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Synthesis, utility and medicinal importance of 1,2- & 1,4-dihydropyridines

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Dihydropyridine (DHP) is among the most beneficial scaffolds that have revolutionised pharmaceutical research with unprecedented biological properties. Over the years, metamorphosis of easily accessible 1,2- and 1,4-dihydropyridine (1,4-DHP) intermediates by synthetic chemists has generated several drug molecules and natural products such as alkaloids. The 1,4-dihydropyridine (1,4-DHP) moiety itself is the main fulcrum of several approved drugs. The present review aims to collate the literature of 1,2- and the 1,4-DHPs relevant to synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds, including the strategies which can furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. We will also elaborate the significance of DHPs towards the synthesis of natural products of medicinal merit.

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1. Introduction

Arthur Hantzsch added one of the most valuable scaffolds to the toolbox of medicinal chemists, reporting the synthesis of dihydropyridine (DHP) in 1882. Among five possible regio-isomers only 1,2- and the 1,4-DHP (Fig. 1) have gained significant attention. The 1,4-DHP scaffold has served as a nucleus for several blockbuster drugs such as nifedipine and amlodipine.[1] Close resemblance to nicotinamine adenine dinucleotide (NADH) coenzyme, which has an important role in biological oxidation–reduction reactions, has made the 1,4-DHP core even more lucrative. Perhaps less studied in the past, the potential of 1,2-dihydropyridines has recently been explored as a critical scaffold for the synthesis of alkaloids and other drugs. 1,2-DHPs are now popular as a precursor for the synthesis of the 2-aza-bicyclo[2.2.2]octanes (isoquinuclidines) ring system present in alkaloids, ibogaine and dioscorine. The anti-influenza drug, oseltamivir phosphate (Tamiflu), is also synthesised from 1,2-DHP *via* an isoquinuclidine intermediate (Fig. 1).[2]

Recently, we reviewed reactions of 1,2- and the 1,4-dihydropyridines.[3a] The present manuscript aims to highlight the importance of 1,2- and the 1,4-dihydropyridines relevant to both synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds. We then focus on strategies which can

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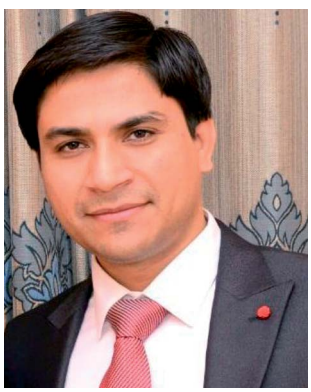

Vivek received his PhD degree in Chemistry in 2014 from University of Delhi, India. Currently he is working as Postdoctoral Fellow at RNA Therapeutics Institute, University of Massachusetts Medical School, USA. His current research interests include development of low-cost microfluidic gene synthesis, to improve in vivo delivery of peptide nucleic acid (PNA), and study the effect of neutral linkage between conformationally locked nucleotides for gene silencing applications.

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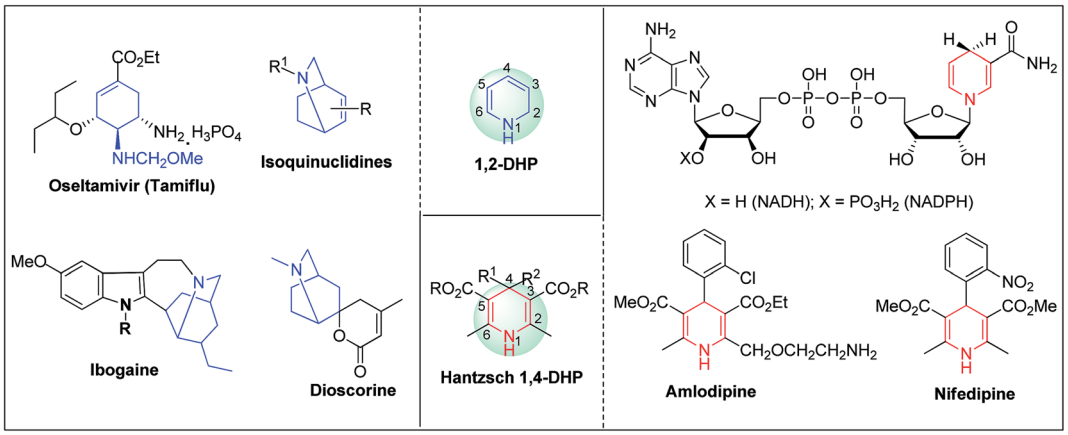
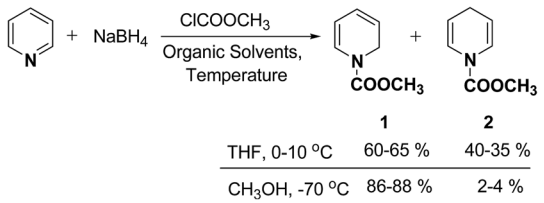
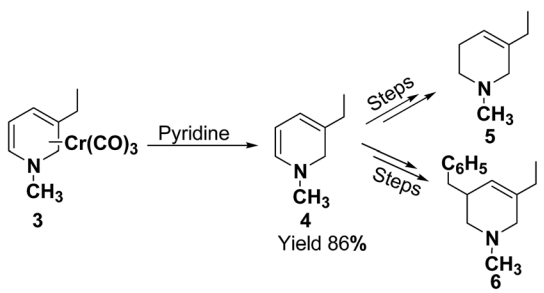


Fig. 1 Structures of 1,2-DHP, Hantzsch 1,4-DHP, NADH/NADPH and some medicinally important compounds/cores accessible from DHPs.

furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. We will also spotlight the utility of DHPs towards the synthesis of natural products of medicinal merit. In 2002, Rodolfo Lavilla compiled the synthesis, reactivity, and applications of DHPs in medicinal chemistry.[3b]



Scheme 1 Synthesis of 1,2- and 1,4-dihydropyridines 1 and 2 by reduction of pyridine using $NaBH_4$.



Scheme 2 Dihydropyridine 4 generated from precursor chromium complex 3.

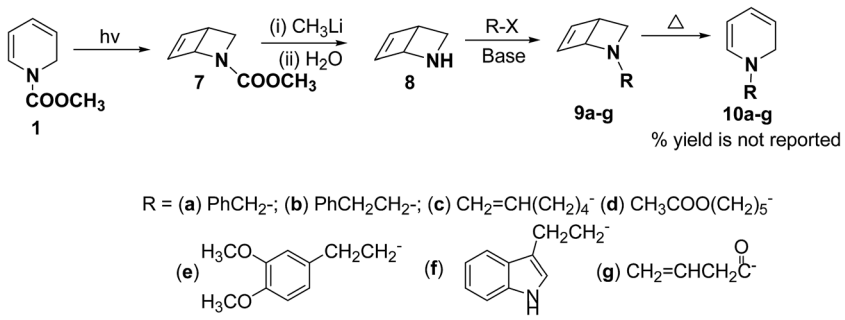
2. Synthesis of dihydropyridines

Substituted dihydropyridine are usually prepared either by the cyclization reactions (Hantzsch ring closure) or by reduction of pyridinium ions. The reviews by Eisner and Kuthan,[3c] and Stout and Meyers[3d] covers the chemistry of DHPs from early development till 1982. Beside these, R. Lavilla[3b] in 2002 and Silva, *et al.*[3e] in 2013 also compiled the literature for the synthesis of DHPs.

2.1. Synthesis of 1,2-dihydropyridine

In 1972, Fowler *et al.*[4] reported the synthesis of both *N*-carbomethoxy-1,2- and 1,4-dihydropyridine by treating a mixture of pyridine and sodium borohydride with methyl chloroformate in various organic solvents like, ether, glyme, THF, methanol and water. They observed that reaction in THF at 0 °C gave a mixture of dihydropyridines containing about 35–40% of 1,4-dihydropyridine along with the 1,2-dihydropyridine. However, the amount of 1,4-isomer can be reduced to 2–4% by performing the reaction in methanol at −70 °C giving 1,2-DHP in 86–88% yields (Scheme 1).

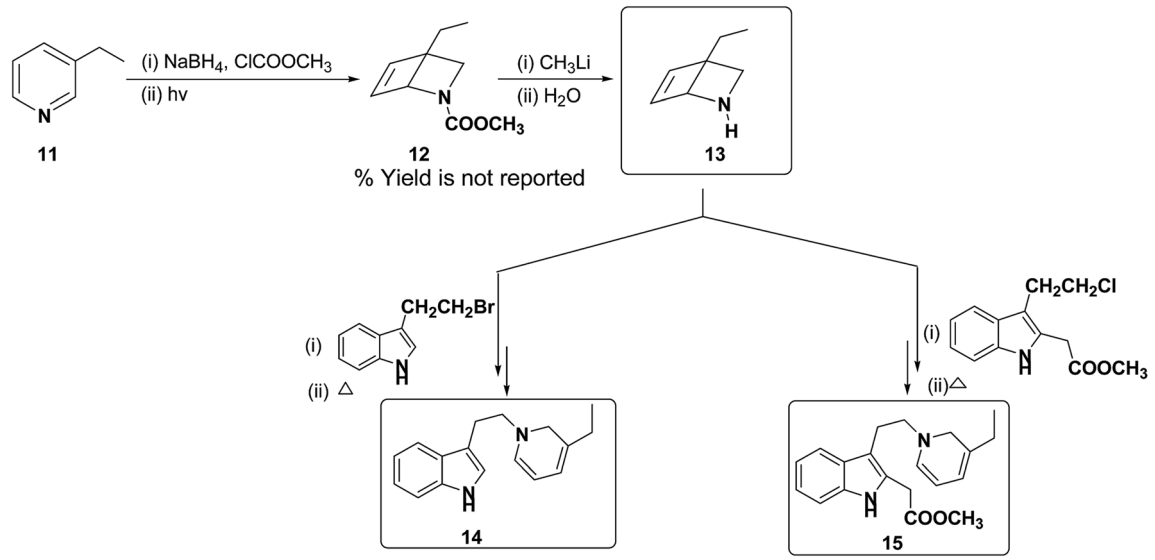
Kutney, *et al.*[5] have described the synthesis of novel and stable chromium complex of *N*-methyl-3-ethyl-1,2-



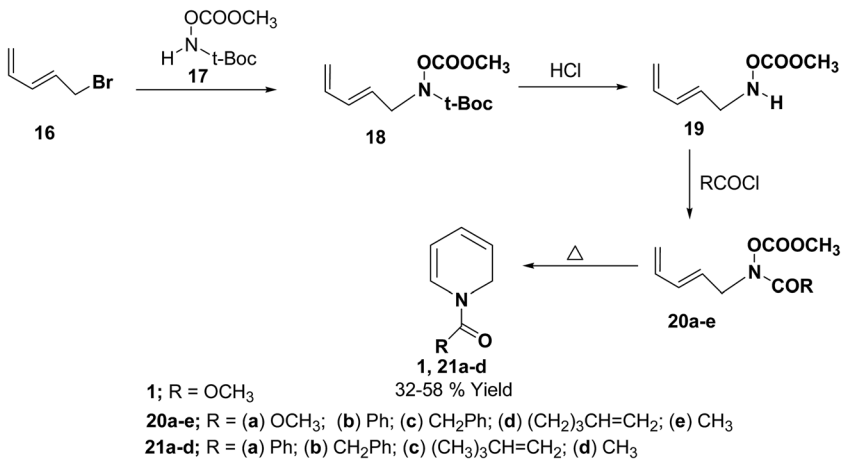
Scheme 3 Synthesis of *N*-substituted 1,2-dihydropyridines 10a–g.

dihydropyridine. This metal carbonyl complex **3** has been used for the synthesis of essentially pure *N*-methyl-3-ethyl-1,2-dihydropyridine **4**, which can be used as a precursor to synthesize a number of useful heterocyclic compounds such as **5** and **6** (Scheme 2).

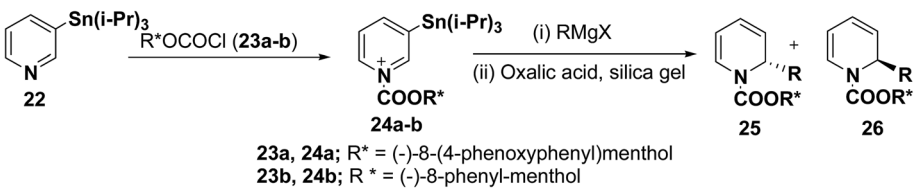
Beeken, *et al.*[6] have developed a synthetic methodology for the synthesis of 1,2-dihydropyridines **10a–g** *via* 2-azabicyclo [2.2.0]hex-5-ene **8** as a synthetic equivalent. The amine **8** was conveniently synthesized by methyl lithium mediated hydrolysis of carbamate derivative of 1,2-dihydropyridine **7** which in turn was photochemically synthesized from compound **1**. Alkylation and acylation of amine **8** has lead to the formation of **9a–g** which were easily isolated. The alkylated/acylated analogues **9a–g** were converted into the corresponding 1,2-dihydropyridines **10a–g** under thermal heating condition (Scheme 3).



Scheme 4 Synthesis of 1,2-dihydropyridines **14** and **15** from 3-ethyl pyridine **11**.



Scheme 5 Synthesis of 1,2-dihydropyridines **1**, **21a–d** by thermal cyclisation of hydroxamic acid derivatives.



Scheme 6 Asymmetric synthesis of 1-acyl-α-alkyl-1,2-dihydropyridines **25** and **26**.

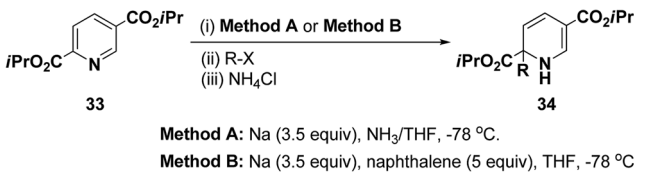
Further, Fowler *et al.* have successfully prepared dihydropyridines **14** and **15** from 3-ethyl pyridine **11** (Scheme 4). 3-Ethyl pyridine **11** was first converted into *N*-carboxymethyl amine **12** using $ClCOOCH_3$ and sodium borohydride, which on hydrolysis yield amine **13**. This method is significantly important as it can be applied to relatively more complex 1,2-DHP structures which may serve as an intermediate for the synthesis of alkaloids, *e.g.* compound **15** is an intermediate in a biomimetic synthesis of *Strychnos* alkaloids.

Fowler, *et al.*[7] has synthesized the 1,2-dihydropytidines **1**, **21a–d** by the thermal cyclisation of hydroxamic acid esters **20**. Reaction of the hydroxamic acid ester **17** with 5-bromopenta-1,3-diene **16** gave the compound **18**. The removal of *t*-Boc protecting group from compound **18** followed by acylation with various acid chlorides gave the hydroxamic acid derivatives **20**. Evaporation of these hydroxamic acid derivatives through a hot tube gave the 1,2-dihydropyridines **1**, **21a–d** as the only isolable products in 32 to 58% yields (Scheme 5).

2-Substituted-1,2-dihydropyridine analogues are useful intermediate for the synthesis of natural products such as piperidine, indolizidine, quinolizidine and *cis*-decahydroquinoline alkaloids. Comins, *et al.*[8] have reported the asymmetric synthesis of 2-substituted-1,2-dihydropyridines **25** & **26** from *N*-acyl pyridinium salt **24**, which was synthesized *via* the addition of 3-(triisopropylstannyl)pyridine **22** to an enantiopure chloroformate **23a–b** derived from (−)-8-(4-phenoxyphenyl)menthol or (−)-8-phenyl-menthol. The reaction of *N*-acyl pyridinium salt **24** with different Grignard reagents followed by treatment of the reaction mixture with silica gel containing oxalic acid provided chiral 1,2-dihydropyridines **25** and **26** (Scheme 6, Table 1).

Table 1 Synthesis of 1-acyl-2-alkyl-1,2-dihydropyridines **25** and **26**

Entry	R*OCOCl	RMgX	Product	Yield%	de
1	**23a**	*n*-PrMgCl	**25a**	72	82
2	**23b**	*n*-PrMgCl	**25b**	81	78
3	**23a**	*n*-HexMgCl	**25c**	81	91
4	**23a**	$PhCH_2MgCl$	**25d**	58	76
5	**23a**	VinylMgBr	**25e**	71	90
6	**23a**	PhMgCl	**25f**	85	89
7	**23b**	PhMgCl	**25g**	87	84
8	**23a**	*p*-MePhMgBr	**25h**	86	92

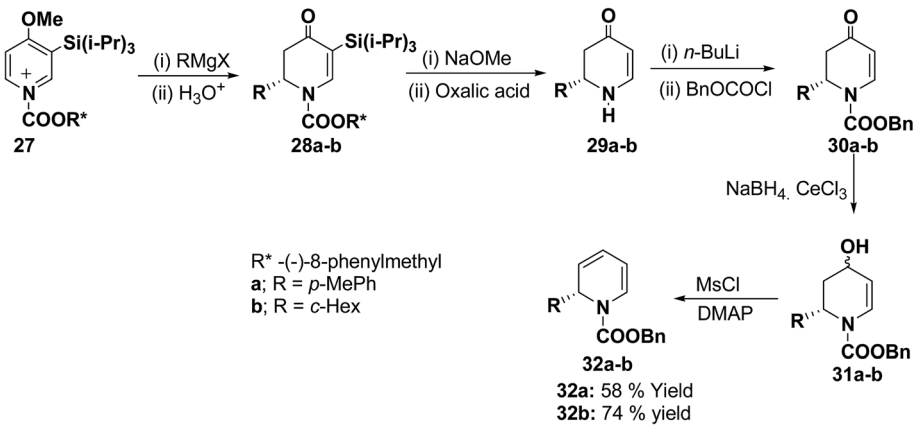


Scheme 8 Reduction of electron deficient pyridine **33**: preparation of 1,2-dihydropyridines **34**.

Table 2 Reduction of pyridine **33** by using method A or B and their alkylation[a]

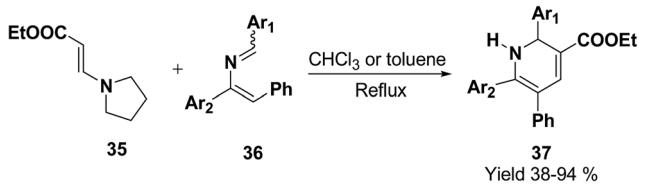
Entry	R–X	R	Method	Yield (%)
1	MeI	Me	A	99
2	MeI	Me	B	86
3	EtI	Et	A	98
4	EtI	Et	B	78
5	iBuI	iBu	A	93
6	Epibromohydrin		B	84
7	Allyl-Br	Allyl[c]	A	90
8	$I(CH_2)_3Cl$	$(CH_2)_3Cl$	A	96
9	$I(CH_2)_3Cl$	$(CH_2)_3Cl$	B	96
10	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	A	99
11	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	B	91
12	$I(CH_2)_5Cl$	$(CH_2)_5Cl$	A	97
13	$I(CH_2)_5Cl$	$(CH_2)_5Cl$	B	94

[a] Method A: Na (3.5 equiv.), NH_3/THF, −78 °C, then R–X (3.5 equiv.), then NH_4Cl after 5–30 s (time delay depends upon the electrophile). Method B: Na (3.5 equiv.), naphthalene (5 equiv.), THF, −78 °C, then R–X (3.5 equiv.), then NH_4Cl after 5–30 s (time delay depends upon the electrophile). b = formed as a mixture of diastereomers. c = this compound will aromatize in approximately 24 h at room temperature and should be stored in the freezer.

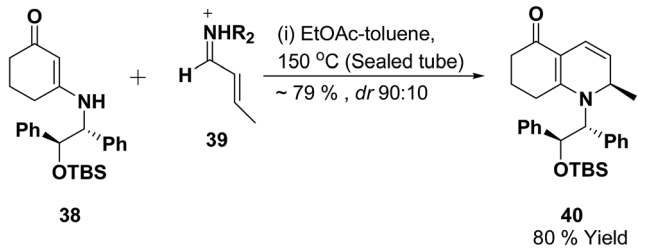


Scheme 7 A highly enantioselective synthesis of 1,2-dihydropyridines **32a–b**.

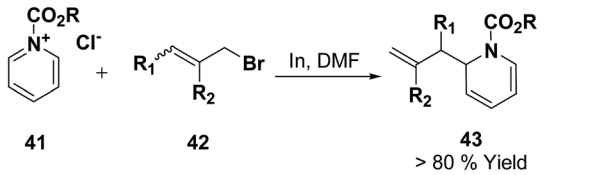
The presence of the chiral auxiliary in **25** may find application in the several transformations. Another asymmetric synthesis was developed for the synthesis of 1,2-dihydropyridines as shown in Scheme 7. The chiral salt **27** prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine and (−)-8-phenylmethyl chloroformate, was treated with Grignard reagent (RMgX) to give tetrahydropyridone **28a–b** in high yield and high diastereomeric excess (de). The chiral auxiliary and the triisopropyl silyl groups were removed from purified diastereomers **28** with sodium methoxide/methanol and oxalic acid to give enantiopure dihydropyridones **29a** (88% yield) and **29b** (81% yield) *via* one pot reaction. Deprotonation of **29** with *n*-BuLi and addition of benzyl chloroformate provided **30** in almost quantitative yield. Reduction of **30** to alcohols and subsequent dehydration gave the desired enantiomerically pure 1-(benzyloxycarbonyl)-1,2-dihydropyridine **32a** and **32b** in 58 and 74% yields, respectively (Scheme 7).



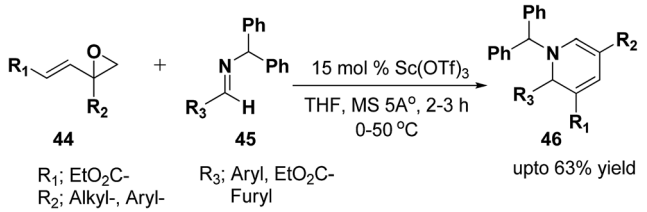
Scheme 9 Regioselective synthesis of 1,2-dihydropyridine.



Scheme 10 1,2-Dihydropyridine *via* [3 + 3] cycloaddition reaction.



Scheme 11 Indium catalysed synthesis of 1,2-dihydropyridine.



Scheme 12 Vinylogous imino-aldol reaction with vinyloxiranes: synthesis if 1,2-dihydropyridines.

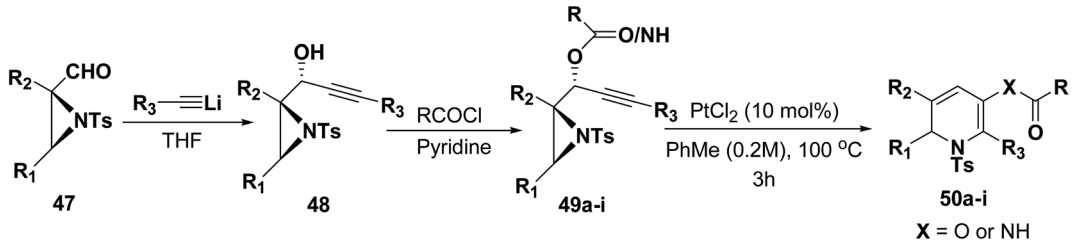
Donohoe, *et al.*[9] has used Birch conditions or sodium naphthalene in THF for the partial reduction of electron deficient pyridines for the synthesis of 1,2-dihydropyridines **34**. Reductive alkylation of electron deficient pyridine diester **33** under Birch type conditions (Scheme 8, method A, quenching the reaction with an electrophile followed by a proton source) gave excellent yield of the corresponding monoalkylated dihydropyridine **34**. The partial reduction using sodium and naphthalene in THF (Scheme 8, method B) was also accomplished, thus avoiding the use of liquid ammonia. Moreover, both sets of reducing conditions were compatible with a range of electrophiles (Table 2).

Palacios, *et al.*[10] has reported the synthesis of 1,2-dihydropyridine **37** using enamines **35** and 2-azadienes **36** (readily prepared by aza-Wittig reactions). The compounds and **36** under reflux in toluene form a broad variety of substituted dihydropyridines **37** in a regiospecific manner (Scheme 9).

Vinylogous amides **38** undergo [3 + 3] cycloaddition reaction with α,β-unsaturated iminium ions **39** to yield 1,2-dihydropyridines **40**. Intramolecular and stereoselective versions of this process have been successfully developed (Scheme 10).[11]

Loh, *et al.*[12] has reported the indium-promoted allylations of *N*-acetylpyridinium salt **41** with allyl bromide **42** in DMF, to furnish 1,2-dihydropyridines **43** regioselectively in good yields (Scheme 11).

Brunner, *et al.*[13] has synthesized the functionalized 1,2-dihydropyridine in moderate to good yield by using vinyloxiranes as dienolates in imino-aldol reactions. Under the optimized reaction condition the reaction of vinylepoxide **44** (1.5 equiv.) with benzhydril protected aldimine **45** (1.0 equiv.) in the presence of catalytic amount of $Sc(OTf)_3$ (15.0 mmol) lead to the formation of stable 1,2-dihydropyridine **46** in upto 63% yield (Scheme 12). Further it has been illustrated by the author



Scheme 13 Pt(II) catalyzed synthesis of 1,2-dihydropyridines.

that the reaction proceeds *via* the vinylogous imino-aldol type reaction.

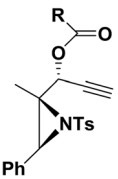
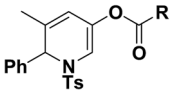
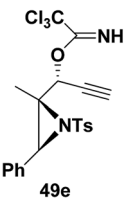
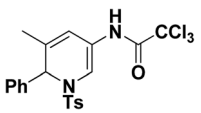
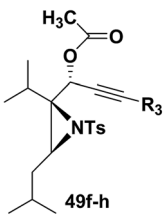
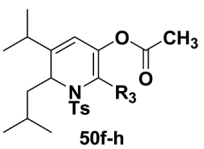
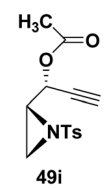
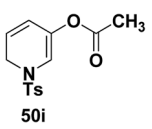
Motamed, *et al.*[14] has reported the first Pt(II) catalyzed cycloisomerisation of aziridinyl propargylic esters **49a–i** to afford 1,2-dihydropyridines **50a–i** (Scheme 13). The aziridinyl propargylic ester substrates (Table 3) were prepared by acylation of the corresponding aziridine propargylic alcohols **48**, which were synthesized from aziridinyl aldehyde **47** *via* a highly diastereoselective (dr > 95%) 1,2-addition of the corresponding alkyllithium or Grignard reagent. The aziridinyl propargylic esters **49a–i** on cycloisomerisation using Pt(II) catalysis (10 mol% of $PtCl_2$, 0.2 M in toluene, 100 °C, 3 h) afforded the corresponding 1,2-DHP products **50a–i** in moderate to good yields (Table 3).

To explore the scope of the substrates that participate in the reaction, other substituents at the aziridine nitrogen were explored. The *N*-acyl substrates **49j–m** (Scheme 14) were subjected to the Pt(II) catalyzed reaction to afford the 1,2-dihydropyridines **50j–m** in 65–74% yield along with the another heterocycle **51a–d** as by product, which were not isolated.

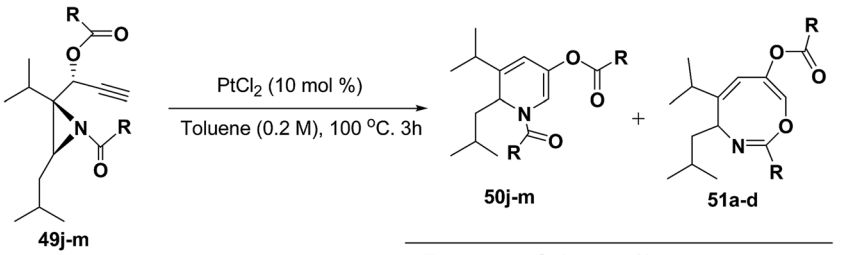
Hodgson, *et al.*[15] have developed a new methodology of radical deoxygenation process on 3-azatricyclo[2.2.1.$0^{2,6}$] heptan-5-ols **53** using tributyltin hydride to afford the 1,2-dihydropyridines. 3-Azatricyclo[2.2.1.$0^{2,6}$]heptan-5-ols **54a–b** were synthesized from the corresponding epoxide **52** (readily available from cycloaddition of the *N*-Boc pyrrole and tosyl ethyne, followed by the epoxidation of the resulting bicyclic diene), which on radical deoxygenation (*via* the xanthate) using Bu_3SnH (2.0 equiv.) gave the 1,2-dihydropyridines **54a–b** in 37 and 10% yields, respectively (Scheme 15).

