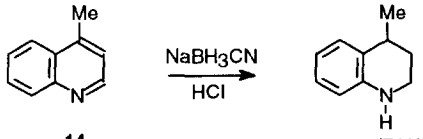
Alcohol-sodium systems have also been applied but are less selective in causing reduction of the carbocyclic ring, thus for example **18** is reduced to a mixture of **19** and **20**.[121]



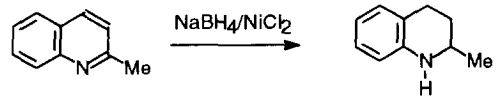
18 **19** **20**

(50%, isolated)

Alternatively, quinolines are reduced by borohydrides under strongly acidic conditions,[43] for example, **14** to **15**. However, better results are obtained when borohydrides are applied in the presence of nickel dichloride,[89,122,123] as illustrated by the example of the conversion of **12** to **13**.[123]

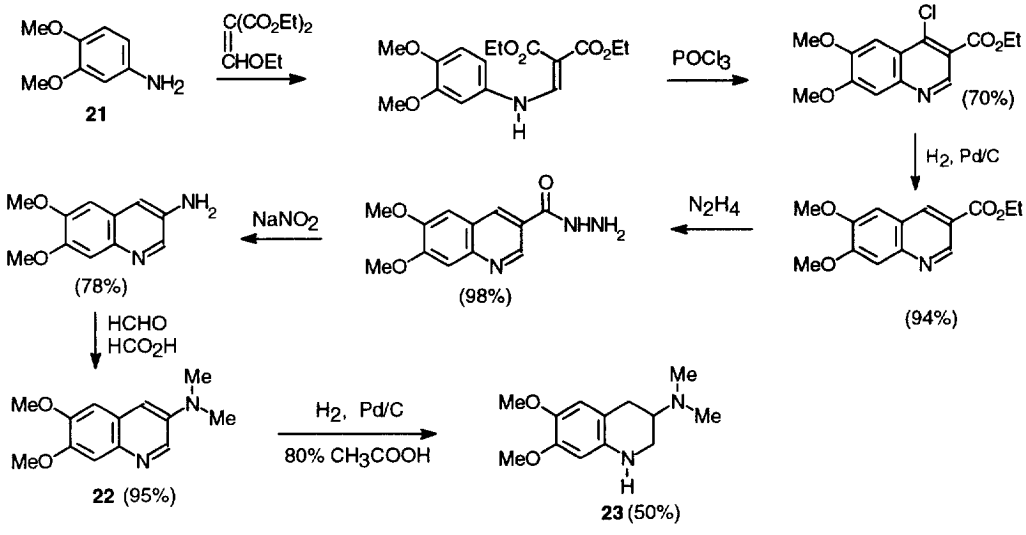


14 **15** (71%)



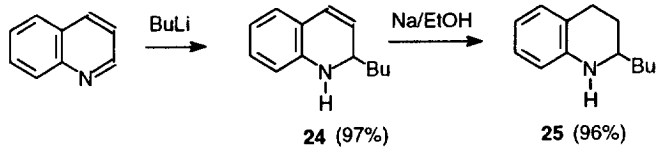
12 **13** (94%)

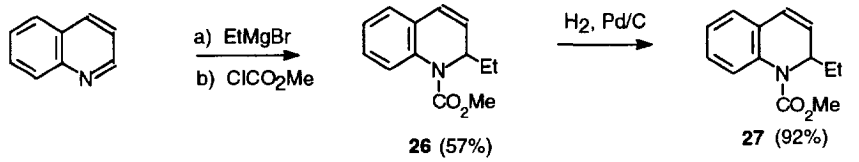
As shown above, reduction of the heterocyclic ring of quinolines is a simple method for the preparation of 1,2,3,4-tetrahydroquinolines. However, when the starting quinolines have to be prepared, the complexity of their synthesis may outweigh the simplicity of the reduction step. Although such approaches are still widely used, *e.g.*, conversion of aniline **21** to tetrahydroquinoline **23** via quinoline **22**,[54] construction of the saturated heterocyclic ring of 1,2,3,4-tetrahydroquinolines from building blocks containing the desired substituents can frequently provide a better alternative.



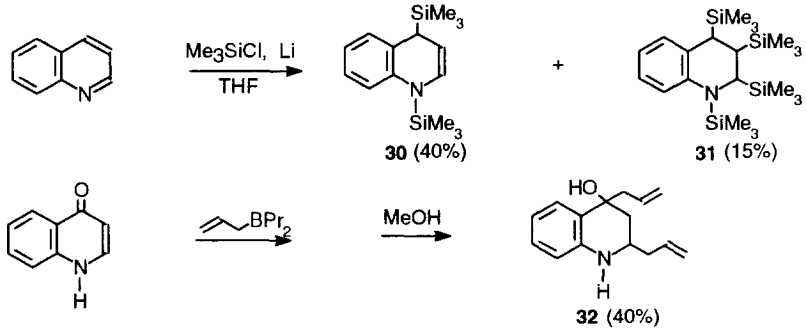
2b. Conversions of Quinolines to 1,2,3,4-Tetrahydroquinolines via 1,2-Dihydroquinolines

Strong nucleophiles add readily to the C=N bond of quinolines providing 2-substituted 1,2-dihydroquinolines, which can be converted upon subsequent reduction to 2-substituted 1,2,3,4-tetrahydroquinolines. Thus, the reaction of quinoline with butyllithium gives dihydroquinoline **24**, which is then reduced to 2-butyl-1,2,3,4-tetrahydroquinoline (**25**) in excellent yield.[42,124] Reaction of quinoline with ethylmagnesium bromide followed by methyl chloroformate gives dihydroquinoline **26**, which is then reduced to tetrahydroquinoline **27**.[125] Quaternization of the nitrogen atom of quinoline allows the attack of even weaker nucleophiles, as it is illustrated by the preparation of **29** via **28**.[126]

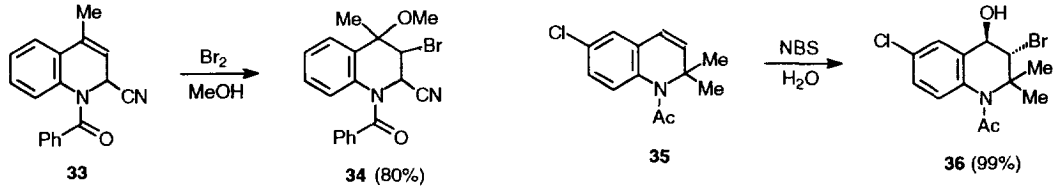


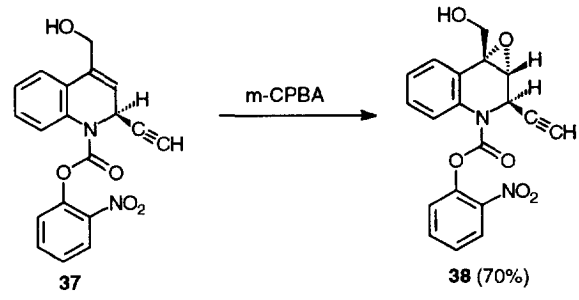


In some instances, the addition does not stop on 1,2-dihydroquinolines, but the process continues until the heterocyclic ring becomes saturated. Reactions with an organosilicon reagent[127] (**30** and **31**) and with an organoboron reagent[128] (**32**) depicted below illustrate such cases.



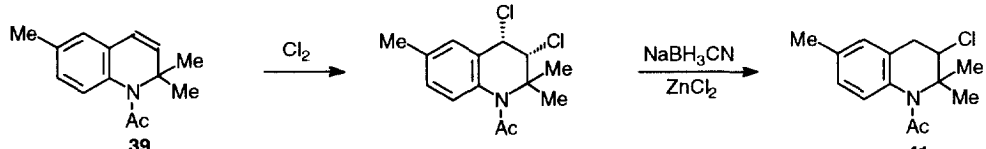
Reduction is not the only method for the conversion of 1,2-dihydroquinolines into 1,2,3,4-tetrahydroquinolines. The C(3)-C(4) bond of 1,2-dihydroquinolines has the typical properties of an electron rich double bond which allows a wide range of addition reactions. These additions are usually stereospecific. Thus, bromination of dihydroquinoline **33** in methanol yields the pentasubstituted 1,2,3,4-tetrahydroquinoline **34**.[129] Formation of only one stereoisomer of **34** was reported; however, the stereochemistry was not assigned.[129] In another example, bromination with NBS in water converts dihydroquinoline **35** into tetrahydroquinoline **36**.[130] *m*-Chloroperbenzoic acid converts dihydroquinoline **37** into epoxy-1,2,3,4-tetrahydroquinoline **38**.[9] These additions enable the preparation of highly substituted 1,2,3,4-tetrahydroquinoline systems.





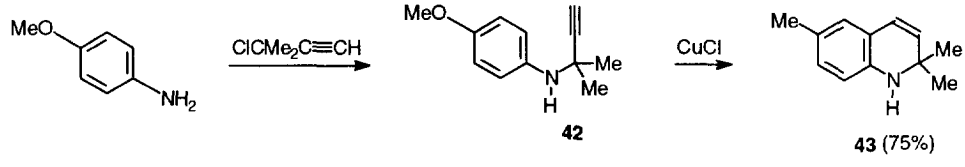
37 **38** (70%)

Sodium cyanoborohydride reduces 3,4-dichlorotetrahydroquinoline **40** (obtained by chlorination of dihydroquinoline **39**) to give monochloro derivative **41**, which illustrates the high lability of a tetrahydroquinoline substituent at C-4.[24]

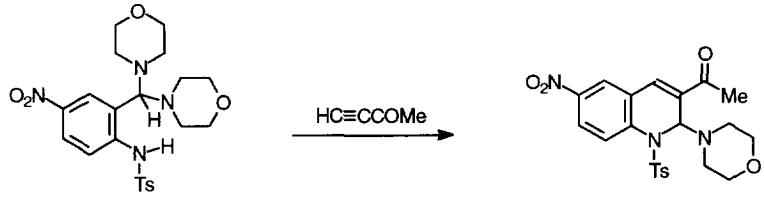


39 **40** **41**

1,2-Dihydroquinolines suitable for conversion to tetrahydro analogs can be obtained on several other synthetic routes besides nucleophilic additions to quinolines. Cyclocondensation-additions of anilines to alkynes are the most common. Thus, alkylation of p-toluidine with dimethylpropargyl chloride gives the N-propargyl derivative **42**, which in the presence of a cuprous chloride catalyst is converted to dihydroquinoline **43**.[24] Conversion of the aniline derivative **44** to dihydroquinoline **45** is another such synthesis.[131]

