REVIEW

Recent developments in the chemistry of dihydropyridines

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1 Introduction

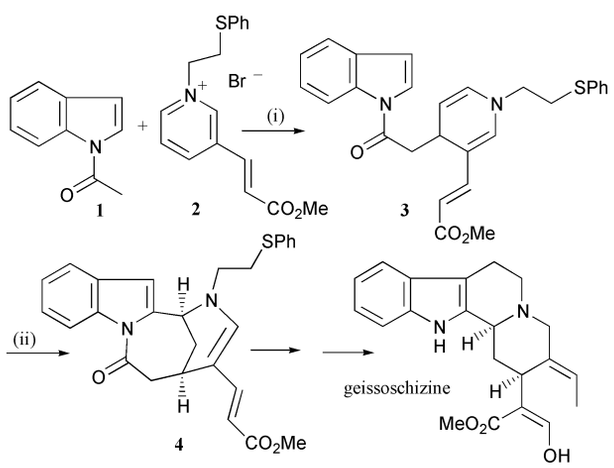
The study of dihydropyridines began early in 1882, when Hantzsch disclosed the first synthesis of these compounds. Major landmarks were the isolation of NADH and its role as a reductive cofactor, and the breakthrough of Hantzsch dihydropyridines as antihypertensive drugs. Afterwards, research also focused on NADH (reduced nicotinamide adenine dinucleotide) mimics and on the synthetic aspects of these heterocyclic systems, especially with regard to natural products and bioactive agents. The present review deals with new accomplishments in the dihydropyridine field: their reactivity, their use in organic synthesis, and their incidence in medicinal chemistry as well as in other applications. Oxo-derivatives (pyridones) and dihydropyridinylidene compounds (anhydrobases) are excluded from this work. Two points will be peripherally mentioned: the Hantzsch synthesis and the pharmacology of calcium channel blockers, and the biological chemistry of NADH. Only the more appealing references (from the point of view of an organic chemist) to these topics will be provided, as they have received such massive attention that extensive coverage would result in an unbalanced review. On the other hand, the comprehensive report on the area is also a challenging task (*dihydropyridine* as a keyword appears in more than 340 documents in *Chemical Abstracts* in the year 2000 alone). Some selection would therefore seem to be needed, and any author whose work, while significant, is not cited must excuse my unintentional oversight. The reader is referred to major works and previous reviews.[1]

2 Synthesis of dihydropyridines

2.1 Nucleophilic addition to *N*-alkylpyridinium salts

The addition of a broad variety of nucleophiles to pyridinium salts is, probably, the method of choice for the preparation of complex and/or functionalized dihydropyridines, especially those involved in the synthesis of natural products.

The interaction of enolates with *N*-alkylpyridinium salts followed by an intramolecular electrophilic trapping of the resulting dihydropyridine (the so-called "Wenkert procedure") has been successfully implemented in the synthesis of indole alkaloids.[2] Hence, the enolate of 1-acetylindole **1** and the salt **2** formed the intermediate dihydropyridine **3**, which upon acidic treatment gave the tetracycle **4**. Further transformations then allowed completion of a formal synthesis of (±)-geissoschizine.[3] The beneficial effect of lithium iodide in the acid-induced cyclization was used to increase the otherwise low yield of these processes (Scheme 1).[4a] Also worthy of note is the malonate addition taking place upon a "deactivated" pyridinium salt (lacking the β-electron-withdrawing group).[4b]

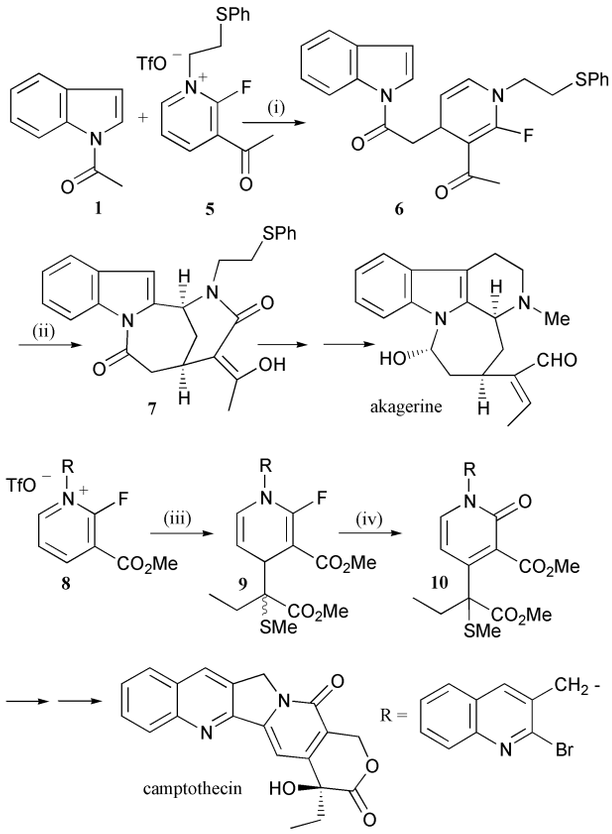


Scheme 1 *Reagents and conditions*: i, LDA (20%); ii, TsOH–C_6H_6, LiI (40%).

In a similar manner, the new vallesiachotamine lactone from *Cephaelis dichroa*,[5] compounds having the ring system of apogeissoschizine,[6] and structures related to akuammiline-type alkaloids[7] have been prepared through the addition of the appropriate ester enolate to the corresponding pyridinium salt, followed by acid-promoted cyclization.

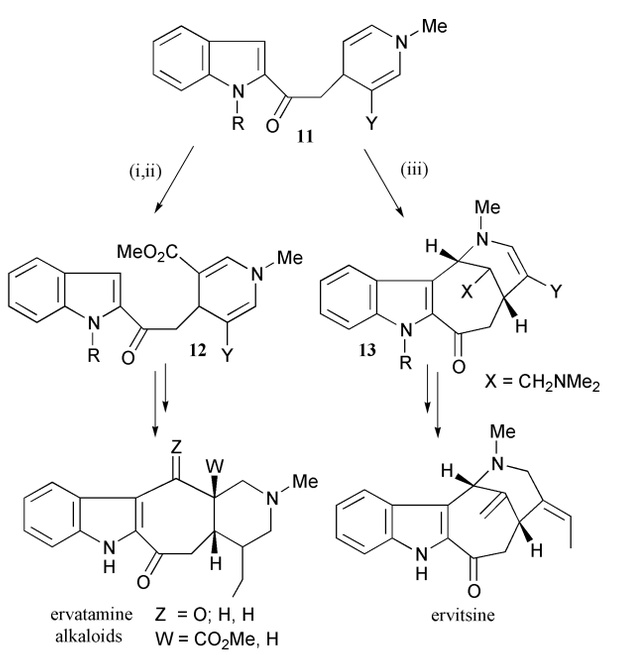
The use of 2-fluoropyridinium salts has enabled the preparation of pyridone and lactam structures using the same addition–cyclization protocol, which included, in these cases, the hydrolysis of the C–F bond either at the dihydropyridine stage or upon further oxidation. The formal syntheses of akagerine[3] and camptothecin[8] were accomplished in this way (Scheme 2).

Trapping the intermediate dihydropyridine with electrophiles other than a proton allows interesting functionalizations of the β-position at the enamine moiety. Several syntheses of



Scheme 2 *Reagents and conditions*: i, LDA (23%); ii, TsOH–C_6H_6, LiI, MeOH (58%); iii, methyl α-(methylsulfanyl)butyrate, LDA; iv, DDQ (≈50% overall yield).

ervitsine-ervatamine alkaloids have been described using this modified method. Thus, treatment of dihydropyridines **11** with trichloroacetic acid anhydride (TCAA), followed by the base-induced degradation of the trihalomethyl ketone, resulted in the formation of the methoxycarbonyl derivatives **12**, which were further elaborated to accomplish the preparation of ervatamine alkaloids.[9] On the other hand, interaction of **11** with Eschenmoser's salt, and subsequent cyclization of the resulting iminium ion, afforded tetracycle **13** *en route* to the total synthesis of ervitsine (Scheme 3).

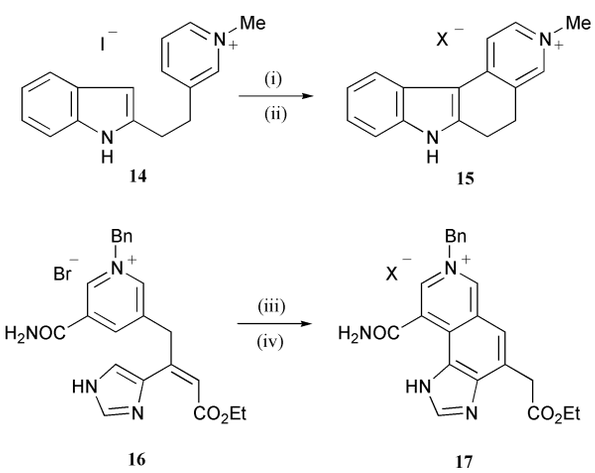


Scheme 3 *Reagents and conditions*: i, TCAA; ii, MeONa, MeOH; iii, $Me_2N^+{=}CH_2\ I^-$.

Two enantioselective syntheses of indole alkaloids using the Wenkert procedure have been reported. (+)-Vallesiachotamine and (−)-isovallesiachotamine have been prepared by addition of chiral enolates to pyridinium salts.[10] Also, the use of a chiral pyridinium salt (prepared by attachment of (*S*)-*O*-methylprolinol to the carbonyl present at the β-position of the pyridine ring) has allowed the synthesis of (−)-N_a-methylervitsine.[11]

α-Addition of esters, nitriles, and ketones to *N*-alkylquinolinium and isoquinolinium salts under sonochemical activation has been described.[12] In the first two cases, the nucleophile was generated by interaction of a silyl precursor with a fluoride source, whereas in the third, NaOH was used as the base. The processes showed good regioselectivity and yields ranging from moderate to nearly quantitative.