Wan, *et al.*[16] have reported the three component sequential reaction enaminones **55**, α,β-unsaturated aldehydes **56a–b** and amines **57a–k** to afford 1,2-dihydropyridines **58** in highly regioselective manner. This novel regioselectivity has been

Table 3 Pt(II)-Catalyzed synthesis of 1,2-dihydropyridines[a]

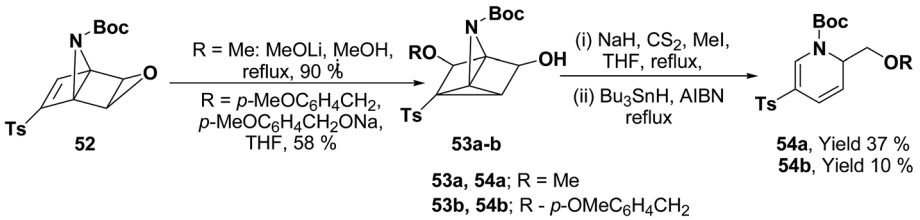
Entry	Substrate	Product	Yield[b] (%)
1	 **49a-d** (**a**) R = Me (**b**) R = *p*-ClPh (**c**) R = t-Bu (**d**) R = Ph	 **50a-d** (**a**) R = Me (**b**) R = *p*-ClPh (**c**) R = t-Bu (**d**) R = Ph	(**50a**) 76%, (**50b**) 72%, (**50c**) 76%, (**50d**) 76%
2	 **49e**	 **50e**	(**50e**) 56%
3	 **49f-h** (**f**) R_3 = Cyclopropyl (**g**) R_3= Ph (**h**) R_3 =H	 **50f-h** (**f**) R_3 = Cyclopropyl (**g**) R_3 = Ph (**h**) R_3 =H	(**50f**) 62%, (**50g**) 69%, (**50h**) 70%
4	 **49i**	 **50i**	(**50i**) 76%

[a] Standard conditions: 10 mol% of $PtCl_2$, 0.2 M in toluene at 100 °C over 3 h. [b] Isolated yields after column chromatography.

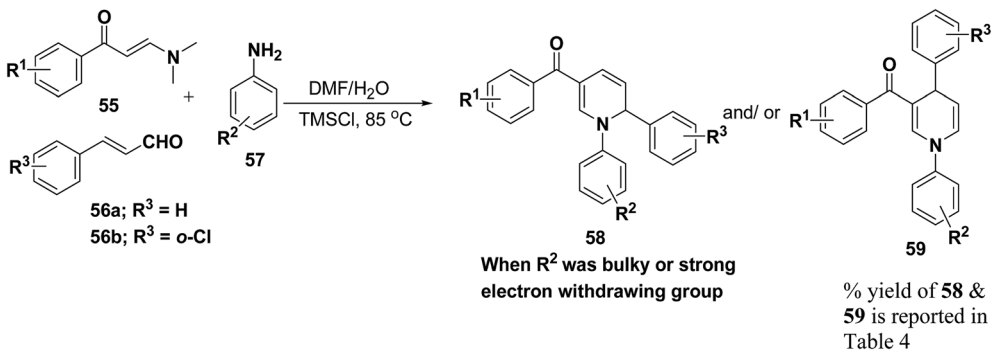


Entry	Substrate 49	% Yield of 50
1	(**j**) R = Me	71
2	(**k**) R = Ph	74
3	(**l**) R = *p*-Tol	69
4	(**m**) R = *p*-ClPh	65

Scheme 14 Pt(II)-Catalyzed cycloisomerization of acylated aziridines substrates to 1,2-dihydropyridines.



Scheme 15 Bu_3SnH catalyzed radical deoxygenation on xanthate: synthesis of 1,2-dihydropyridines.

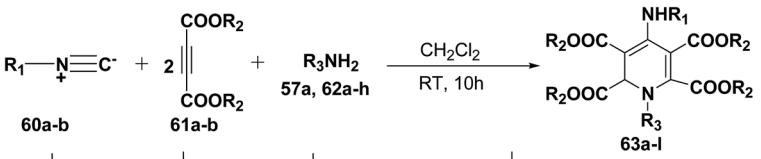


Scheme 16 Regioselective synthesis of 1,2-dihydropyridines.

Table 4 Regioselective synthesis of 1,2-DHPs and 1,4-DHPs[a]

Entry	R^1	R^3	R^2 (**57a–k**)	% yield[b] of **58**	% yield[b] of **59**
1	H	H	(**57a**) *p*-NO_2	(**58a**) 63	nd
2	*p*-OCH_3	H	(**57a**) *p*-NO_2	(**58b**) 14	(**59c**) 53
3	H	H	(**57b**) *o*-F	(**58c**) nd[c]	(**59c**) 70
4	*p*-OCH_3	H	(**57b**) *o*-F	(**58d**) nd	(**59d**) 52
5	H	H	(**57c**) *o*-Cl	(**58e**) 59	(**59e**) nd
6	*o*-Cl	*o*-Cl	(**57d**) H	(**58f**) 52	(**59f**) nd
7	*o*-Cl	H	(**57c**) *o*-Cl	(**58g**) 60	(**59g**) nd
8	H	H	(**57e**) *o*-Br	(**58h**) <10	(**59h**) 46
9	H	H	(**57d**) *o*-I	(**58i**) 27	(**59i**) 51
10	H	H	(**57g**) *o*-CH_3	(**58j**) nd	(**59j**) 65
11	H	H	(**57h**) 2,4,6-trimethyl	(**58k**) <10	(**59k**) 51

[a] General conditions: 0.3 mmol of enaminones, 0.35 mmol of aldehyde, 0.3 mmol of amine, 0.3 mmol of TMSCl mixed in 1 mL of solvents (0.5 mL H_2O + 0.5 mL of DMF), stirred at 85 °C for 10 h. [b] Isolated yield based on the corresponding enaminone. [c] nd = not determined.



60a-b 61a-b 63a-l

60	R_1
a	cHexyl
b	*t*-Bu

61	R_2
a	Me
b	Et

62	R_3
a	Bn
b	*p*-Tolyl-CH_2
c	4-$MeOC_6H_4CH_2$
d	2-$ClC_6H_4CH_2$
e	4-$ClC_6H_4CH_2$
f	1-NaphthylCH$_2$
g	*n*-Bu
h	4-$MeOC_6H_4$

63	R_1	R_2	R_3	Yield (%)
a	cHexyl	Me	Bn	80
b	cHexyl	Me	*p*-Tolyl-CH_2	95
c	cHexyl	Me	4-$MeOC_6H_4CH_2$	91
d	cHexyl	Me	2-$ClC_6H_4CH_2$	75
e	cHexyl	Me	4-$ClC_6H_4CH_2$	83
f	cHexyl	Me	1-NaphthylCH$_2$	87
g	cHexyl	Me	*n*-Bu	88
h	*t*-Bu	Me	*p*-Tolyl-CH_2	93
i	*t*-Bu	Me	4-$MeOC_6H_4CH_2$	90
j	cHexyl	Me	4-$MeOC_6H_4$	87
k	*t*-Bu	Me	4-$O_2NC_6H_4$	59
l	cHexyl	Et	Bn	69
m	cHexyl	Et	Bn	83
n	cHexyl	Et	4-$MeOC_6H_4CH_2$	80
o	cHexyl	Et	2-$ClC_6H_4CH_2$	85
p	cHexyl	Me	Bn	71

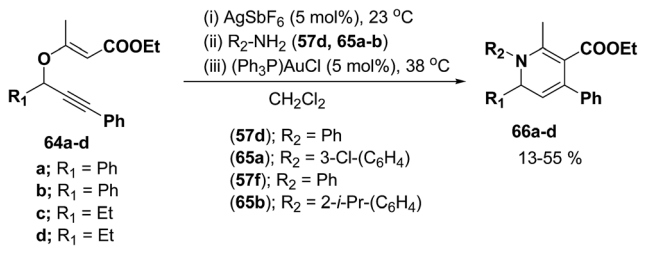
Scheme 17 Three component one-pot synthesis of functionalized 1,2-dihydropyridines **63a–l**.

Scheme 18 Four component one-pot synthesis of functionalized 1,2-dihydropyridines **63m–p**.

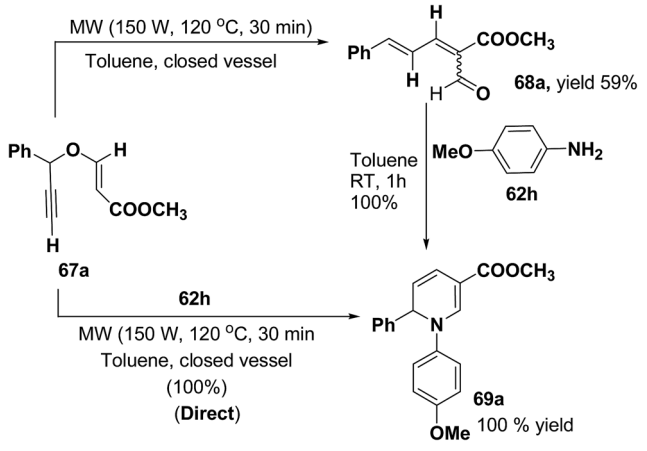
assigned to both steric and electronic effects originating from the amine partner (Scheme 16).

To examine the factors contributing to the selectivity, a series of reactions by taking *p*-nitroaniline and *ortho*-substituted anilines, have been carried out with enaminones and α,β-unsaturated aldehydes. The results are highlighted in Table 4. As shown in Table 4 both 1,2-DHPs **58** and/or 1,4-DHPs **59** could be furnished depending on the properties of the substituent on phenyl ring of the anilines. *p*-Nitroaniline mainly offered 1,2-DHPs **58** as a major product, while with different *ortho*-anilines indicate that the regioselectivity was affected by both the size and the electronic profiles of the *ortho* groups. The reaction of *o*-haloanilines, fluoro- and bromoaniline gave 1,4-DHP **59c**, **59d** and **59h** as the major product (entries 3, 4, and 8), while *o*-chloroaniline gave 1,2-DHP **58e**, **58f** and **58g** as the only isolated product (entries 5–7). Integrating the 1,2- and/or 1,4-DHP furnished in the 2-iodoaniline, 2-methylaniline, and 2,4,6-trimethylaniline entries (entries 9–11), it is evident that the bulky *ortho* group is important, but not the only inducing factor for 1,2-DHP formation. Further it was observed that the sequence of adding the reactants did not make a visible difference in the regioselectivity of the reactions.

Yavari, *et al.*[17] has reported one pot synthesis of highly functionalized 1,2-dihydropyridines from alkyl isocyanide **60a–b**,

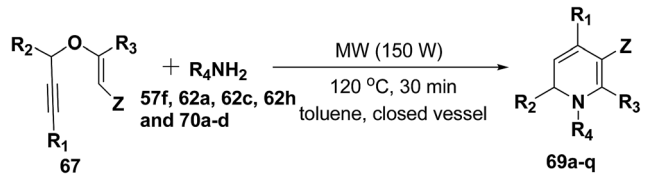


Scheme 19 Synthesis of 1,2-dihydropyridines **66a–d** from propargyl ethers.



Scheme 20 Two step *versus* domino reaction: synthesis of 1,2-dihydropyridine **69a**.

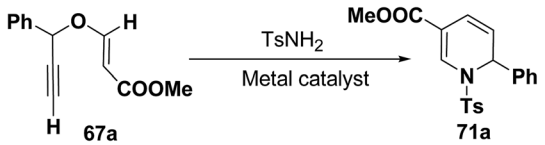
Table 5 Domino synthesis of 1,2-dihydropyridines **69a–q** from propargyl enol ethers **67** and primary amines[a]



Entry	R_1	R_2	R_3	67	R_4NH_2	69	Yield (%)
1	H	Ph	H	**a**	*p*MeOC_6H_4 (**62h**)	**a**	100
2	H	H	H	**b**	*p*MeOC_6H_4 (**62h**)	**b**	51[b]
3	H	Me	H	**c**	*p*MeOC_6H_4 (**62h**)	**c**	87
4	h	*n*Pent	H	**d**	*p*MeOC_6H_4 (**62h**)	**d**	71
5	Ph	Ph	H	**e**	*p*MeOC_6H_4 (**62h**)	**e**	95
6	*c*Hex	Ph	H	**f**	*p*MeOC_6H_4 (**62h**)	**f**	55
7	H	Ph	Me	**g**	*p*MeOC_6H_4 (**62h**)	**g**	24[c]
8	H	Me	Me	**h**	*p*MeOC_6H_4 (**62h**)	**h**	17[c]
9	H	Ph	H	**i**	*p*MeOC_6H_4 (**62h**)	**i**	80[d]
10	H	Ph	H	**a**	Bn (**62a**)	**j**	83
11	H	Ph	H	**a**	Allyl (**70a**)	**k**	72
12	H	Ph	H	**a**	Ad[e] (**70b**)	**l**	87
13	H	Ph	H	**a**	(*S*)PhCHMe (**70c**)	**m**	83[f]
14	H	Ph	H	**a**	PMB[g] (**62c**)	**n**	78
15	H	Ph	H	**a**	Ph (**57f**)	**o**	93
16	H	Ph	H	**a**	4-Cl-C_6H_4 (**70d**)	**p**	88
17	H	Ph	H	**a**	*p*MeOC_6H_4 (**62h**)	**q**	100[h]

[a] Propargyl vinyl ether **67** (1.0 equiv.), primary amine **62h** (1.1 equiv.) in toluene (5 mL). Z = CO_2CH_3. [b] 300 W, 150 °C, 2 h. [c] 300 W, 150 °C, 3 h, Z = $CO_2CH_2CH_3$. [d] Z = SO_2Tol. [e] Ad = adamantyl. [f] 50% de. [g] PMB = *p*-methoxybenzyl. [h] (*R*)-1-Phenylprop-2-yn-1-ol was used to prepare enantiopure (*R*)-**69q**; product **69q** obtained as a racemic mixture.

Table 6 Optimization of reaction conditions[a]

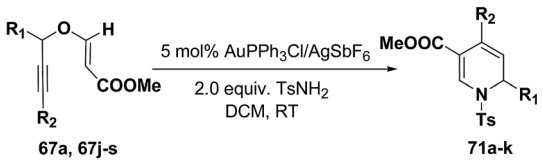


Entry	Catalyst (mol%)	Solution	$TsNH_2$ (mol%)	Yield (%)
1	$AuCl_3$	DCM	200	NR[b]
2	$PPh_3AuCl/AgOTf$	DCM	200	NR[b]
3	$PPh_3AuCl/AgBF_4$	DCM	200	84
4	$PPh_3AuCl/AgSbF_6$	DCM	200	92
5	PPh_3AuCl	DCM	200	NR[b]
6	$AgSbF_6$	DCM	200	NR[b]
7	$PdCl_2(CN)_2$	DCM	200	NR[b]
8	$PtCl_2$	DCM	200	NR[b]
9	$PPh_3AuCl/AgSbF_6$	Toluene	200	Trace[c]
10	$PPh_3AuCl/AgSbF_6$	CH_3CN	200	NR[b]
11	$PPh_3AuCl/AgSbF_6$	DCE	200	77
12	$PPh_3AuCl/AgSbF_6$	DCM	120	80

[a] Reactions were conducted with 0.4 mmol of **1a** in 3 mL of solvent at room temperature. [b] No reaction. [c] Most of the material decomposed.

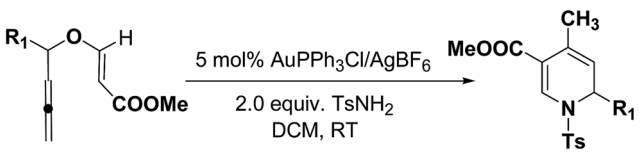
acetylenic esters **61a–b** and primary alkylamine (**62a–i**). The reaction of alkyl isocyanides **60a–b**, dimethyl acetylenedicarboxylate (**61a**), and primary amines **57a, 62a–h**, proceeded smoothly in CH_2Cl_2 at room temperature and produced tetramethyl 4-(alkylamino)-1-alkyl(aryl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **63a–k** in good yields after purification (Scheme 17). Similarly, taking two equivalent of diethyl acetylenedicarboxylate **61b** in above reaction gives **63l** in 69% yield. A wide range of structurally varied primary amines were employed in this cyclocondensation reaction. Addition of a solution of equimolar amounts of primary amine **62a**, **62c** & **62d** and **61a** to a 1 : 1 mixture of cyclohexyl isocyanide (**60a**), and diethyl acetylenedicarboxylate (**61b**) in CH_2Cl_2 at rt, produced 5,6-diethyl 2,3-

Table 7 Tandem synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and $TsNH_2$[a]



Entry	R_1	R_2	67	Product	Yield[b] (%)
1	C_6H_5	H	**67a**	**71a**	92
2	2-Me-C_6H_4	H	**67j**	**71b**	90
3	4-Me-C_6H_4	H	**67k**	**71c**	91
4	3-Me-C_6H_4	H	**67l**	**71d**	80
5	3,4-Di-Me-C_6H_3	H	**67m**	**71e**	78
6	2-MeO-C_6H_4	H	**67n**	**71f**	89
7	4-CI-C_6H_4	H	**67o**	**71g**	85
8	2-CI-C_6H_4	H	**67p**	**71h**	84
9	2-Naphthyl	H	**67q**	**71i**	88
10	*n*-Hexyl	H	**67r**	**71j**	82
11	C_6H_5	*n*-Pentyl	**67s**	**71k**	60

[a] Reactions were conducted with 0.4 mmol of **67** in 3 mL of solvent. [b] Isolated yield after column chromatography.



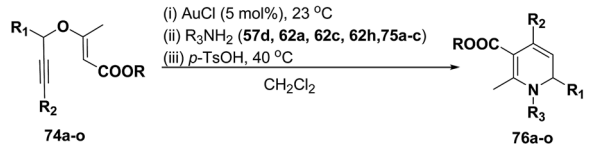
R_1	Product	Yield (%)
C_6H_5	**73a**	69
2-Me-C_6H_4	**73b**	67
4-Me-C_6H_4	**73c**	65
3-Me-C_6H_4	**73d**	56
4-Cl-C_6H_4	**73e**	55
4-Br-C_6H_4	**73f**	48
2-naphthyl	**73g**	62
n-hexyl	**73h**	NR

Scheme 21 Tandem synthesis of 1,2-dihydropyridines **73a–h** from allenic vinyl ethers and $TsNH_2$.

dimethyl 4-(cyclohexylamino)-1-(arylmethyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **63m–o** which contain two different ester groups (Scheme 18). Similarly reaction of **62a** and **61b** in a 1 : 1 mixture of **60a** & **61a** yields **63p**. The formation of a single product when two different acetylenic esters are used is presumably controlled by the sequence in which the reaction is carried out.

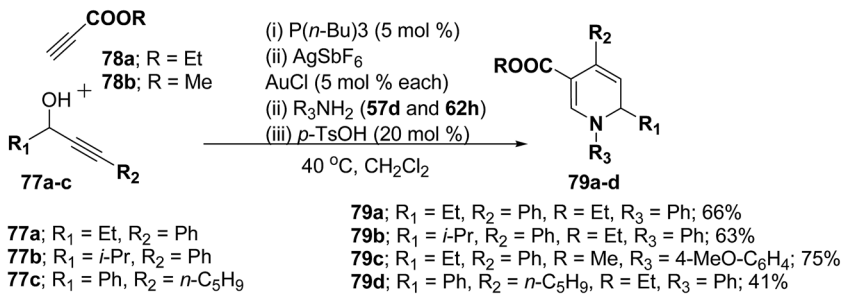
Binder and Kirsch *et al.*[18] has synthesized 1,2-dihydropyridines **66a–d** from propargyl vinyl ethers **64a–d** through a sequence of propargyl-Claisen rearrangement, condensation, and heterocyclization (Scheme 19). The scope of this protocol was quite limited, only four examples of 1,2-dihydropyridines with low to moderate yields are known.

Tejedor, *et al.*[19] has developed a convenient domino access to substituted alkyl 1,2-dihydropyridine-3-carboxylates from propargyl enol ethers and primary amine. After some experimental work, it has been found that microwave irradiation of a solution of **67a** in toluene (150 W, 120 °C, 30 min) afforded the corresponding dienal **68a**, which could be isolated as a mixture of *E*/*Z* (1 : 1) isomers in 59% yield after flash-chromatographic purification (Scheme 20). Subsequent treatment of dienal **68a** with *p*-anisidine (**62h**; 1.0 equiv.) at room temperature in toluene for 1 h afforded 1,2-dihydropyridine **69a** in quantitative yield. The direct microwave irradiation of **67a** with **62h** in toluene (150 W, 120 °C, 30 min) afforded the

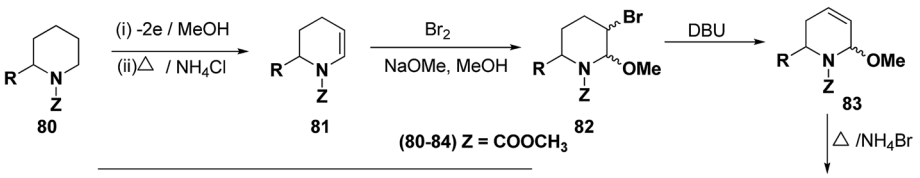


74 & 76	R_1	R_2	R_3	R	Yield (%)
a	Et	Ph	Ph (**57d**)	Et	88
b	Et	Ph	PMB (**62c**)	Et	62
c	Et	Ph	*i*-Pr (**75a**)	Et	75
d	Et	Ph	(*S*)-PhCHMe (**70c**)	Et	67
e	Et	Ph	4-Br-C_6H_4 (**75b**)	Me	69
f	Et	Ph	3-NO_2-C_6H_4 (**75c**)	Me	78
g	Et	Ph	4-MeO-C_6H_4 (**62h**)	Me	85
h	Et	Ph	Bn (**62a**)	Me	81
i	Me	Ph	Ph (**57d**)	Et	84
j	i-Pr	Ph	Ph (**57d**)	Et	77
k	Ph	Ph	Ph (**57d**)	Et	72
l	H	ph	Ph (**57d**)	Et	55
m	CH_2CH_2Ph	*n*-C_5H_9	Ph (**57d**)	Et	55
n	Et	4-MeO_2C-C_6H_4	Ph (**57d**)	Et	74
o	Et	4-MeO-C_6H_4	Ph (**57f**)	Et	89

Scheme 22 The conversion of **74a–o** in 1,2-dihydropyridines **76a–o**.

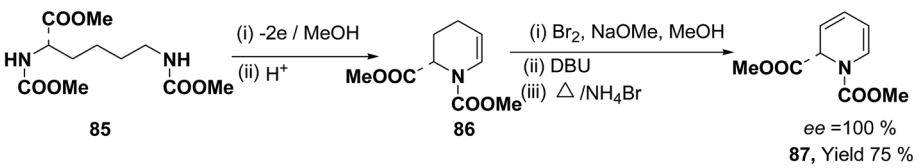


Scheme 23 One pot synthesis of 1,2-dihydropyridines **79a–d** starting from propargylic alcohols **77a–c**.



80-84	R	% Yield 81	82	83	84
a	H	83	80	72	65
b	Me	64	80	50	65
c	Et	74	84	74	89
d	CH_2COOMe	60	56	78	85

Scheme 24 Electrochemical synthesis of 1,2-dihydropyridines **84a–d**.



Scheme 25 Electrochemical synthesis of enantiomerically pure 1,2-dihydropyridine **87**.

corresponding 1,2-dihydropyridine **69a** in almost quantitative yield.

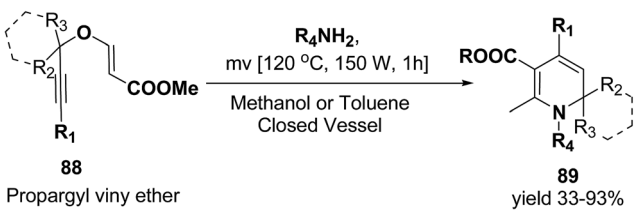
After the development of one step domino process the scope of this reaction has been extended with regard to the propargylic component and amine (Table 5). In general, the reaction presented a broad spectrum for the amine although aromatic amines gave better yields than aliphatic amines (compare entries 1, 15 and 16 with entries 10–14). The effect of diastereo induction by the amine component was studied with the chiral amine **70c**, which in turn yields chiral 1,2-dihydropyridine **69m** with a significant 50% de (entry 13).

Wei, *et al.*[20] has reported the synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and allenic vinyl ethers by gold-catalyzed Claisen rearrangement and 6π-aza-electrocyclization. No reaction occurred with $AuCl_3$ or $AuPPh_3Cl/AgOTf$ (5 mol% each) in CH_2Cl_2 at room temperature (entries 1 and 2, Table 6). 1,2-Dihydropyridine was obtained in 84% yield when $AuPPh_3Cl/AgBF_4$ (5 mol%) was used (entry 3). It was interesting result that 92% yield was realized by using $AuPPh_3Cl/AgSbF_6$ (5 mol%) at room temperature (entry 4). Ag(I) could serve to abstract the chloride from $AuPPh_3Cl$ to form a more electrophilic catalyst. On the contrary, when $Au(PPh_3)Cl$ or $AgSbF_6$ was used alone (entries 5 and 6), the tandem reaction did not take place at all. On the other hand, other transition metal catalysts such as $PtCl_2$ or $PdCl_2(CN)_2$ did not promote any transformation (entries 7 and 8). The investigation on the solvent effect showed that the best choice of the solvent was CH_2Cl_2 (entries 9–11). However, the yield decreased when the amount of $TsNH_2$ was reduced from 2.0 to 1.2 equivalents (entry 12). Thus the use of 5 mol% of $AuPPh_3Cl/AgSbF_6$, with 2.0 equivalents of $TsNH_2$ in CH_2Cl_2 at room temperature constituted the optimal reaction conditions.

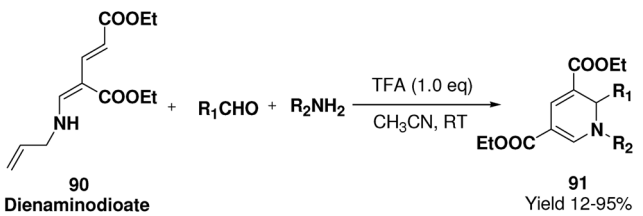
The scope of the reaction has been explored in gold catalysed tandem reaction by studying a wide variety of substrates (Table 7). Substrates containing electron-rich or electron-deficient aryl groups at the propargylic position gave good to excellent yields of desired 1,2-dihydropyridines (entries 2–9).

The scope of this reaction has been extended by Wei, *et al.* on allenic vinyl ethers **72a–h** and it has been found that 5 mol% $AuPPh_3Cl/AgBF_4$ in presence of 2.0 equiv. $TsNH_2$ gave the moderate to good yield of diversified 1,2-dihydropyridines **73a–h** (Scheme 21).

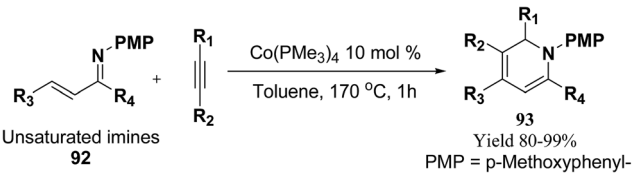
1,2-Dihydropyridines **76a–o** were synthesized in good to excellent yields by using a standardized protocol of Kirsch



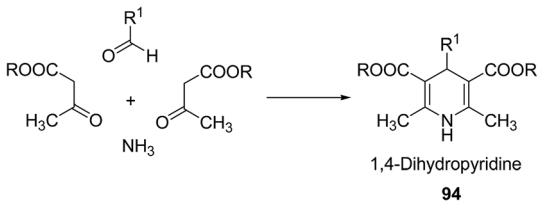
Scheme 26 Microwave-assisted domino synthesis of 1,2-dihydropyridines **89** from propargyl vinyl ether **88**.



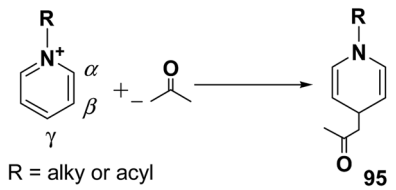
Scheme 27 Cascade synthesis of 1,2-dihydropyridine **91** by variation of aldehydes and amines.