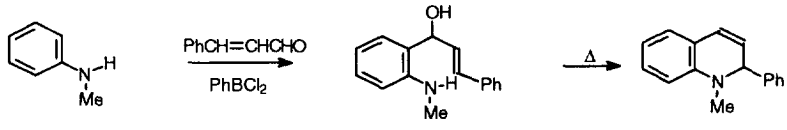


42 **43** (75%)



44 **45** (83%)

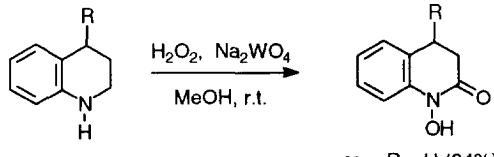
A further method involves reactions of anilines with α,β-unsaturated carbonyl compounds. As an example, condensation of N-methylaniline with cinnamaldehyde in the presence of phenylboron dichloride gives aminoalcohol **46**, which is then cyclized to dihydroquinoline **47**.[132]



46 **47** (57%)

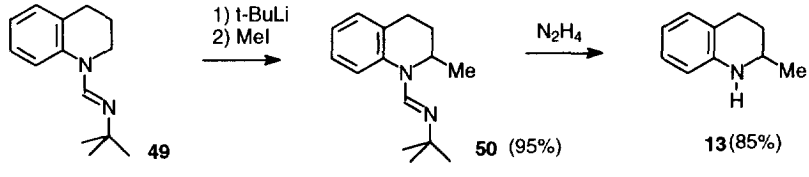
2c. Derivatization of 1,2,3,4-Tetrahydroquinolines

Easily available 1,2,3,4-tetrahydroquinoline and its simple alkyl derivatives can be used as sources for more complex analogs. A well developed method for derivatization of 1,2,3,4-tetrahydroquinolines at C-2 is oxidation by hydrogen peroxide in the presence of sodium tungstate.[133,134] This is illlustrated by formation of hydroxamic acids **48a** and **48b** from 1,2,3,4-tetrahydroquinoline and its 4-methyl derivative, respectively. The hydroxamic acids thus obtained can be easily converted to the corresponding 2-oxo-1,2,3,4-tetrahydroquinolines by hydrogenation over a platinum catalyst.[135]

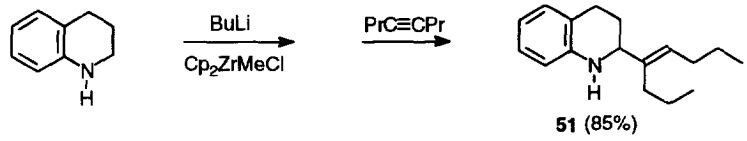


48a, R = H (84%)
48b, R = Me (83%)

Several methods of regioselective lithiation of 1,2,3,4-tetrahydroquinolines on C-2 followed by treatment with electrophiles have been developed. According to one of these methods, 1,2,3,4-tetrahydroquinoline is first converted to a formamidine derivative (**49**). The formamidine substituent in these derivatives plays both the role, of an activating and a directing group. Lithiation of **49** and treatment with electrophiles gives 2-substituted 1-formamidinotetrahydroquinolines, *e.g.* **50**. Finally, the protection is removed in a reaction with hydrazine to give tetrahydroquinoline **13**.[136] Use of organozirconium reagents allows for milder reaction conditions (no need for *tert*-butyllithium), simplifying the whole procedure, as shown by the preparation of compound **51**.[137-140]

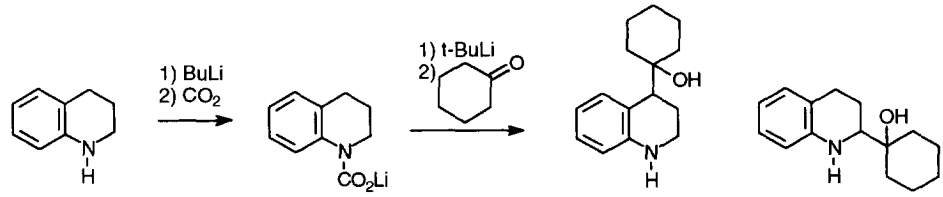


49 **50** (95%) **13**(85%)



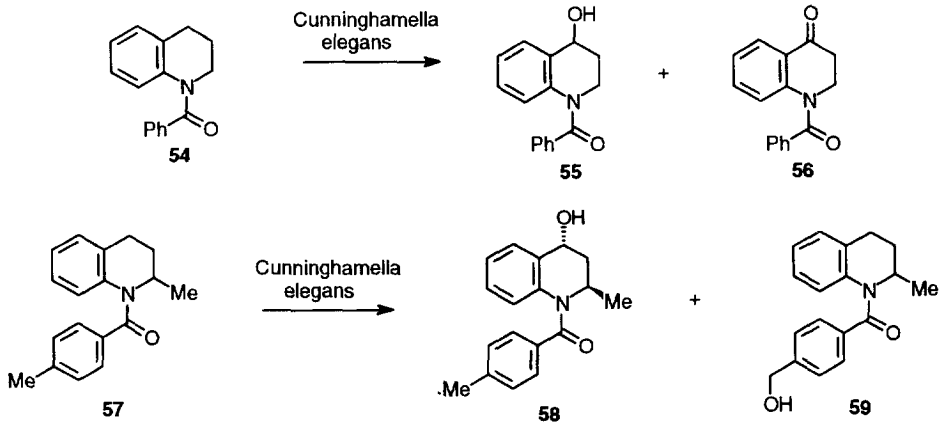
51 (85%)

In another approach,[141a] tetrahydroquinoline is converted to its lithium carbamate derivative **52** by consecutive treatment with butyllithium and carbon dioxide. In the following step, carbamate **52** is lithiated by treatment with *tert*-butyllithium, and finally subjected to a reactions with electrophiles to give substituted 1,2,3,4-tetrahydroquinolines; it was originally thought that lithiation occured at the 2-position giving, *e.g.*, compound **53b** from a reaction with cyclohexanone,[141a] but it has since been shown that the lithiation takes place at the 4-position and that **53a** is the correct structure of the product.[141b]



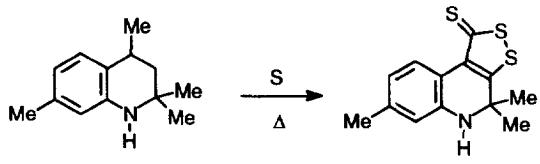
52 **53a** (55%) **53b**

Biochemical oxidation of tetrahydroquinolines by the fungus Cunninghamella elegans occurs exclusively on C-4.[142,143] Conversions of **54** to a mixture of **55** and **56**, and of **57** to a mixture of **58** and **59** illustrate such biochemical oxidation. Contrary to the above methods, a reaction with elemental sulfur allows for simultaneous derivatization at C-3 and C-4; thus, converting tetrahydroquinoline **60** into the tricyclic dihydroquinoline derivative **61**.[144]



54 **55** **56**

57 **58** **59**



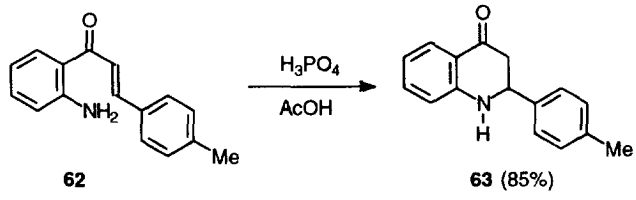
60 61 (47%)

3. Heterocyclic Ring Synthesis by Closure of one Bond

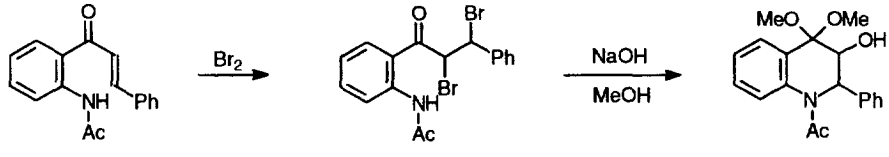
Very often, desired substitution of the heterocyclic ring in tetrahydroquinolines, is more simply achieved by constructing this ring from smaller fragments than from the corresponding quinoline. The heterocyclic ring can be constructed in many ways.

3a. Formation of the N-(C1) Bond

In general, N-C bond formation is one of the simpler tasks in organic synthesis and, if appropriately ortho-substituted anilines are available, cyclization to the corresponding 1,2,3,4-tetrahydroquinolines is easy. Convenient syntheses of 2'-aminochalcones[145] makes them attractive starting materials for the preparation of 2-aryl-1,2,3,4-tetrahydro-4-quinolines. In a given example, 2'-amino-4-methylchalcone (**62**) is converted to 2-(4-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinoline (**63**) in a cyclization process catalyzed by phosphoric acid.[146] The carbonyl group of **63** can be subjected to reduction and addition reactions providing a wide range of substitution on C-4.[147] Bromination of the double bond of chalcone **64**, followed by cyclocondensation of the bromo derivative **65** in methanolic sodium hydroxide, leads to a tetrahydroquinoline additionally substituted on C-3 (**66**).[146]

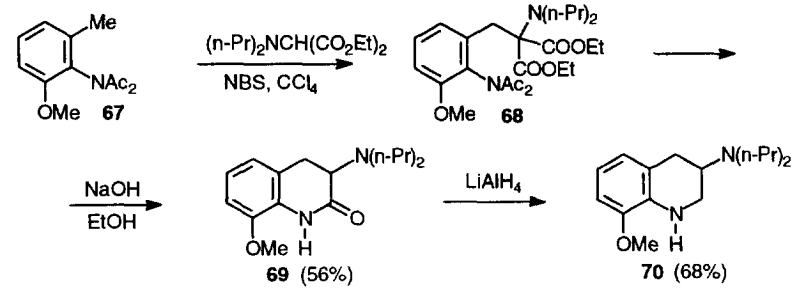


62 63 (85%)