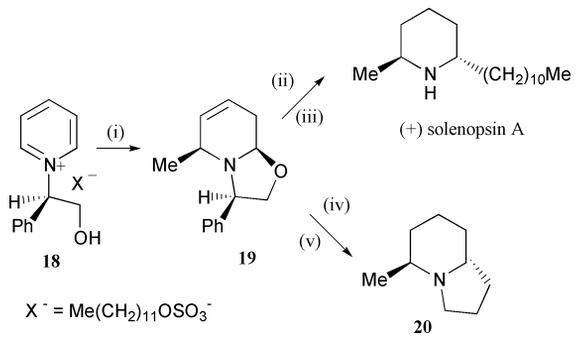
Base-promoted addition of azoles (indoles and pyrrole by their β- and α-positions respectively) to azinium salts (*N*-alkylpyridinium, quinolinium and isoquinolinium) proceeds in homogeneous solvents or in phase transfer conditions (PTC) (DMSO or toluene–H_2O, respectively). Regioselectivity is strongly influenced by the solvent, PTC favoring γ-attack.[13] The intramolecular version of these reactions has been reported. Of the several systems studied, only the one having an ethylene bridge linking the indole and pyridinium moieties **14** undergoes the desired cyclization, affording (after oxidation) the pyridocarbazole **15**. Similar trends hold for reaction with the corresponding *N*-acetylpyridinium salt.[14] In the study of a chemical model for the urocanase reaction (a rare process where NAD^+ suffers a nucleophilic attack by an imidazole), the salt **16** affords on treatment with base (also after oxidation of the initially formed dihydropyridine) the tricyclic system **17** (Scheme 4).[15]



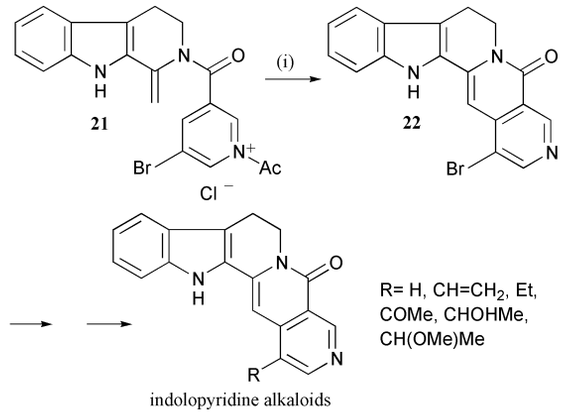
Scheme 4 *Reagents and conditions*: i, NaOH–CH_2Cl_2, Bu_4NHSO_4; ii, spontaneous oxidation (84% overall yield); iii, Al_2O_3–MeOH–CH_3CN; iv, spontaneous oxidation.

The addition of organocopper reagents to β-substituted *N*-alkylpyridinium salts has been described. The resulting dihydropyridines were stabilized by treatment with TCAA. Regioselectivity seems to depend on the type of organometallic reagent used, but is also modulated by the substituents on the heterocyclic ring.[16] Regio- and diastereoselective additions of Grignard reagents have been performed upon homochiral *N*-alkylpyridinium **18** and isoquinolinium salts.[17] These compounds are conveniently prepared *via* the Zincke reaction, and when the chiral auxiliary bears a hydroxy group, the addition process may be repeated, and stereoselective double alkylations become feasible. Several piperidines, indolizidines and isoquinoline derivatives have been prepared in enantiopure form (Scheme 5).

The thermal and photoinduced alkylation of pyridinium, quinolinium, and isoquinolinium tetraalkylborates produced



Scheme 5 *Reagents and conditions*: i, MeMgCl (70%, de 90%); ii, n-$C_{11}H_{23}MgBr$ (66%, de 32%); iii, H_2, HCl, Pd/C (60%); iv, 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (77%, de 54%); v, H_2, HCl, Pd/C (75%).



Scheme 6 *Reagents and conditions*: i, CH_2Cl_2, 40 °C (42%).

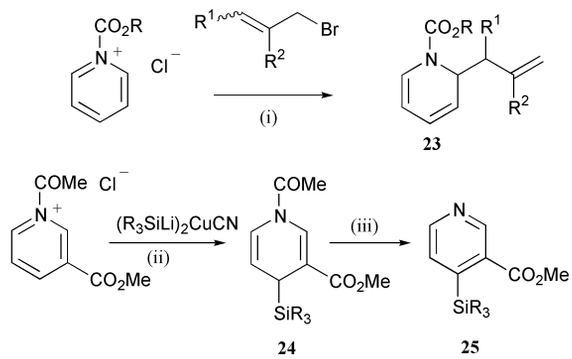
trialkylborane and the corresponding α-alkyldihydroazines in good yields and reasonable regioselectivity. These reactions proceed also in the solid state.[18] The use of pyridine as the base in a Pudovik reaction [the addition of esters of phosphorus(III) acids containing a P–H bond to unsaturated systems] afforded 1,2-dihydropyridin-2-ylphosphonates, arising from dialkyl phosphite addition to the pyridinium salt formed *in situ* (resulting from the interaction of the conjugated alkyne with the pyridine).[19a] The addition of phosphites and phosphines to *N*-(halovinyl)pyridinium salts, however, regioselectively yields the γ-substituted-1,4-dihydropyridines.[19b]

2.2 Nucleophilic addition to *N*-acylpyridinium salts

Analogous synthetic approaches involving *N*-acylpyridinium salts (or similar species) have been implemented during this period. This strategy offers the advantage of using the more reactive (electrophilic) pyridinium salts, and furnishes more stable (resistant to spontaneous oxidation) dihydropyridine adducts which may be conveniently transformed into a broad variety of substituted pyridines, tetrahydropyridines and piperidines. Usually the processes are compatible with functionalized substrates and proceed with high degrees of regio- and stereocontrol. On the other hand, the pyridinium salt (often formed *in situ*) is in equilibrium with the pyridine and the acid derivative; some limitations in terms of solvents, nucleophiles, and experimental conditions to be employed, arise from this phenomenon. The use of a triflate† counterion (prepared by the exchange of chlorides with silyl triflates) leads to increased yields in addition reactions.[20] This has been attributed to the higher reactivity of the salts thus formed (the new anion being less nucleophilic) and to an equilibrium shift favoring the formation of the *N*-acylpyridinium salt.

Pyrrole addition to an *N*-acetylpyridinium chloride affords the corresponding 4-(pyrrol-2-yl)-1,4-dihydropyridine in low yield. Quinolinium and isoquinolinium derivatives react in a similar way, yielding the bis-adducts (2,5-disubstituted pyrroles), which were DDQ oxidized to the fully aromatic systems.[13] An intramolecular enamide addition taking place on 3,5-disubstituted *N*-acetylpyridinium salt **21** was used to regioselectively build the common pentacyclic intermediate for the synthesis of six indolopyridine alkaloids.[21] In this case, oxidation and hydrolysis of the initially formed dihydropyridine afforded the desired compound **22** (Scheme 6).

Additions of organometallic reagents have been widely used in the preparation of natural products, pharmaceuticals, and liquid crystalline compounds. Representative examples involve the interaction of organocopper,[22] organozinc,[23] and Grignard reagents,[24] including stereoselective processes with remote asymmetric induction.[25] Indium-promoted allylations take place in DMF, to regioselectively furnish 1,2-dihydropyridines **23** with good yields.[26] The introduction of silyl substituents at the γ-position of the pyridine ring has been achieved through the silylcupration of *N*-acetylpyridinium salts.[27] In this case, oxidation of the initial product **24**, leads to the silylated pyridines **25** (Scheme 7).



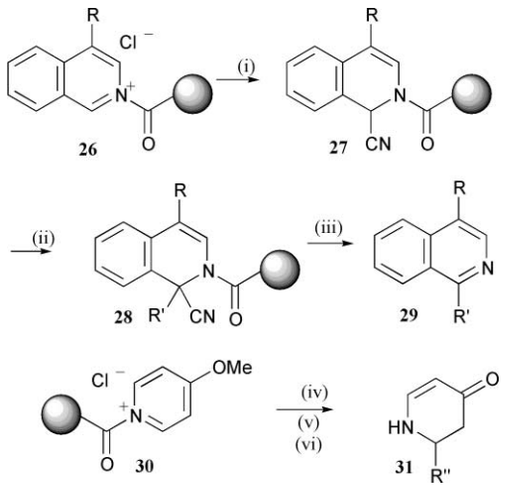
Scheme 7 *Reagents and conditions*: i, In, DMF (≈70%); ii, THF, −78 °C (≈80%); iii, *p*-chloranil, toluene (≈60%).

The use of *N*-trifluoromethylsulfonylpyridinium triflates (prepared by interaction of pyridines with triflic anhydride) allows the addition of phosphines, phosphites,[28] and ketones (directly, without preforming the corresponding silyl enol ethers).[29] Treatment of the 1,4-dihydroadducts with base leads to the γ-substituted pyridines.

Solid-phase techniques have been recently introduced in this field.[30] The generation of *N*-acylpyridinium salts attached to functionalized polystyrene resins opens a new way for preparing combinatorial libraries of pyridine-type compounds. In this respect, Reissert reactions (using traceless linkers)[31] and Grignard additions,[32] have been applied to the synthesis of substituted isoquinolines and dihydropyridones (Scheme 8).

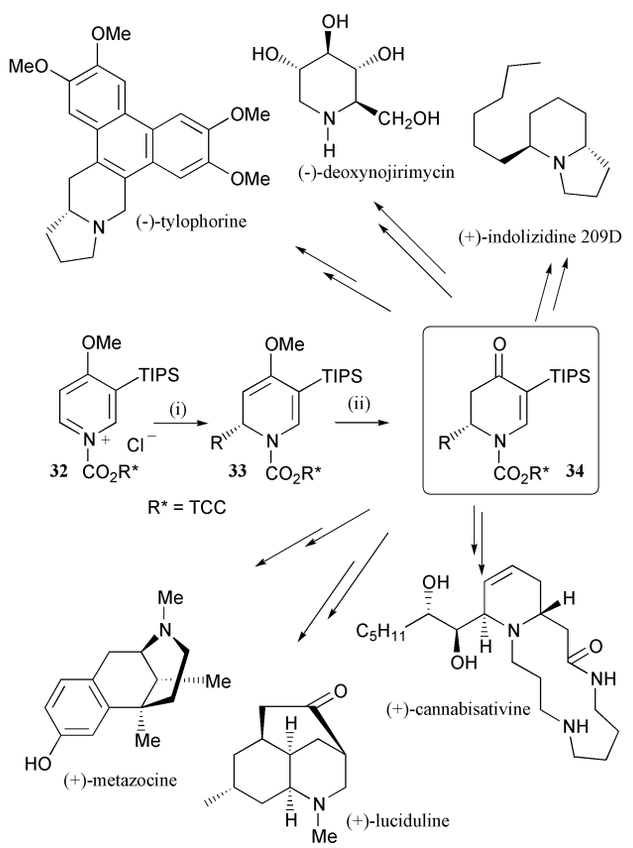
Some asymmetric syntheses of dihydroazines based on diastereoselective additions taking place on *N*-acyliminium salts, with the participation of chiral auxiliaries have been successfully carried out. For instance, enantiomerically pure carboxylic acid chlorides (being linked to the heterocyclic nitrogen),[33] chiral diamines (to form aminals with an aldehyde placed at the β-position of the azine ring),[34] or nonracemic substituted oxazolidinones and thiazolidine-2-thiones (attached by an amide bond to a nicotinic acid derivative)[35] have been effectively used in the synthesis of chiral heterocyclic systems. The Comins protocol, in which a 4-methoxypyridinium salt **32** [formed by reaction of the pyridine with the chloroformate of (+)-*trans*-2-(α-cumenyl)cyclohexanol (TCC)] reacts with nucleophiles to yield enantiomerically enriched 1,2-dihydropyridines **33**, deserves special mention. Subsequent hydrolysis of the enol ether affords the key intermediate **34**, a 2,3-dihydro-4-pyridone which can be stereo-, chemo-, and regioselectively transformed into a broad variety of diversely

† The IUPAC name for triflate is trifluoromethanesulfonate.