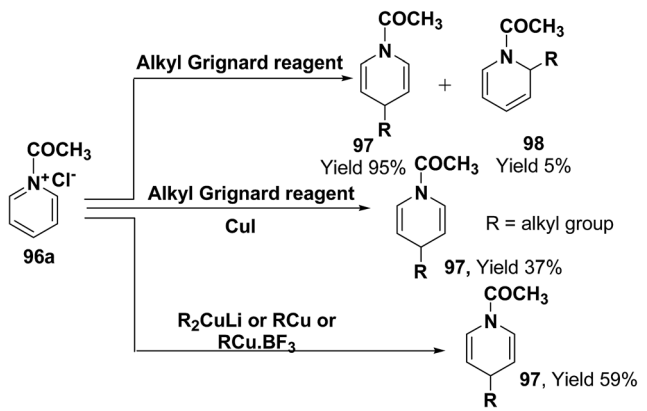
Scheme 28 Annulation reaction between unsaturated imines and alkynes for the formation of 1,2-dihydropyridines **93**.



Scheme 29 Hantzsch dihydropyridine synthesis.

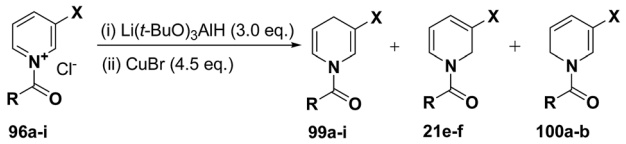


Scheme 30 An example of Kröhnke procedure.



Scheme 31 Grignard and organocopper reagents catalyzed exclusive synthesis of 1,4-dihydropyridine **97**.

et al.[21] with internal alkynes **74a–o** and used a sequential addition of reagents and catalysts to obtain reproducibly high yields [(i) AuCl (5 mol%), 23 °C; (ii) R_3NH_2 (**57d**, **62a**, **62c**, **62h** and **75a–c**); (iii) *p*-TsOH (20 mol%), 40 °C, CH_2Cl_2] (Scheme 22). The formation of 1,2-dihydropyridines **76a–o** tolerated substitution of R_1 and R_2 with both aryl and alkyl groups (Scheme 22). Compound **76l** bearing no substituent in the 2-position ($R_1 = H$) was obtained in only moderate yield.



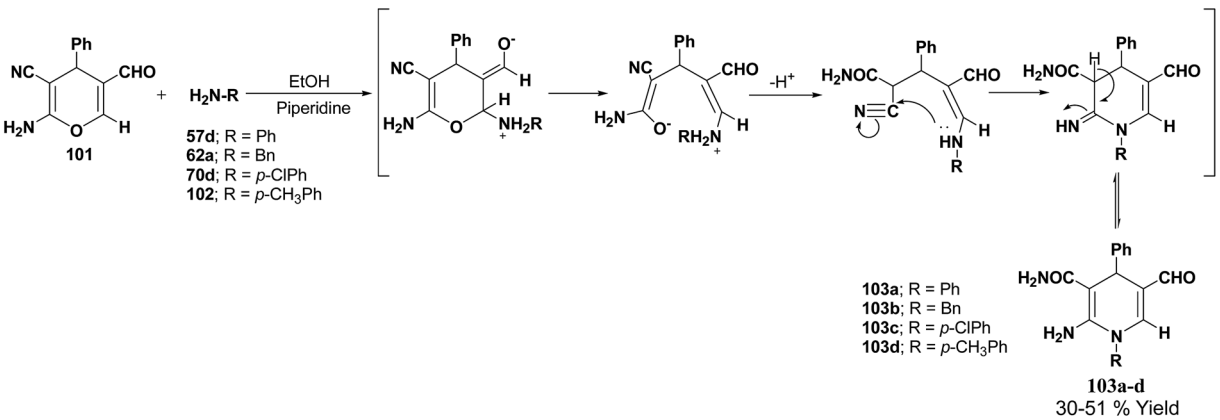
X	R	Yield, %	Product ratio 99	21	100
H	-CH_3 (**96a**)	65	100 (99a)		
H	-OC_6H_5 (**96b**)	35	100 (99b)		
H	-$OCH_2C_6H_5$ (**96c**)	20	100 (99c)		
H	-OEt (**96d**)	36	100 (99d)		
H	-*n*Bu (**96e**)	32	100 (99e)		
Me	-OC_6H_5 (**96f**)	52	98.2 (99f)	0.9 (**21e**)	0.9 (**100a**)
Et	-OC_6H_5 (**96g**)	40	98.5 (99g)	<1.5 (**21f**)	<1.5 (**100b**)
Cl	-OC_6H_5 (**96h**)	40	100 (99h)		
COOMe	-OC_6H_5 (**96i**)	45	>90 (99i)		

Scheme 32 Comins copper hydride catalyzed regioselective synthesis of 1,4-dihydropyridines **99a–i**.

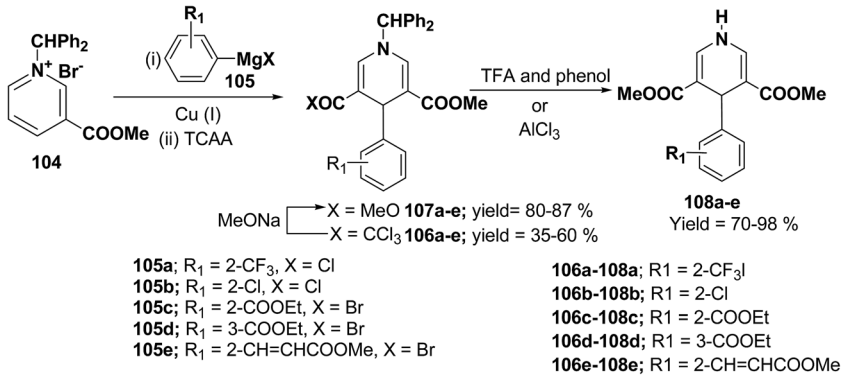
Further this one-pot procedure is extended by an additional step that is the formation of the propargyl vinyl ethers. When propargylic alcohols **77a–c** were reacted with 1.0 equiv. of ethyl propiolate **78a**/methyl propiolate **78b** and 5 mol% of $P(n\text{-}Bu)_3$, the Michael-addition remained an efficient process. Subsequent addition of both AuCl and $AgSbF_6$ (5 mol% each) furnished the allenylcarbonyl compounds. Notably, only the use of both catalysts together provided good and reproducible results; neither one was able to catalyze the reaction on its own. The sequence was terminated by condensation with 1.5 equiv. of an amine and 0.2 equiv. of *p*-TsOH at 40 °C for 15 h to give the desired products in good yields (Scheme 23). It is of particular note that this one-pot procedure presents the possibility to access 1,2-dihydropyridines **79a–d** even in cases when the required propargyl vinyl ether is not accessible due to poor stability.

Shono, *et al.*[22] have developed a convenient and regioselective method for the synthesis of 1,2-dihydropyridines, especially those possessing substituents at certain positions of the pyridine nucleus. 2-Substituted 1-(methoxycarbonyl)-1,2-dihydropyridines have been synthesized from piperidines electrochemically (Scheme 24).

Optically active 1,2-dihydropyridine **87** has been synthesized starting from L-lysine derivative **85** by electrochemically in two steps *via* the synthesis of tetrahydropyridine **86** in 75% yield, ee ~ 100% (Scheme 25).



Scheme 33 Synthesis of 1,4-dihydropyridines **103a–d** from 2-amino-5-formyl-4*H*-pyran **101**.

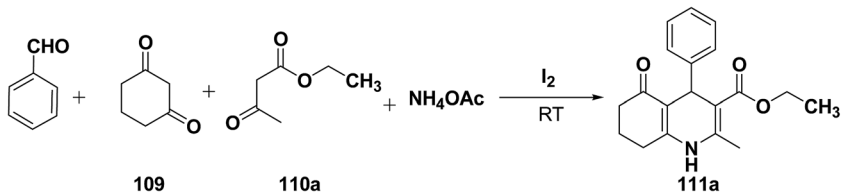


Scheme 34 Synthesis of 4-functionalized 3,5-diacyl-4-aryl-1,4-dihydropyridines **108a–e**.

Tejedor, *et al.*[23] has developed a general and practical metal-free protocol for the synthesis of 1,2-dihydropyridines (Scheme 26) with variety of structural/functional diversity at the ring and featuring mono, double, or spiro substitution at the sp^3 hybridized carbon position. The protocol contains a microwave-assisted domino reaction of propargyl vinyl ether **88** (secondary or tertiary) and a primary amine (aliphatic or aromatic) in toluene or methanol.

Challa, *et al.*[24] has developed a convenient synthesis of 1,2-dihydropyridine (**91**) from dienaminodioate **90** and an imine (generated *in situ*) mediated by CF_3COOH in a one-pot cascade synthesis. The advantages associated with this transformation include conditions that are metal-free, room temperature,

Table 8 Optimizing the reaction conditions[a]

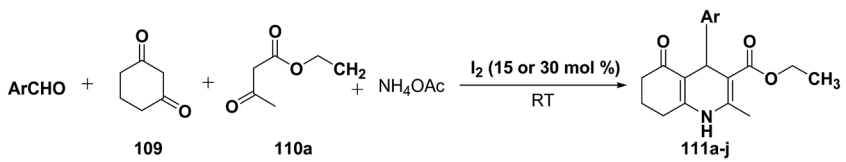


109 110a 111a

Entry	Iodine (mol%)	Time (h)	Yield[b] (%)
1	0	4	56
2	15	4	99
3	30	2.5	99
4	50	1.5	70

[a] Benzaldehyde : 1,3-cyclohexanedione : ethyl acetoacetate : ammonium acetate (1 : 1 : 1 : 1). [b] Crude isolated yield.

Table 9 Iodine catalyzed synthesis of 1,4-dihydropyridine derivatives through Hantzsch reaction



109 110a 111a-j

Entry	105	Ar	Iodine (mol%)	Time (h)	Yield[a] (%)
1	**111a**	C_6H_5	30	2.5 h	99
2	**111a**		15	30 min	93
3	**111b**	*p*-Me-C_6H_4	30	1.5 h	90
4	**111b**		15	35 min	99
5	**111c**	*p*-Me-C_6H_4	30	4 h	97
6	**111c**		15	40 min	87
7	**111d**	*p*-F-C_6H_4	30	3.5 h	91
8	**111d**		15	35 min	87
9	**111e**	*p*-CI-C_6H_4	30	6 h	99
10	**111e**		15	40 min	90
11	**111f**	*p*-OH-C_6H_4	30	2.5 h	99
12	**111f**		15	45 min	92
13	**111g**	*o*-NO_2-C_6H_4	30	1.5 h	94
14	**111g**		15	25 min	91
15	**111h**	*m*-NO_2-C_6H_4	30	1.5 h	99
16	**111h**		15	25 min	92
17	**111i**	*p*-NO_2-C_6H_4	30	3 h	99
18	**111i**		15	25 min	85
19	**111j**	Isopropyl	30	5 h	99
20	**111j**		15	40 min	99

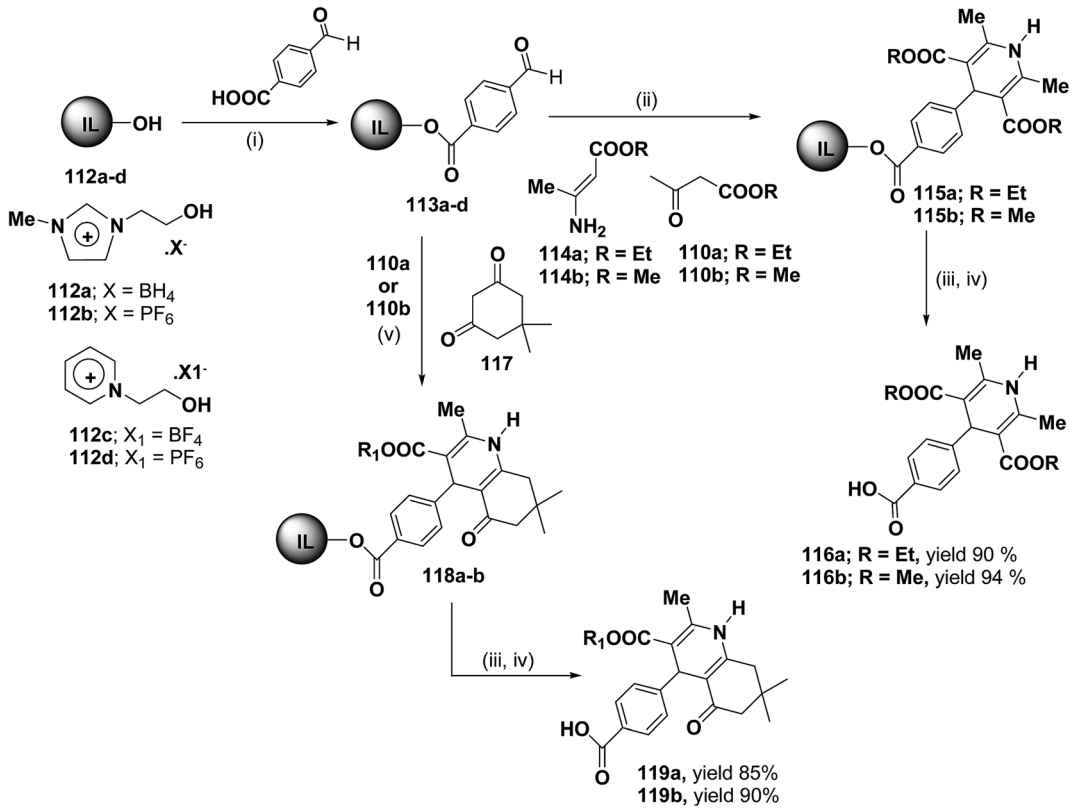
[a] Crude isolated yield.

undistilled solvent, and expeditious in excellent yields. Out of the several acid catalyst used for the optimisation of the reaction condition trifluoroacetic acid was found to me excellent, which yield 1,2-dihydropyridine in excellent yield (Scheme 27). The substrate scope has been demonstrated with various aromatic, heteroaromatic, unsaturated aldehydes, and anilines, benzylic amines in impressive yields.

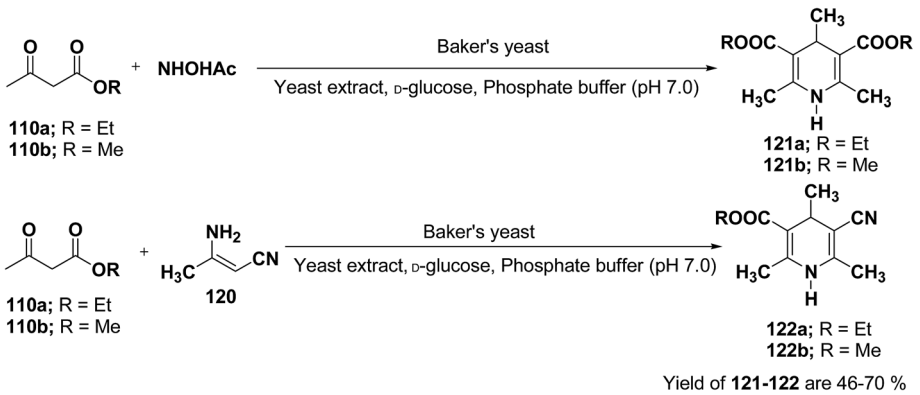
Fallon, *et al.*[25] has developed a convenient one-pot synthesis of highly substituted 1,2-dihydropyridines **93** from unsaturated imines **92** and alkynes *via* C–H activation/6π-electrocyclisation pathway (Scheme 28). The reaction proceeds with high regioselectivity, and the author has disclosed the first example of isolated 1,2-dihydropyridines lacking substitution at 2 position. A low valent cobalt complex without reducing agents or additives provides C–H activation.

2.2. Synthesis of 1,4-dihydropyridines

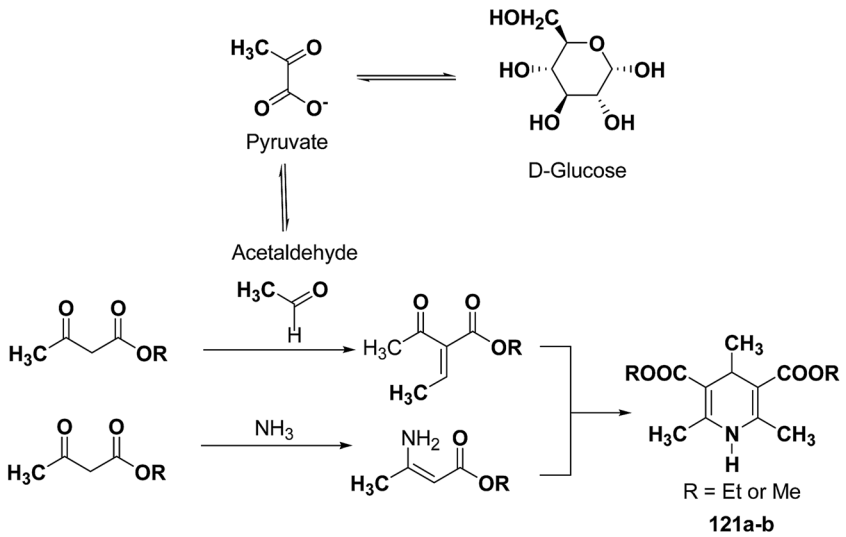
Over the years many outstanding discoveries have been made in the field of drug development and research with multifaceted



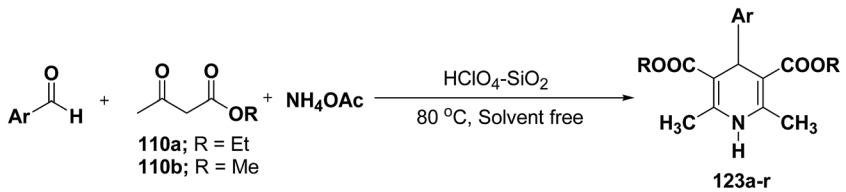
Scheme 35 Ionic liquid supported synthesis of 1,4-DHPs. Reagents and conditions (i) DCC (1.0 equiv.), DMAP (5%), dry MeCN, rt, 24 h; (ii) method A: **110** (1.0 equiv.), **114** (1.0 equiv.), mw: 120 °C (power level: 50%, 150 W), 10 min or method B: **110** (2.0 equiv.), NH_4OAc (2.0 equiv.), mw: 120 °C (power level: 50%, 150 W); (iii) MeONa 30%, MeOH, reflux, 18 h; (iv) LiOH 60%, THF, rt, 20 h then 3 M HCl; (v) **110** (1.0 equiv.), **117** (1.0 equiv.), NH_4OAc (2.0 equiv.), mw: 120 °C (power level: 50%, 150 W).



Scheme 36 Baker's yeast catalyzed synthesis of 1,4-DHPs **121** and **122**.



Scheme 37 Proposed mechanism for the baker's yeast catalysed synthesis of 1-4-DHPs.



Scheme 38 Heterogeneous catalyst ($HClO_4$–SiO_2) catalyzed synthesis 1,4-DHPs **123**.

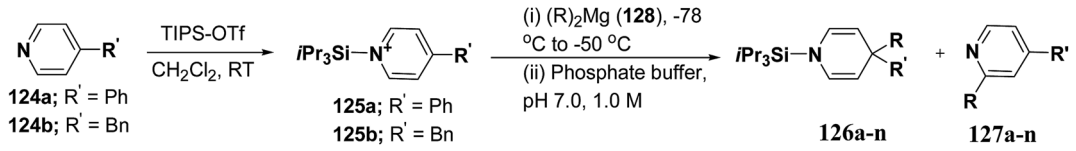
drugs having great potential. 1,4-Dihydropyridine is one such privileged structure which has revolutionized the pharmaceutical industry. It is a well explored scaffold which binds to multiple receptors, possesses a wide variety of biological features and also has its basis in biologically active natural products. The first synthesis of 1,4-dihydropyridines was reported by Arthur Hantzsch in 1882.[26] He observed that in the process of synthesizing pyridine by a one pot three-component condensation reaction of acetoacetic ester, aldehyde and ammonia, an intermediate 1,4-dihydropyridine (1,4-DHP) **94** is formed, which could be isolated easily. Since then this reaction has been successfully employed in the synthesis of 1,4-DHPs and bears his name as "Hantzsch dihydropyridine synthesis" (Scheme 29).

The addition of nucleophiles to α- and γ- positions of *N*-substituted pyridinium salts gives both 1,2- and 1,4-dihydropyridines. The regioselectivity of the addition reaction depends on the hardness of the nucleophile: hard nucleophiles preferentially attack at C-2 whereas soft ones attack at C-4 position of the pyridinium salts. The addition is also believed to proceed at both the α- and γ-carbon centres under kinetic control and only at the γ-carbon under thermodynamic control.[27] The Kröhnke procedure[28–30] and sodium dithionite reduction[31–33] are examples of reactions involving addition of nucleophiles at γ-position. The Kröhnke procedure,[28–30] consisting of base-catalysed reaction of ketones with alkyl or *N*-acyl pyridinium salts, was investigated years ago (Scheme 30). It is of particular synthetic interest since it constitutes a useful method of forming new carbon–carbon bonds to give γ-substituted 1,4-dihydropyridines **95**.[22]

Table 10 One-pot synthesis of 1,4-DHP under solvent free conditions using $HClO_4$–SiO_2[a]

Entry	(Ar) **123**	**110**	Reaction time (min.)	% yield
1	C_6H_5 (**123a**)	**110b**	20	95
2	*p*-CH_3-C_6H_4 (**123b**)	**110b**	25	90
3	*p*-CH_3O-C_6H_4 (**123c**)	**110b**	28	92
4	*p*-Cl-C_6H_4 (**123d**)	**110b**	20	89
5	*p*-OH-C_6H_4 (**123e**)	**110b**	26	90
6	*o*-NO_2-C_6H_4 (**123f**)	**110b**	35	92
7	*o*-Cl-C_6H_4 (**123g**)	**110b**	26	87
8	*p*-NO_2-C_6H_4 (**123h**)	**110a**	33	92
9	*o*-CH_3O-C_6H_4 (**123i**)	**110a**	42	90
10	*p*-Br-C_6H_4 (**123j**)	**110a**	40	92
11	*o*-Br-C_6H_4 (**123k**)	**110a**	40	89
12	2-Furyl (**123l**)	**110a**	52	86
13	2-Thienyl (**123m**)	**110a**	56	90
14	3-Pyridyl (**123n**)	**110a**	55	82
15	C_6H_5 (**123o**)	**110b**	20	94
16	*p*-CH_3-C_6H_4 (**123p**)	**110b**	25	92
17	*o*-CH_3O-C_6H_4 (**123q**)	**110b**	25	90
18	*o*-NO_2-C_6H_4 (**123r**)	**110b**	22	91

[a] The structures of the products were determined from their spectroscopic (IR, NMR and MS) data.



Scheme 39 Synthesis of 1,4-DHPs **126a–n** *via* addition reaction of Grignard reagent to *N*-triisopropylsilylpyridinium ions **125a–b**.

Comins, *et al.*[34] and Yamaguchi, *et al.*[35] have reported the reaction of 1-acetylpyridinium chloride with alkyl Grignard reagent, which lead to the formation of 1,4-dihydropyridines **97** and 1,2-dihydropyridines **98**.[34a] However, when a catalytic amount of CuI is present, the addition is regiospecific and resulted in the exclusive formation of 1,4-dihydropyridines **97**. Stoichiometric organocopper reagent (*e.g.* R_2CuLi, RCu, $RCu\cdot BF_3$) also give 1,4-addition product and resulted into the formation of 1,4-dihydropyridines **97** (Scheme 31).[36]

Several hydride reagents *e.g.* $NaBH_4$,[3] $NaBH_3CN$, $(PPh_3)_2CuBH_4$,[37] $(Ph_2MeP)_3CuBH_4$,[38] Semmelhack's "$NaCuH_2$"[39] and Semmelhack's "$LiCuH_2$"[39] has been used for the regioselective synthesis of 1,4-dihydropyridines from 1-(phenoxycarbony1) pyridinium chloride **99a** (generate *in situ* by the reaction between pyridine and phenyl chloriformate), but none of these procedure resulted into the regioselective formation of 1,4-DHP. Comins, *et al.*[40] has used a copper hydrido reagent prepared from lithium tri-*tert*-butoxyaluminum hydride (3.0 equiv.) and copper bromide (4.5 equiv.) as a reducing agent for the regioselective reduction of 1-(phenoxycarbony1)pyridinium chloride **96a** in almost quantitative yield (Scheme 32). Further this procedure has been extended to the variety of the 1-(alkoxy/aryloxy/acyloxycarbony1)pyridinium chlorides **99b–i** (generated *in situ* by the reaction between substituted pyridine and corresponding alkyl/phenyl chloroformate or acid chloride). This convenient one-pot preparation of 1-(alkoxycarbonyl)-1,4-dihydropyridines by using the Comins' copper hydride complements the two-step procedure developed by Fowler.[4]

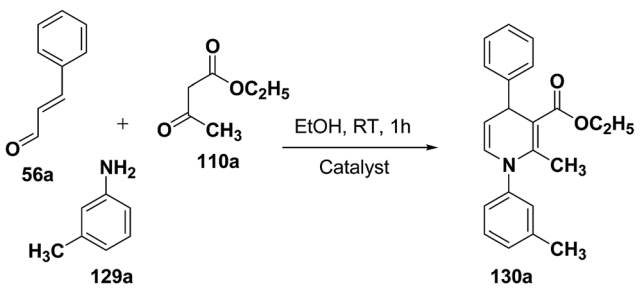
De Lucas, *et al.*[41] have developed a novel methodology for the synthesis of *N*-substituted 1,4-dihydropyridines **103a–d** by the reaction of 2-amino-5-formyl-4*H*-pyran **101** with primary amines **57d**, **62a**, **70d** and **102** in moderate yield (Scheme 33). The formation of 1,4-dihydropyridines involves cleavage of the 4*H*-pyran ring by nucleophilic attack of the respective amine and subsequent 6-*exo*-dig cyclisation.

Bennasar, *et al.*[42] have developed a regioselective synthesis of 4-functionalized 3,5-diacyl-4-aryl-1,4-dihydropyridines **108a–e** by the copper-mediated addition of functionalized arylmagnesium reagent **105a–e** to the *N*-benzhydrilpyridinium salt **104**,

Table 11 Addition of various dialkylmagnesium reagents to *N*-triisopropylsilylpyridinium ions **125a–b**

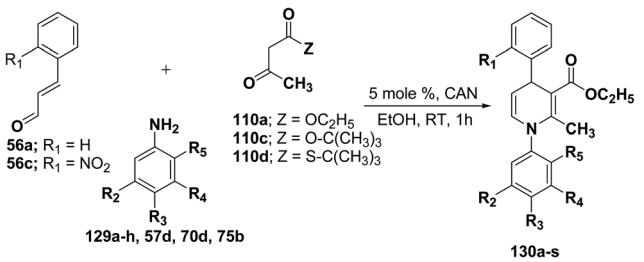
Entry	125	R_2Mg (128)[a]	Product	% yield[b]	Product ratio 126/127/125 (%)[c]
1	**125a**	Et_2Mg	**126a, 127a**	78	90/4/6
2	**125a**	nBu_2Mg	**126b, 127b**	82	100/0/0
3	**125a**	Bn_2Mg	**126c, 127c**	92	95/2/3
4	**125a**	Ph_2Mg	**126d, 127d**	0	5/95[d]/0
5	**125a**	Me_2Mg	**126e, 127e**	0	0/59/41
6	**125a**	iPr_2Mg	**126f, 127f**	91	99/0/1
7	**125a**	tBu_2Mg	**126g, 127g**	56	80/3/17[e]
8	**125a**	$Allyl_2Mg$	**126h, 127h**	20	20/78[d]/2
9	**125b**	Et_2Mg	**126i, 127i**	73	86/2/12
10	**125b**	nBu_2Mg	**126j, 127j**	54	54/6/40
11	**125b**	Bn_2Mg	**126k, 127k**	85	95/0/5
12	**125b**	iPr_2Mg	**126l, 127l**	78	100/0/0
13	**125b**	tBu_2Mg	**126m, 127m**	5	6/0/94[f]
14	**125b**	$Allyl_2Mg$	**126n, 127n**	12	21/70/9

[a] After addition of the organomagnesium compound R_2Mg to the *N*-silylpyridinium ion **125** at −78 °C the mixture was slowly warmed to −50 °C. [b] Isolated yield. [c] According to ^1H NMR of the crude reaction product. [d] Sum of **127** and non oxidized 1,2-addition product, which were both present. [e] Yield 63%, ratio 86/2/12 when addition performed by warming the mixture from −78 °C to room temperature. [f] Yield 29%, ratio 32/0/68 when addition performed by warming the mixture from −78 °C to room temperature.