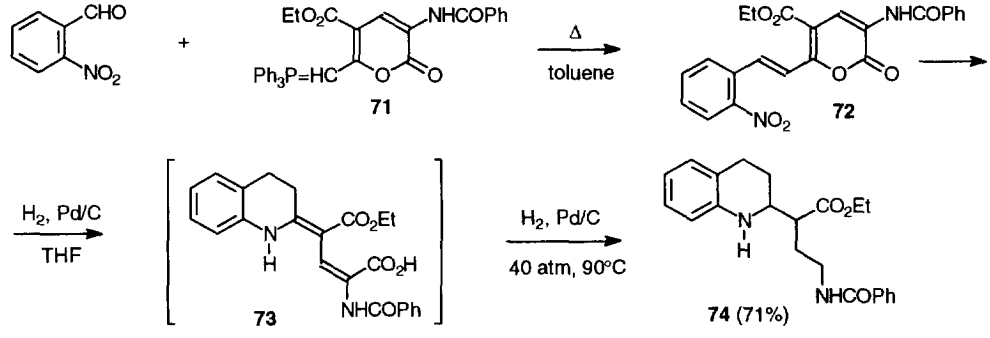


64 65 66 (25%)

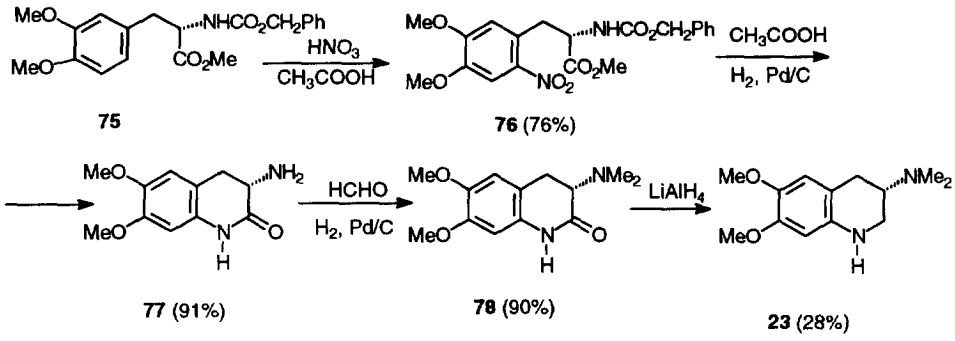
A 3C linkage at the *ortho* position of aniline can be constructed by the addition of 1C and 2C fragments. Thus, bromination of the toluidine derivative **67** with NBS followed by condensation with diethyl malonate yields derivative **68**, which is then cyclized to 2-oxotetrahydroquinoline **69** upon treatment with sodium hydroxide in ethanol.[47] Subsequent reduction with lithium aluminum hydride eliminates the 2-oxo function giving 3-aminotetrahydroquinoline **70** in good yield.[47]



In another example, the 3C linkage (in **72**) is constructed onto 2-nitrobenzaldehyde in a Wittig reaction with **71**. In the next step, catalytic reduction on palladium, the nitro group is reduced to an amino group followed by cyclization to give derivative **73**.[148] When the hydrogenation is carried out at room temperature and atmospheric pressure, compound **73** can be isolated from the reaction mixture (54%). At elevated temperature and 40 atm of H_2, the reaction does not stop on **73**, which is then decarboxylated and reduced to tetrahydroquinoline **74**.[148]

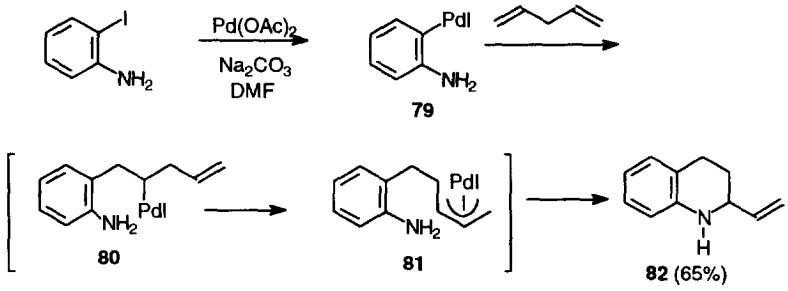


In another approach, the *ortho* nitro group is added later, after the 3C linkage unit is already constructed, as shown in the example given.[54] Nitro derivative **76** is prepared by nitration of **75** under mild conditions. Catalytic hydrogenation of **76** reduces the nitro group and then removes protection from the amino group to give 2-oxo-tetrahydroquinoline **77**. Methylation of the amino group at C-3 gives **78**, which is consecutively reduced to 6,7-dimethoxy-3-(dimethylamino)-1,2,3,4-tetrahydroquinoline (**23**), a precursor of positive inotropic agents. This synthesis of **23** can be compared with the alternative approach, which proceeds through quinoline system **22**.



75 76 (76%) 77 (91%) 78 (90%) 23 (28%)

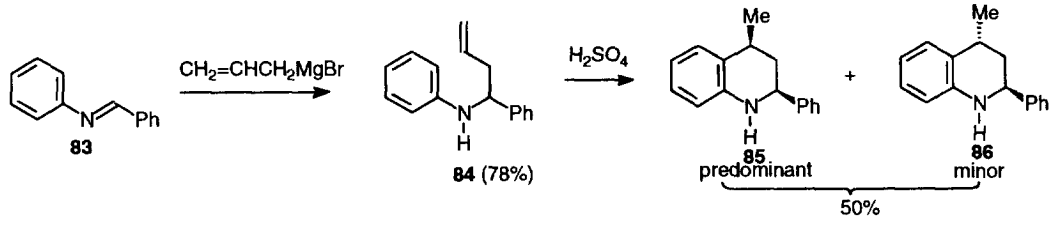
The 3C linkage can be added in one step by palladium catalyzed annulation of 1,4-dienes using *ortho* iodoanilines.[149] For example, the palladium intermediate **79**, obtained by treatment of 2-iodoaniline with palladium acetate, reacts with 1,4-pentadiene to give 2-vinyl-1,2,3,4-tetrahydroquinoline (**82**), *via* **80** and **81**.[149]



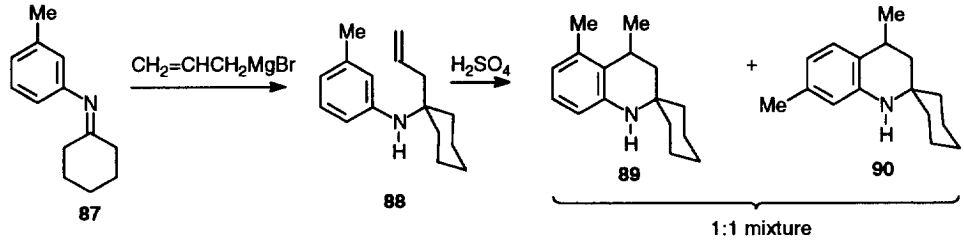
79 80 81 82 (65%)

3b. Formation of the C(4) - C(4a) Bond

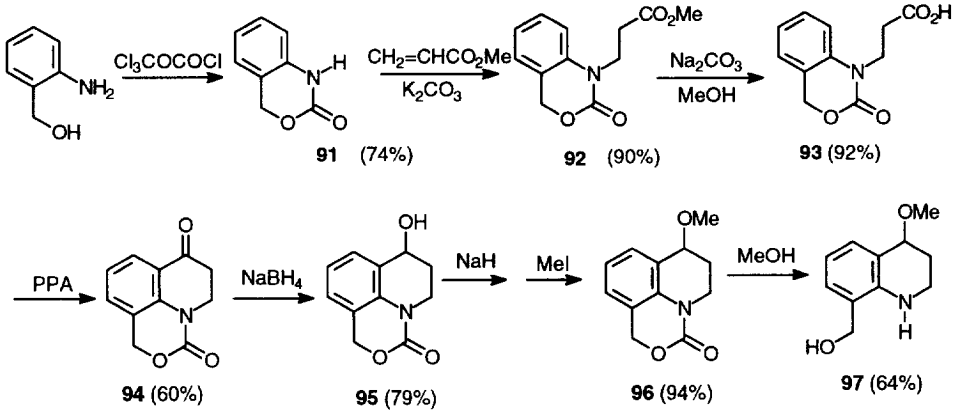
The high reactivity of the aniline *ortho* carbon atoms towards electrophiles allows easy cyclization of anilines with an N-alkyl group carrying an electrophilic center at the C-3 atom. As shown below, such compounds can be obtained by reactions of N-alkylideneanilines with allylmagnesium bromide. In the first example, derivative **84**, obtained from the reaction of N-benzylideneaniline (**83**) with allylmagnesium bromide, undergoes sulfuric acid catalyzed cyclization to a mixture of *cis* (**85**) and *trans* (**86**) 4-methyl-2-phenyl-1,2,3,4-tetrahydroquinolines.[150] In the second example, a mixture of tetrahydroquinolines **89** and **90** is produced by the cyclization of intermediate **88**, obtained from N-cyclohexylidene-3-methylaniline (**87**).[151]



83 84 (78%) 85 86

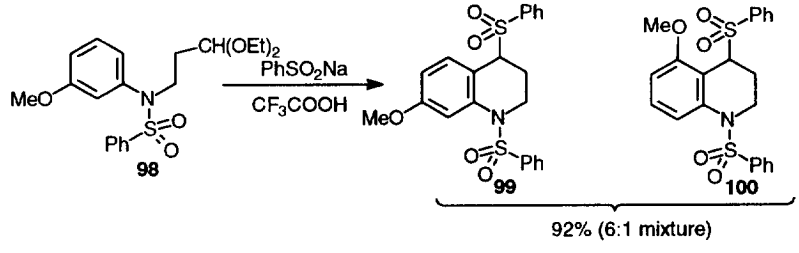


The concept is well illustrated by the synthesis of tetrahydroquinoline **97**, a key intermediate in the preparation of antiulcer agents.[51] In the first step, the hydroxy and the amino group in 2-(hydroxymethyl)-aniline are protected as benzoxazine **91** by reaction with trichloromethyl chloroformate. The N-H bond of **91** adds to methyl acrylate to give aminopropionate **92** in high yield. Hydrolysis of the ester function gives acid **93**, which undergoes cyclocondensation in the presence of polyphosphoric acid to form 4-oxotetrahydroquinoline



system **94**. Reduction of the carbonyl group of **94** followed by methylation and deprotection of the N-H and OH functions leads to tetrahydroquinoline **97**, via intermediates **95** and **96**.