Scheme 8 *Reagents and conditions*: i, TMSCN, CH_2Cl_2; ii, LDA, R′X; iii, aq. KOH, THF; iv, R″MgX, THF; v, aq. HCl, THF; vi, NaOH, MeOH.

functionalized piperidine-based systems. This versatile approach has allowed the total synthesis of alkaloids belonging to different skeletal types, like indolizidines and phenanthroindolizidines,[36] lycopodium alkaloids,[37] polyamine alkaloids,[38] benzomorphans,[39] hydroxypiperidines,[40] together with derivatives of histrionicotoxin.[41] Additional studies on the reactivity of dihydropyridones further expand the usefulness of the methodology (Scheme 9).[42]

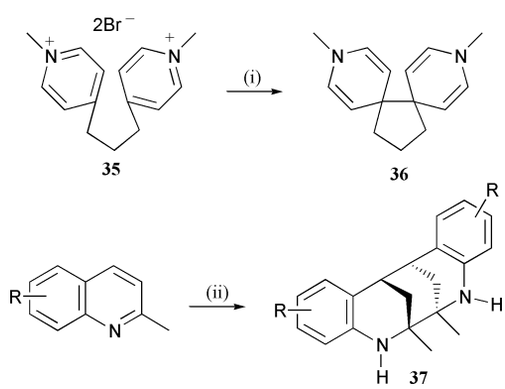


Scheme 9 *Reagents and conditions*: i, RMgBr, THF; ii, oxalic acid, H_2O, THF.

Recently, a catalytic enantioselective Reissert reaction has been disclosed. The synthesis of nonracemic 2-cyano-1,2-dihydroquinolines (up to 96% ee) arises from the interaction of the chiral bifunctional catalyst (a Lewis acid–Lewis base structure based on a binaphthyl motif) which coordinates simultaneously with both the *N*-acylquinolinium salt and the nucleophile. Application to the preparation of a NMDA (*N*-methyl-D-aspartic acid) receptor antagonist using a solid-supported version of the catalyst was also reported.[43]

2.3 Reduction of pyridinium salts

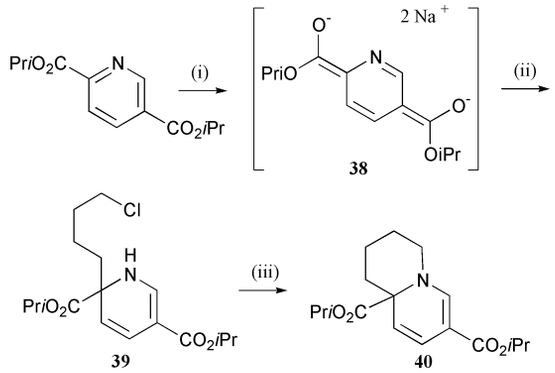
The classic dithionite reduction of pyridinium salts continues to be the most general, regioselective and reliable method for the synthesis of 1,4-dihydropyridines starting from *N*-alkylpyridinium salts. Spectroscopic studies of the process suggest that the mechanism involves an intramolecular hydride transfer from an intermediate sulfinic ester, derived from the *O*-addition of the dithionite anion.[44] Customary preparations are often found in heterocyclic synthesis.[45] *N*-Tryptophyl-1,4-dihydropyridines, obtained by this method, are useful intermediates in the total synthesis of indole alkaloids, as they are readily and stereoselectively cyclized to indoloquinolizidines.[46] Pyridinium salts bearing a chiral auxiliary derived from phenylglycinol are reduced to the corresponding dihydropyridines; and after intramolecular hydroxy addition to the enamine moiety, useful tetrahydropyridines are formed with good yields.[47] Borohydride reduction of *N*-acylpyridinium salts, although not completely regioselective, is also commonly used in the preparation of dihydroderivatives.[48] A ruthenium formyl complex efficiently reduces NAD^+-like compounds to the corresponding 1,4-dihydropyridines.[49] Also, electroreduction of pyridine dicarboxylic esters (and pyridinium salts as well) affords 1,2- or 1,4-dihydropyridines, depending on the relative position of the substituents; appropriate experimental conditions (cathode, supporting electrolyte, temperature and additives) are crucial for high yields.[50] One-electron reduction of pyridinium salts generates dihydropyridyl radicals which undergo spontaneous dimerization. Studies on the mechanism and regio- and stereoselectivity of such processes have been reported.[51] Trapping of the intermediate radical with olefins yields 4-substituted-1,4-dihydropyridines.[52] Sodium interaction with bispyridinium salt **35** produces the dispirodihydropyridine **36**, by intramolecular coupling of the initially formed diradical.[53] Zinc in acetic acid promotes the reductive dimerization–cyclization of substituted 2-methylquinolines to form pentacyclic derivatives **37**, in a cascade process which also yields minor amounts of different polyheterocyclic compounds (Scheme 10).[54]



Scheme 10 *Reagents and conditions*: i, 2.8% Na amalgam, H_2O–hexane; ii, Zn, AcOH–THF (≈60–90%).

Pyridinium salts can be reduced by Zn, presumably by 2-electron transfer to give an anion, which may be alkylated *in situ*. This procedure yields very reactive 4-substituted dihydropyridines which are generally transformed by further reduction into stable compounds.[55]

Birch reduction of electron-deficient pyridines produces dianions such as **38** which can be selectively trapped by alkylation, to furnish α-substituted-1,2-dihydropyridines **39** in high yields (Scheme 11).[56]

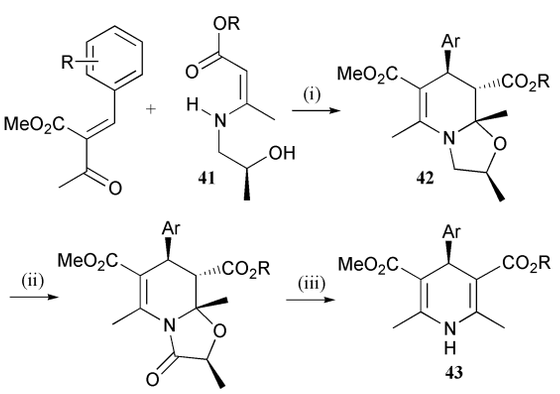


Scheme 11 *Reagents and conditions*: i, Na, NH_3, −78 °C; ii, 1-chloro-4-iodobutane, then NH_4Cl (one pot, 100%); iii, DBU, acetone (88%).

2.4 Condensation procedures

The venerable Hantzsch synthesis of dihydropyridines has been adapted to the needs of combinatorial chemistry, and two solid-phase versions of this process have been described. Attachment of one β-dicarbonyl component to an amine-functionalized PAL or Rink resin (to form a linked aminocrotonate), followed by interaction with the second β-dicarbonyl and the aldehyde components, and final acidic cleavage, yields libraries of Hantzsch dihydropyridines with good overall yields (≈70%).[57a] A modification consisting of the use of a Wang resin and the linkage of the β-dicarbonyl through an ester bond was recently disclosed.[57b]

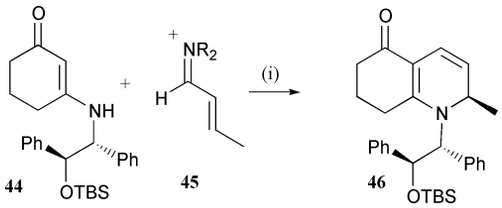
Related condensations include the 3-component interaction of β-dicarbonyl compounds (or β-cyano, β-nitro and other derivatives) with aminocrotonates and aldehydes.[58] Aminocrotonates condense with trifluoromethyl substituted β-dicarbonyl compounds to afford fluorinated dihydropyridines and pyridines.[59] The employment of aminocrotonates with chiral *N*-linked substituents **41** allows the preparation of enantiopure dihydropyridines **43** with excellent stereoinduction, in a 3-step protocol, involving condensation (to form **42**), oxidation, and subsequent hydrolysis and elimination (Scheme 12).[60]



Scheme 12 *Reagents and conditions*: i, MeOH, reflux (≈45%); ii, benzyltriethylammonium permanganate, CH_2Cl_2 (≈30%); iii, KOH, MeOH (≈80%).

In a related process, reaction of β-enaminonitrile with α,β-unsaturated carbonyls (ketones and aldehydes) affords 1,4-dihydropyridines after acid-catalyzed dehydration of the initial adduct.[61] Vinylogous amides **44** interact with α,β-unsaturated iminium ions **45** in a stepwise formal [3 + 3] cycloaddition to yield 1,2-dihydropyridines **46**. Intramolecular and stereoselective versions of this process have been successfully developed (Scheme 13).[62]

Other approaches have also shown their relevance. Lanthanide triflates promote the condensation of aldehydes with primary amines to furnish 2,3-dihydropyridinium ions in good yields.[63] (Vinylimino)phosphoranes (2 equivalents) react with



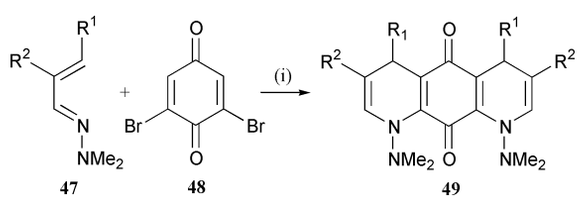
Scheme 13 *Reagents and conditions*: i, EtOAc–toluene, 150 °C (sealed tube), (79%, dr 90 : 10).

aryl (or α,β-unsaturated) aldehydes to produce 1,4-dihydropyridines, bypassing the alternative aza-Wittig process.[64] In a one-pot multicomponent reaction, nitroenones, aromatic aldehydes and anilines condense to form dihydropyridines in a stereoselective manner.[65] Heterocyclic *o*-aminothioaldehydes react with alkynes (conjugated with electron-withdrawing groups) in a stepwise transformation to produce *b*-fused dihydropyridines.[66] Vinylogous amidinium salts, aldehydes and malononitrile condense to form 2-amino-4*H*-pyrans, which on treatment with amines are smoothly converted (through a ring opening–ring closure sequence) into the corresponding 1,4-dihydropyridines.[67] Dienamines bearing ω-nitro or ester groups undergo aza-annulations with aldehydes to give 1,2- or 1,4-dihydropyridines.[68]

2.5 Pericyclic reactions

Photocyclization of 3-styrylpyridines under anaerobic conditions takes place with high regioselectivity to give dihydroazaphenanthrenes, which are further oxidized to the fully aromatic systems.[69] The thermal electrocyclization of 1-azatrienes was found to be facilitated remarkably by the presence of carbonyl and alkenyl substituents at the 4- and 6- positions respectively; 1,2-dihydropyridines can be obtained through this method. When hydroxylamine derivatives are employed, a final elimination gives rise to the corresponding pyridines.[70] Theoretical studies on these systems have been performed.[71] Lithiathed allenes add to isothiocyanates, and after *S*-alkylation and thermal isomerization, the 2-azatriene system thus generated undergoes cyclization to afford 2,3 dihydropyridines.[72]

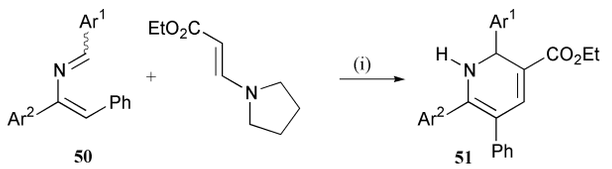
Hetero Diels–Alder reactions involving azadienes or azadienophiles have been used in the synthesis of dihydropyridines, although they are more frequently found in the preparation of tetrahydro derivatives. 1-Azadienes **47** undergo a smooth and regioselective double cycloaddition in the presence of bromo quinone **48**, to produce (after base-induced HBr elimination) the tricyclic diazaanthraquinone **49**. Further heating (loss of Me_2NH) causes aromatization of the adduct (Scheme 14).[73]



Scheme 14 *Reagents and conditions*: i, Et_3N, rt.