Catalyst	Mole % of catalyst	Isolated yield (%)
$InCl_3$	20	45
$PPh_3.HClO_4$	20	50
$KHSO_4$	40	45
CAN	5	71

Scheme 40 Screening of the catalysts for the three-component domino reaction between **56a**, **129a** and **110a**.

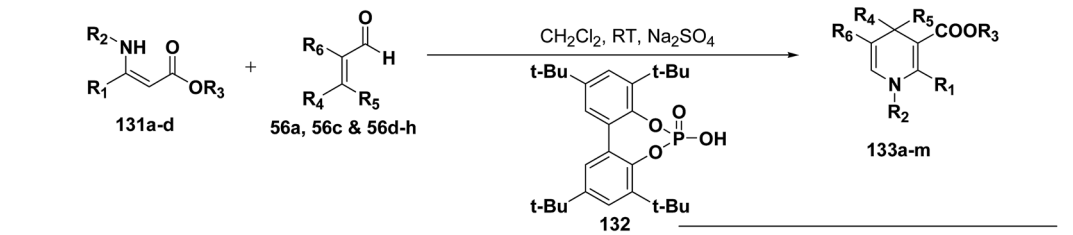


Scheme 41 Three-component domino reaction between **56**, **110** and **129a–h**, **57d** & **70d**.

Table 12 Scope and yields of the CAN-catalyzed synthesis of 1,4-dihydropyridines **130a–s**

Entry	Compound	110	56	R_2	R_3	R_4	R_5	Amine	Time (h)	Yield (%)
1	**130a**	**110a**	**56a**	CH_3	H	H	H	**129a**	1	74
2	**130b**	**110a**	**56a**	H	H	H	H	**57d**	1	71
3	**130c**	**110a**	**56a**	H	CH_3	H	H	**129b**	1	70
4	**130d**	**110a**	**56a**	H	F	H	H	**129c**	1	76
5	**130e**	**110a**	**56a**	H	Cl	H	H	**70d**	1	74
6	**130f**	**110a**	**56a**	CH_3	CH_3	H	H	**129d**	1	70
7	**130g**	**110a**	**56a**	Cl	H	H	H	**129e**	1	72
8	**130h**	**110a**	**56a**	H	Br	H	H	**75b**	1	74
9	**130i**	**110a**	**56a**	CH_3	H	CH_3	H	**129f**	1	72
10	**130j**	**110a**	**56a**	OCH_3	H	H	H	**129g**	1	65
11	**130k**	**110a**	**56c**	H	H	H	H	**57d**	1	50
12	**130l**[a]	**110a**	**56a**	H	CH_3	H	CH_3	**129h**	1	72
13	**130m**	**110c**	**56a**	H	H	H	H	**57d**	2	52
14	**130n**	**110c**	**56a**	H	CH_3	H	H	**129b**	2	61
15	**130o**	**110c**	**56a**	H	Cl	H	H	**70d**	2	65
16	**130p**	**110d**	**56a**	H	H	H	H	**57d**	1	61
17	**130q**	**110d**	**56a**	H	F	H	H	**129c**	1	62
18	**130r**	**110d**	**56a**	H	Cl	H	H	**70d**	1	63
19	**130s**	**110d**	**56a**	H	CH_3	H	H	**129b**	1	61

[a] Isolated as an 1.1 : 1 rotamer mixture.

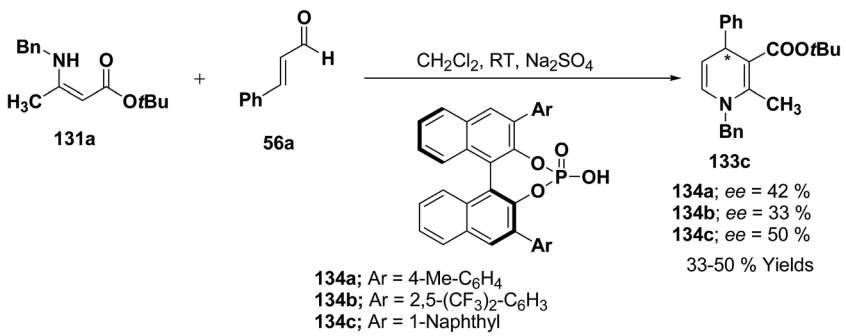


131a; $R_1 = CH_3$, R_2 = Bn, R_3 = *t*-Bu
131b; $R_1 = CH_3$, R_2 = Bn, R_3 = Et
131c; R_1 = Ph, R_2 = Bn, R_3 = Et
131d; $R_1 = CH_3$, R_2 = Ph, R_3 = *t*-Bu

56d; $R_4 = R_5 = CH_3$, R_6 = H
56e; $R_4 = R_6 = CH_3$, R_5 = H
56f; R_4 = *p*-NO_2-C_6H_4, $R_5 = R_6$ = H
56g; R_4 = p-OCH_2Ph-C_6H_4, $R_5 = R_6$ = H
56h; R_4 = p-$N(CH_3)_2$-C_6H_4, $R_5 = R_6$ = H

131	56	133	(%) Yield
131a	56d	133a	89
131a	56e	133b	70
131a	56a	133c	89
131a	56f	133d	79
131a	56g	133e	39
131a	56h	133f	66
131a	56c	133g	84
131b	56a	133h	54
131c	56a	133i	71
131c	56f	133j	71
131c	56a	133k	77
131d	56d	133l	31
131d	56e	133m	32

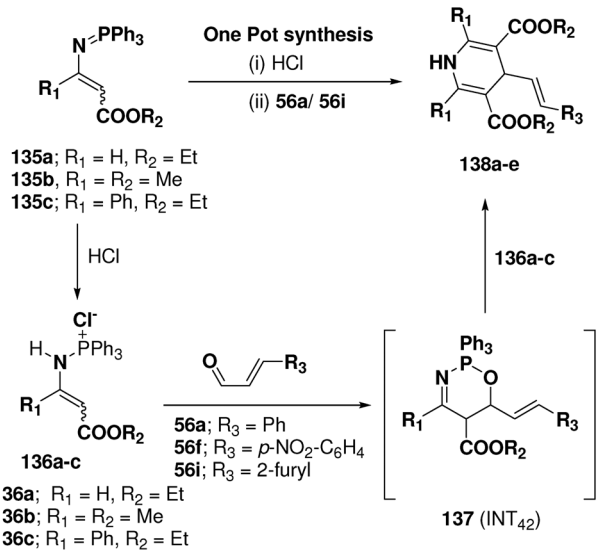
Scheme 42 Synthesis of 1,4-dihydropyridines **133a–m** catalyzed by Brønsted acid **132**.



134a; *ee* = 42 %
134b; *ee* = 33 %
134c; *ee* = 50 %
33-50 % Yields

134a; Ar = 4-Me-C_6H_4
134b; Ar = 2,5-$(CF_3)_2$-C_6H_3
134c; Ar = 1-Naphthyl

Scheme 43 Enantioselective synthesis of 1,4-dihydropyridine **133c** catalyzed by chiral Brønsted acids **134a–c**.



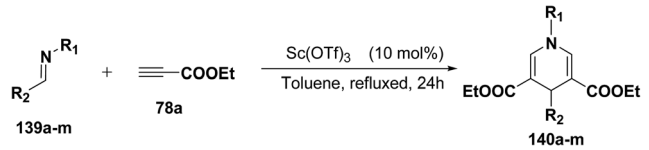
Starting Material	Product	R_1	R_2	R_3	Reaction conditions T (°C)	Time (h)	Yield (%)[a]
136a/56a	138a	H	Et	C_6H_5	40	19	66
136a/56f	138b	H	Et	p-NO_2-C_6H_4	40	30	62
136b/56a	138c	Me	Me	C_6H_5	40	20	65
136c/56a	138d	Ph	Et	C_6H_5	40	25	51[b]
136c/56i	138e	Ph	Et	2-furyl	40	48	57[b]

[a] Purified by chromatography. [b] Obtained in "one pot" process from phosphazene **135c**.

Scheme 44 Reaction of enamino-phosphonium salts **136** with α,β-unsaturated aldehydes **55a**, **56f** and **56i**: preparation of symmetrical dihydropyridines **138a–e**.

followed by acylation with trichloroacetic anhydride. The subsequent haloform reaction on **106a–e** yields **107a–e**, which on *N*-deprotection gives **108a–e** (Scheme 34).

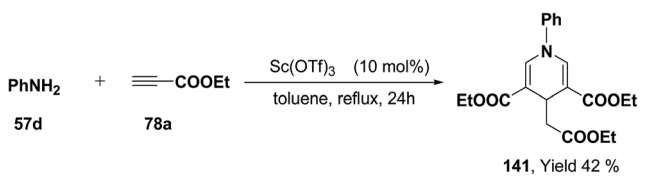
Table 13 The reaction of imines **139a–m** with **78a**[a]



Entry	Imine	R_1	R_2	Product **140**	Yield[b] (%)
1	**139a**	*c*-Hex	Ph	**140a**	22[c]
2	**139b**	*t*-Bu	Ph	**140b**	18
3[d]	**139c**	Bn	Ph	**140c**	28
4	**139d**	$CHPh_2$	Ph	**140d**	35
5	**139e**	Ph	Ph	**140e**	45[c]
6	**139f**	p-$MeOC_6H_4$	Ph	**140f**	75[c]
7[d]	**139g**	p-MeC_6H_4	Ph	**140g**	62[c]
8[d]	**139h**	2,6-MeC_6H_3	Ph	**140h**	77
9	**139i**	p-$MeOC_6H_4$	p-MeC_6H_4	**140i**	78
10	**139j**	p-$MeOC_6H_4$	p-CI-C_6H_4	**140j**	54
11	**139k**	p-$MeOC_6H_4$	p-FC_6H_4	**140k**	47
12	**139l**	p-$MeOC_6H_4$	p-$NO_2C_6H_4$	**140l**	34
13	**139m**	p-$MeOC_6H_4$	$PhCH_2CH_2$	**140m**	0

[a] **133** (0.5 mmol), **78a** (1.25 mmol), Sc(OTf) (0.05 mmol) in toluene (5 mL) at reflux for 24 h. [b] Isolated yield. [c] GC yield. [d] BTF was used as a solvent instead of toluene.

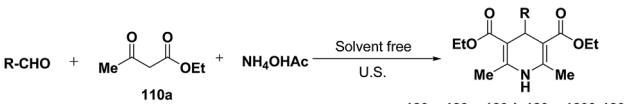
Yao, *et al.*[43] have developed a simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives with excellent product yields at room temperature using catalytic amount of molecular iodine. Initially, benzaldehyde, 1,3-cyclohexanedione **109**, ethyl acetoacetate **110a** and ammonium acetate were stirred at room temperature in a few mL of ethanol. After 4 hours, only 56% of product **111a** was realized after recrystallization of the crude product from ethanol (entry 1, Table 8). To improve the product yields and to optimize the reaction condition, molecular iodine was used in catalytic amount (15 mol%) and a reaction was carried out under similar reaction conditions to give the product **111a** in 99% yield (entry 2). The increase in the quantity of molecular iodine from 15 to 30 mol% not only reduced the reaction time from 4 to 2.5 h, but also enhanced the product yield from 56% to 99% (entry 3). Similarly, using 50 mol% of iodine as catalyst the reaction time further reduced to 1.5 h along with a decrease in the yield of the product **111a** (70%) (entry 4).



Scheme 45 $Sc(OTf)_3$ catalyzed reaction of aniline **57d** and **78a**: preparation of 1,4-DHP **141**.

A range of aryl and alkyl aldehydes were subjected to react with **109**, **110a** and NH_4OAc in the presence of either 15 or 30 mol% of iodine to generate corresponding 1,4-DHP **111b**. The results are summarized in Table 9, *e.g.* with 30 mol% of iodine as catalyst, *p*-chlorobenzaldehyde is converted into the product in 6 h with 99% yield, whereas the same reaction takes place within 40 min with 15 mol% of iodine without significant loss of yield (Table 9, entries 9 & 10). In general, the yields are little less with 15 mol% of catalyst and the reaction times are also short. Both aliphatic and aromatic aldehydes react equally good to give the products with excellent yields. The aryl group substituted with different groups and same groups located at different positions of the aromatic ring has not shown much effect on the formation of the final product.

Bazureaua, *et al.*[44] have developed a three component one pot microwave dielectric heating assisted liquid phase synthesis of 1,4-dihydropyridines using task specific ionic liquid as a soluble solid support. They synthesized the ILP bound aldehydes **113a–d** in high yields by the esterification of PEG-ILPs **112a–d** with 4-formylbenzoic acid in dry MeCN with dicyclohexylcarbodiimide (DCC) and 5% of dimethylamino pyridine (DMAP) as catalyst. The ILP bound 1,4-dihydropyridines **115** has been synthesized in an excellent yields *via* two methods. Method A involves the condensation of aldehydes **113a–d** and 1.0 equiv. of β-ketoester ethyl acetoacetate **110a** or methyl acetoacetate **110b** and 1.0 equiv. of aminocrotonate **114** under microwave irradiation (120 °C, 150 W, 50% power level, time exposure: 10 min), in the method B the IL-phase bound 1,4-DHP **115** was prepared by the condensation from β-ketoester **110a** or **110b** (2.0 equiv.) and NH_4OAc (2.0 equiv.) using the same



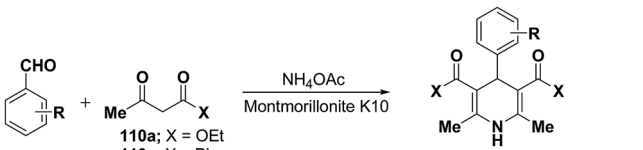
110a

123a, 123c, 123d, 123e, 123f, 123g & 142a-f

Entry	Product	Solvent	Time (min)	Isolated yield[a] (%)
1	C_6H_5 (**123a**)	No	40	87
2	4-Cl-C_6H_4 (**123d**)	No	50	94
3	4-OH-C_6H_4 (**123e**)	No	40	85
4	2-NO_2-C_6H_4 (**123f**)	No	45	80
5	3-NO_2-C_6H_4 (**142a**)	No	25	98
6	3-NO_2-C_6H_4 (**142a**)	Ethanol	60	74
7	4-CH_3O-C_6H_4 (**123c**)	No	60	90
8	2-Cl-C_6H_4 (**123g**)	No	60	82
9	C_6H_5-CH=CH (**142b**)	No	70	90
10	3,4-(OCH_2O)-C_6H_3 (**142c**)	No	35	97
11	3-Cl-C_6H_4 (**142d**)	No	30	87
12	4-OH-$^3CH_3$-C_6H_3 (**142e**)	No	70	82
13	2,4-Cl_2-C_6H_3 (**142f**)	No	30	99

[a] Isolated yield based on the corresponding aldehydes.

Scheme 46 Synthesis of 1,4-dihydropyridines under ultrasound at room temperature.



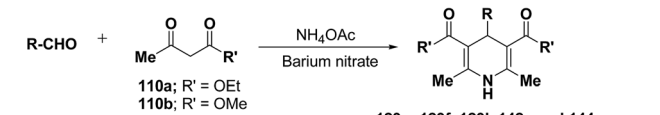
110a; X = OEt
110e; X = Ph

123a, 123b, 123g, 123i, 142a and 143a-c

143a; X = Ph, R = *m*-NO2
143b; X = Ph, R = *o*-Cl
143c; X = Ph, R = H

Entry	Product (R)	Time (min)	Isolated yield (%)
1	H (**123a**)	30	65
2	*o*-OMe (**123i**)	40	83
3	*m*-NO_2 (**142a**)	30	75
4	*o*-Cl (**123g**)	70	60
5	*p*-Me (**123b**)	60	60
6	*m*-NO_2 (**143a**)	60	40
7	*o*-Cl (**143b**)	50	35
8	H (**143c**)	40	40

Scheme 47 Synthesis of 1,4-dihydropyridines catalyzed by montmorillonite K10 clay.



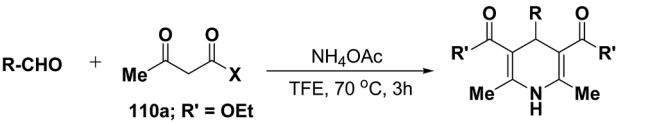
110a; R' = OEt
110b; R' = OMe

123n, 123f, 123l, 142a and 144a-q

Entry	Product (R)	104	Time (min)	Isolated yield (%)
1	3-pyridyl (**123n**)	**110a**	25[a]	93
2	4-Cl-C_6H_4 (**144a**)	**110b**	20	91
3	4-pyridyl (**144b**)	**110a**	10 [b]	90
4	4-Br-C_6H_4 (**144c**)	**110b**	10	89
5	Me_2N-C_6H_4 (**144d**)	**110b**	25	93
6	Me_2N-C_6H_4 (**144e**)	**110a**	15	91
7	2-pyridyl (**144f**)	**110a**	20 [c]	93
8	3-NO_2-C_6H_4 (**142a**)	**110a**	5	95
9	3-NO_2-C_6H_4 (**144g**)	**110b**	20	92
10	2-NO_2-C_6H_4 (**123f**)	**110a**	25	92
11	2-Furyl (**123l**)	**110a**	10	95
12	2-Furyl (**144h**)	**110b**	15	98
13	*β*-Naphthyl (**144i**)	**110a**	22	88
14	*β*-Naphthyl (**144j**)	**110b**	25	89
15	CH_3CH=CH (**144k**)	**110b**	15	93
16	CH_3CH=CH (**144l**)	**110a**	15	94
17	C_6H_4CH=CH (**144m**)	**110b**	20	86
18	2,3-$(OH)_2$-C_6H_3 (**144n**)	**110b**	25	89
19	C_6F_5 (**144o**)	**110a**	45	90
20	C_6F_5 (**144p**)	**110b**	45	90
21	4-CF_3-C_6H_4 (**144q**)	**110a**	30	95

[a,b,c] Reaction time 5, 6, 3, and 3 hrs respectively at 80 °C without any catalyst.

Scheme 48 Synthesis of 1,4-dihydropyridines in presence of 5 mol% of the barium nitrate.



110a; R' = OEt
110b; R' = OMe

123a, 123b, 123d, 123e, 123h, 123j, 123l, 144m and 145a-b

Entry	Product (R)[a]	R'	yield (%)[b]
1	C_6H_5 (**123a**)	OEt	97
2	*p*-Cl-C_6H_4 (**123d**)	OEt	96
3	C_6H_5CH=CH (**144m**)	Me	95
4	cyclohexane (**145a**)	OEt	96
5	2-Furyl (**123l**)	OEt	98
6	*p*-Me-C_6H_4 (**123b**)	OEt	98
7	*p*-Br-C_6H_4 (**123j**)	OEt	97
8	*p*-OH-C_6H_4 (**123e**)	OEt	95
9	*p*-NO_2-C_6H_4 (**123d**)	OEt	96
10	*n*-hexane (**145b**)	OEt	97

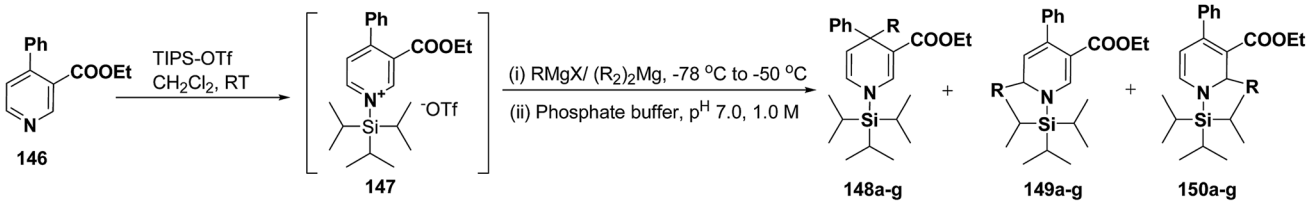
[a] Reaction condition: aldehyde (1.0 mmol), acetoacetate ester (2.0 mmol), NH_4OAc (1 mmol), TFE (2 mL), 3 h. [b] Isolated yield.

Scheme 49 Synthesis of 1,4-dihydropyridines through Hantzsch reaction in TFE.

microwave reaction conditions (120 °C, 10 min) (Scheme 35). IL-phase, the bound products **115a–b** were subjected to cleavage by: (i) transesterification with 30% of MeONa in refluxed MeOH during 18 h, (ii) saponification with 60% of LiOH in THF at room temperature, followed by controlled acidification with a solution of 3.0 M HCl to obtain the desired 1,4-DHP **116a–b** in an good yield. Similarly **118a–b** was synthesized by the condensation of **113a–d** with **110a** or **110b** (1.0 equiv.) and **117** (1.0 equiv.) and NH_4OAc (2.0 equiv.) under the same microwave radiation condition. **118a–b** on transesterification followed by saponification yielded **119a–b**.

J. H. Lee[45] has described an efficient method for the synthesis of 1,4-DHP under mild reaction condition using Baker's yeast. In a typical procedure a solution of 100 mL of pH 7.0 phosphate buffer, 5.0 g of D-glucose, and 2.0 g of yeast extract was warmed at 35 °C. Further 5.0 g of dry active Baker's yeast was added to this solution and the mixture was stirred at 30 °C for 30 min, after which, acetoacetic ester **110a** or **110b** (1.0 mmol) and ammonium acetate or 3-amino crotonitrile **120** were added. The mixture was stirred at room temperature for 24 h and then extracted with diethyl ether. The organic layer was dried and concentrated *in vacuo* and the resulting crude products were recrystallized using ether–*n*-hexane to afford pure products **121a–b** and **122a–b** in 46–70% yields (Scheme 36).

The glycolytic pathway from D-glucose to pyruvate is one of the most universal metabolic pathway known. In yeast, glycolysis is supposed to be the main pathway for the catabolism of glucose. According to the classical concept of glycolysis, metabolic acetaldehyde, resulting in the formation of acetoin, should be released from pyruvate in aerobic conditions. It is assumed that this acetaldehyde is involved in this Hantzsch-type reaction (Scheme 37).



Entry	Nucleophile ($RMgx/R_2Mg$)[a]	Cu(I)-salt (15 mol%)	Product/educt ratio[b]		1,4-dihydropyridines	
			148/149/150	(148+149+150)/146	Product No.	Yield[c] (%)
1	MeMgBr	-	-[d]	-	148a	e
2	Me_2Mg	-	-[d]	-	148a	e
3	EtMgCl	-	61/35/4	58/42	148b	20
4	Et_2Mg	-	64/35/4	98/2	148b	55
5	EtMgCl	$CuBe.SMe_2$	97/3/0	33/67	148b	15
6	EtMgCl	CuCN	99/1/0	70/30	148b	25
7	Et_2Mg	$CuBr.SMe_2$	76/14/1	44/55	148b	23
8	*i*PrMgCl	-	99/1/0	70/30	148c	63
9	ipr_2Mg	-	100/0/0	97/3	148c	91
10	*t*BuMgCl	-	94/6/0	40/60	148d	47
11	tBu_2Mg	-	86/14/0	89/11	148d/149d	56/5[f]
12	AllMgCl	-	-[d]	-	148e	e
13	All_2Mg	-	-[d]	-	148e	e
14	BnMgCl	-	72/28/0	69/31	148f/149f	38/7
15	Bn_2Mg	-	50/49/1	98/2	148f/149f	45/24
16	BnMgCl	$CuBe.SMe_2$	95/5/0	95/5	148f	41
17	BnMgCl	Me_2S[g]	85/15/0	46/54	148f	40
18	Bn_2Mg	$CuBr.SMe_2$	62/38/0	66/34	148f	28
19	BnMgCl	CuCN	99/1/0	95/5	148f	31/25
20	BnMgCl	CuCN[h]	59/41/0	95/5	148f/149f	38
21	BnMgCl	$Bu_4N^+I^-$	90/1-/0	60/40	148f	39
22	BnMgCl	$Bu_4N^+Br^-$	92/8/0	46/54	148f	44
23	BnMgCl	$Bu_4N^+Cl^-$	85/15/0	43/57	148f/149g	7
24	PhMgCl	-	90/10/0	13/87	148g	46
25	Ph_2Mg	-	98/2/0	63/37		

[a] Compound **146** was dissolved in CH_2Cl_2 and treated with 1.0 equiv. of silyl triflate at room temperature. After 15 min the solution was cooled to -75 °C and 2.0 equiv. of the corresponding organomagnesium reagent was added. Work up was performed by addition of phosphate buffer (pH 7.0, c= 1.0 M) and extraction of the aqueous layer with CH_2Cl_2. [b] According to ^1H NMR of the crude product. [c] Isolated yield. [d] Not determinable. [e] Not isolated. [f] Contaminated with 9% **148d**. [g] Addition of 20 mol %. [h] 1.0 equiv.

Scheme 50 Addition of various organomagnesium reagents to *N*-triisopropylsilylpyridinium ions **147**: preparation of 1,4-dihydropyridines.

Sridhar, *et al.*[46] have reported an efficient and convenient procedure for the one-pot synthesis 1,4-dihydropyridine derivatives **123a–r** in excellent yields (Scheme 38) by the condensation of β-dicarbonyl compounds **110a** or **110b**, aldehydes and ammonium acetate, by using heterogeneous catalyst ($HClO_4$–SiO_2) under solvent-free conditions. The experimental procedure has been found very simple, convenient, and has the ability to tolerate a variety of other functional groups on phenyl ring of the aromatic aldehydes such as methoxy, nitro, hydroxyl and halides under the reaction conditions. Further the optimized reaction condition has been examined to prove the universality of this catalyst application. Various aromatic, aliphatic and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of heterogeneous catalyst ($HClO_4$–SiO_2). The results of this study are summarized in (Table 10).

Wanner, *et al.*[47] have synthesized *N*-silyl protected 1,4-DHP **126a–n** by the addition reaction of dialkylmagnesium reagents (R_2Mg) to *N*-triisopropylsilylpyridinium ions **125a–b** (Scheme 39). The *N*-triisopropylsilylpyridinium ions **125a–b** were generated *in situ* by the reaction of 4-substituted pyridines **124a–b** and triisopropylpyridinium-triflate (TIPS-OTf). The regioselectivity of 4-addition product of this reaction was quite satisfactory (Table 11, entries 1, 2, 3, 6, 7, 9, 10, 11 and 12).

Perumal, *et al.*[48–50] has carried out an initial study in search for the suitable catalyst and solvent for the synthesis of 1,4-DHP using cinnamaldehyde **56a**, *m*-toluidine **129a** and ethyl acetoacetate **110a**. Author first assayed indium trichloride,[44] triphenylphosphonium perchlorate,[45] and potassium hydrogen sulfate as catalysts,[46] which have been successfully employed in related condensation reactions, but the yields obtained were only moderate, even with high catalyst loadings. The best results were obtained with cerium ammonium nitrate (CAN) in ethanol, which gave the desired dihydropyridine derivative in 71% isolated yield (Scheme 40). Further Perumal, *et al.*[51] have developed cerium ammonium nitrate (CAN) catalyzed three-component domino reaction between aromatic amines **57d**, **70d** & **129a–h**, α,β-unsaturated aldehydes **56a** & **56c** and alkyl acetoacetate **110a**, **110c** & **110d** to afford the 1,4-dihydropyridines **130a–s** in moderate to good yields (Scheme 41, Table 12).

Renaud, *et al.*[52] has developed Brønsted acid **132** catalyzed addition of β-enaminoacrylates **131a–d** to α,β-unsaturated aldehydes **56a**, **56c** and **56d–h** to afford the corresponding *N*-substituted 1,4-dihydropyridines **133a–m** in 31–89% yields (Scheme 42).

Further author have also reported the enantioselective synthesis of 1,4-dihydropyridine **133c** starting from **131a** and **56a** using three different chiral Brønsted acids **134a–c** in ee 33–50% (Scheme 43).