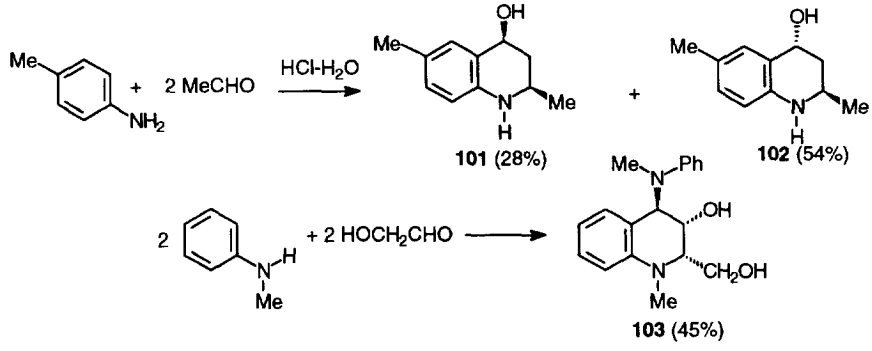
Use of aldehydes or their derivatives in the cyclization step instead of carboxylic acids allows simplification of the procedure by obviating reduction of the carbonyl group. Soft nucleophiles present in the reaction mixture tend to substitute hard nucleophiles at C-4, stabilizing the products and preventing side reactions. Combination of both these ideas was utilized in the work presented below. Thus, the derivative **98**,



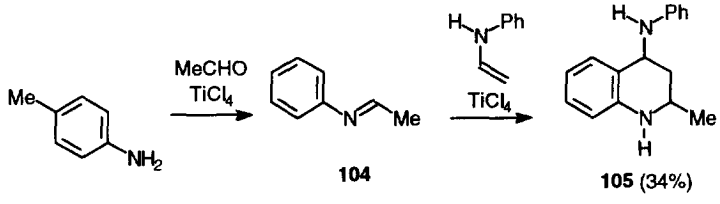
obtained in a reaction of 3-methoxyaniline with 3-iodopropionaldehyde diethyl acetal followed by treatment with benzenesulfonyl chloride, undergoes first cyclocondensation, then a substitution reaction with the benzene-sulfinate anion to give a mixture of tetrahydroquinolines **99** and **100** in high yield.[152]

4. Condensations of Anilines with Two Molecules of an Aldehyde.

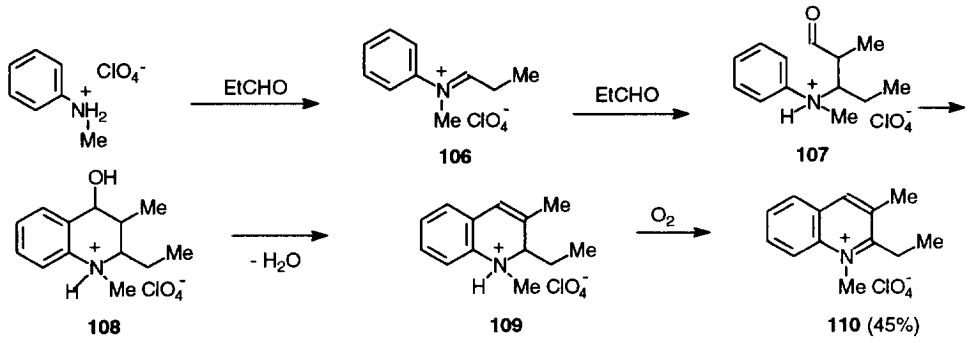
As known for over one century, anilines react with enolizable aldehydes.[153,154] However, the stereochemistry of the 4-hydroxy-1,2,3,4-tetrahydroquinolines produced was not known until X-ray crystallography and high field NMR spectroscopy became widely available. Thus, according to a recent report,[155] *p*-toluidine and two molecules of acetaldehyde gives a mixture of the *cis* (**101**) and *trans* (**102**) isomers of 2,6-dimethyl-4-hydroxy-1,2,3,4-tetrahydroquinoline in an approximate ratio of 1:2. The isomers were separated by selective recrystallization, and their stereochemistry was assigned by NMR methods.[155] Under a different set of reaction conditions (1:1 molar ratio and lack of acidic catalysis), *N*-methylaniline and glycolaldehyde give tetrahydroquinoline **103**, the stereochemistry of which was assigned based on X-ray crystallography data.[156]



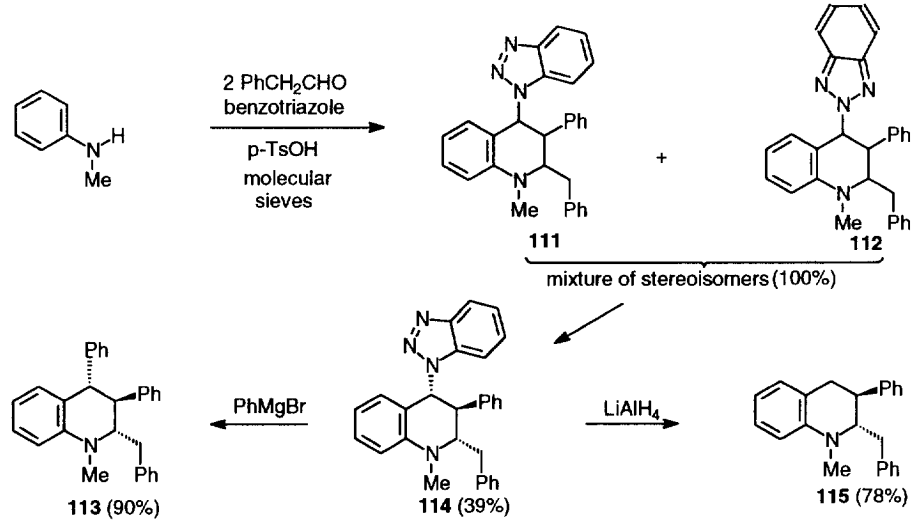
The probable mechanism leading to product **103** is substitution of the 4-hydroxy group in the corresponding 4-hydroxytetrahydroquinoline by excess *N*-methylaniline; however other possibilities cannot be excluded. Thus, formation of a similar product, tetrahydroquinoline **105**, is explained by a two step process: first, condensation of aniline with acetaldehyde to imine **104**; second, cycloaddition of **104** to its enamine tautomer.[157] The stereochemistry of **105** was not reported.



The detailed mechanism of such reactions is discussed in a recent paper.[158] Thus, condensation of N-methylanilinium perchlorate with propionaldehyde gives iminium salt **106**. Addition of another molecule of propionaldehyde to **106** produces aldehyde **107**, which undergoes cyclization to tetrahydroquinoline **108**. Under the reactions, refluxing in chloroform for 14 h, compound **108** is unstable undergoing dehydration to **109** and then oxidation to quinolinium salt **110**. Other aldehydes, unbranched at the α-position, react similarly producing homologs of **110** with yields in the range of 5-30%.[158]



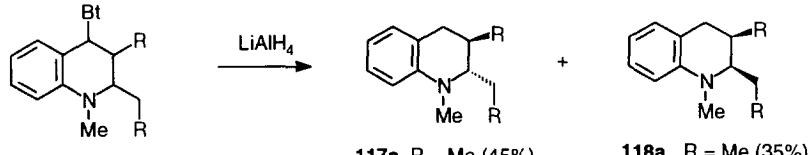
According to our own findings, addition of benzotriazole to the reaction mixture stabilizes the tetrahydroquinoline system by substitution with the benzotriazol-1-yl or 2-yl moiety of the hydroxy group in **108**, and in analogues obtained from other aldehydes.[159] Thus, in the case of phenylacetaldehyde, an almost



quantitative yield of a mixture of stereoisomers **111** and **112** is achieved, from which the predominant isomer **114** is separated by recrystallization. The benzotriazolyl moiety on C-4 of tetrahydroquinoline **114** can be

relatively easily substituted by strong nucleophiles, as illustrated by preparation of tetrahydroquinolines **113** and **115**.

Mixtures of isomers **116** obtained from reactions of *N*-methylaniline with typical aliphatic aldehydes are difficult to separate.[159] However, the corresponding pairs of diastereomeric 2,3-dialkyltetrahydroquinolines (**117a** and **118a**, or **117b** and **118b**), obtained after reduction with lithium aluminum hydride, are easily separated by column chromatography.

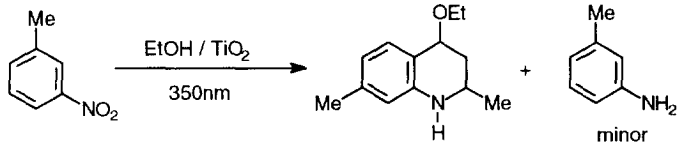


116
Bt = benzotriazol-1-yl or -2-yl

117a, R = Me (45%)
117b, R = Pr (55%)

118a, R = Me (35%)
118b, R = Pr (33%)

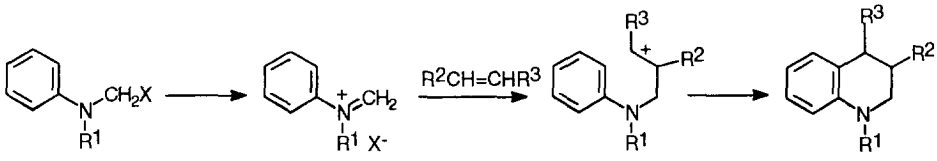
Irradiation of a solution of a nitrobenzene in ethanol, in the presence of titanium(IV) oxide, produces the corresponding 4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (*e.g.*, **119**), via reduction of the nitro to the amino group, oxidation of ethanol to acetaldehyde, and subsequent condensation of these reagents.[160]



119 (71%)
minor

5. Reactions of N-Aryl Methyleneiminium Cations with Olefins

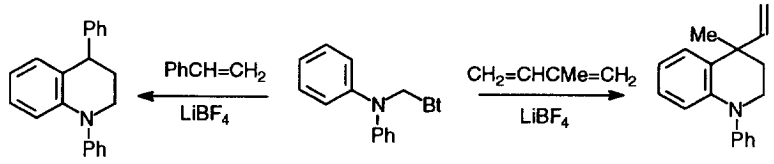
This approach allows the preparation of various 3,4-disubstituted 1,2,3,4-tetrahydroquinolines unsubstituted at C-2. The concept is to generate from an aniline derivative **120** a methyleneiminium cation **121** which by electrophilic attack on an olefin leads to an intermediate cation **122** and spontaneous cyclization to tetrahydroquinoline **123**. Because the addition step follows the Markovnikov rule, regioselectivity is achieved in the reaction when the substituents R^2 and R^3 differ significantly in their electronic character.