Unsaturated sulfinimines react with enol ethers to afford the corresponding tetrahydropyridines which, on attempted removal of the sulfinyl group, evolve to dihydropyridines.[74] Dihydroquinolines have been prepared through a [4+2] cycloaddition between ynamines (or alkoxyacetylenes) and *o*-azaxylylenes generated *in situ*, in the course of a general route to hydroquinolines.[75] 1-Azadienes react with electron-deficient alkynes[76] and alkynyl Fischer carbene complexes[77] to afford the corresponding substituted 1,4-dihydropyridines with good yields. A rare process involving the interaction of 1-azadienes and allenic esters has been disclosed, 4-aryl-1,4-dihydropyridines being the

result of such cycloadditions.[78] Enamines and 2-azadienes **50** (readily prepared by aza-Wittig reactions) interact to form a broad variety of substituted dihydropyridines **51** (after pyrrolidine elimination) in a regiospecific manner[79] (Scheme 15). A rationalization of the reactivity and the regioselectivity of these processes was made with the aid of semiempirical calculations.[80]



50 **51**

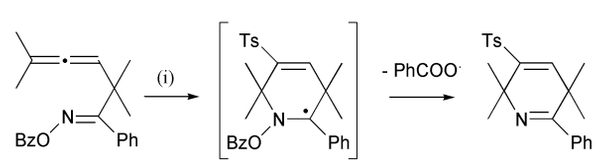
Scheme 15 *Reagents and conditions*: i, $CHCl_3$ or toluene, reflux (≈60%).

High pressure (up to 1500 bar) significantly increases the yield of the Diels–Alder reaction between a substituted butadiene and perfluorooctanonitrile, this allowed the synthesis of the elusive 2,5-dihydropyridine system.[81] An intramolecular inverse electron demand hetero Diels–Alder reaction between the C2–C3 portion of an indole ring and *C*-linked 1,2,4-triazines stereoselectively forms, after the usual N_2 extrusion, 3,4-dihydropyridines, in good yields (≈80–90%) when applied to substituted tryptamines.[82]

2.6 Miscellaneous preparations

Interaction of diisopropylzinc with substituted-2,2-bipyridines, produces the N–H 1,2-dihydropyridines (arising from a single addition). These revert to the starting heterocycles by an autooxidative process, thus cleaving the C–C bond previously formed.[83] Interesting observations regarding the reactivity of alkyllithium derivatives with pyridines have been described: the preparation and structural determination of the *N*-lithio-1,4-dihydropyridine arising from the addition of butyllithium to pyridine,[84] and the formation of hydrazinopyridines from the interaction of the 1,2-intermediate adduct with azodicarboxylates.[85] Regio- and stereoselective addition of organolithium reagents to nicotinoyl derivatives linked to an iron-based chiral auxiliary gave the corresponding 1,4-dihydropyridines in good yields.[86] Also, the addition of a trimethylsiliconide anion to pyridine, affords the 4-trimethylsilyl-1,4-dihydropyridine which can be *N*-acylated or oxidized to the γ-silylpyridine.[87]

Intramolecular addition of allyl radicals onto benzoyloximes forms 2,5-dihydropyridines **53** through a 6-*endo*-cyclization, in a process triggered by the addition of tosyl or tributylstannyl radicals to the allene moiety. Depending on the substitution pattern of the starting α-allenylbenzoyloximes **52**, products from a 5-*exo* ring closure are also formed (Scheme 16).[88] An aryl radical underwent an intramolecular [1,7] addition in a 3-aminosulfonylpyridine to give rise to the 1,4-dihydropyridine, and its oxidized analogue.[89]



52 **53**

Scheme 16 *Reagents and conditions*: i, TsBr, AIBN, cyclohexane (94%).

Fischer alkynylcarbene complexes react with conjugated imines[90] or with 4-amino-1-azadienes[91] to form 1,4- and 3,4-dihydropyridines respectively. In a series of related experiments, interaction of these organometallic compounds with anhydrobases produced spiro-fused 1,2- or 1,4-dihydropyridines.[92]

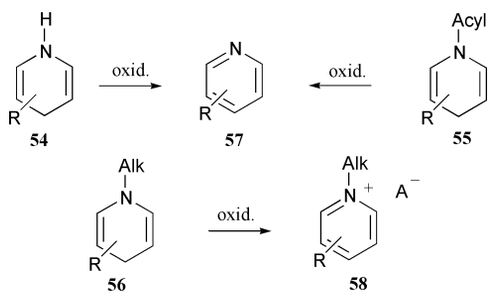
3 Reactivity of dihydropyridines

Reactions involving electrophilic additions to the enamine moiety (and the subsequent nucleophilic trapping of the iminium ion generated) and reductions to tetrahydropyridines and piperidines have been mentioned in the corresponding sections dealing with the preparation of dihydropyridines.

3.1 Oxidation

The oxidative conversion of dihydropyridines to the corresponding pyridinium salts is perhaps the most typical and general reaction of this heterocyclic system. Even so, research on this topic remains very active. The biomimetic NADH–NAD^+ chemistry, is the object of the next subsection.

There are a large number of oxidizing conditions available for achieving nearly quantitative transformations of *N*–H **54**, *N*-acyl- **55**, or *N*-alkyldihydropyridines **56** to the pyridines **57** or pyridinium salts **58** (Scheme 17).



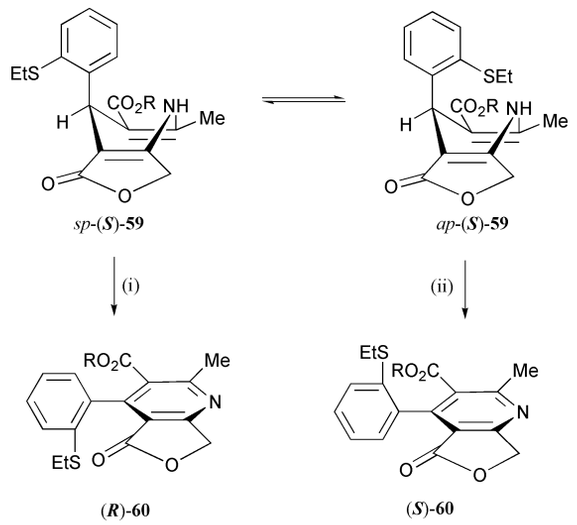
54 **57** **55** **56** **58**

Scheme 17

The list of new results includes the use of O_2 (in a process catalyzed by $RuCl_3$),[93] Magtrieve™ (CrO_2),[94] *in situ* generated HNO_3,[95] $Mn(OAc)_3$,[96] $Bi(NO_3)_3$,[97] PIFA (phenyliodine (III) bis-(trifluoroacetate)),[98] S (under microwave irradiation),[98] DDQ (used in a practical two step synthesis of 4-substituted pyridines, based on the faster oxidation of 1,4-dihydropyridines in competition with 1,2- or 1,6-regioisomers),[99] nitric oxide,[100] *S*-nitrosoglutathione,[101] and nitrosonium ions.[102] A common problem, often found in these oxidations, is the easy dealkylation of the substituents located at position 4 (especially in the benzyl and isopropyl series), which may be partially avoided using some of the above reagents. A spontaneous oxygen-mediated aromatization with concurrent dealkylation at C-2 has also been reported.[83]

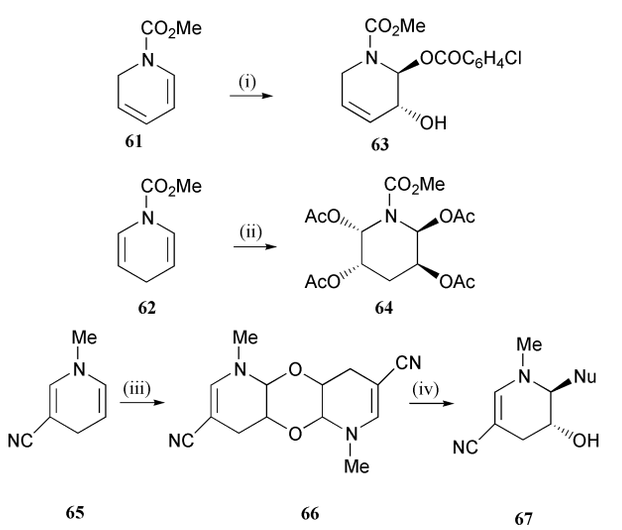
Photoinduced oxidations of Hantzsch 1,4-dihydropyridines have been performed through SET processes with CCl_4,[103] and quinones.[104] Electrochemical oxidation of 4-(pyridinium-3-yl)-1,4-dihydropyridines and 1,2-dihydropyridines (arising from [3 + 2] cycloadditions) affords the aromatized compounds; occasional cyclizations at the 4-substituent to yield indolizines have also been reported.[105] Remarkable oxidations of enantiomerically pure Hantzsch-type dihydropyridines have allowed the enantioselective synthesis of atropoisomeric γ-arylpyridines; in this way $NOBF_4$ reacts with dihydropyridine (*S*)-**59** to yield pyridine (*R*)-**60** (95% ee), whereas MnO_2 or $TEMPO^+$-BF_4^- affords (*S*)-**60** (93% ee).[106] The different accessibility of H-4 in the two rotamers of the starting dihydropyridine seems to be the most reasonable cause for the observed results. Bulky reagents would be forced to interact with the antiperiplanar (*ap*) rotamer, whereas $NOBF_4$ would select the more stable synperiplanar (*sp*) (Scheme 18). Moderate stereoselectivity results from the electroreduction of **60** to the parent dihydropyridines **59**.