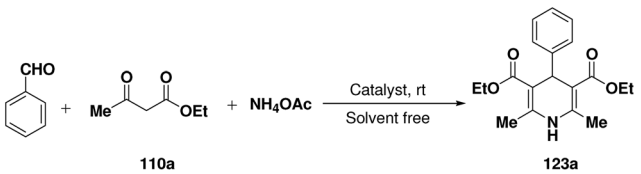
Palacios, *et al.*[53] explored the reactivity of enaminophosphonium salts **136a–c** derived from phosphazenes **135a–c** with α,β-unsaturated aldehydes **56a**, **56f** and **56i** (Scheme 44). The reaction of enaminophosphonium salt **135a**, prepared by hydrochloric acid treatment of *N*-vinylic phosphazene **135a**, with cinnamaldehyde **56a** or *p*-nitrocinnamaldehyde **56f** in refluxing CH_2Cl_2 led to the formation of 4-(2-phenylethenyl)-3,5-diethoxycarbonyl-1,4-dihydropyridine **138a** and 4-[2-(4-nitrophenyl)ethenyl]-3,5-diethoxycarbonyl-1,4-dihydropyridine **138b** in 66 and 62% yields, respectively. The formation of these dihydropyridines **138** could be explained by means of a formal [4 + 2]-cyclization process involving an initial 1,4-addition of the γ-carbon atom of the enaminophosphonium salt **136a** to the carbonyl group of the aldehydes **56a** to give the cycloadduct intermediate 1,2,5-oxaazaphosphoranes **137** (INT_{42}) followed by regioselective attack of a second molecule of the phosphonium salt **130a** (Scheme 44). 1,4-DHPs **138d** and **138e** were also obtained in "one pot" process from phosphazene **135c** in 51 and 57% yields, respectively.

Fukuzawa, *et al.*[54] have developed a procedure for the synthesis of *N*-substituted-1,4-dihydropyridines **140a–m** in moderate to good yields by scandium(III) triflate catalyzed reaction of imines **139a–m** with ethyl propiolate **78a** (2.5 equiv.) in toluene or benzotrifluoride (BTF) under refluxed conditions (Table 13).

Further, it has also been reported by the author's that the $Sc(OTf)_3$ catalyzed reaction of aniline **57d** and ethyl propiolate **78a** (3.2 equiv.) yielded another 1,4-dihydropyridine **141** bearing three ester groups in 42% yield under the same reaction conditions (Scheme 45).

Wang, *et al.*[55] has developed a three-component one pot condensation of aldehydes, ethyl acetoacetate **110a** and ammonium acetate to afford the 1,4-dihydropyridines **123a**, **123c**, **123d**, **123e**, **123f**, **123g** and **142a–f** in 82–99% yields under ultrasound irradiation without solvent and catalyst at room temperature (Scheme 46). The main advantages of this procedure are mild reaction condition, shorter reaction time and high product yield.

Zonouz, *et al.*[56] have developed a three-component one pot condensation of aldehydes ethylacetoacetate **110a**/



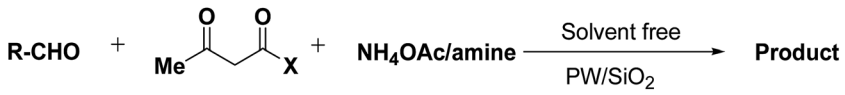
110a **123a**

Entry	Catalyst	Time (min)	yield (%)[a]
1	40 wt% PW/K10 (0.2g)	11	80
2	40 wt% PMo/K10 (0.2g)	10	80
3	40 wt% SiW/K10 (0.2g)	15	91
4	40 wt% PW/KSF (0.2g)	16	95
5	40 wt%PMo/KSF (0.2g)	20	94
6	40 wt% SiW/KSF(0.2g)	20	96
7	40 wt% PW/γ-Al_2O_3 (0.2g)	20	90
8	40 wt% SiW/g-Al_2O_3 (0.2g)	20	91
9	40 wt% PW/C (0.2g)	25	70
10	40% PMo/C (0.2g)	20	58
11	40% SiW/C (0.2g)	25	59
12	40 wt% SiW/SiO_2 (0.2g)	30	52
13	40 wt% PMo/siO_2 (0.2g)	18	85
14	40 wt% PW/SiO_2 (0.2g)	5	85
15	20 wt% PW/SiO_2 (0.2g)	5	90
16	60 wt% PW/SiO_2 (0.2g)	9	35
17	40 wt% PW/SiO_2 (0.14g)	9	50
18	40 wt% PW/SiO_2 (0.4g)	5	40
19		5	30

[a]Isolated yield, based on benzaldehyde
$H_3PW_{12}O_{40}$ (PW), $H_4SiW_{12}O_{40}$ (SiW), and $H_3PMo_{12}O_{40}$ (PMo).

Scheme 51 Effect of different catalyst on the yield of 1,4-dihydropyridine.

Table 14 Synthesis of Hantzsch 1,4-dihydropyridines by the condensation of aldehydes, β-dicarbonyl compounds and ammonium acetate/amines using PW/SiO_2 as catalyst



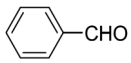
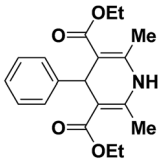
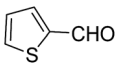
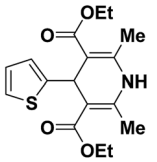
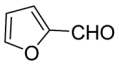
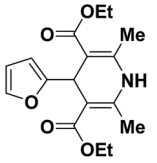
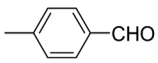
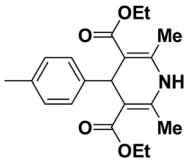
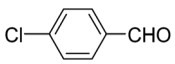
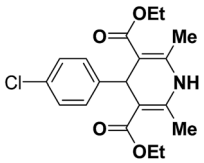
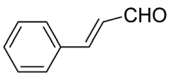
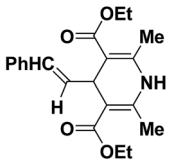
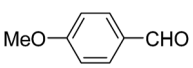
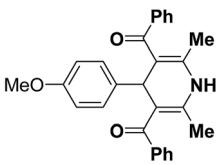
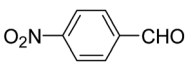
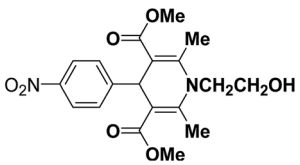
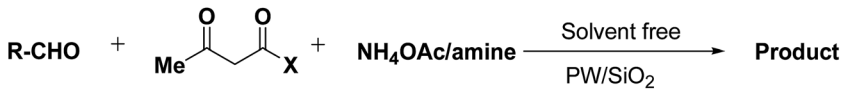
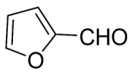
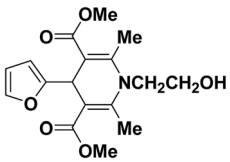
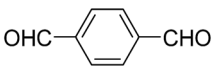
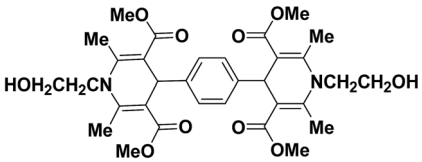
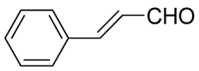
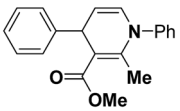
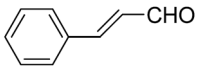
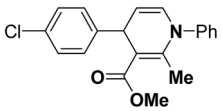
Entry	Aldehyde	X	Amine	Product	Product no.	Time (min)/ % yield[a] (%)
1		OEt	NH_4OAc		**123a**	5/190
2		OEt	NH_4OAc		**123m**	13/94
3		OEt	NH_4OAc		**123l**	4/98
4		OEt	NH_4OAc		**123b**	35/96
5		OEt	NH_4OAc		**123d**	8/92
6		OMe	NH_4OAc		**142b**	20/91
7		Ph	NH_4OAc		**151a**	32/55
8		OMe	$OH(CH_2)_2NH_2$		**151b**	15/86

Table 14 (*Contd.*)

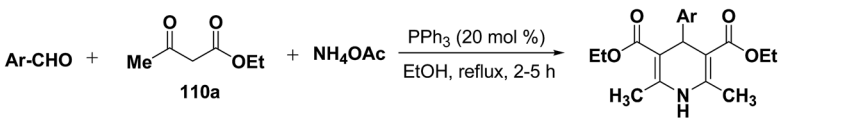


Entry	Aldehyde	X	Amine	Product	Product no.	Time (min)/ % yield[a] (%)
9		OMe	$OH(CH_2)_2NH_2$		**151c**	20/84
10[b]		OMe	$OH(CH_2)_2NH_2$		**151d**	20/80
11		OEt	$PhNH_2$		**151e**	45/82
12		OEt	4-Cl-$PhNH_2$		**1451f**	17/83

[a] Isolated yield, based on aldehyde. [b] Aldehyde : β-dicarbonyl compound : ethanolamine (1 : 3 : 1.5).

phenylacetylacetone **110e** and NH_4OAc in the presence of a solid catalyst (montmorillonite K10 clay) to afford 1,4-dihydropyridines **123a**, **123b**, **123g**, **123i**, **142a** and **143a–c** in good yields (Scheme 47). This procedure has advantages such as short reaction time, high yield and simple reaction workup conditions.

Rawat, *et al.*[57] have developed an efficient methodology for the three-component one pot condensation of aldehydes, alkylacetoacetate **110a**/**110b** and NH_4OAc using barium nitrate as a efficient catalyst to afford 1,4-dihydropyridines **123n**, **123f**, **123l**, **142a** and **144a–q** (Scheme 48).



123a, 123b, 123c, 123d, 123h, 123j, 123l 123m, 142a, 142b, 142d and 152

Entry	Product (Ar)	Time (h)	Yield[a] (%)
1	C_6H_5 (**123a**)	3	72
2	4-Me-C_6H_4 (**123b**)	3.5	90
3	4-MeO-C_6H_4 (**123c**)	3	75
4	3-Cl-C_6H_4 (**142d**)	3	85
5	4-Cl-C_6H_4 (**123d**)	2	81
6	3-NO_2-C_6H_4 (**142a**)	4.5	94
7	4-NO_2-C_6H_4 (**123h**)	2	92
8	4-Br-C_6H_4 (**123j**)	3.5	93
9	3,5-Cl_2-C_6H_3 (**152**)	4	80
10	Stryl (**142b**)	4	95
11	2-Thienyl (**123m**)	5	91
12	2-Furyl (**123l**)	5	94

[a] Isolated yield.

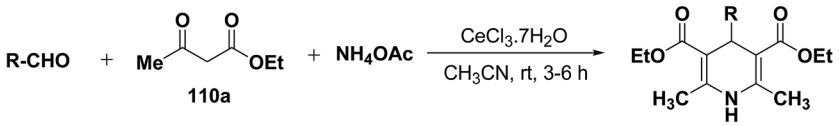
Scheme 52 Triphenylphosphine-catalyzed Hantzsch synthesis of 1,4-dihydropyridines.

Heydari, *et al.*[58] has synthesized 1,4-dihydropyridines **123a**, **123b**, **123d**, **123e**, **123h**, **123j**, **123l**, **144m** and **145a–b** in excellent yields by the reaction of aldehydes, alkyl acetoacetate **110a–b**, and ammonium acetate (Scheme 49) at 70 °C in trifluoroethanol (TFE). The advantage of this reaction was the solvent (TFE), which can be readily separated from reaction products and recovered in excellent purity for reuse.

Wanner, *et al.*[59] have developed a methodology for the synthesis of 4,4-disubstituted 1,4-dihydronicotinates **148a–g** by the regioselective addition of Grignard reagents RMgX or R_2Mg to nicotinic acid ester **146**, activated with triisopropylsilyl triflate **147** (Scheme 50). The regioselectivity of this reaction, where 4-unsubstituted and 4-substituted pyridine derivatives were employed as starting materials, was examined. Depending on the structure of the organomagnesium reagent varying ratios of 1,2- (**149a–g**), 1,4- (**148a–g**), and 1,6-regioisomers (**150a–g**) were obtained but in all the cases 1,4-addition products were predominating one.

Rafiee, *et al.*[60] have prepared 12-tungstophosphoric acid (PW) supported on different metal oxides and their catalytic performances have been evaluated in the three component condensation of benzaldehyde, ethyl acetoacetate **110a** and ammonium acetate to afford the corresponding 1,4-dihydropyridine **123a** (Scheme 51). A high catalytic activity was found over silica supported PW. Effect of PW loading, catalyst loading and solvent has been studied by the author to find out the best reaction condition. 40% PW onto SiO_2 (0.2 g) under solvent-free condition has been found to be the best catalyst for the synthesis of 1,4-dihydropyridines.

A series of 4-aryl, *N*-alkyl, and *N*-aryl substituted 1,4-dihydropyridines **123a**, **123b**, **123m**, **123l**, **123d**, **142b** and **151a–f** have been synthesized using different aldehydes in good to excellent yield in short reaction times (Table 14).

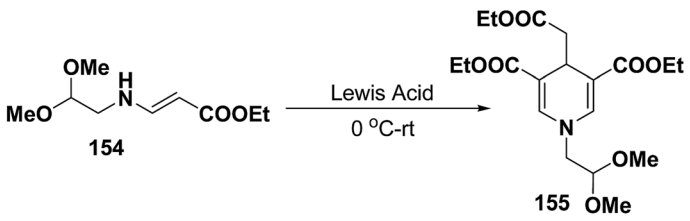


123a, 123b, 123c, 123d, 123f, 123h, 123i, 123l, 123m,142a, 144i,153a-d

Entry	Product (R)	Time (h)	Yield[a] (%)
1	C_6H_5 (**123a**)	3	80
2	4-OMe-C_6H_4 (**123c**)	4	82
3	4-F-C_6H_4 (**153d**)	3.5	86
4	4-Cl-C_6H_4 (**123d**)	4	91
5	4-$CH(CH_3)_2$-C_6H_4 (**153a**)	5	81
6	4-$C(CH_3)_3$-C_6H_4 (**153b**)	5	86
7	4-NO_2-C_6H_4 (**123h**)	3.5	82
8	2-NO_2-C_6H_4 (**123f**)	5.6	65
9	3-NO_2-C_6H_4 (**142a**)	5	71
10	β-Naphthyl (**144i**)	5	72
11	4-Me-C_6H_4 (**123b**)	3	82
12	2-OMe-C_6H_4 (**123i**)	6	61
13	2-Furyl (**123l**)	5.5	92
14	2-Thienyl (**123m**)	5	94
15	Isopropyl (**153c**)	5	89

[a] Isolated yield.

Scheme 53 $CeCl_3 \cdot 7H_2O$-catalyzed synthesis of Hantzsch 1,4-dihydropyridines.



Lewis Acid	Amount (equiv.)	Solvent	Time	Recovered 154 (%)	155 (%)
$BF_3.OEt_2$	0.3	THF	10h	-	17
$AlCl_3$	0.3	THF	3h	-	<10
Me_2AlCl	0.5	THF	10h	98	-
$TiCl_4$	0.2	DCM	10h	-	33

Scheme 54 Optimization of Lewis acid catalysts for the synthesis of 1,4-dihydropyridine **155**.

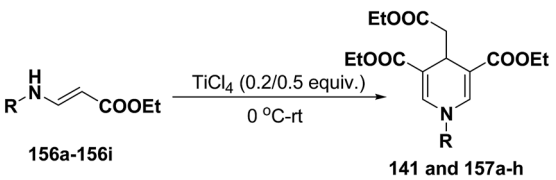
Debache, *et al.*[61] have developed triphenylphosphine-catalyzed Hantzsch three-component reaction of an aromatic aldehydes, ethyl acetoacetate **110a** and ammonium acetate to afford Hantzsch 1,4-dihydropyridines **123a**, **123b**, **123c**, **123d**, **123h**, **123j**, **123l**, **123m**, **142a**, **142b**, **142d** and **152** in good to excellent yields (Scheme 52).

Yadav, *et al.*[62] have developed an efficient one-pot synthesis of 1,4-dihydropyridines **123a**, **123b**, **123c**, **123d**, **123f**, **123h**, **123i**, **123l**, **123m**, **142a**, **144i**, **153a–d** in good to excellent yields *via* the $CeCl_3 \cdot 7H_2O$-catalyzed Hantzsch three-component reaction of an aromatic aldehydes, ethyl acetoacetate **110a** and ammonium acetate (Scheme 53).

Ajavakom, *et al.*[63] have screened several Lewis acid catalysts such as $BF_3 \cdot OEt_2$, $AlCl_3$, and $TiCl_4$ on β-amino acrylates **154**, for the synthesis of 1,4-dihydropyridine **155** (Scheme 54). The yield of product **155** obtained from these initial screening of the Lewis acid catalyst were not satisfactory, which may be likely due to the decomposition of the acetal group in β-amino acrylate **154** under acidic conditions. Out of the several screened Lewis acid catalyst $TiCl_4$ in dichloromethane was found to be best catalyst for the synthesis of 1,4-dihydropyridine **155**.

Several 1,4-dihydropyridines derivatives **141** and **157a–h** has been synthesized from β-amino acrylates **156a–i** using $TiCl_4$ as a Lewis acid catalyst (0.2/0.5 equiv.) at 0 °C – rt (Scheme 55).

Li, *et al.*[64] have screened several experimental conditions to synthesize 1,4-dihydropyridines by the condensation of (*Z*)-3-(4-methoxyphenylamino)-1-phenylprop-2-ene-1-one (**158a**) with *p*-nitrobenzaldehyde in the presence of catalytic amount of Lewis acids. The reaction of **158a** with *p*-nitrobenzaldehyde in the presence of a catalytic amount of $TsOH \cdot H_2O$, TFA or $NaAuCl_4 \cdot 2H_2O$ yielded the desired 1,4-DHP **159a** in 71–79% yield (Table 15, entries 2–4). Increase in the aldehyde equivalent from 0.75 to 1.0 not only lessened the reaction time, but also enhanced the yield of the desired product (Table 15, entry 2 *vs.* 6). The high yield of the 1,4-DHP **159** was achieved in the presence of $TsOH \cdot H_2O$ as a catalyst (85–87%; Table 15, entries 6 and 7).



156a-156i

141 and 157a-h

Entry	Acrylate	R	$TiCl_4$ (equiv)	Product	Yield (%)
1	**156a**	*n*-Bu	0.2	**157a**	81
2	**156b**	n-$C_{18}H_{37}$	0.2	**157b**	83
3	**156c**	Bn	0.2	**157c**	79
4	**156d**	$HOCH_2CH_2$	0.2	**157d**	81
5	**156e**	Ph	0.5	**141**	82
6	**156f**	*p*-MeO-C_6H_4	0.2	**157e**	52
7	**156f**	*p*-MeO-C_6H_4	0.5	**157e**	76
8	**156g**	*p*-I-C_6H_4	0.2	**157f**	58
9	**156g**	*p*-I-C_6H_4	0.5	**157f**	79
10	**156h**	*p*-F-C_6H_4	0.5	**157g**	70
11	**156i**	*m*-Cl-C_6H_4	0.5	**157h**	76

Scheme 55 $TiCl_4$ catalysed synthesis of 1,4-dihydropyridines **141** and **157a–h**.

Tamaddon, *et al.*[65] have developed a green, efficient one-pot synthesis of various 4-alkyl/aryl-1,4-dihydropyridines in an excellent yields *via* the Hantzsch three-component reaction of an aromatic/aliphatic aldehydes, alkyl acetoacetate **110a**/**110b** and ammonium carbonate in water (Scheme 56).

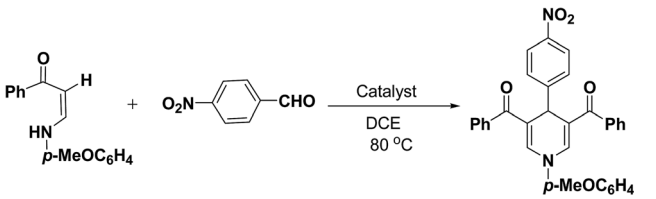
Shimizu, *et al.*[66] have developed an efficient one-pot synthesis of 1,4-dihydropyridines **161a–z** in moderate to good yields *via* the $Yb(OTf)_3$-catalyzed Hantzsch three-component reaction of an aromatic aldehydes, 3,3-dimethoxy propionate **160** and aromatic amines in 1,4-dioxane at 90 °C (Scheme 57).

Wang, *et al.*[67] have developed an efficient one-pot synthesis of 1,4-dihydropyridines in an excellent yields *via* the Hantzsch three-component reaction of an aromatic/aliphatic aldehydes, alkyl acetoacetate **110a**/**110b** and ammonium acetate in PEG-400 as solvent at 90 °C (Scheme 58). PEG-400 facilitates the reactants converting into corresponding products smoothly in excellent yields because of its good immiscibility with a number of organic reagents. Moreover, PEG-400 is inexpensive, thermally stable, nonvolatile, and nontoxic.

2.3. Synthesis of enantiopure 1,4-dihydropyridines

2.3.1. Resolution of racemic 1,4-dihydropyridine carboxylic acids *via* diastereomeric salt formation. Chiral crystallization

Table 15 Optimization of catalyst for the synthesis of 1,4-dihydropyridine **159a**

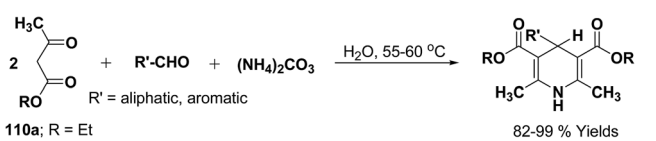


158a

159a

Entry	*p*-NO_2-C_6H_4-CHO (eq.)	Catalyst (mol%)	Time (h)	% yield of **159a**[a]
1	0.75	$Sc(OTf)_3$ (5)	12	34
2	0.75	$TsOH \cdot H_2O$ (10)	3	75
3	0.75	TFA (10)	5	71
4	1.0	$NaAuCl_4 \cdot 2H_2O$ (5)	1	79
5	1.0	TFA (5)	20	91
6	1.0	$TsOH \cdot H_2O$ (10)	1	85
7	1.0	$TsOH \cdot H_2O$ (5)	1	87
8	1.0	$FeCl_3 \cdot 6H_2O$ (10)	3	48
9	1.0	—	10	NR[b]

[a] Isolated yields. [b] NR = no reaction.

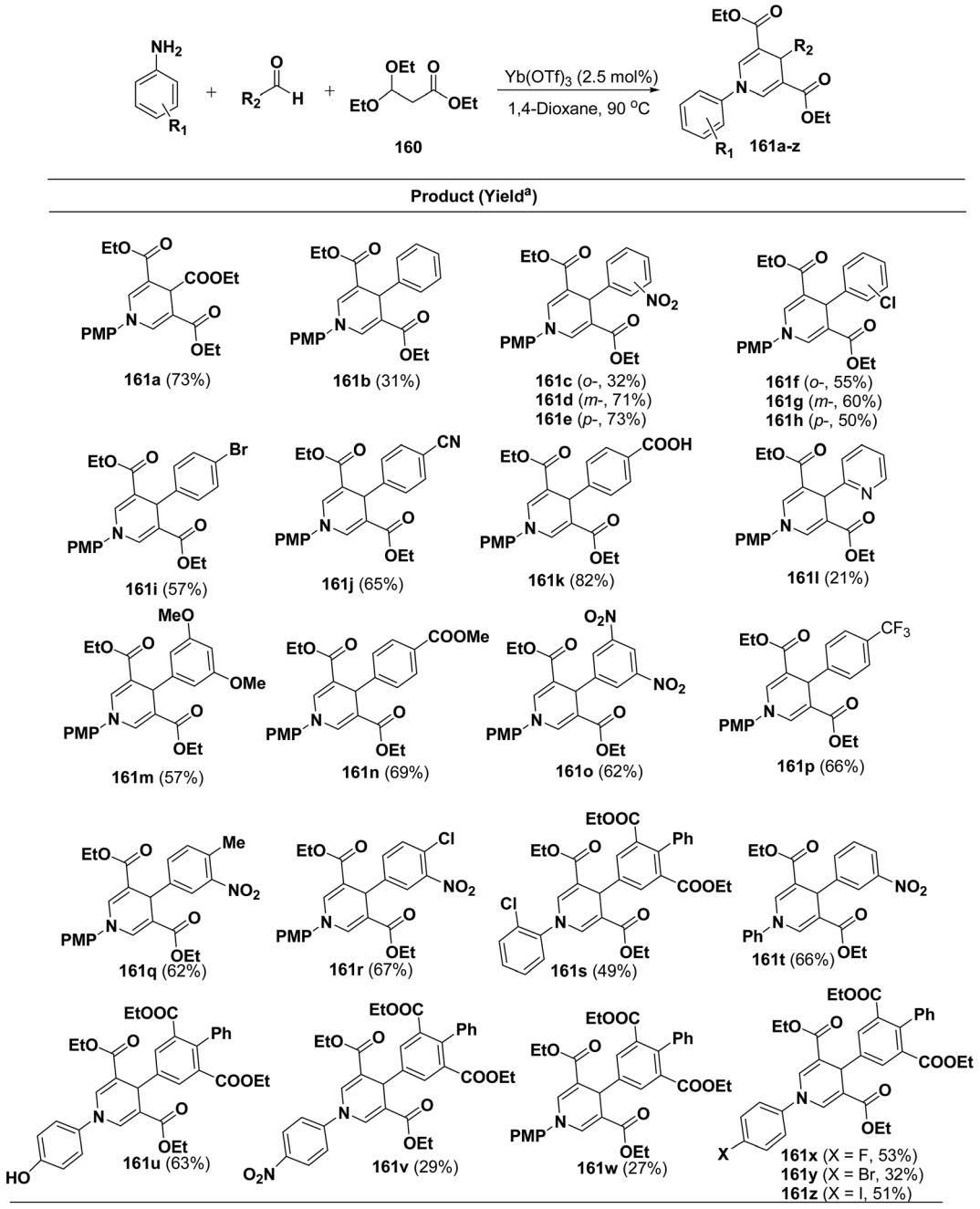


110a; R = Et
110b; R = Me

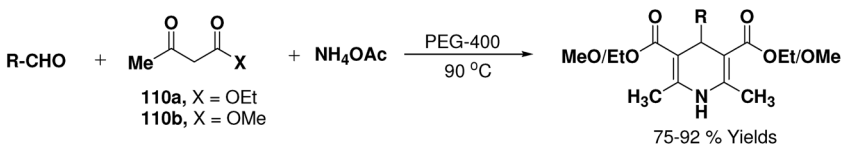
82-99 % Yields

Scheme 56 Synthesis of 1,4-dihydropyridines using ammonium carbonate in water.

with the use of resolving agents to form diastereomeric salts is a widely used technique for resolving chiral compounds. Cinchonidine, cinchonine and quinidine are the most commonly used natural chiral amine bases applied which are used to resolve racemic 1,4-dihydropyridinecarboxylic acid *via* forming their diastereomeric salts. It has been observed that these alkaloids



Scheme 57 $Yb(OTf)_3$ catalyzed one-pot synthesis of 1,4-DHPs **161a–z**.



Scheme 58 Synthesis of 1,4-dihydropyridines in PEG-400.

behave as quasi-mirror images and are used in a complementary way to obtain both enantiomers of 1,4-dihydropyridines in a pure form. The method involves treatment of racemic acid with a chiral base which leads to the formation of diastereomeric salts (Scheme 59). The enantiomer is then obtained in pure acid form by repeated crystallization followed by acidification. The other enantiomer is recovered from the mother liquor and resolved using other suitable chiral base reagent by going through the same procedure. The first resolution of racemic dihydropyridinecarboxylic acids through this method was carried out by Shibanuma, *et al.*[68] to synthesize nicardipine from 1-ethoxymethyl-5-methoxycarbonyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (±)-**162** using cinchonine and cinchonidine (Scheme 59). Various other 1,4-dihydropyridine derivatives have been synthesized similarly through optical resolution of racemic mixture of 1-ethoxymethylated dihydropyridines and by subsequently removing the ethoxymethyl group.[69]

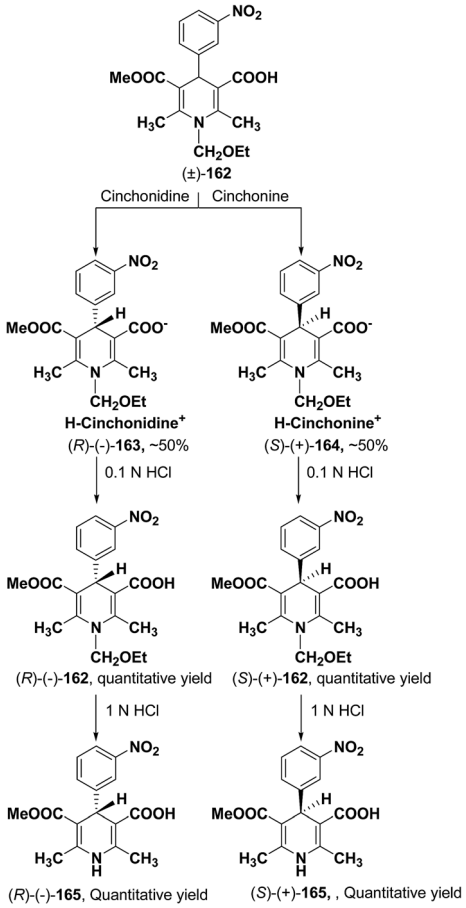
Synthesis of optically-active 1,4-dihydropyridine derivatives from 1-ethoxymethylated carboxylic acid **162** involves protection and deprotection approach for NH group in 1,4-DHP ring. Use of unprotected racemic acid for direct resolution has also been investigated in detail. Zhang, *et al.*[70] treated racemic acid (±)-**165** with cinchonidine to form diastereomeric salt (*S*)-(+)-**167** (Scheme 60). (*S*)-(+)-**167** enantiomer was formed by repeated crystallization and further treatment with hydrochloric acid. When quinidine was used (*R*)-(−)-**166** was formed.