120 **121** **122** **123**

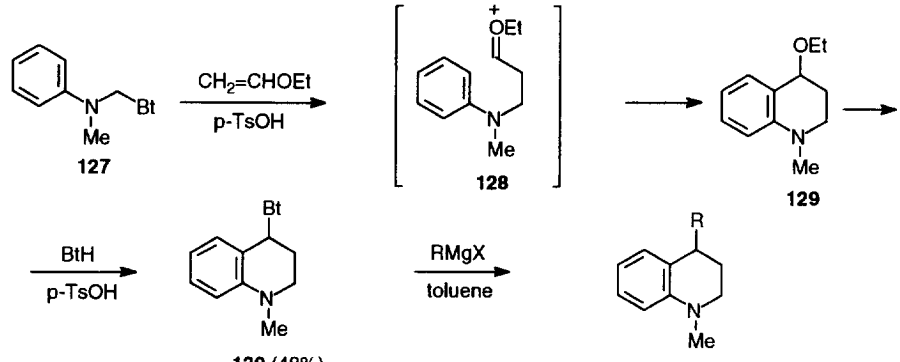
5a. Benzotriazole Methodology

The benzotriazolyl substituent Bt (benzotriazol-1-yl and/or -2-yl) is very advantageous as group X in these reactions: it renders derivatives **120** stable enough to be separated and characterized, but also reactive enough to produce readily iminium cations **121**. In practice, species **120** and **121** coexist at equilibrium in solutions.[161] In two examples of such reactions, diphenylamine derivative **125** (obtained readily by condensation of diphenylamine with formaldehyde and benzotriazole) reacts, with styrene to give **124** and isoprene to give **126**.[162]



124 (45%) **125** **126** (60%)

The reaction proceeds even better when olefins are activated by a heteroatom[163] Thus, *N*-methylaniline derivative **127** with ethyl vinyl ether yields an intermediate adduct **128** stabilized by the ethoxy group, eventually undergoing cyclization to 4-ethoxytetrahydroquinoline **129**. Compound **129** can be isolated when the reaction is stopped in its earlier stage; however, the ethoxy group is usually quickly substituted by benzotriazole giving finally the more stable product **130**. Compound **130** can conveniently be used as a starting material for the synthesis of 4-substituted tetrahydroquinolines, as shown by three examples, **131a-131c**.[163]

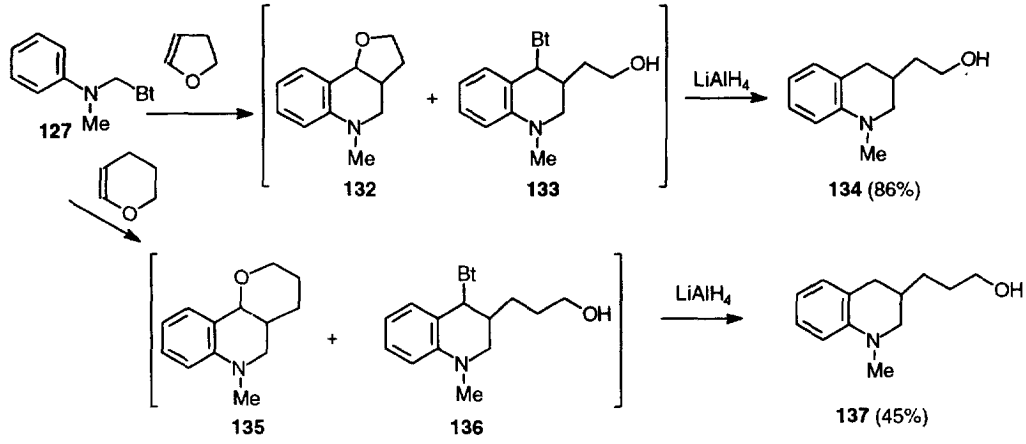


127 **128** **129** **130** (48%)

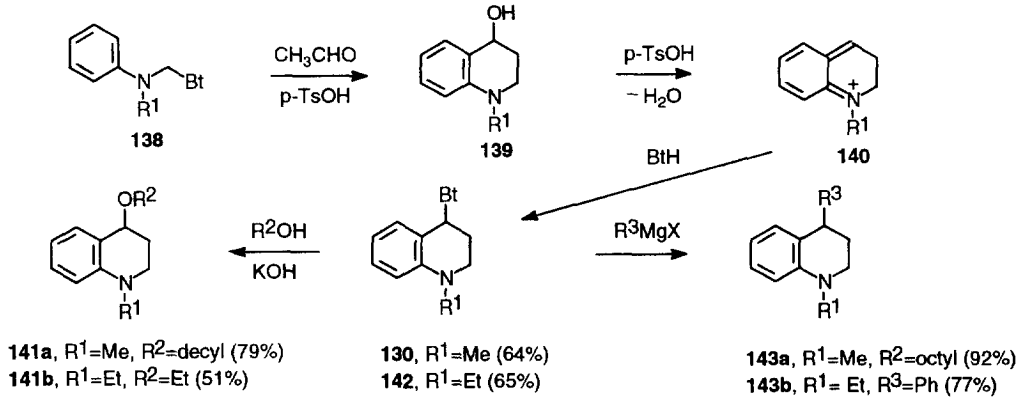
131a, R = Me (79%)
131b, R = Bu (46%)
131c, R = Ph (62%)

With 2,3-dihydrofuran, compound **127** gives a mixture consisting of tricyclic system **132** and four benzotriazolyl derivatives **133** (two pairs of diastereomeric benzotriazol-1-yl and -2-yl isomers). Product **132**

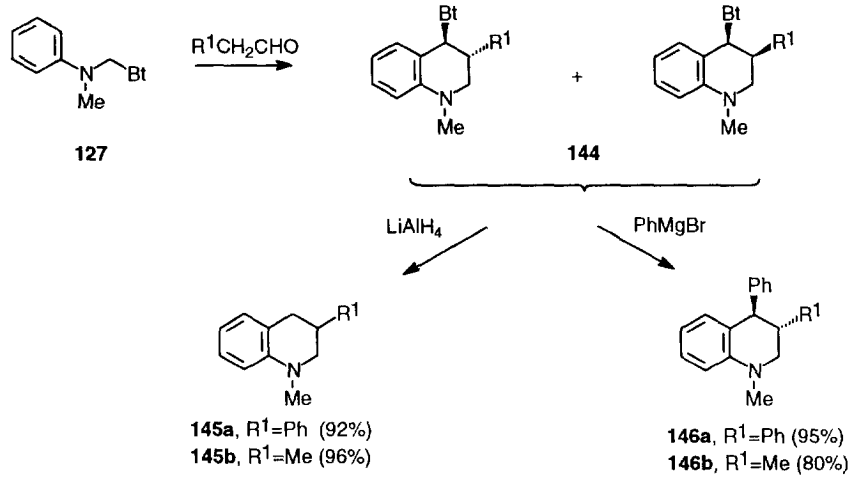
can be separated from the reaction mixture by fractional distillation (in 61% yield); however, treatment with lithium aluminum hydride in refluxing anisole converts the whole mixture into a single product **134**.[163] The reaction of **127** with 3,4-dihydro-2H-pyran proceeds similarly yielding 3-(3-hydroxypropyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**137**), via intermediates **135** and **136**.[163]



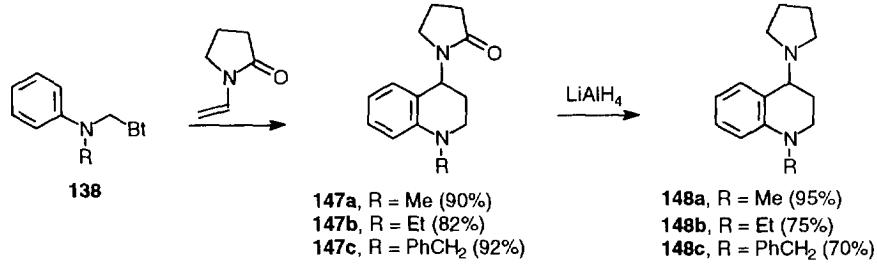
Reactions of *N*-[(benzotriazol-1-yl)methyl]anilines **138** with enolizable aldehydes proceeds similarly to those with enol ethers. However, in reactions of **138** with acetaldehyde, the assumed hydroxy intermediates **139**, cannot be isolated, as the hydroxy group undergoes rapid substitution with benzotriazole to give products **130** and **142**. Iminium cation **140** is implicated as a key intermediate for the preparation of compounds **130** and **142**, and also in subsequent conversions in which the benzotriazolyl moiety is substituted by an electrophile. 4-(Benzotriazol-1-yl)tetrahydroquinolines are convenient starting materials in preparation of other 1,4-disubstituted tetrahydroquinolines due to their reactivity with electrophiles, as demonstrated by conversion of **130** to tetrahydroquinolines **141a** and **143a**, and conversion of **142** to tetrahydroquinolines **141b** and **143b**.[159]

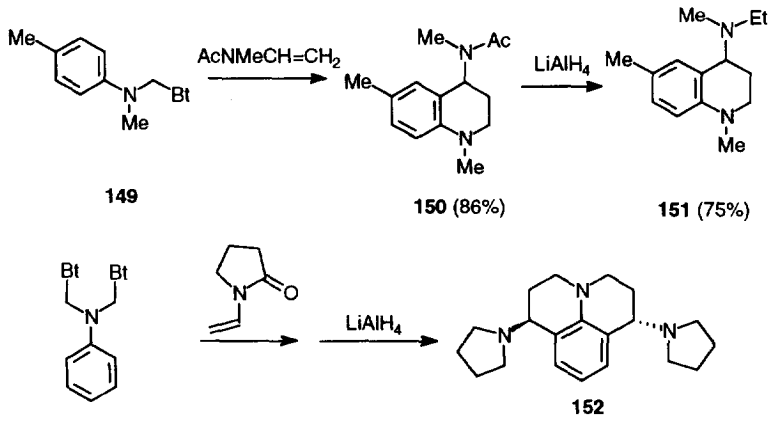


Reactions of **127** with higher aldehydes produce mixtures of diastereomers **144**, each as a pair of benzotriazol-1-yl and 2-yl isomers. These complex mixtures, without purification, in reactions with lithium aluminum hydride, are converted into single products (**145a** and **145b**). Reactions with phenylmagnesium bromide similarly give single products **146a** and **146b**.[159] This is the best method currently available for the introduction of a substituent at C-3 of the tetrahydroquinoline ring.[164]