In a conceptually different approach, oxidation of dihydropyridines can occur through bonding with electronegative atoms, bypassing the natural (*biomimetic*) electron transfer to form pyridinium salts. These, so-called *nonbiomimetic* oxidations constitute a family of chemically productive processes,



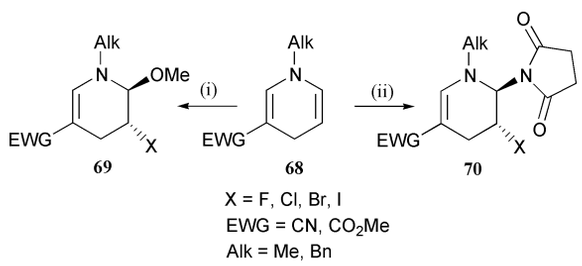
Scheme 18 *Reagents and conditions*: i, $NOBF_4$, CH_3CN (82%, 95% ee); ii, $TEMPO^+BF_4^-$, CH_3CN (94%, 93% ee).

yielding functionalized tetrahydropyridines or piperidines with potential use in organic synthesis. In this respect, 1,2- and *N*-acyl-1,4-dihydropyridines **61** and **62** have been oxidized through interaction with MCPBA and OsO_4 to form the corresponding *trans*-hydroxyester **63** (arising from *m*-chlorobenzoic addition to the transient oxirane) and the tetraacetoxypiperidine **64**, respectively.[48a] Similar reactions have been used in the synthesis of azasugars and alkaloid derivatives.[48b,107] On the other hand, dimethyldioxirane promotes the formal epoxidation of the more labile *N*-alkyl-1,4-dihydropyridines **65** to form the dimeric dioxanes **66** (other oxidants only promote the biomimetic process to the corresponding pyridinium salts). The α-alkoxyamino moiety present in **66** is a suitable iminiun ion precursor and, on Lewis acid catalysis, allows the stereoselective incorporation of different nucleophiles at the α-position of the tetrahydropyridine ring (Scheme 19).[48a,108]



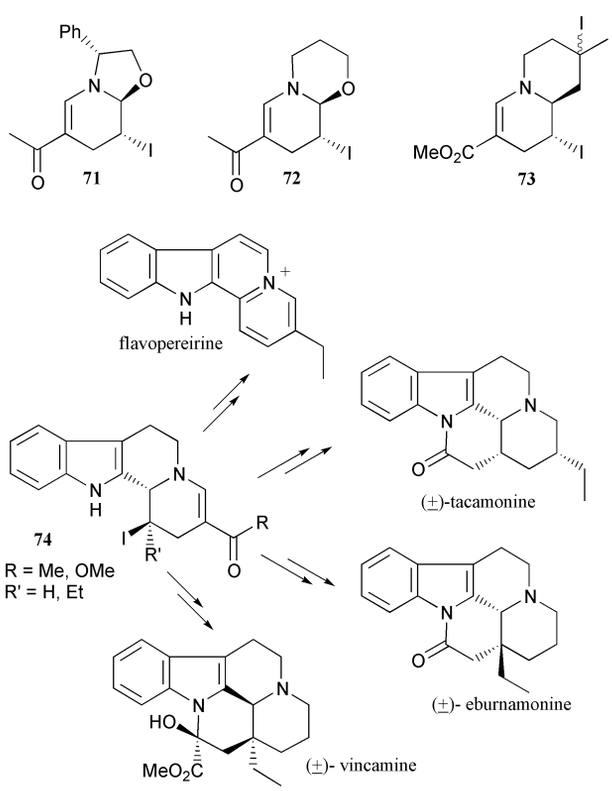
Scheme 19 *Reagents and conditions*: i, MCPBA, CH_2Cl_2 (65%); ii, OsO_4 cat., 4-methylmorpholine *N*-oxide, acetone–H_2O, then Ac_2O (77%); iii, dimethyldioxirane, acetone (72%); iv, nucleophile, Lewis acid.

Contrary to expectations, oxidative electrophilic additions to dihydropyridines take place with high yields and regioselectivity. Iodometric titrations of dihydropyridines, once thought to give the pyridinium salts, yield instead the Markovnikov-type compounds. Thus, alkoxyhalogenations of **68** afford the corresponding 3-halo-2-alkoxy-1,2,3,4-tetrahydropyridines **69**. The procedure involves the use of halogens or halonium ion sources (*N*-halosuccinimides or *N*-fluoropyridinium triflate) and allows the introduction of I, Br, Cl and even F atoms at the dihydropyridine β-position; the iminium ion generated in the event being trapped by the solvent or by the succinimide anion (to yield **69** and **70**, respectively) (Scheme 20).[109]



Scheme 20 *Reagents and conditions*: i, I_2, NXS or *N*-fluoropyridinium triflate, MeOH (74–90%); ii, NXS, THF (≈75%).

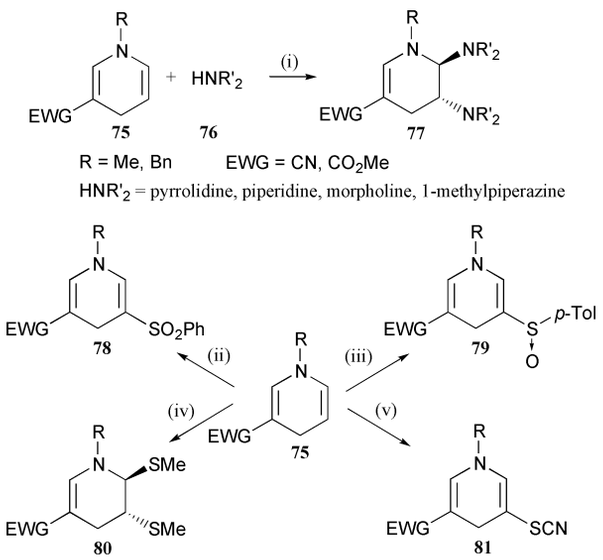
Intramolecular nucleophilic trapping of the intermediate β-halodihydropyridinium ion enables the preparation of bi- or polyheterocyclic structures. Hydroxy groups, alkenes, and activated aromatic rings (conveniently linked to the heterocyclic nitrogen), acting as internal nucleophiles, have been successfully used in these stereoselective one-pot addition–cyclization reactions. In this way, oxazolidines (including enantiomerically pure examples, like **71**, arising from a chiral dihydropyridine), oxazinanes **72**, quinolizines **73**, and indoloquinolizines **74** were prepared.[110] The ready access to these systems permits their use in multistep synthesis; in this way, the cytotoxic alkaloid flavopereirine and its 6,7-dihydro derivative were prepared through a dehydrohalogenation–biomimetic (DDQ) oxidation sequence.[111] A versatile route to Vinca, Eburnea, and Tacamine alkaloids based on the peculiar stereoselectivity of the carbon-centered radicals generated from the haloindoloquinolizines **74** has been recently implemented (Scheme 21).[112]



Scheme 21

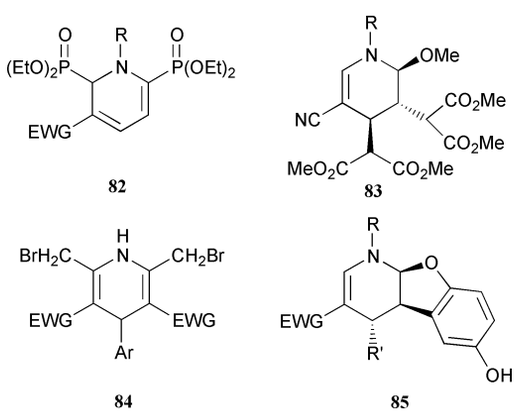
The introduction of nitrogen functionalities was based on the *nonbiomimetic* oxidative methodology; thus the cohalogenation process involved the interaction of dihydropyridines **75** with iodine in the presence of an excess of secondary amines **76**. The

high yields of the *trans*-diamines **77** thus far obtained suggest a fast iodination of the enamine moiety (precluding extensive oxidation of the amines), trapping of the iminium ion by an amine, subsequent aziridinium ion formation (from the resulting 2-amino-3-iodotetrahydropyridine) and ring opening, promoted by a second equivalent of the amine. Primary amines, azides, and sulfonamides can also be attached to the tetrahydropyridine framework using related protocols. Following this electrophilic approach, sulfones **78**, sulfoxides **79**, sulfides **80**, and thiocyanates **81** were also prepared (Scheme 22).[113]



Scheme 22 *Reagents and conditions*: i, I_2, Na_2CO_3, THF (≈85%); ii, I_2, Bu_4N^+ $PhSO_2^-$, Et_3N, CH_2Cl_2 (≈75%); iii, *p*-TolSOCl, Et_3N, CH_2Cl_2 (≈50%); iv, Br_2, THF, then Na^+ MeS^- (≈55%); v, $(SCN)_2$, C_6H_6 (≈90%).

Other bond-forming oxidations affecting dihydropyridines have been described: the double phosphonylation of pyridinium salts to yield diphosphonates **82**;[114] a double malonate addition to β-cyanopyridinium salts, a cascade process involving malonate ionic (nucleophilic) and radical reactions, to stereoselectively form tetrahydropyridines **83**;[115] an allylic halogenation of the α-methyl groups of Hantzsch dihydropyridines (to give **84**);[116] and the 1-aza-9-oxafluorene **85** formation on interaction of *N*-alkyl or acetyldihydropyridines with *p*-benzoquinones (Scheme 23).[117]

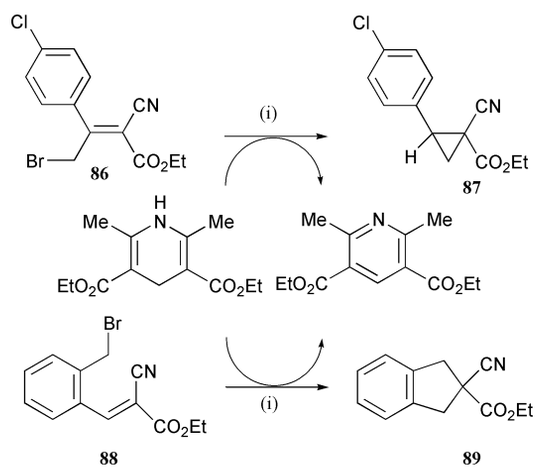


Scheme 23

3.2 NADH-NAD$^+$ chemistry

The hydride transfer from NADH-type compounds in biological or chemical reductions has been analyzed regarding mechanistic details, preparative transformations, NADH mimics for enantioselective synthesis, enzyme research, and other applications. For instance, computational models of the transition state structures for the hydride transfer step in dihydrofolate and glutathione reductases have been described.[118] The spontaneous enolization on the NADH radical cations seems to be an important event in the oxidation of these compounds.[119] Also deprotonation and fragmentation of C–C bonds may take place in the radical cation intermediates, depending on the nature of the groups attached to the 4-position of the NADH analogues.[120] Hantzsch dihydropyridines (as NADH models) were oxidized by nitric oxide to yield the corresponding pyridines (dealkylation was observed in some cases) through a hydrogen atom transfer from the nitrogen to generate an aminyl radical,[121] whereas the tropylium cation (as an oxidant) promotes one-step hydride transfer.[122] Hammett's free energy relationships for the oxidation of *N*-(*p*-substituted phenyl)-1,4-dihydronicotinamides with quinolinium, tropylium and xanthylium ions have been used to suggest that the mechanism of the first reaction would involve a direct hydride transfer, whereas the other two oxidations would take place through a sequential mechanism initiated by a single electron transfer.[123] Guidelines for the assignment of the mechanism (in terms of concerted *versus* multistep hydride transfer) were presented on the basis of the free energy changes of the elementary steps involved in the interaction of NADH models with several cations and quinones.[124]