The separation of (*R*)- and (*S*)-amlodipine **170** has been achieved by treatment of racemic acid **168** with cinchonidine in methanol. Dilution with water formed a crystalline precipitate which was recrystallized to yield diastereomerically pure cinchonidine salt **169**, which was further converted to enantiomerically pure (*R*)- and (*S*)-amlodipine in several synthetic steps (Scheme 61).[71]

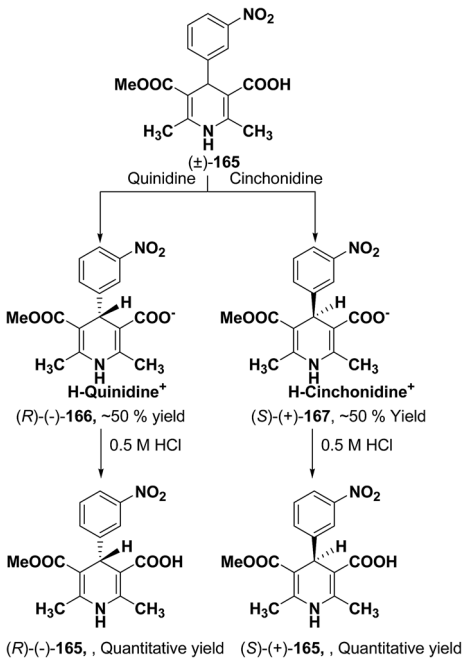
Various chiral acids have been used for the separation of racemic basic dihydropyridines. Racemic amlodipine **170** has been resolved using (1*S*)-(−)-camphanic acid chloride (Scheme 62) by Goldmann, *et al.*[72] The diastereomeric amides **171** obtained were easily separated chromatographically on Chiralcel OD column followed by crystallization from DMF/water.

Another remarkable method to get *R*-(+) and *S*-(−) amlodipine **170** is through L or D-tartaric acid respectively in DMSO.[73] It has been reported that (*R*)-amlodipine tartrate crystallizes out preferentially when naturally occurring L-tartaric acid is used with racemic amlodipine in DMSO. Recently it has been described that (*S*)-isomer of amlodipine could also be obtained with L-tartaric acid just by changing the solvent system (Scheme 63). By using DMF/H_2O (85 : 15 ratio) desired (*S*)-(−)-**172** crystallized out with 99% purity.[74] By reacting **172** with benzenesulfonic acid, active pharmaceutical ingredient (*S*)-(−)-amlodipine besylate hemipentahydrate salt **173** was obtained.

2.3.2. Separation of racemic 1,4-dihydropyridines by using chiral auxiliary. This synthetic strategy utilizes chiral auxiliary for the synthesis of optically active 1,4-dihydropyridines by forming diastereomeric esters which can be separated and eventually the chiral auxiliary can be regioselectively removed. Synthesis of 5-cyano-1,4-dihydropyridines from isoxazolo[5,4-*b*]



Scheme 59 Synthesis of enantiopure 1,4-dihydropyridines **165** *via* diastereomeric salt formation method.



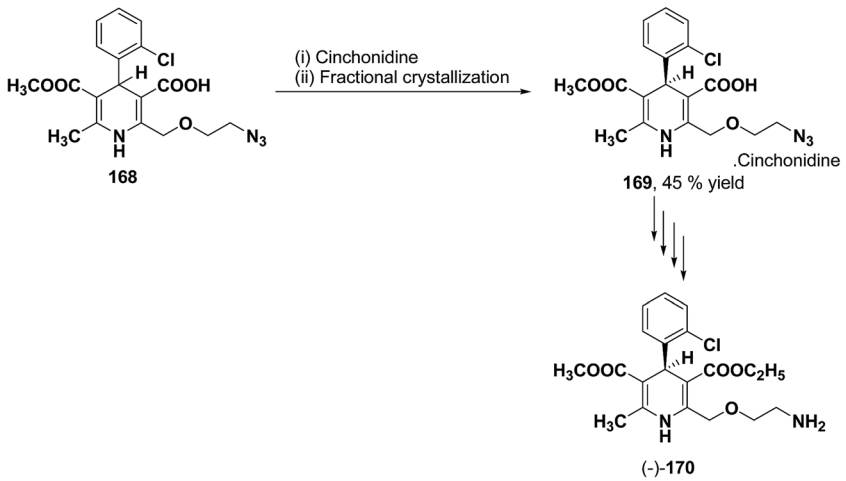
Scheme 60 Synthesis of chiral 1,4-dihydropyridine **165** *via* diastereomeric salt formation method.

pyridines have been achieved by Taylor, *et al.*[75] The monoester derivative **174** was reacted with nitrile oxide to produce isoxazolo[5,4-*b*]pyridine **175** in 74% yield (Scheme 64). Its saponification formed an acid which was then re-esterified with (−)-menthol. The resulting diastereomeric esters **176** were separated through flash chromatography, which on hydrolysis and decarboxylation yielded the desired 5-cyano-1,4-dihydropyridine-3-carboxylic acid **177**.

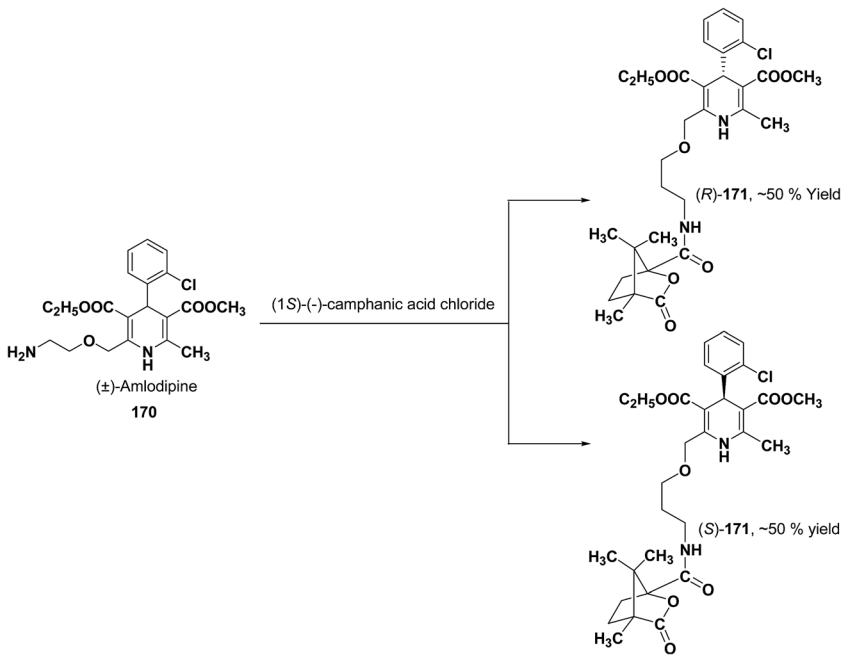
Arrowsmith, *et al.*[76] esterified (±)-**178** using optically pure (*S*)-(+)-2-phenylethanol to give diastereomeric mixture **179.** It was chromatographically separated on silica gel to form pure diastereomers and further treatment with sodium ethoxide and finally reduction of azide group by palladium on calcium carbonate yielded pure enantiomers (*R*)-(−)-amlodipine and (*S*)-(+)-amlodipine **170** (Scheme 65).

Lamm, *et al.*[77] disclosed the formation of pure enantiomers of felodipine **185**, a calcium channel antagonist by chromatographic separation of diastereomeric esters **183** prepared from (*R*)-1-(*p*-toluenesulfonyl)-3-tritylpropan-2-ol **181** (Scheme 66). This chiral auxiliary was removed easily by β-elimination reaction using potassium hydroxide in methanol at room temperature. Esterification of **184** with iodomethane successfully yielded (*R*)- and (*S*)-enantiomers of felodipine **185**.

Racemic isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridinylpyridine-5-carboxylate isomers with *in vitro* calcium channel modulating activities have been described by Vo, *et al.*[78] Out of them the most promising 4-(2-pyridinyl) compound was resolved into pure enantiomers with the help of L-threonine **186** (Scheme 67). Through a multistep synthesis L-threonine was converted to β-aminocrotonate derivative **187**, which through



Scheme 61 Separation of (*R*)- and (*S*)-amlodipine **170** by treatment of racemic acid **168** with cinchonidine in methanol.



Scheme 62 Resolution of racemic amlodipine **170** using (1*S*)-(−)-camphanic acid chloride.

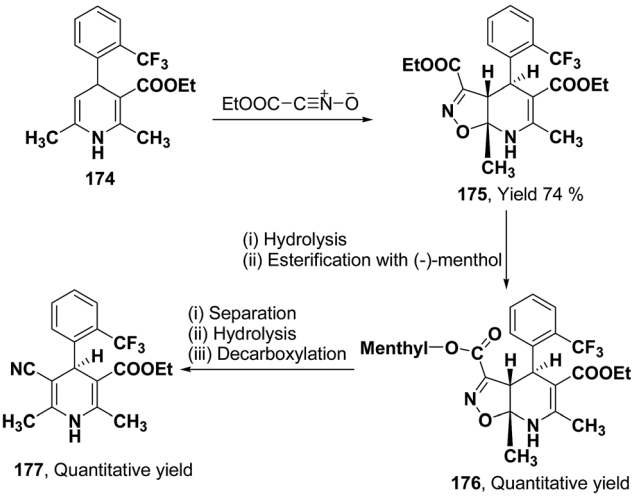
Hantzsch condensation afforded the mixture of 1,4-DHP diastereomers **188** separable by silica gel column chromatography. This was followed by removal of chiral auxiliary using DBU to yield **189** and desired enantiopure (−)-**190** and (+)-**190** were synthesized using isopropyl bromide and potassium carbonate in DMF.

Similarly synthesis of (*S*)-(−)- and (*R*)-(+)-enantiomers of 2-nitrooxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate[79] **192** exhibiting dual cardioselective agonist/smooth muscle selective antagonist activity[80] were synthesized utilizing D-threonine **191** as chiral auxiliary (Fig. 2). In both the cases the chiral esterifying group was easily removed by non-nucleophilic base 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU).

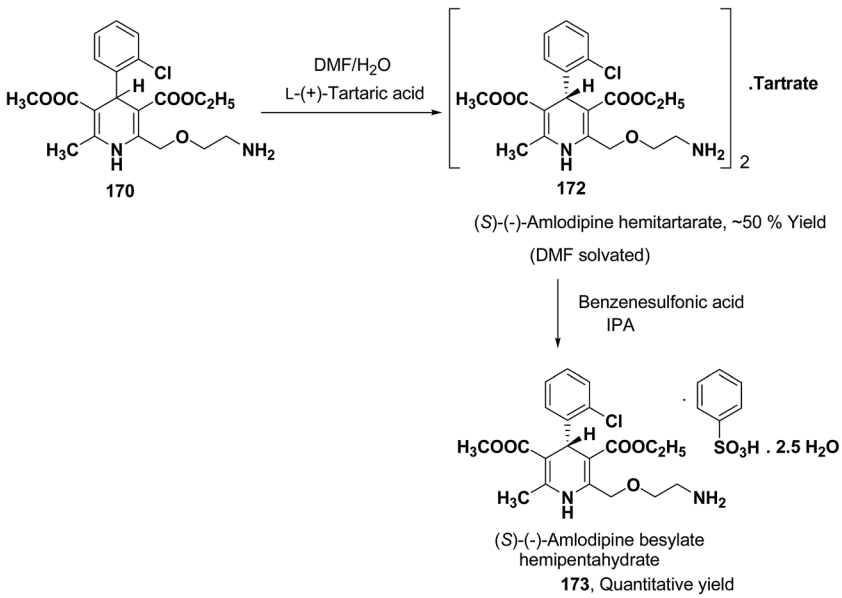
To synthesize chiral β-ketoester **195**, (4*R*,5*R*)-(−)-2,3-*O*-isopropylidine-D-threitol was used as chiral auxiliary (Scheme 68).[81] Using **195** as chiral β-ketoester, phenylpropargyl aldehyde **194** and benzyl 3-amino-3-phenyl-2-propenoate **193**, 1,4-DHP diastereomers **196** were obtained which were resolved through HPLC. 2,2-Dimethyl-1,3-dioxolane-4-methanol and 2,3-*O*-isopropylidine-D-threitol moieties on the chiral ester were replaced by ethyl group through deprotection of diol by acidic treatment followed by transesterification in ethanol to afford **197**.

2.3.3. Synthesis of enantiomerically pure 1,4-DHPs using chiral aldehydes. Synthetic methodology to synthesize 4-alkyl-3,5-dialkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **200a–c** has been developed by utilizing chiral aldehydes **198a–c** (Scheme 69).[82] Enantiomerically pure 1,4-DHPs **200a–c** were synthesized by Michael addition of ethyl aminocrotonate **114a** to chiral α-acetylacrylates **199a–c**. The synthesis of α-acetylacrylates **199a–c** was carried out by knoevenagel condensation of methylacetyl acetate and the corresponding chiral aldehyde.

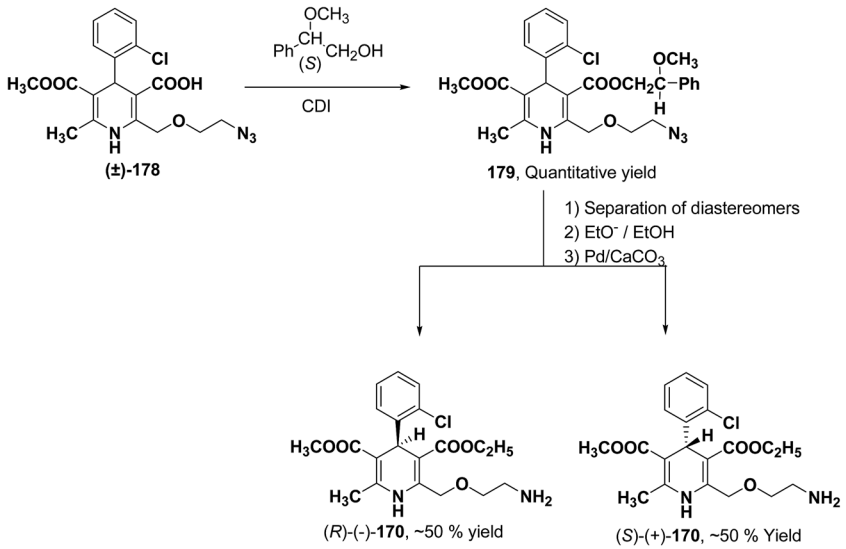
2.3.4. Organocatalytic asymmetric synthesis to form enantiomerically enriched dihydropyridines. Chiral phosphonic acids **134b**, **201a–c** and **202** have been recognized as promising catalysts for asymmetric synthesis of 1,4-dihydropyridines (Scheme 70). A three-component cyclization of an α,β-unsaturated aldehyde **56f**, a primary amine **62h** and ethyl acetoacetate **110a** in presence of chiral phosphonic acids **134b**, **201a–c** and **202** have been explored to generate chiral 1,4-dihydropyridines **203** with excellent ee upto 98% (Scheme 70).[83] The screening of phosphonic acids **134b**, **201a–c** and **202** showed that increasing size of substituents at 3,3′-positions of the chiral catalyst and increase in the reaction temperature leads to enhanced enantioselectivities (Table 16). It was concluded that in PhCN at 50 °C phosphonic acids **201c** and **202** afforded **203** with 89% and 90% ee, respectively. Decreasing the amount of **202** from 20 mol% to 10 mol% led to an improved ee of **203** up to 92%.



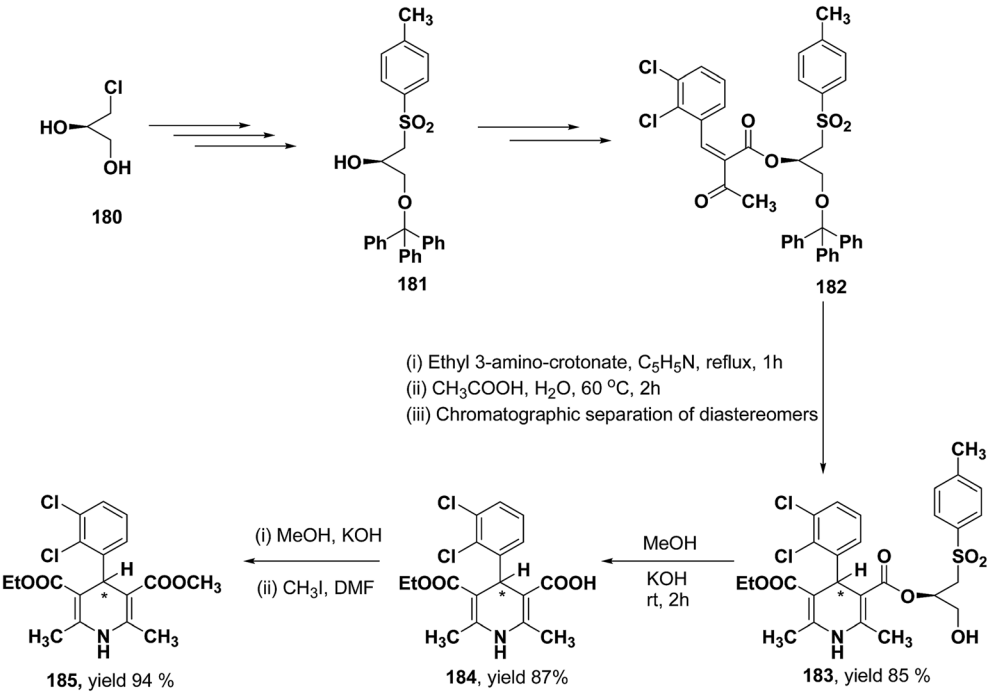
Scheme 64 Separation of **174** using nitrile oxide as a chiral auxiliary.



Scheme 63 Resolution of *R*-(+) and *S*-(−) amlodipine **170** *via* diastereomeric salt formation with L or D-tartaric acid, respectively in DMSO.



Scheme 65 Resolution of **170** from **178** using optically pure (*S*)-(+)-2-phenylethanol.



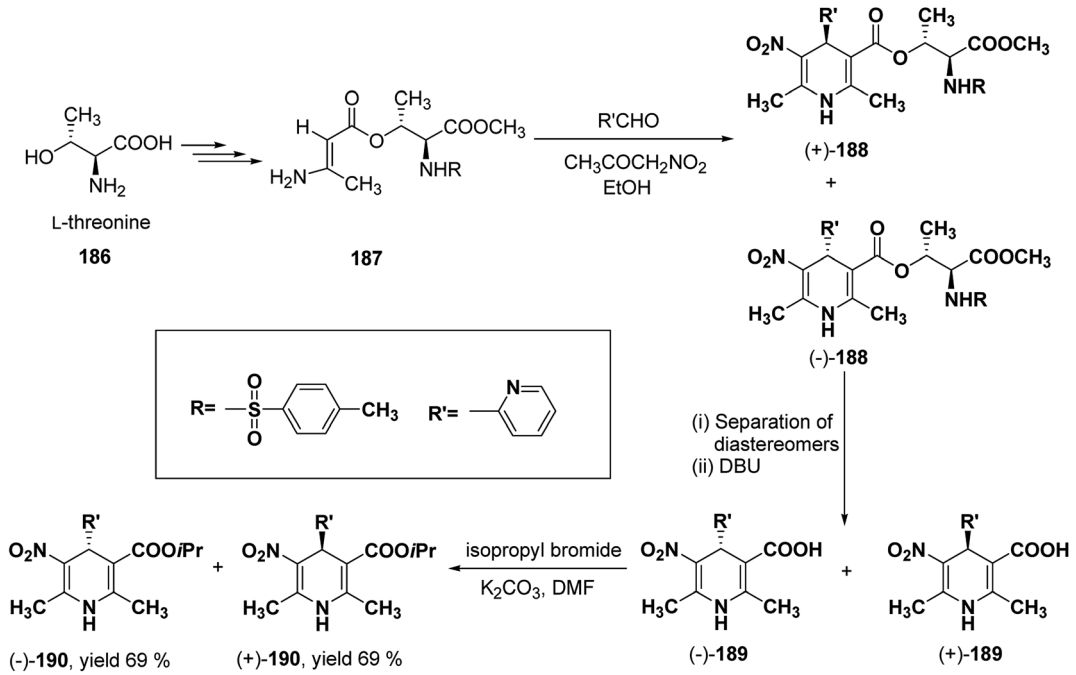
Scheme 66 Formation of enantiopure **185** using chiral auxiliary.

Yamamoto, *et al.*[84] described an efficient asymmetric synthesis of 1,4-dihydropyridine derivatives. The key step of this reaction was the stereoselective Michael addition using *t*-butyl ester of L-valine **207** as a chiral auxiliary to achieve good ee of **209** (>95%) and moderate yield (Scheme 71). With this method, (+)-4-(3-chlorophenyl)-6-dimethoxymethyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxylic acid cinnamyl ester (+)-**209** was obtained and was characterized as a promising N-type calcium channel blocker with improved selectivity over L-type compared to its (−)- and racemic isomers.

3. Utility of dihydropyridines in the synthesis of natural products

3.1. Utility of 1,2-dihydropyridines in the synthesis of natural products

Kutney, *et al.* have synthesized two pyridocarbazole alkaloids, olivacine **212** and guatambuine **213** by utilizing the tricarbonylchromium complex **211** of the suitable 1,2-dihydropyridine, which was synthesized from indole **210** (Scheme 72).[85]



Scheme 67 Resolution of racemic isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridinylpyridine-5-carboxylate using L-threonine.

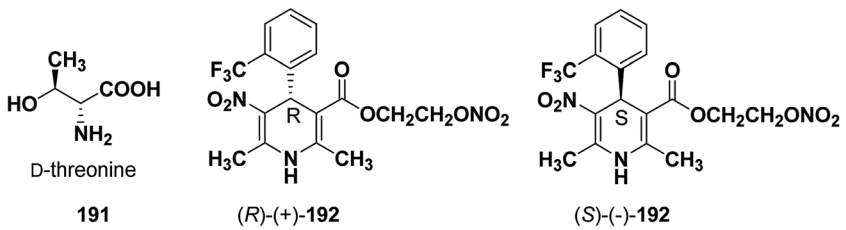


Fig. 2 Structures of D-threonine **191** and 2-nitrooxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate **192**.

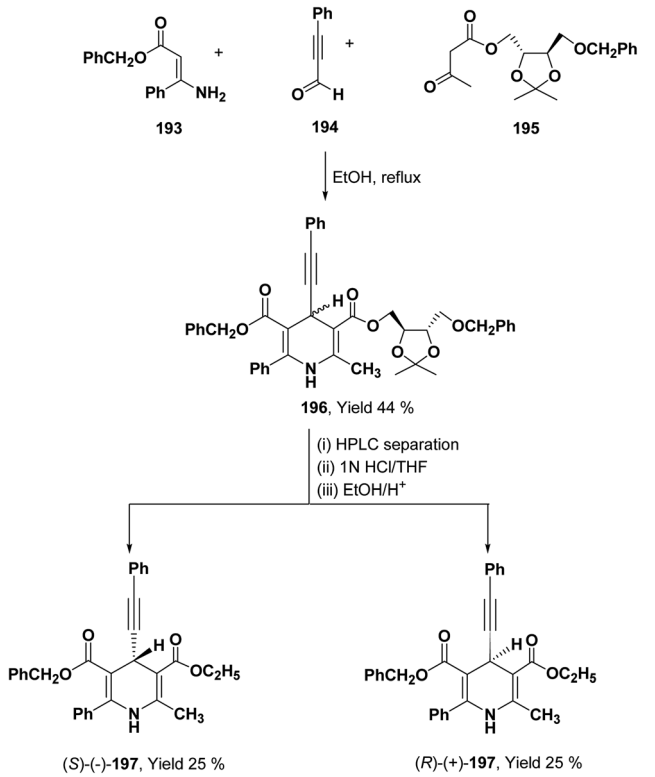
The synthesis of (±)-elaeokanine A **216** has been achieved in a regioselective manner from 1-methoxycarbonyl salt of 3-$(iPr)_3$ silyl pyridine **214** by Comins and Myoung.[86] The 1-methoxycarbonyl salt of 3-$(iPr)_3$ silyl pyridine was first converted into the 1,2-dihydropyridine derivative **215**, which was then converted into the (±)-elaeokanine A into several number of synthetic steps (Scheme 73).

2-Substituted-1,2-dihydropyridine and piperidines has been synthesized in regio- and stereoselective manner from unsubstituted pyridinium salt. The approach relies on stereoselective formation of (*E*)-isomer of *N*-pyridinium imidate **218** from amide **217** in which the nitrogen lone pair is oriented at the proper position to direct the addition of Grignard reagent **219** at the 2-position. This approach has been used for the synthesis of 2-substituted-1,2-dihydropyridine **220** and *R*-(−)-coniine **221** (Scheme 74).[87]

2,3-Disubstituted-1,2-dihydropyridines **224** and **225** have been synthesized from the 3-substituted pyridinium salts **222** and **223**, respectively (Scheme 75). This methodology has been applied for the synthesis of (−)-L-733 061 (**226**) and (−)-CP-99 994 (**227**), two members of a new class of highly potent, nonpeptide, substance P antagonists.[88]

A simple synthesis of the fused tetrahydro-imidazopyridine **229** was accomplished *via* selective addition of protected guanidine **228** to *N*-carbomethoxy-1,2-dihydropyridine **1** in the presence of bromine at room temperature. Base-mediated semicleavage of the aminal gave 4-substituted 2-aminoimidazole **230** (Scheme 76). With this new method, natural marine metabolite 3-amino-1-(2-aminoimidazol-4-yl)-prop-1-ene (marine C_6N_4 2-aminoimidazole alkaloids) **231** and its derivatives may be prepared starting from pyridine.[89]

The asymmetric synthesis of 2,6-disubstituted 3-piperidinols having a 2,3-*cis* and 2,6-*trans* relative stereochemistry has been accomplished from 2-substituted 1,2-dihydropyridine **233** (synthesized from unsubstituted pyridinium salt **232**) *via* a one-pot, highly diastereoselective epoxidation-nucleophilic addition with a heteroatom nucleophile or an organometallic reagent. This methodology was applied to the expedient asymmetric synthesis of (+)-julifloridine **234** in four steps (Scheme 77).[90]

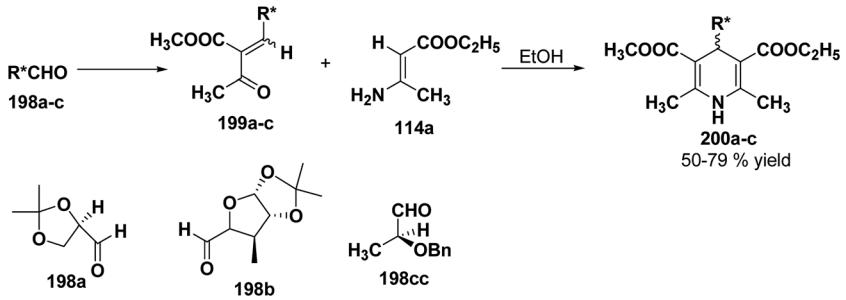


Scheme 68 Use of (4*R*,5*R*)-(−)-2,3-*O*-isopropylidine-D-threitol was used as chiral auxiliary in the separation of 1,4-DHP.