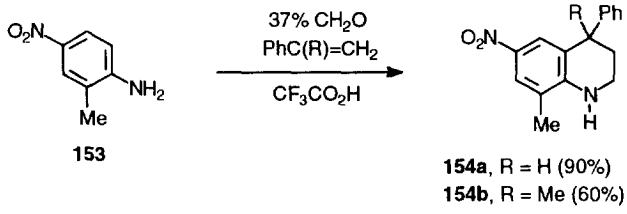
4-(Dialkylamino)tetrahydroquinolines can be also conveniently prepared using benzotriazole methodology. Thus, reactions of *N*-[benzotriazol-1-yl)methyl]anilines **138** with 1-vinyl-2-pyrrolidinone give 4-(2-pyrrolidinon-1-yl)tetrahydroquinolines **147** in high yields.[165] Reduction of the carbonyl group with lithium aluminum hydride converts these products into 4-(pyrrolidin-1-yl)tetrahydroquinolines **148**. *N*-Vinylacetamide reacts similarly, as it is shown in preparation of **151** from **149**, via amido intermediate **150**. This method allows also for convenient syntheses of julolidines substituted at C-1 and/or C-7 with dialkylamino groups, for example, julolidine **152**.[164]



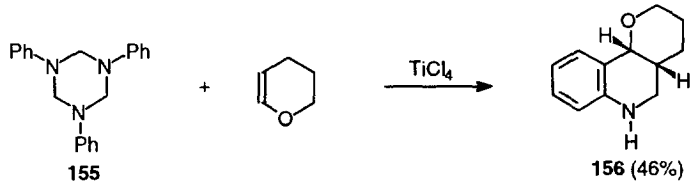


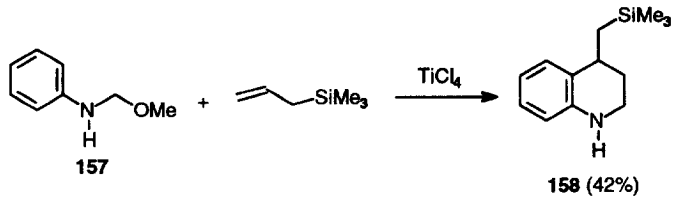
5b. Other Groups X in the $ARNCH_2X$ System

Condensations of anilines with formaldehyde under acidic conditions allow direct trapping of generated *N*-arylmethyleneiminium cations by added alkenes.[166] Nitrotoluidine **153** is thus converted into tetrahydroquinolines **154a** and **154b** upon treatment with formaldehyde and a styrene in the presence of trifluoroacetic acid.[167]



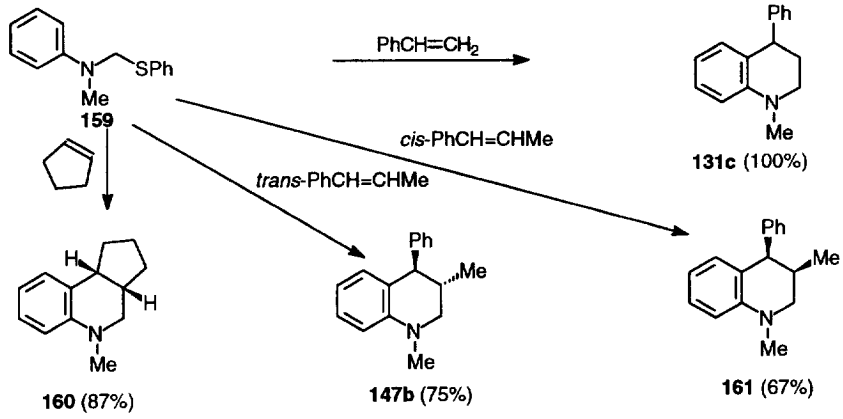
Other methods for the generation of the methylene iminium cations **121** involve ionization of triphenylhexahydro-1,3,5-triazine (**155**), prepared by condensation of aniline with formaldehyde[168] and N-(alkoxymethyl)anilines (**157**), prepared by electrochemical[169,170] or ruthenium catalyzed[171] oxidation of N-methylanilines in alcohols. Despite some inconvenience in the preparation and handling of these reagents, these methods have been used in the synthesis of tetrahydroquinolines, *e.g.* **156**[172] and **158.**[173]



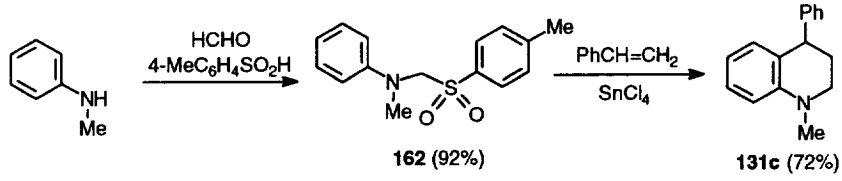


157 **158** (42%)

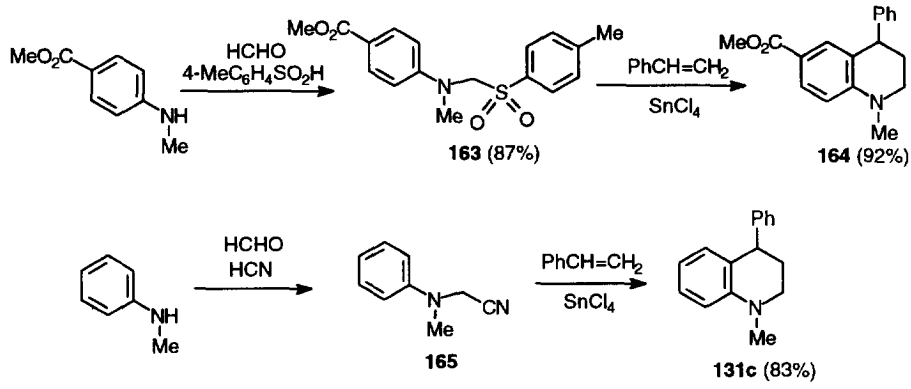
N-(Phenylthiomethyl)anilines, available by reactions of anilines with formaldehyde and thiophenol[174] seem to provide a good alternative, except for odor problems. Four examples of syntheses of tetrahydroquinolines, based on reactions of *N*-methyl-*N*-(phenylthiomethyl)aniline (**159**) with styrene (**131c**), cyclopentane (**160**), *trans*-1-phenylpropene (**147b**), and *cis*-1-phenylpropane (**161**) catalyzed by $TiCl_4$-PPh_3, are given below.[175]



Crystalline α-arylaminosulfones, prepared by condensation of anilines with formaldehyde and arylsulfinic acid are convenient reagents.[176] Thus, two examples of reactions of α-arylaminomethyl sulfones **162** and **163** with styrene to give tetrahydroquinolines **131c** and **164**, respectively, illustrate this approach. α-Arylaminomethylnitriles react similarly, as in the conversion of **165**[177] to tetrahydroquinoline **131c**.[176]

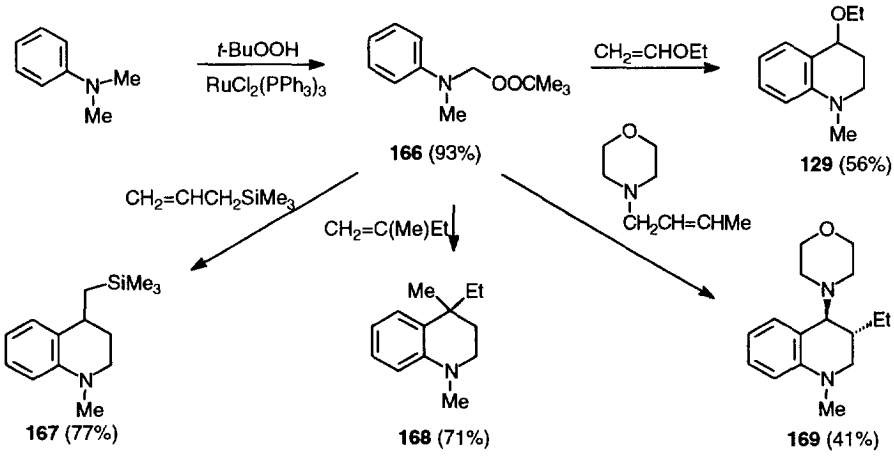


162 (92%) **131c** (72%)

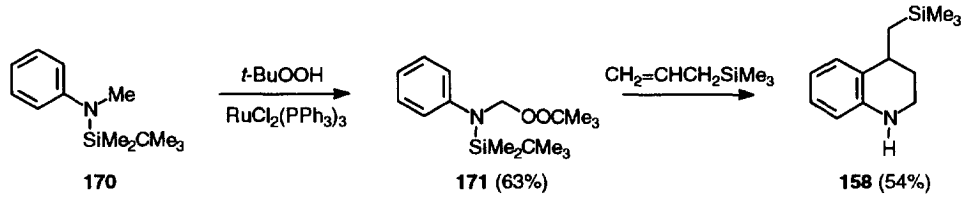


5c. Oxidation of N-Methylanilines

Oxidation of N-methylanilines can give *N*-arylmethyleneiminium cations. Thus, *N*-(*t*-butylperoxymethyl)-*N*-methylaniline (**166**) is prepared conveniently from *N,N*-dimethylaniline in a reaction with *tert*-butyl hydroperoxide.[178] In the presence of Lewis acids, compound **166** eliminates *tert*-butylperoxide anion producing *N*-methyl-*N*-phenylmethyleneiminium cation. Four examples using **166** in syntheses of tetrahydroquinolines (**129** and **167-169**) from the corresponding olefins are shown below.[179]

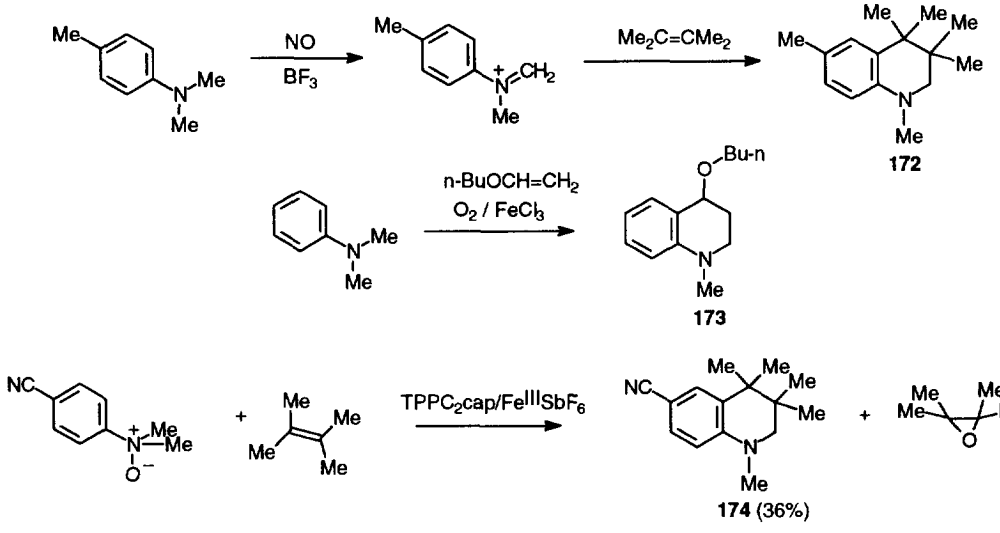


Tetrahydroquinolines unsubstituted at N atom can also be produced by this method using *N*-silyl protection: *e.g.*, conversion of derivative **170** to tetrahydroquinoline **158** via intermediate **171**.[179] Titanium tetrachloride is used as a Lewis catalyst in these reactions.