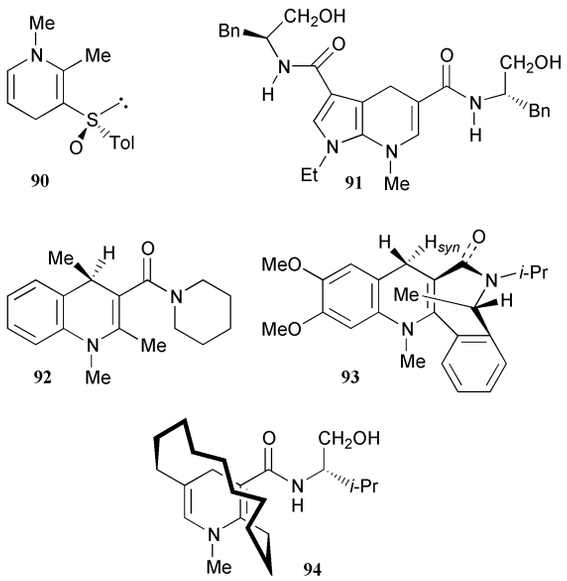
An interesting synthetic application involves the use of Hantzsch dihydropyridines to promote the reductive cyclization of allylic **86** and benzylic bromides **88** through hydride transfer to the conjugated double bond and subsequent nucleophilic displacement of the bromide, to yield the cyclopropane **87** and the indane derivative **89**, respectively (Scheme 24).[125]



Scheme 24 *Reagents and conditions*: i, deaerated CH_3CN, rt, 2 equivalents of dihydropyridine (≈90%).

Enantioselectivities ranging from low to moderate (26–55% ee) have been achieved in the former cyclopropane-forming reaction by using chiral NADH models,[126] or through chiral induction by inclusion in cyclodextrins.[127]

Research following on from the seminal work of Ohnishi and Ohno on the enantioselective reduction of carbonyl derivatives by chiral NADH analogs has continued in this period at a good pace. Thus, the use of dihydropyridines bearing a chiral sulfinyl group at the β-position (**90**, Scheme 25) allows high ee's (99%) in the reduction of the reference compound (methyl benzoylformate).[128] A polymer-supported version of this reducing agent has been prepared and allows recycling while maintaining good levels of asymmetric induction.[129] The double incorporation of chiral auxiliaries [a pinyl residue, derived from (+)-*trans*-myrtanal, at the 4-position, and a chiral amide at position 3] in a Hantzsch dihydropyridine results in moderate (72%) to low (7%) enantiomeric excesses in the reference reduction.[130] Homochiral NADH models based on pyrrolo[2,3-*b*]pyridines **91** bearing one or two chiral auxiliaries display good asymmetric induction in the



Scheme 25

reduction of benzoylformate, and show the interesting feature of tuning the enantioselectivity by adjusting the Mg^{++} ion concentration, going from 70% ee [1 eq. $Mg(ClO_4)_2$] favoring the (*S*)-methyl mandelate to 77% ee [with 8 eq.] of the (*R*)-enantiomer. Reduction of *N*-acetyl enamides also proceeds satisfactorily, using the same models.[131] Nitroalkenes and arylketones were efficiently reduced by related NADH models in the presence of $MgBr_2$.[132] A chiral oxazaphospholidine oxide at the β-position of a 1,4-dihydroquinoline does not increase the levels of enantioselectivity in the control reduction (45% ee).[133]

The electronic effect of the carbonyl group promoting the transfer of the *syn* hydrogen in NADH, prompted the preparation of pertinent models in which restricted mobility of the amide group was enforced by cyclization or by steric hindrance with a contiguous ring substituent. The study of this effect included systematic experimentation on different dihydropyridines, with the determination of relative *syn* : *anti* ratios and kinetic isotopic effects, to positively prove the hypothesis. Interestingly, in the absence of Mg^{2+}, the more reactive hydrogen is the one *anti* with respect to the carbonyl dipole.[134] Quinoline compounds offer advantages over other models in terms of higher reactivity and asymmetric induction levels, thus **92** reduces the reference compound with more than 99% ee[135] In a related approach, an axially chiral NADH mimic, the tetracyclic dihydroquinoline **93** enantioselectively reduces benzoylformate (84% ee), with transfer of the *syn* hydrogen (conclusive deuteration experiments).[136] Macrocyclic bridged ansa-type NADH models (like **94**) are presented as miniature NADH-reductases, bearing the active cofactor together with the oligomethylene moiety mimicking the "enzyme wall" necessary for stereoselection; again excellent asymmetric induction and selectivity in the hydride transfer are observed.[137] Progress in this area prior to 1996 is reported in two reviews.[138]

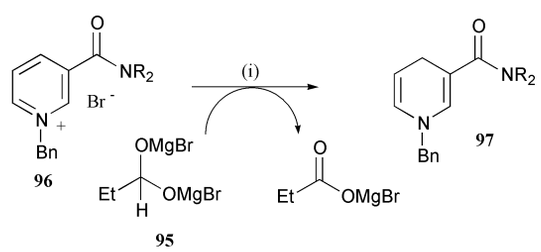
Regarding NADH-related biochemical processes, the stereochemistry of the hydride transfer from NADPH to FAD catalyzed by a reductase in the valanimycin biosynthesis, has been determined, (the 4-*pro R* hydrogen is transferred).[139] The electrocatalyzed oxidation of NADH by a diaphorase (an oxidase which uses a redox mediator as an electron acceptor) with ferrocene carboxylic acid has been described, details of the mechanism being dicussed.[140]

Much effort has been invested in the cofactor regeneration of NADH-reductases, a pivotal issue in the industrial use of these enzymes. Cross-linked enzyme crystals of HLDH (horse liver alcohol dehydrogenase) with NADH bound were prepared by crystallization in the presence of the cofactor and treatment with glutaraldehyde. This material showed good reactivity (including enantioselectivity), stability towards organic solvents, and allowed an efficient recycling (just adding butanediol to reform NADH).[141] A monooxygenase (flavin dependent) which catalyzes the *o*-hydroxylation of phenols was recycled employing indirect chemical or electrochemical NADH regeneration techniques (a Rh complex which acts as a mediator and is itself regenerated by cathodic reduction or with formate).[142] A related approach involving cross-linked lactate dehydrogenase, with electroenzymatic regeneration (methyl viologen and lipoamide dehydrogenase immobilized on a Nafion membrane) also offered good biocatalytic properties.[143] A pH-controlled protocol efficiently overcomes the inhibition caused by formate and the alkaline shift inactivation in the formate dehydrogenase NADH regeneration.[144] Microemulsions (W/O, water/oil) constitute a gentle and safe medium for the activity of alcohol dehydrogenases, and they also foster the NADH recycling.[145]

Acetone treatment of microorganism resting cells (*Geotrichum candidum*) dramatically improves the natural enantioselectivity of the enzyme-mediated reduction of ketones; cyclopentanol is used for the regeneration of NADPH. Selective inhibition of the recycling system of one group of reductases which do not accept cyclopentanol as a substrate (for instance the enzymes producing *R*-isomers) consequently causes an increase in the proportion of the *S*-alcohols.[146]

The complementary processes, *i.e.* NAD^+-mediated oxidations, also received considerable attention. Molecular mechanics force field parameters have been developed for NAD^+ and NADH nucleotides.[147] Mechanistic studies on the hydride transfer to NAD^+ from formate[148] and benzimidazoline,[149] included the use of quantum mechanics–molecular mechanics hybrid methods and kinetic isotopic effects. Additional studies on the molecular dynamics simulations for the NAD^+ reduction in the active sites of formate dehydrogenase,[150] and liver alcohol dehydrogenase[151] have been published. A correlation between the ^{13}C and ^{15}N NMR chemical shifts of a series of NAD^+ analogs and their hydride acceptor capabilities has been established.[152]

The biomimetic oxidation of the propanal equivalent **95** with pyridinium salts **96** (as NAD^+ analogs) allowed detection of the hydride transfer with formation of the 1,4-dihydropyridine **97** (minor amounts of the corresponding 1,2-dihydropyridine were noticed) in the first aldehyde to carboxylic acid mimicked reaction (Scheme 26).[153]

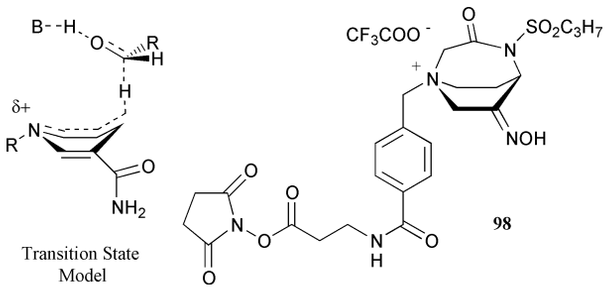


Scheme 26 *Reagents and conditions*: i, THF, rt (up to 90%).