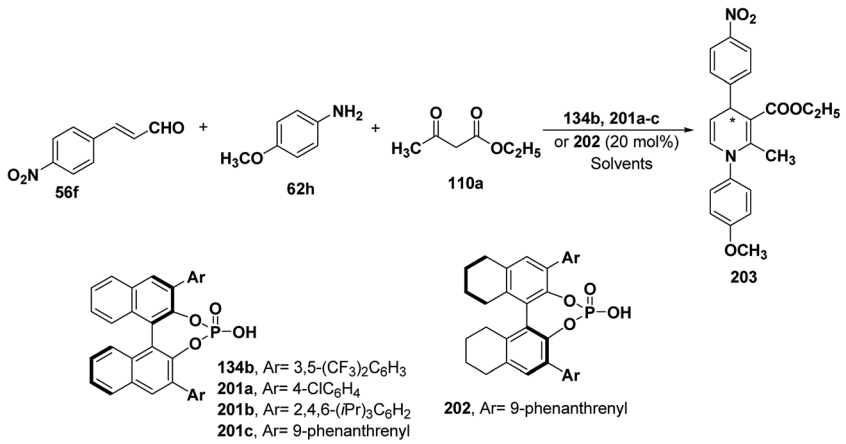
Table 16 Effect of phosphonic acids **134b**, **201a–c** and **202** and increase in the reaction temperature on the enantioselectivity of **203**

Catalyst	Solvent	Temperature (°C)	Yield (%)	ee (%)	Product
201a	$CHCl_3$	25	72	19	(*S*)-**203**
134b	$CHCl_3$	25	85	19	(*S*)-**203**
201b	$CHCl_3$	25	62	31	(*S*)-**203**
201c	$CHCl_3$	25	67	73	(*S*)-**203**
201c	$CHCl_3$	40	80	80	(*S*)-**203**
201c	$CHCl_3$	50	85	82	(*S*)-**203**
201c	PhCN	50	82	89	(*S*)-**203**
202	$CHCl_3$	25	69	64	(*R*)-**203**
202	$CHCl_3$	50	86	72	(*R*)-**203**
202	PhCN	50	83	90	(*R*)-**203**
202 (10 mol%)	PhCN	50	82	92	(*R*)-**203**

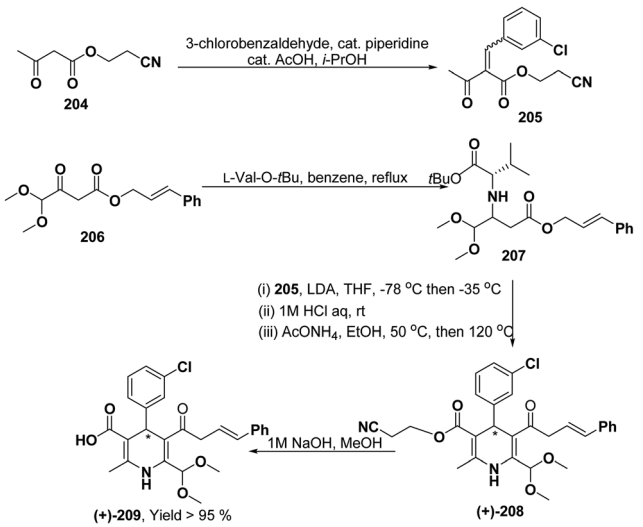
Marine metabolites pyrrole-2-aminoimidazole oroidine, hymenidin and clathrodine have been synthesized *via* one pot oxidative bromine mediated addition of 2-aminopyrimidine **237** to the *N*-acyl-1,2-dihydropyridine **236** to form compound **238**. The *N*-acyl-1,2-dihydropyridine was synthesized by the reaction of pyrrole-2-carbonyl chloride **235** with pyridine followed by the reduction using sodium borohydride. The compound **238** was treated with hydroxylamine hydrochloride and resulted into the formation of amide **239** and **240**. The treatment of amide **239** and **240** with trifluoroacetic acid in dichloromethane resulted



Scheme 69 Synthesis of chiral 1,4-DHPs **200a–c** using chiral aldehydes.



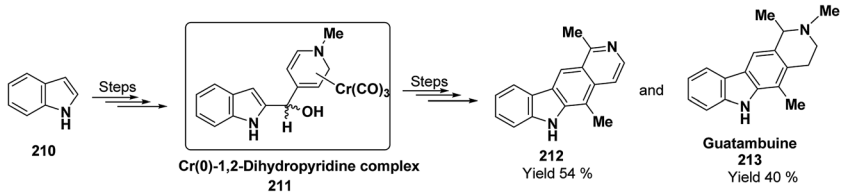
Scheme 70 Chiral phosphonic acids catalyzed synthesis of 1,4-DHP **203**.



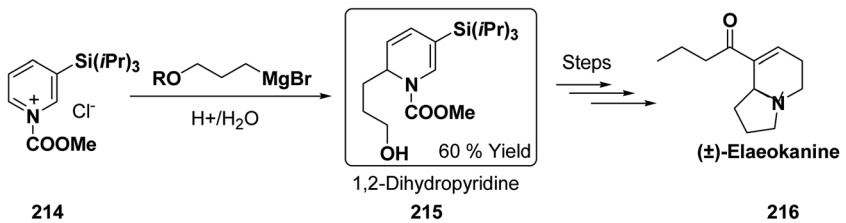
Scheme 71 Stereoselective synthesis of 1,4-dihydropyridine **209**.

into the formation of oroidine **241** and hymenidine **242** or clathrodine **243** in good yields (Scheme 78).[91]

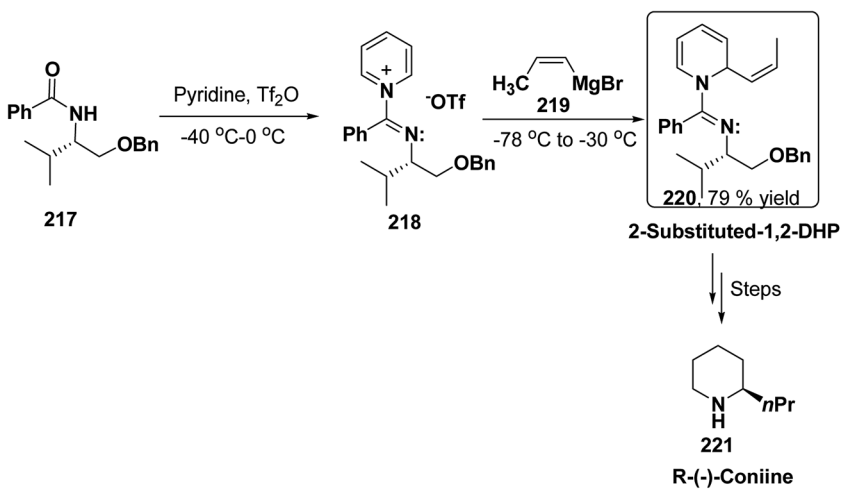
Stereoselective synthesis of L-picolic acid and (2*S*,3*S*)-3-hydroxypipecolic acid were achieved from a chiral 1,2-dihydropyridine intermediate **244**. L-Picolic acid **248** has been obtained *via* reduction of **244** to **245**, removal of chiral auxiliary yields **246**, oxidation yields **247** and basic hydrolysis of **247** yields L-picolic acid **248**. (2*S*,3*S*)-3-Hydroxypipecolic acid **253** was obtained in five steps (i) tandem hetero Diels–Alder reaction of **244** with oxygen to yield **249**, (ii) alane reduction to yield **250**, (iii) *N* and *O*-protection to afford **251**, (iv) reduction of double bond to yield **252**, and (v) sharpless oxidation to yield **253** (Scheme 79). L-Picolic acid is a naturally occurring non-proteinogenic α-amino acid and many biological alkaloids contain this moiety as a key structural unit or are derived from it. (2*S*,3*S*)-3-Hydroxypipecolic acid is found in febrifugine a potent antimalarial agent. Both L-picolic acid and (2*S*,3*S*)-3-hydroxypipecolic acid are conformationally constrained amino acids relevant to the study of peptide structure and drug design.[92]



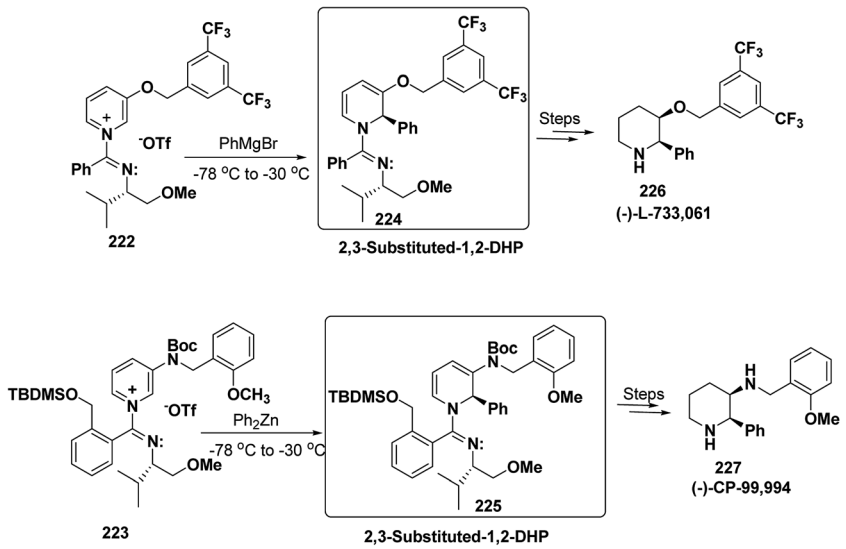
Scheme 72 Synthesis of pyridocarbazole alkaloids.



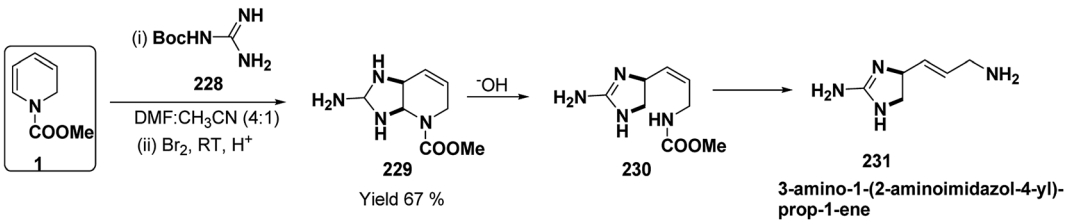
Scheme 73 Synthesis of (±)-elaeokanine A using 1,2-dihydropyridine derivative.



Scheme 74 Synthesis of *R*-(−)-coniine.



Scheme 75 Synthesis of 2,3-disubstituted-1,2-DHP: synthesis of (–)-L-733, 061 and (–)-CP-99, 994.



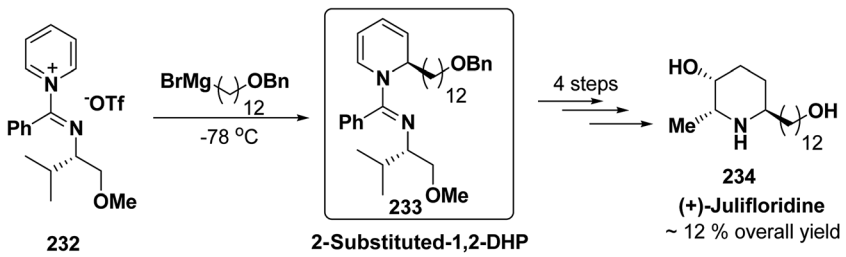
Scheme 76 Synthesis of marine C_6N_4 2-aminoimidazole alkaloids.

3.2. Utility of 1,4-dihydropyridine in the synthesis of natural products

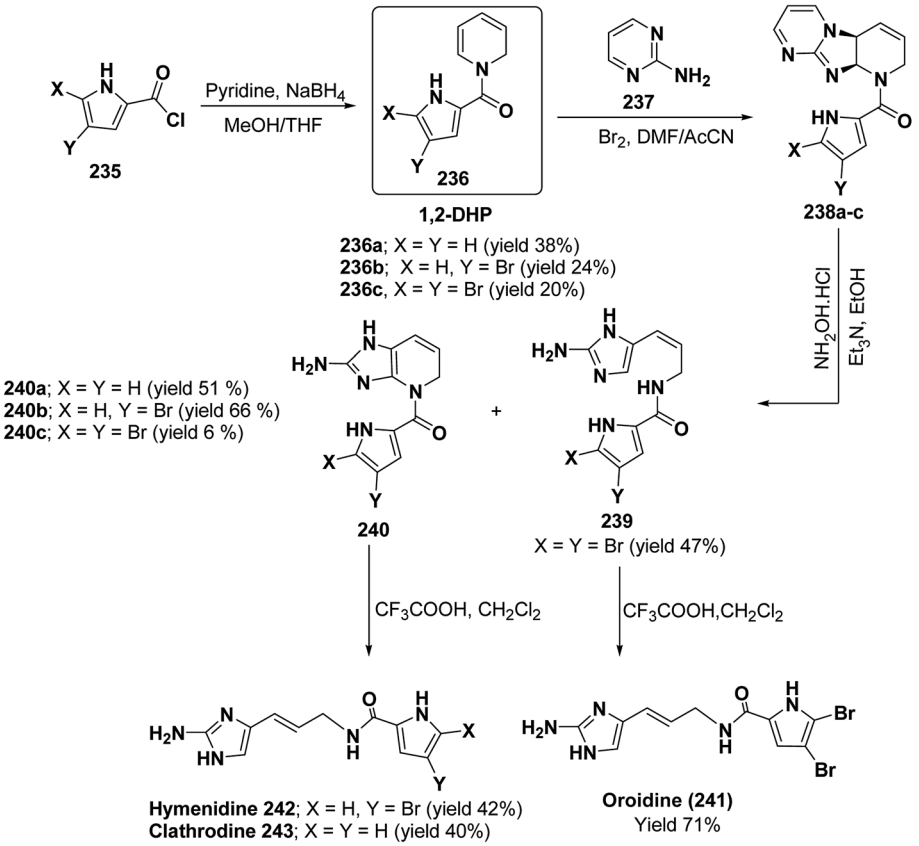
Yohimbines are pentacyclic indole alkaloids containing five chiral centres. A convergent six steps synthesis of (±)-pseudo-yohimbines has been accomplished from methyl-β-(β-pyridyl) acrylate **254** (Scheme 80). Methyl-β-(β-pyridyl)acrylate **254** was converted into pyridinium salt **256** using tryptophyl bromide **255**, which was then converted into 1,4-dihydropyridine derivative **257**. The 1,4-dihydropyridine **257** was converted into (±)-pseudo-yohimbines **258** in several steps.[93]

Indoloquinolizine alkaloid, deplancheine has been synthesized starting from pyridinium salt **256**. The pyridinium salt **256** was reduced to 1,4-dihydropyridine derivative **259** using sodium dithionate. The treatment of 1,4-dihydropyridine with HCl·MeOH resulted into the formation of cyclised product **260**. The chloride salt **261** was synthesized using $HCl \cdot H_2O$ from **260**, which was reduced selectively to yield (±)-deplancheine **262** in good yield (Scheme 81).[94]

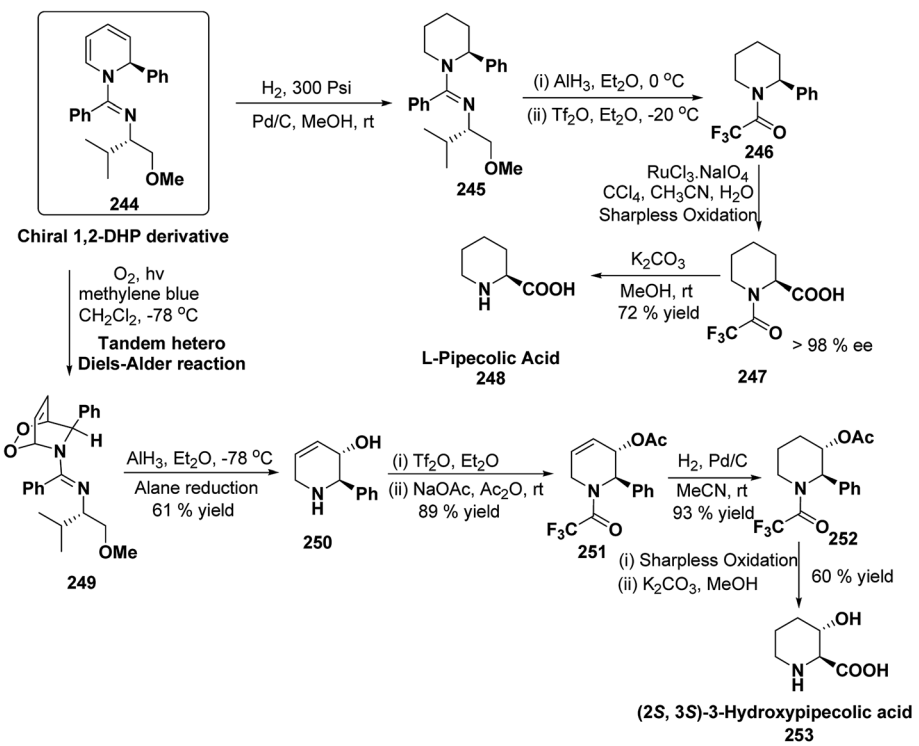
Vinoxine is amino indole alkaloid and its first total synthesis is based on the intramolecular cyclisation of suitably substituted 1,4-dihydropyridine–indole conjugate **265**. The dihydripyridine–indole conjugate was synthesized by the reaction between methyl 2-(1*H*-indol-1-yl)acetate **263** and pyridinium salt **264** in the presence of LDA in THF. The intramolecular cyclization reaction on compound **265** was



Scheme 77 Synthesis of (+)-julifloridine from 1,2-dihydropyridine.



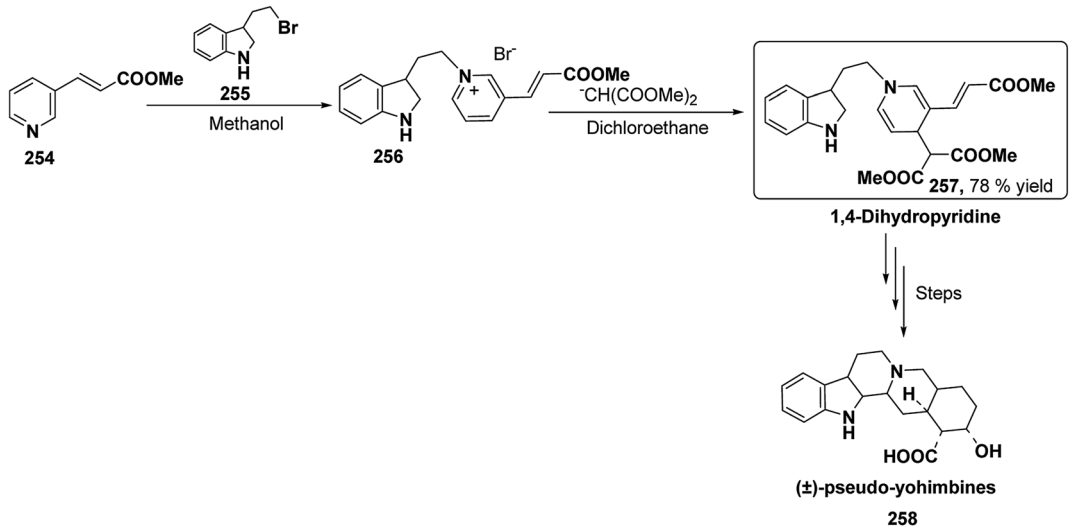
Scheme 78 Synthesis of oroidine, hymenidine and clathrodine using 1,2-dihydropyridine as an intermediate.



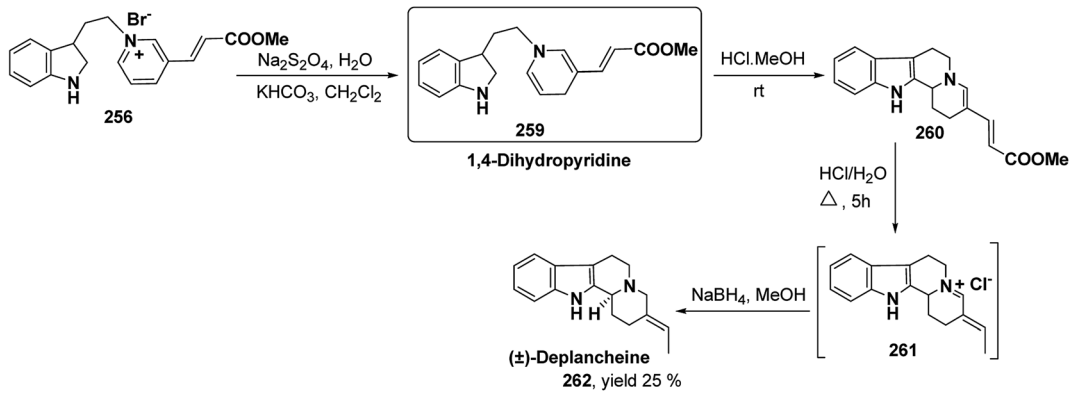
Scheme 79 Synthesis of L-picolic acid and (2*S*,3*S*)-3-hydroxypipecolic acid.

carried out using $C_6H_6 \cdot HCl$ to afford **266.** The chloride salt **267** of **266** was synthesized using 4 N HCl followed by the esterification and selective reduction afford the vinoxine **268b** in good yield (Scheme 82).[95]

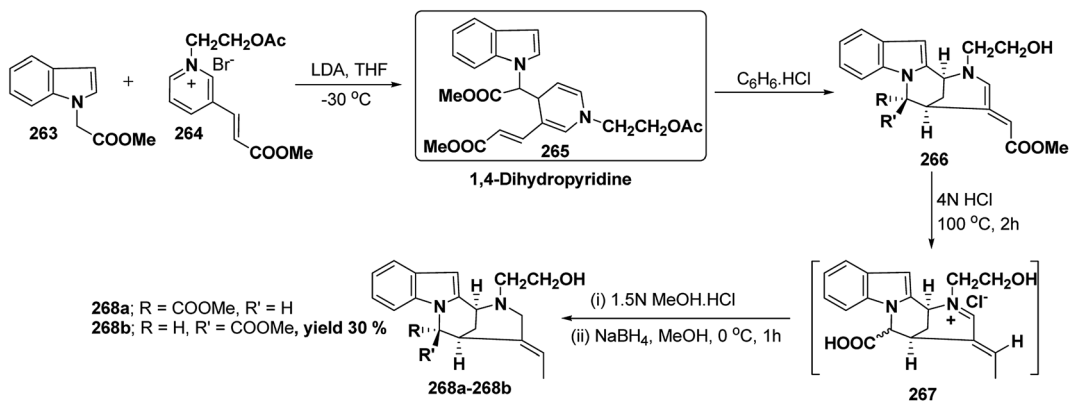
Bosch, *et al.*[96] has reported the synthesis of vinoxine analogue bearing C-16 methoxycarbonyl substituent, 19,20-dihydro-16-epivinoxine **275.** The synthesis of 19,20-dihydro-16-epivinoxine **275** has been achieved from 3-ethyl-4-pyridine



Scheme 80 Synthesis of (±)-pseudo-yohimbines.



Scheme 81 Synthesis of (±)-deplancheine.

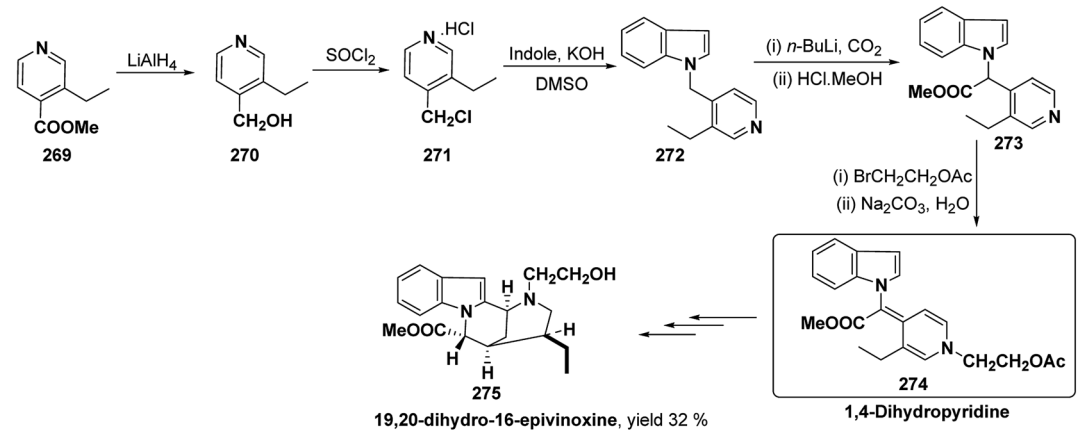


Scheme 82 Synthesis of vinoxine **268b**.

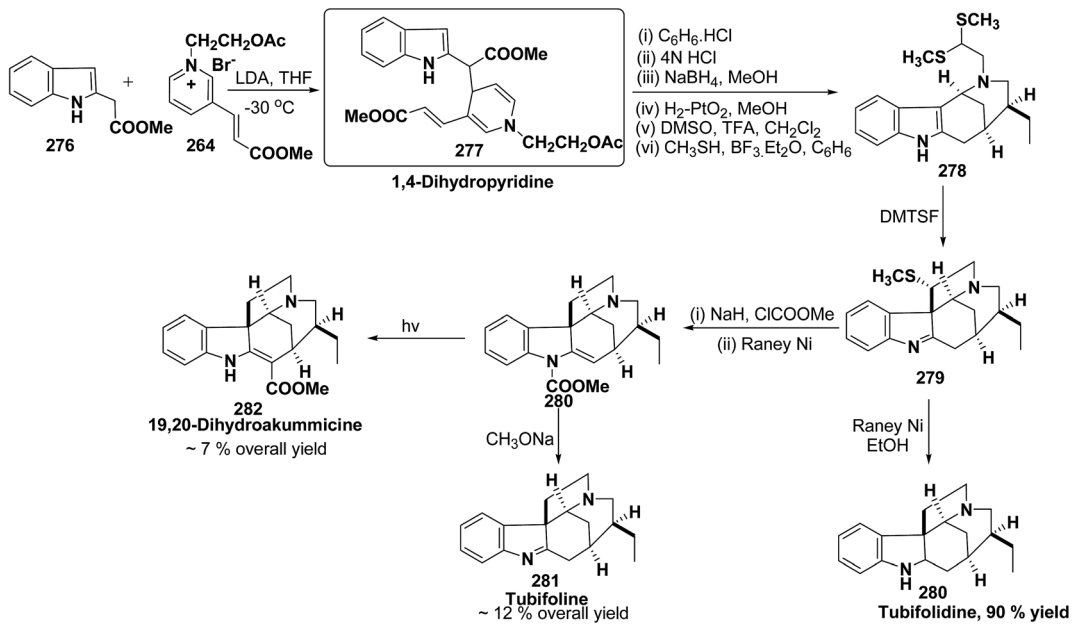
carboxylate **269** *via* the synthesis of 1,4-dihydropyridine analogue **274** (Scheme 83).

An efficient route for the synthesis of tetracyclic ABCD ring substructures of *Strychnos* alkaloids has been carried out by synthesizing the 1,4-dihydropyridine **277** derivative from indole-2-carboxylate **276** and **264**. The compound 1,4-dihydropyridine **277** was converted into disulfane analogue **278** in six steps, which was converted into pentacyclic compound **279** by generating the carbanion of compound **278** using DMTSF (dimethyl(methylthio)sulfonium fluoroborate). The resulting pentacyclic compound has been converted into tubifolidine **280** by treating **279** with RANEY® Ni. Tubifoline **281** and 19,20-dihydroakummicine **282** were synthesized by first *N*-protection with methyl carboxylate and desulferisation to yield **281** followed by treatment with sodium methoxide and photolysis, respectively (Scheme 84).[97]

Ervitsine **289** is a minor 2-acylindole alkaloid isolated in 1977 from *Pandaka boiteau*. The first total synthesis of ervitsine **289** through a straightforward, biomimetic sequence involving only three separate synthetic steps (Scheme 85) has been reported by Bennasar, *et al.*[98] The key intermediate was the iminium cation **286.** The iminium cation **286** was synthesized from 1,4-dihydropyridine derivative **285** using $Me_2N^+{=}CH_2I^-$. The 1,4-dihydropyridine derivative **285** was synthesized using 2-acetyl indole **283** and pyridinium salt **284.** The iminium cation **286** would undergo regioselective cyclization to the bridged tetracyclic system **287**, which was converted into *N*-methyl ervitsine **289a** and ervitsine **289b** into two synthetic steps first by treatment with *m*CPBA to yield **288** followed by borohydride reduction. A short four-step synthesis of *N*-methyl ervitsine involving the nucleophilic addition of acetyl indole to pyridinium salt, with subsequent C_6H_5SeBr-promoted cyclization



Scheme 83 Synthesis of 19,20-dihydro-16-epivinoxine **275**.