170 **171** (63%) **158** (54%)

N-(Arylamino)-*N*-methylmethyleneiminium cations can be directly observed by NMR during oxidation of *N,N*-dimethylanilines with nitric oxide in the presence of Lewis acids.[180] The cations can be trapped by olefins to give tetrahydroquinolines, *e.g.*, **172**. Iron salts catalyze oxidation of *N,N*-dimethylaniline with oxygen to methyleneiminium cations, which are efficiently trapped by vinyl ethers to give 4-alkoxytetrahydroquinolines (example: **173**).[181] Reaction of aniline *N*-oxides with olefins in the presence of an iron(III) C_2-capped porphyrin catalyst also gives tetrahydroquinolines (**174**), but the mechanism involved is believed to have radical character.[182]



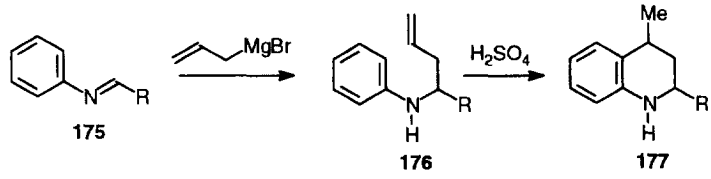
172 **173** **174** (36%)

6. Preparation of 2-Substituted Tetrahydroquinolines from Aniline Imines

Condensations of anilines with two molecules of an enolizable aldehyde RCH_2CHO give 1,2,3,4-tetrahydroquinolines possessing both an RCH_2 group on C-2 and an R group on C-3. In instances where it is desired that C-2 be substituted, but not C-3, direct derivatization of tetrahydroquinolines discussed earlier may be a solution.

6a. Reactions of Schiff Bases

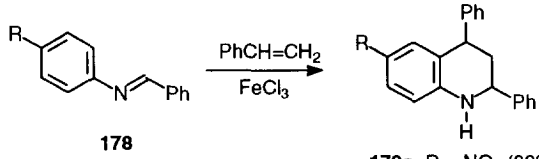
For aryl substituents on C-2, the Schiff bases can be treated with allylmagnesium reagents and the intermediate unsaturated amines obtained cyclized to tetrahydroquinolines under acidic catalysis. The conversion of phenyliminomethylpyridines **175** to 4-methyl-2-pyridyl-1,2,3,4-tetrahydroquinolines (**177**), via amines **176**,[150] illustrates this approach. Some additional examples of such reactions are given earlier (**83-90**).



175 **176** **177**

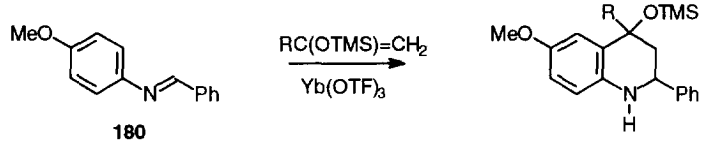
R = 2-, 3-, or 4-pyridyl

Schiff base complexation with Lewis acids activates the α carbon to electrophilic attacks allowing direct cyclization to tetrahydroquinolines with olefins. Comparison of the yields of **179a-c**,[183] shows that electron-withdrawing substituents on the aniline ring of **178** help to prevent side products. The milder yterbium Lewis acid catalyst works well even with electron-donating groups, as shown by examples of conversion of **180** to **181a** and **181b**;[184] the ratio given in parentheses corresponds to two diastereomeric products.



178

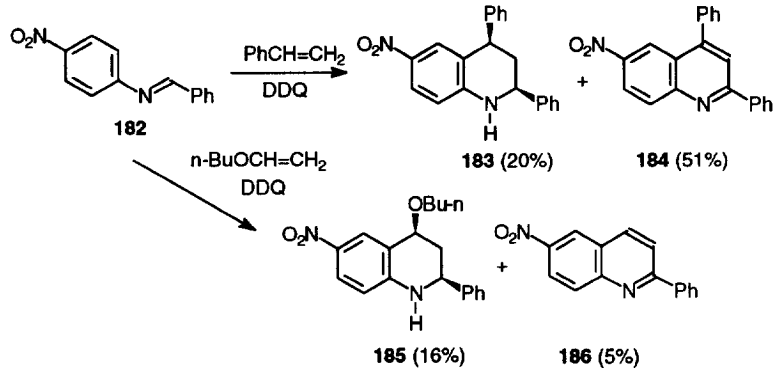
179a, R = NO_2 (99%)
179b, R = CN (80%)
179c, R = H (39%)



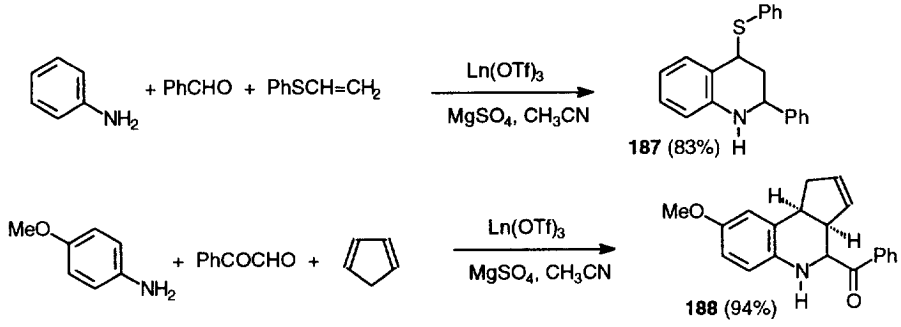
180

181a, R = Ph (88:12, 64%)
181b, R = Me (82:18, 60%)

Treatment of mixtures of Schiff base **182** and an olefin with DDQ produces 2,4-disubstituted tetrahydroquinolines **183** and **185** along with the corresponding quinolines (**184** and **186**).[185]

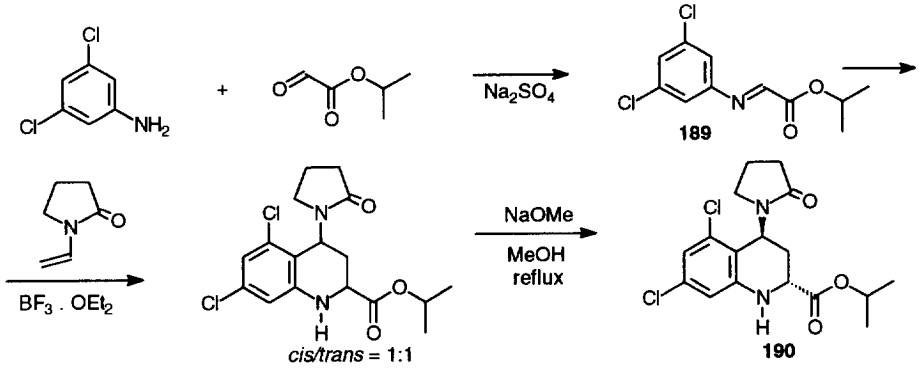


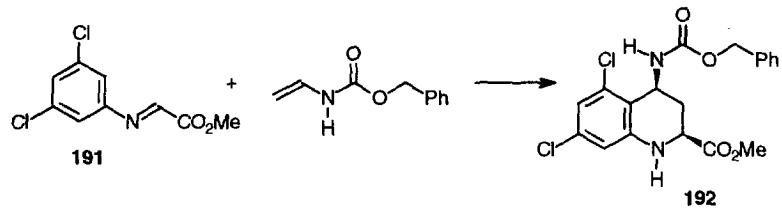
Often, the whole process can be accomplished in one step without isolation of the intermediate Schiff bases. Examples are preparations of tetrahydroquinolines **187** and **188**;[186] however, no proof that structure **188** is the correct regioisomer is provided.



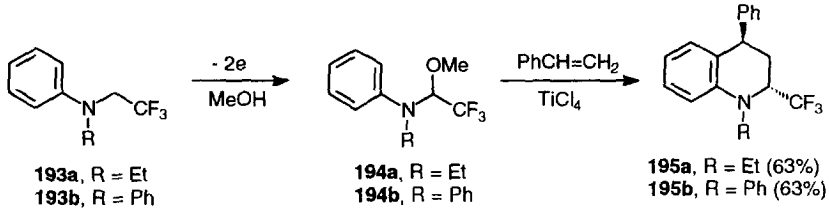
6b. Aniline Alkylimines

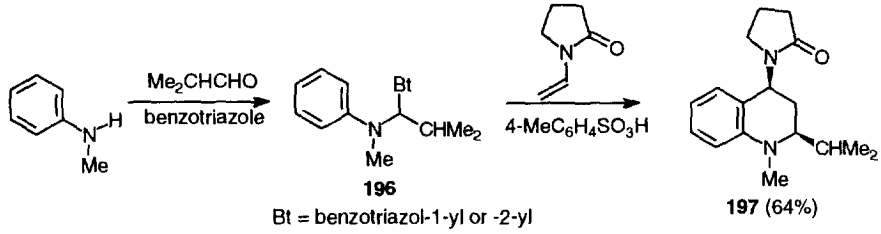
In place of aromatic rings, alkoxycarbonyl groups can stabilize the intermediate imines. Thus, in a synthesis of antagonists for the glycine site of the NMDA receptors, tetrahydroquinolines **190**[25] and **192**[65] are prepared from iminocarboxylic esters **189** and **191**, respectively.