Transition state analogs (like **98**) of the hydride transfer reaction from alcohols to NAD^+ have been prepared with the aim of eliciting catalytic antibodies, opening the way to tailored oxidoreductases (Scheme 27).[154]

NAD^+-dependent enzyme (lactate and alcohol dehydrogenases) electrodes have been prepared and studied for their potential use as biosensors in lactate and ethanol detection.[155]

An NAD^+ analogue, covalently linked to a viologen residue, undergoes selective reduction to the corresponding 1,4-dihydropyridine on irradiation with visible light in the presence of a ruthenium complex.[156] The reaction of dimeric NADH compounds with several oxidants takes place by electron transfer and involves a C–C bond cleavage, to yield monomeric

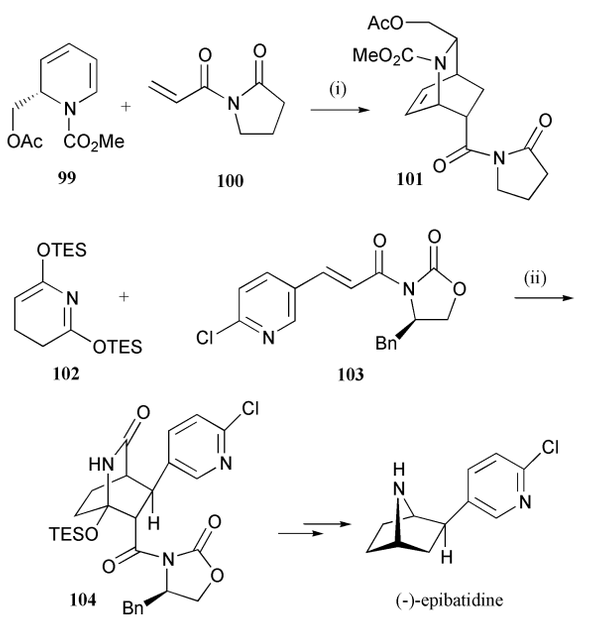


Scheme 27

NAD^+-type pyridinium salts.[157] Photoinduced electron transfer from NADH and dimeric NADH analogues allows one- and two-electron reductions of C_{60}.[158]

3.3 Pericyclic reactions

Diels–Alder cycloadditions have been performed with 1,2-dihydropyridines and electron-deficient alkenes. The use of chiral dihydropyridines enables the asymmetric synthesis of isoquinuclidines. In this way, **99** was reacted with dienophile **100** to furnish, under Lewis acid catalysis, the 2-azabicyclo[2.2.2]octane system **101**, with excellent *endo* selectivity (Scheme 28).[159] A related approach relied on the use of a chiral auxiliary linked to the dihydropyridine nitrogen.[160] Fragmentation processes have been wisely implemented in the transformation of the Diels–Alder cycloadducts in functionalized *cis*- and *trans*-octahydroisoquinolines.[161] A 3,4-dihydropyridine **102** underwent a diastereoselective (20 : 1) [4 + 2] cycloaddition with oxazolidinone **103**, to yield the adduct **104**, which was converted into (−)-epibatidine through a sequence involving ring-opening and ring-closure steps (Scheme 28).[162]

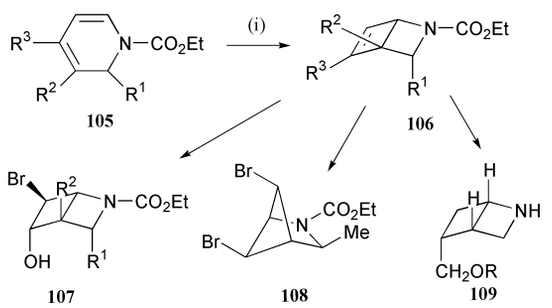


Scheme 28 *Reagents and conditions*: i, $AlCl_3$ (1 equiv.), CH_2Cl_2, 25 °C (77%); ii, Me_2AlCl (2.2 equiv.), CH_2Cl_2, −78 °C (79%).

Hetero Diels–Alder reactions involving 1,2-dihydropyridines and nitrosodienophiles were the starting point for a stereospecific access to azasugar derivatives.[163]

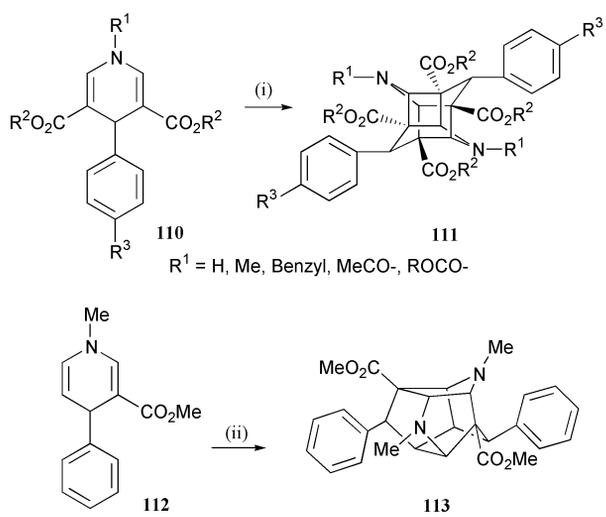
Benzyne, acting as a dienophile, has been reported to interact with 1,2-dihydropyridines under thermal and photochemical conditions.[164] An unsymmetrical isodihydropyridine (an 1-azacyclohexa-2,3-diene prepared by base-induced dehydrohalogenation of a 3-bromo-1,2,5,6-tetrahydropyridine) was efficiently trapped by [4 + 2] and [2 + 2] cycloadditions with furan and styrene, respectively.[165] The photocycloaddition of cyanoethylenes onto 1,4-dihydropyridines has been reported.[166]

Photoirradiation of *N*-alkoxycarbonyl-1,2-dihydropyridines **105** promoted the concerted electrocyclization to yield the 2-azabicyclo[2.2.0]hexene system **106**, which was, afterwards, successfully transformed into a variety of rearranged and non-rearranged skeletal types **107**–**109** (Scheme 29).[167]



Scheme 29 *Reagents and conditions*: i, *hv* (300 nm), acetone (≈20%).

Solid-state and solution photodimerization of Hantzsch-type dihydropyridines **110** takes place through two regioselective and consecutive [2 + 2] cycloadditions, and affords the centrosymmetrical diazatetraasteranes **111** in high yields. Open *syn* dimers also cyclize to the cage compounds on further irradiation.[168] The topology of the crystal packing at the monomer stage determines the feasibility of the solid-state reactions.[169] On the other hand, NADH-type dihydropyridines **112** dimerize only in solution to afford novel cage compounds (**113**, together with a nonsymmetric analogue), probably through a radical coupling-based mechanism (Scheme 30).[170]



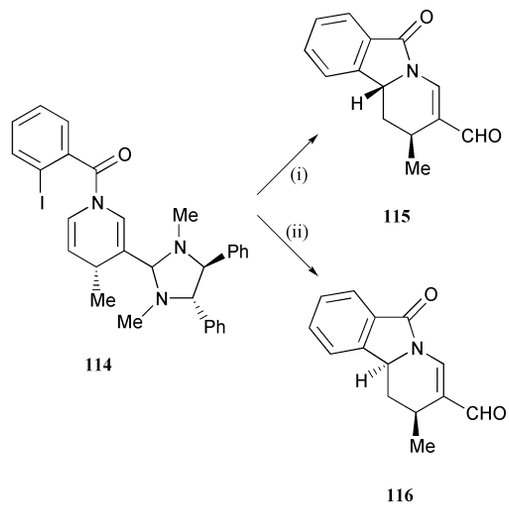
Scheme 30 *Reagents and conditions*: i, *hv* (270 nm), solid state or MeOH–THF (≈100–80%); ii, *hv* (270 nm), MeOH–THF (+ isomer, 80% overall yield).

3.4 Organometallic processes

Metallation of the α-position of *N*-alkoxycarbonyl-1,4-dihydropyridines allowed the introduction of squaric acid based electrophiles, and the resulting addition compounds were subjected to thermolysis to afford the corresponding dihydroquinolines.[171] In a different approach, interaction of a related 2-lithio-1,4-dihydropyridine with hexacarbonylchromium followed by methylation, gave a dihydropyridine Fischer carbene complex, which was reacted with alkynes, in a useful benzannulation, to produce similar dihydroquinolines.[172] The 2-methyl substituent of a Hantzsch-type dihydropyridine was efficiently metallated, and the organolithium derivative thus formed was quenched with different electrophiles (alkyl halides, acetone, TMSCl, disulfides and Davis' oxaziridine) to furnish the modified/functionalized dihydropyridines at this position.[173]

4-Tosyl-1,2-dihydropyridines suffer conjugate additions from organolithium derivatives to yield the corresponding substituted tetrahydropyridines in a stereoselective manner.[174]

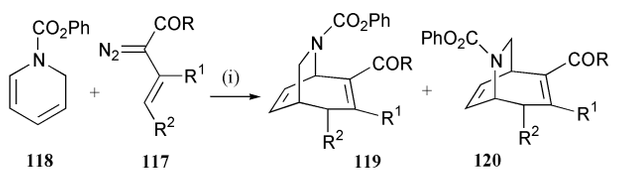
Intramolecular Heck reactions were studied in the cyclization of chiral 1-(*o*-iodobenzoyl)-1,4-dihydropyridines **114**. The stereoselectivity observed is dependent on the reaction conditions, thus the use of a reductive protocol produces (after removal of the chiral auxiliary) tetrahydropyridine **115** (together with the enantiomer of **116**, in a 7 : 3 ratio, partial epimerization at the C-4 position is observed), whereas standard conditions lead to **116** (after hydrolysis and hydrogenation of the double bond) with high ee (Scheme 31).[175]



Scheme 31 *Reagents and conditions*: i, a) $Pd(OAc)_2(PPh_3)_2$, piperidine, HCOOH, b) HCl 5%–Et_2O (35% overall, together with *ent*-**116**); ii, a) $Pd(OAc)_2$, AcOK, DMF, b) HCl 5%–Et_2O, c) H_2, Pd/C (38% overall).

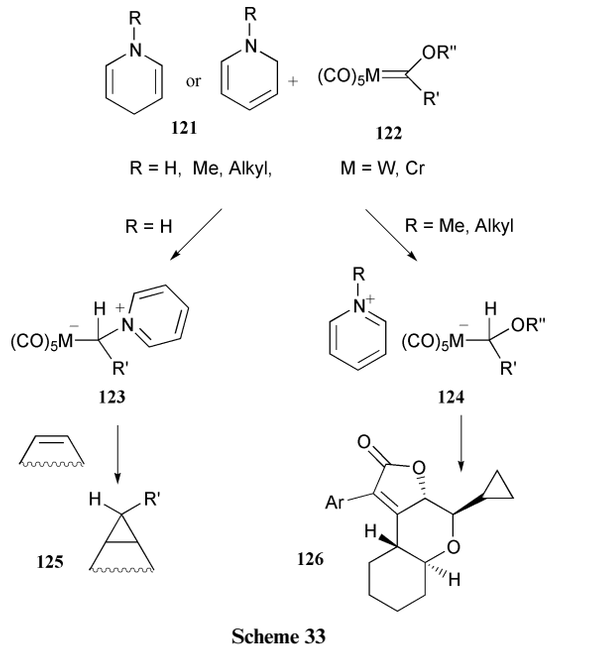
Cationic molybdenum dihydropyridine complexes (prepared from a 3-oxotetrahydropyridine) were selectively alkylated at the α, and/or the α′ positions, to afford, after decomplexation, the corresponding di- or trisubstituted piperidine derivatives with high regio- and stereocontrol.[176]

Vinyldiazomethanes **117** react with *N*-acyldihydropyridine **118** in a rhodium(II) catalyzed process to yield the azabicyclic systems **119** and **120**. The process involves the initial cyclopropanation of one double bond, followed by a Cope rearrangement. The regioselectivity is mainly influenced by the steric bulk of the catalyst, the most suitable being rhodium(II) pivalate (Scheme 32).[177]



Scheme 32 *Reagents and conditions*: i, $Rh_2(OPiv)_4$, toluene, rt to reflux (overall yield ≈70–45%, **119**–**120** ratio from 70 : 1 to 1 : 2).

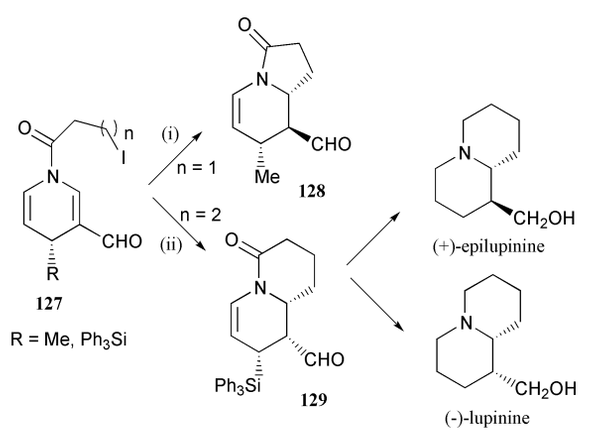
It has recently been shown that dihydropyridines **121** react with Fischer carbene complexes **122** to afford two types of intermediate: pyridinium ylide complexes **123** and *N*-alkylpyridinium tungstates and chromates **124**, depending on the substitution at the heterocyclic nitrogen.[178] These versatile and readily prepared organometallic reagents participate in inter- or intramolecular cyclopropanation reactions (to yield **125**),[178a,179] and in cascade insertion processes with olefins (and alkynes) and carbon monoxide, to form complex polycyclic systems (like **126**).[180] Good to moderate enantioselectivities (ee up to 55%) were observed in the formation of butenolides when using chiral dihydropyridines (Scheme 33).[180c]



Scheme 33

3.5 Radical reactions and other processes

Regioselective radical cyclizations of *N*-(ω-iodoalkanoyl)-1,4-dihydropyridines **127** can be achieved under Luche sonochemical conditions; other methods (tris(trimethylsilyl)silane and Bu_3SnH) gave poorer results.[181] The method also allows good stereocontrol in the synthesis of indolizines **128** and quinolizines **129**, and has been implemented in the total synthesis of lupinine and epilupinine (Scheme 34).



Scheme 34 *Reagents and conditions*: i, Zn, CuI, *i*PrOH–THF (50%); ii, Zn, CuI, *i*PrOH–THF (50%).

The reductive *N*-alkylation of imines with benzyl bromide was achieved in the presence of NADH analogues. In this photoinduced process, the dihydropyridine plays two roles: promoting the formation of the benzyl radicals (by SET to the benzyl halide) and transferring a hydrogen atom to the intermediate carbon radical.[182]

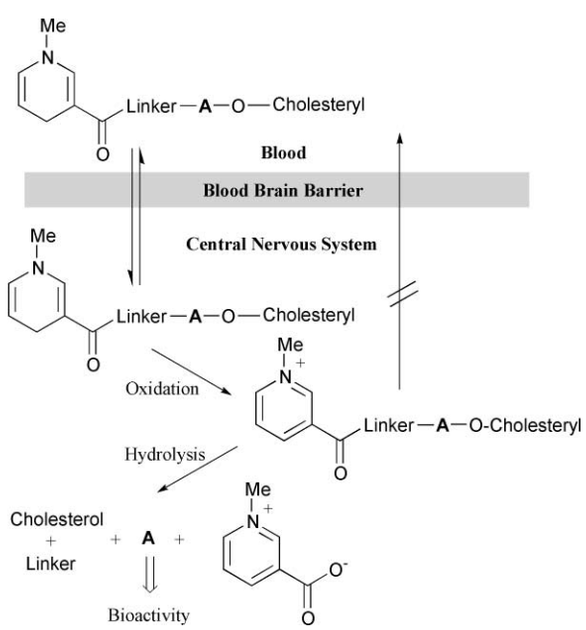
In a final miscellany on the reactivity of dihydropyridines, we may include the thermolysis of Hantzsch dihydropyridines bearing an azido group at the *ortho* position of the 4-aryl group, allowing the preparation of interesting heterocyclic systems;[58a] the cascade processes starting with 2-formyl-1,4-dihydropyridines;[183] and the iminium–enamine chemistry displayed by the transient dihydropyridine formed in the condensation of glutaraldehyde with phenylglycinol, which constitutes the key intermediate for a biomimetic entry to the skeleton of *Nitraria* alkaloids.[184] The preparation of enantiopure Hantzsch

dihydropyridines was achieved by desymmetrization of prochiral analogues or by kinetic resolution of racemates, in both strategies using chemoenzymatic methods based on the selective hydrolysis of a carboxylic ester unit.[185] Doubly protected Hantzsch dihydropyridines allow the controlled introduction of different substituents at the C3 and C5 positions.[186]

4 Biomedical applications

The mechanism of dihydropyridine binding to the L-type Ca^{2+} channel has been disclosed.[187] The conformational analysis of Hantzsch dihydropyridines was studied by theoretical (force field and semiempirical) methods and also experimentally (by X-ray crystallography and NMR spectroscopy), in the search for stable and/or bioactive conformers.[188] Among the studies of new derivatives of the classic Hantzsch structures, the combinatorial synthesis (solid-phase) and screening of a 300 member library of dihydropyridines afforded new potent Ca^{2+} channel blockers.[189] Also, the structure–activity relationships of lipophilic isoxazol-4-yl,[190] coumarin-4-yl,[191] phosphonate,[192] and permanently charged dihydropyridine derivatives[193] were reported. Conjugation of furanoxyl residues to the aryl group of Hantzsch dihydropyridines, endows them with nitric oxide activities, while maintaining the calcium antagonism.[194] The antioxidant (neuroprotective) activity of indol-4-yl-1,4-dihydropyridines has been evaluated, and determined to be independent of the calcium channel blocking activity, the presence of the methyl groups at positions 2 and 6 being critical for the latter function, while not for the former.[195] Also, flavon-4-yl derivatives were positively tested as antioxidants against superoxide radical anions.[196] The synthesis of optically active dihydropyridines labelled with ^{11}C for *in vivo* cardiac PET (positron emission tomography) was successfully carried out.[197]

Dihydropyridines play a crucial role in brain-targeted chemical delivery systems. The attachment of a dihydropyridyl unit to a pharmacophore **A** (together with other cleavable residues, normally through ester or amide linkages) enhances the lipophilicity of the conjugate, improving the access to the central nervous system. Once inside, the enzyme-mediated oxidation to the corresponding pyridinium salt locks this compound in the inner side of the blood brain barrier and subsequent hydrolysis (by esterases) liberates the active compound in place (Scheme 35).[198] This concept has been applied to the transport of neuropeptides,[199] hormone analogues,[200] antioxidants,[201] AZT-derivatives,[202] and even to a Hantzsch dihydropyridine.[203]

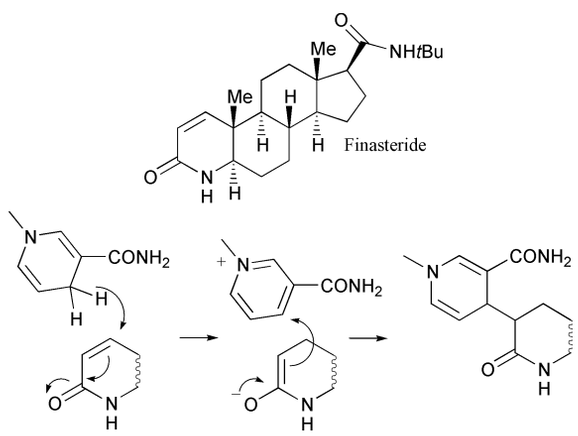


Scheme 35

Remarkable affinities of dihydropyridines for other bioreceptors (among them the α-1A-adrenergic,[204] the A_3 adenosine,[205] and the neuropeptide Y Y_1 receptors[206]) have been measured, resulting in new, selective, and potent antagonists.

Glutapyrone, a hybrid dihydropyridine–amino acid structure, displays complex neuromodulatory activity.[207] Multidrug resistance (the active efflux of drugs across the membrane), which remains the main problem in clinical chemotherapy, may be overcome by new dihydropyridines, without severe side effects.[208] The irreversible inhibition of phospholipase A_2 by a trienal, is the result of the dihydropyridine formation by condensation of the aldehyde with a basic amino acid residue, and subsequent electrocyclization in the enzyme active site.[209] A noncompetitive inhibition of topoisomerase I was observed for dexniguldipine, an antitumor and multidrug resistance reverting dihydropyridine.[210] Radioprotection,[211] and modulation of cocaine dependence in animals[212] were described for Hantzsch-type dihydropyridines.

Finasteride, a 4-azasteroid employed in treatment of benign prostatic hyperplasia, exerts its inhibition on steroid 5α-reductase (a NADPH-dependent enzyme) by forming a covalent dihydropyridine adduct with the $NADP^+$ formed in the reduction of the drug (Scheme 36).[213] Also, the mechanism of action of the tuberculosis drug isoniazid was unravelled; it implies the oxidative activation of the drug to form an acyl radical which adds to the pyridinium ring of the NAD^+, present as the oxidized cofactor of the enoyl–acyl carrier protein (ACP) reductase of the pathogen, yielding a covalent adduct. This causes the irreversible inhibition of the enzyme responsible for the biosynthesis of the mycolic acids, essential for the cell wall integrity.[214]



Scheme 36

Model NMR studies suggest that the formation of a dihydropyridine by condensation of malondialdehyde and lysine residues is involved in the cross-linking mechanism of the collagen of the cardiovascular system.[215]

New and efficient gene delivery systems are based on cationic liposomes formed with charged amphiphilic 1,4-dihydropyridines.[216]

5 Epilogue

The extraordinary versatility of dihydropyridines as synthetic tools is clearly winning the battle over the prejudices (based on alleged *instability*) about using them in multistep sequences. Concise syntheses of complex natural products have been accomplished with the participation of dihydropyridines at critical points. As new reactivity involving these compounds is developed, positive feedback is established regarding their use. On the other hand, their intrinsic value as final products, especially in the therapeutic arena, has not diminished. Even though Hantzsch-type calcium channel blockers have reached maturity, new structural types and applications are still in their

infancy. Combinatorial chemistry will greatly help in the development of these recently found lead compounds. With this scenario, it is tempting to forecast an increasing impact of dihydropyridines on different areas of chemistry and the biosciences.

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