The stabilizing influence of an electron-withdrawing trifluoromethyl group allows the preparation of *N*-(α -methoxyalkyl)anilines **194a** and **194b** by electrophilic anodic oxidation of the corresponding *N*-(2,2,2-trifluoroethyl)anilines **193**. In the presence of titanium tetrachloride, intermediates **194a** and **194b** react with styrene to give tetrahydroquinolines **195a**[170] and **195b**[187], predominantly as *trans* isomers. Because of the higher stability of *N*-[α-(benzotriazol-1-yl)alkyl]anilines, no electron-withdrawing substituents are then necessary: intermediate **196** is simply prepared by condensation of *N*-methylaniline with isobutyraldehyde and benzotriazole. Under acidic conditions, compound **196** reacts with 1-vinyl-2-pyrrolidinone to give tetrahydroquinoline **197**, predominantly as the *cis* isomer.[165]

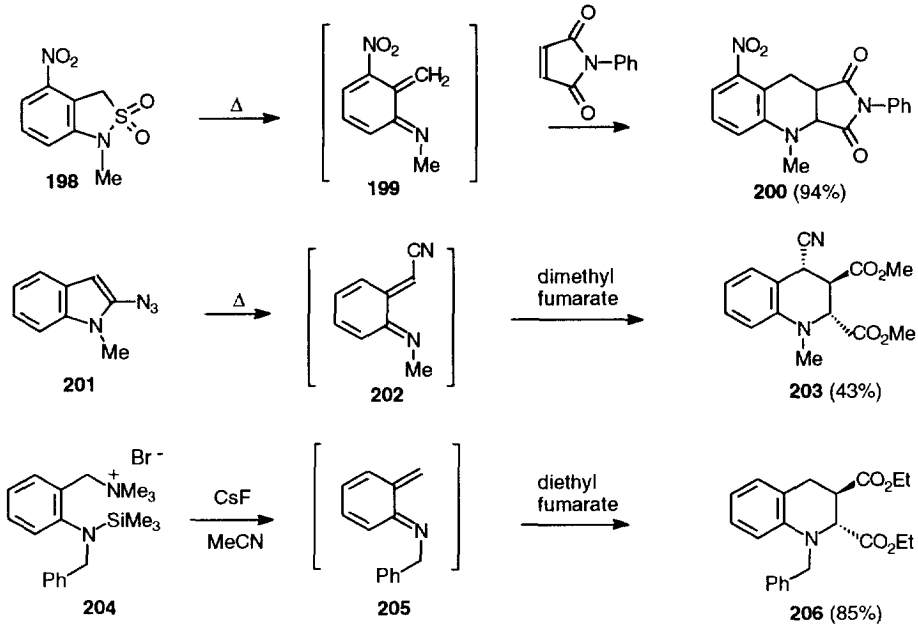




7. Preparation by Insertion of a C(2)-C(3) Fragment

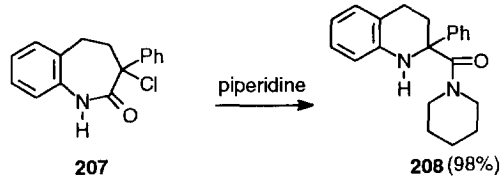
Although less common, this method based on Diels-Alder reactions of *ortho*-methyleneiminoquinones allows for synthesis of 1,2,3,4-tetrahydroquinolines substituted at C-2 and C-3 with substitution patterns difficult to achieve by other methods. Variants of this method, depending primarily on the source of the intermediate *ortho*-methyleneiminoquinone, are summarized below. Thus, 2,1-benzoisothiazoline-2,2-dioxide

(**198**) eliminates sulfur dioxide upon heating to produce *ortho*-methyleneiminoquinone **199**, which is trapped by dienophiles to give 2,3-disubstituted-1,2,3,4-tetrahydroquinolines, *e.g.*, **200**.[188,189] Thermal ring cleavage of 2-azido-1-methylindole (**201**) gives **202**, which is trapped by dimethyl fumarate to yield tetrahydroquinoline **203**.[190] In the last example, 1,4-elimination from silylated ammonium salt **204** catalyzed by fluoride generates *ortho* methyleneiminoquinone **205**, which is trapped by diethyl fumarate to give tetrahydroquinoline **206**.[191]



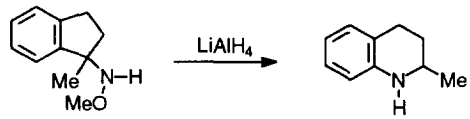
8. Ring Contraction and Ring Expansion

Chlorinations of the corresponding tetrahydrobenzazepines with phosphorus pentachloride, give 3-chloro -2,3,4,5-tetrahydro-1H-1-benzazepin-2-ones which react with amines to form 2-amino-1,2,3,4-tetrahydroquinolines in high yields.[192] As an example, 3-phenyl derivative **207** is converted to 2,2-disubstituted tetrahydroquinoline **208** upon heating with piperidine at reflux for 2 hours.

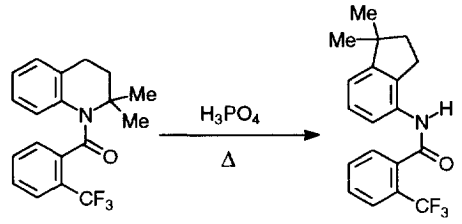


Reductions of 1-methoxyaminoindanes lead to ring expansion to the corresponding tetrahydroquinolines in high yields.[193] Thus, 2-methyl-1,2,3,4-tetrahydroquinoline (**13**) was obtained from 1-(methoxyamino)-1-

methylindane (**209**) upon treatment with lithium aluminum hydride. The opposite conversion, from tetrahydroquinolines to indanes[194] has already found practical applications in preparation of fungicide **211** from tetrahydroquinoline **210**.[74]



209 **13** (92%)



210 **211** (91%)

9. Summary

Table. Recommended Synthetic Methods for Substituted 1,2,3,4-Tetrahydroquinolines

Substitution Pattern	Preferred Methods	Section of this Review
2-monosubstituted	(i) from quinolines by reduction	2a
	(ii) from dihydroquinolines	2b
	(iii) from tetrahydroquinolines by substitution	2c
3-monosubstituted	(i) from quinolines by reduction	2a
	(ii) using benzotriazole methodology	5a
4-monosubstituted	(i) from quinolines by reduction	2a
	(ii) using benzotriaole methodology	5a
	(iii) other $ArNCH_2$ methodology	5b
2,3-disubstituted	(i) from aniline with two moles of RCHO	4
	(ii) from ortho methyleneiminoquinolines	7
2,4-disubstituted	(i) from Schiff bases	6a
3,4-disubstituted	using benzotriazole methodology	5a
2,3,4-trisubstituted	(i) from dihydroquinolines	2b
	(ii) from anilines and two moles of RCHO	4
	(iii) from Schiff bases	6a

Many good synthetic methods for 1,2,3,4-tetrahydroquinolines bearing substituents on the heterocyclic ring have been recently developed. The nature, number and relative location of the substituents are the key parameters to consider before choosing a method. Recommended synthetic methods are summarized in the Table. Benzotriazole methodology is frequently the best method for making 3-monosubstituted 4-monosubstituted and 3,4-disubstituted tetrahydroquinolines. Substitution at the nitrogen atom and at the aromatic ring, not considered in this review, may also influence the choice of the optimum method.

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(*Received* 25 *June* 1996)

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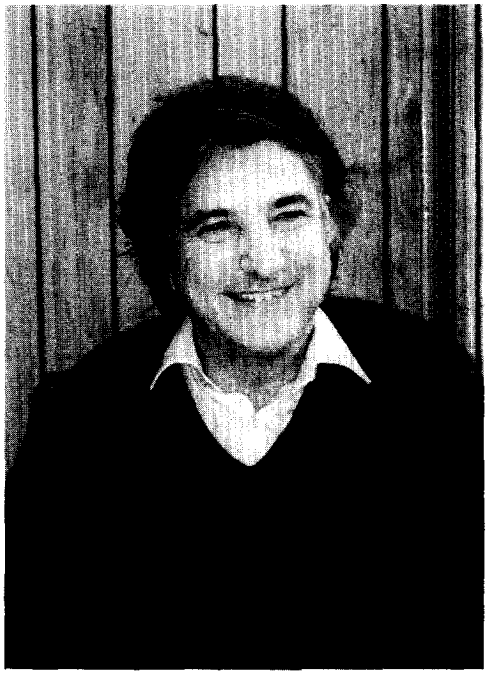

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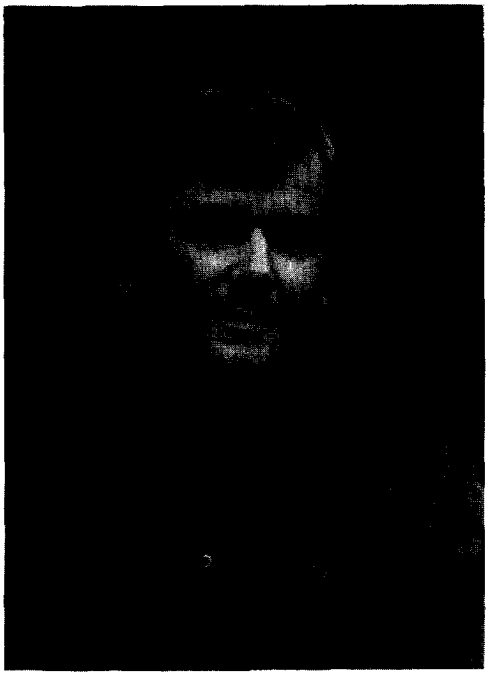

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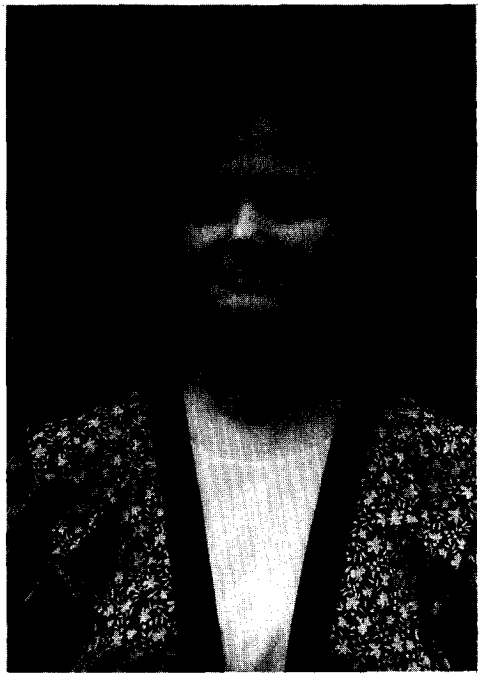

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