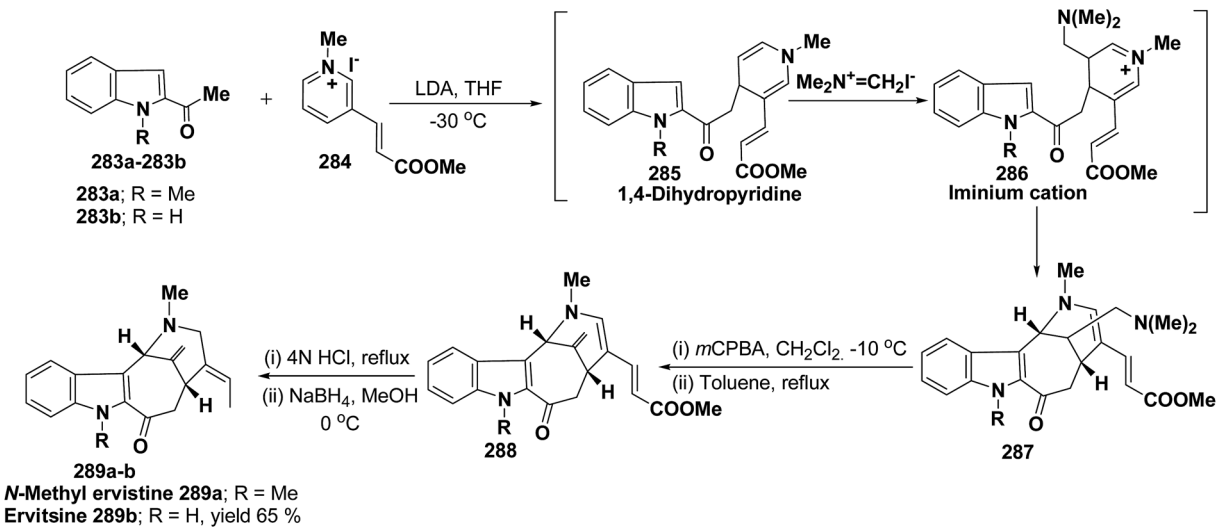
Scheme 84 Synthesis of tubifolidine **280**, tubifoline **281** and 19,20-dihydroakummicine **282**.

of 1,4-dihydropyridine instead of $Me_2N^+{=}CH_2I^-$ promoted cyclization has been further reported by Bennasar, *et al.*[99]

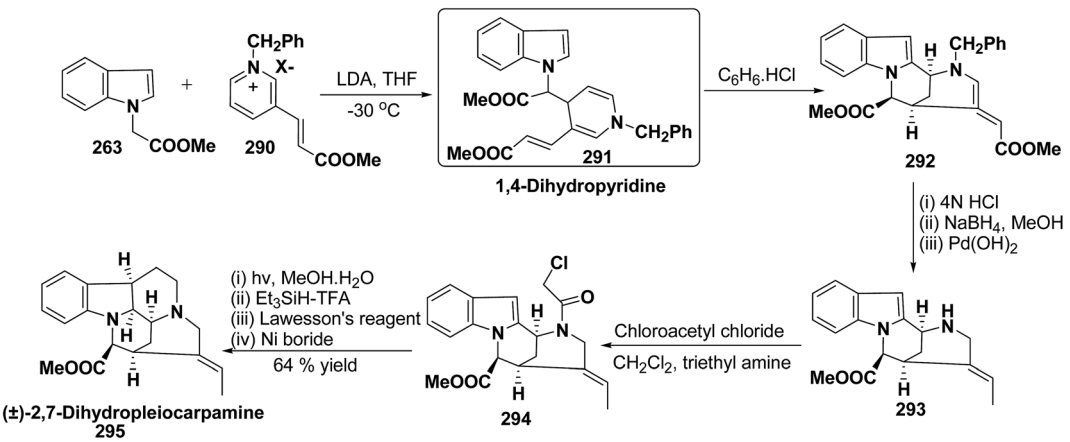
The first total synthesis of (±)-2,7-dihydropleiocarpamine **295** has been reported by Bennasar, *et al.*[100] *via* the synthesis of 1,4-dihydropyridine **291** as an intermediate (Scheme 86). The 1,4-dihydropyridine **291** was synthesized from nucleophilic addition of **263** on pyridinium salt **290** in the presence of LDA in THF. The key step is the photocyclization of the tetracyclic chloroacetamide **294** to give the required six membered ring *via* closure of C-6/C-7 bond formed by diradical coupling, which was not achieved by electrophilic cyclization.

The ervatamine alkaloids (19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**) constitute a group of 2-acylindole alkaloids. Bennasar, *et al.*[101] has reported the total synthesis of 19,20-dehydroervatamine and 20-epiervatamine, whereas ervatamine was synthesized from 19,20-dehydroervatamine *via* catalytic hydrogenation. The intermediate 1,4-dihydropyridine **299** formed *via* the nucleophilic attack of *N*-benzyl-2-acetyl indole **296** to the γ-position of the pyridinium salt **297**. The 1,4-dihydropyridine **298** was functionalized to give 3,5-diacyl-1,4-dihydropyridine **299**, which was reduced to tetrahydropyridine **300**, and was further converted to *cis*-fused pentasubstituted piperidines (19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**) in number of steps by using suitable reagents (Scheme 87).

Bennasar, *et al.*[102] has reported a general route for the synthesis of tetracyclic ring system of silicine–methuenine alkaloids **311** and **312**. The key step in the synthesis was the selective reduction of the intermediate **299** by using PtO_2 followed by debenzylation to afford **301**, which on cyclisation using trimethylsilyl polyphosphate PPSE yielded **310** (Scheme 88). The compound **310** was further converted into tetracyclic ring system of silicine–methuenine alkaloids **311** and **312** in number of steps. The 1,4-dihydropyridine intermediate **299** was synthesized according to the literature procedure reported by Bennasar, *et al.*[101]

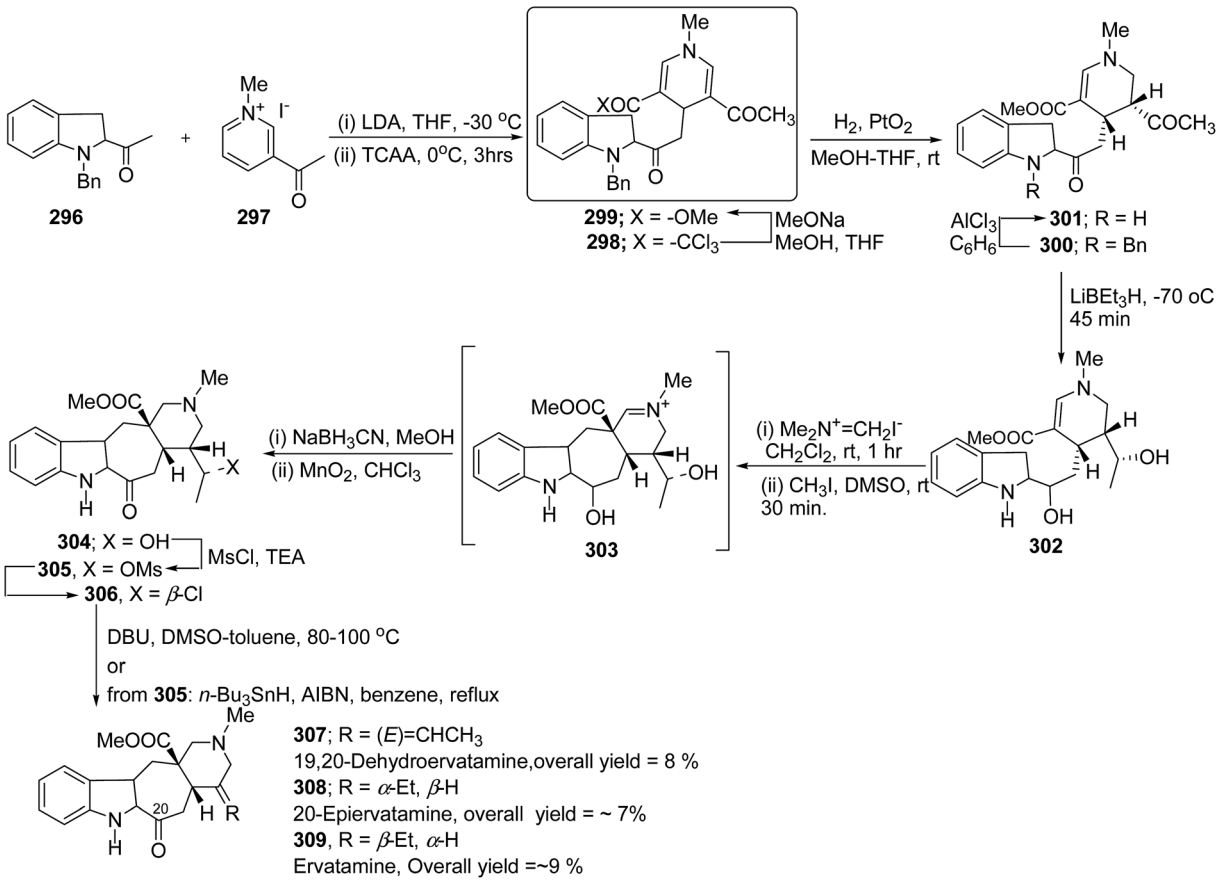


Scheme 85 Synthesis of *N*-methyl ervitsine **289a** and ervitsine **289b**.

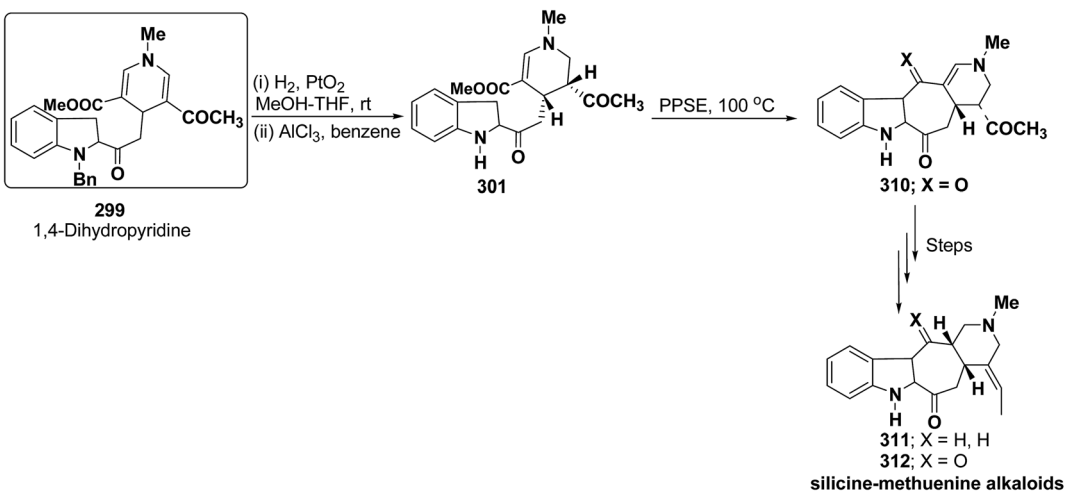


Scheme 86 Synthesis of (±)-2,7-dihydropleiocarpamine **295**.

Bennasar, *et al.*[103] has reported a general route for the synthesis of 6-oxo-16-episilicine **320** (a silicine–methuenine alkaloid), involving the nucleophilic addition of an acetylindole enolate **296** to the pyridinium salt **284** to yield 1,4-dihydropyridine **313** as an intermediate. The 1,4-dihydropyridine **313** was functionalized to give 3,5-diacyl-1,4-dihydropyridine **314**, which was reduced to tetrahydropyridine **315**, and was subjected to PPSE-induced cyclisation to yield **316**. Hydrolysis of compound **316** using $MeOH \cdot H_2O$, HCl followed by decarboxylation using 2,2′-dithiobis-(pyridine-*N*-oxide) yielded **317**, which on *N*-debenzylation yielded **318**. The debenzylated compound **318** on reduction using $NaBH_3CN$



Scheme 87 Synthesis of 19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**.

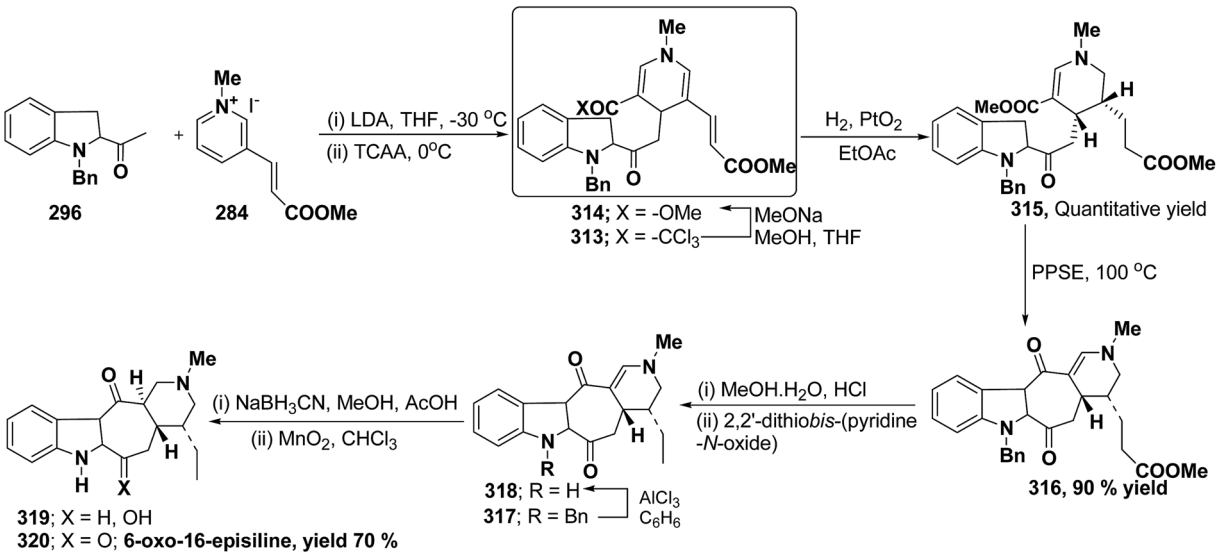


Scheme 88 Synthesis of silicine–methuenine alkaloids **311** and **312**.

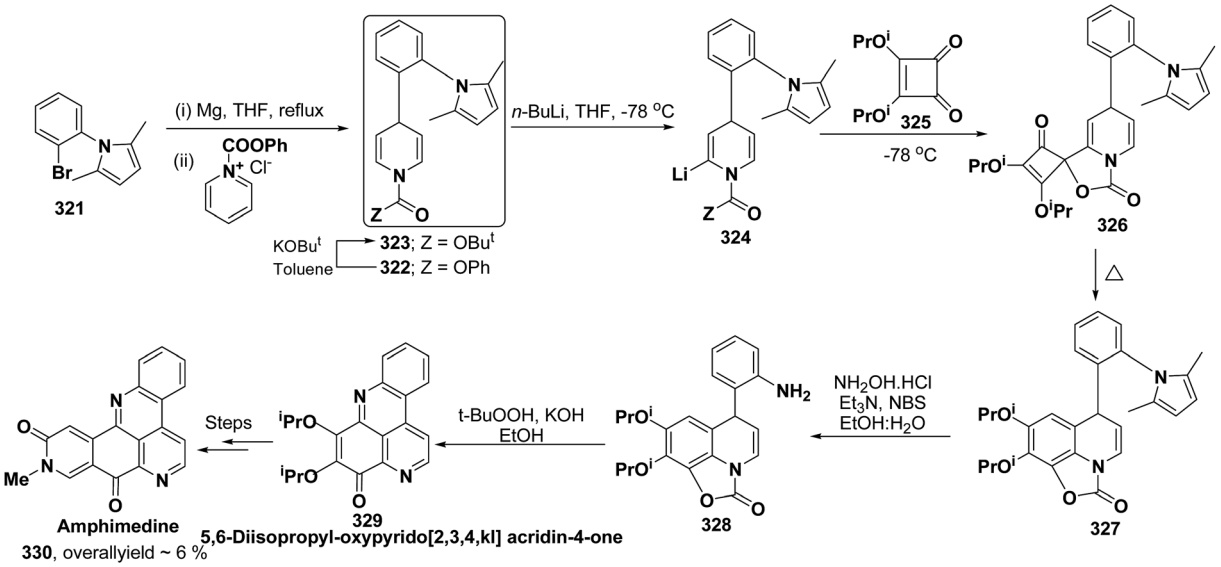
yields **319**, which on oxidation with MnO_2 yield 6-oxo-16-episilicine **320** (Scheme 89).

Pyridoacridines are a family of alkaloids based on 1*H*-pyrido[4,3,2,*mn*]acridine skeleton. The synthesis of pyridoacridine ring **329** of alkaloid amphimedine **330** was achieved by condensing ^{t}butyl-protected 2-lithio-1,4-DHP **324** with 3,4-disubstituted cyclobutanediones **325** to yield **326** followed by thermolysis to yield **327**. The conversion of **327** in aniline derivative **328** was achieved using hydroxylamine hydrochloride and oxidation with ^{t}-BuOOH in presence of KOH yielded dihydroquinoline hydroquinine ring system **329**. The Boc-protected 2-lithio-1,4-DHP was synthesized by the reaction between the Grignard reagent of *N*-(2-bromophenyl)-2,5-dimethylpyrrole **321** with *N*-carboxyphenylpyridinium chloride (Scheme 90).[104]

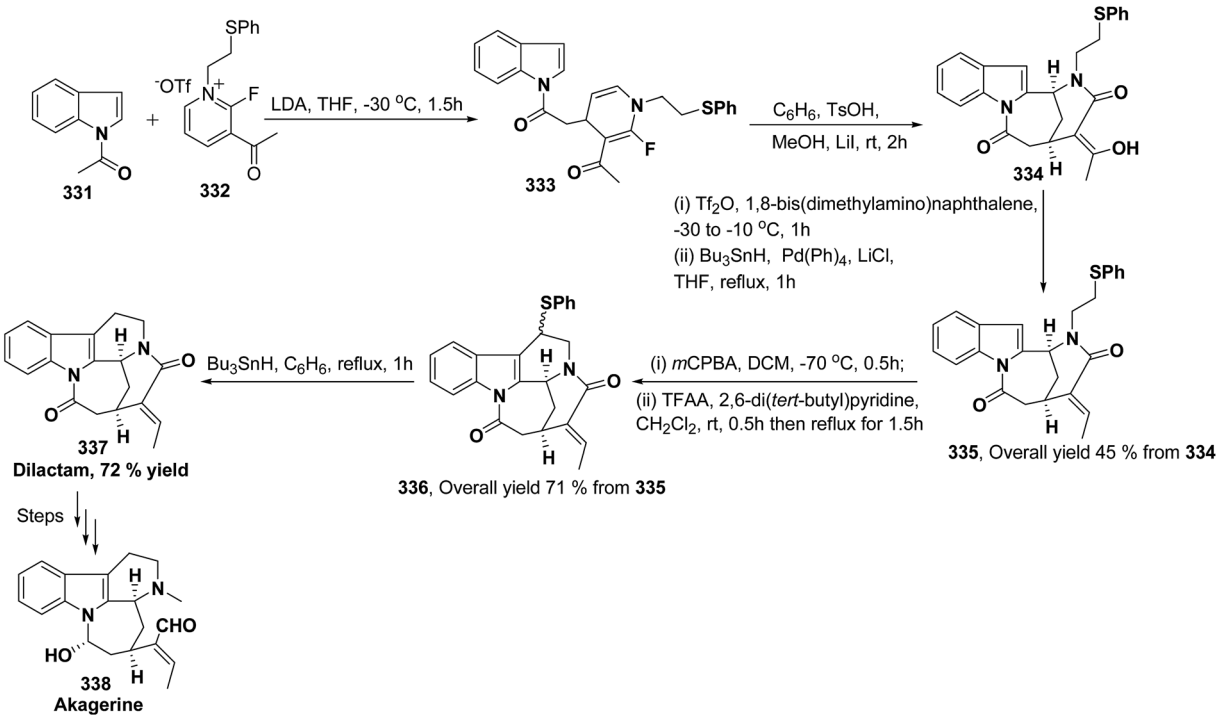
Akagerine **338** is a tetracyclic indole alkaloid. A formal stereoselective synthesis of akagerine **338** had been reported *via* pentacyclic dilactam **337**.[105] The intermediate dilactam **337** was synthesized starting from 1,4-dihydropyridine **333**, which was synthesized from the nucleophilic attack of the *N*-acetyl indole **331** on pyridinium salt **332**. Compound **333** was converted into **334** using sulfonic acid. The hydroxyl group of the compound **334** was removed *via* first triflation followed by reduction to afford compound **335**. The key step is the formation of piperidine ring of compound **336**, which was accomplished by cyclization of thionium ion generated by Pummerer rearrangement using TFAA in presence of 2,6-di(*t*-butyl)pyridine. Dilactam **337** was obtained by the treatment of compound **336** with tributyltin hydride in benzene (Scheme 91).[106]



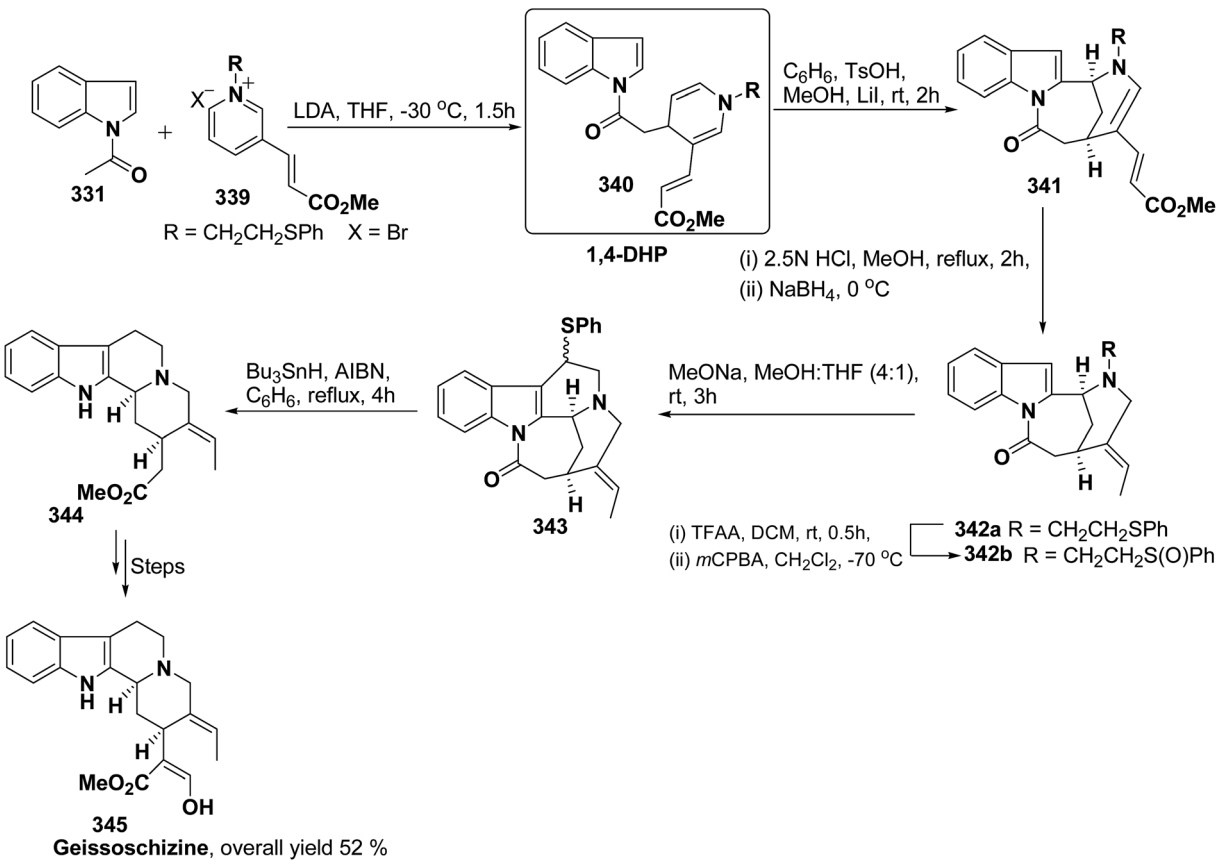
Scheme 89 Synthesis of 6-oxo-16-episilicine **320**.



Scheme 90 Synthesis of 5,6-diisopropyl-oxypyrido[2,3,4,*kl*]acridin-4-one **330**.



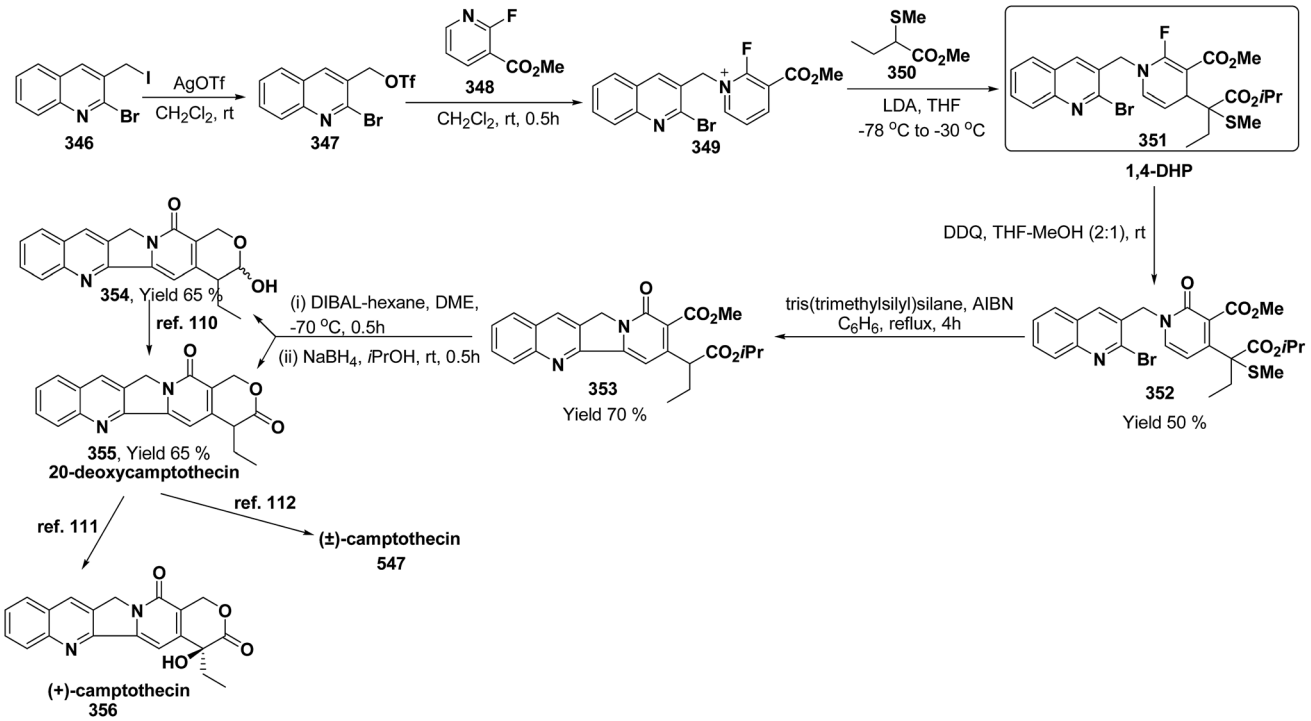
Scheme 91 Synthesis of dilactam **337**.



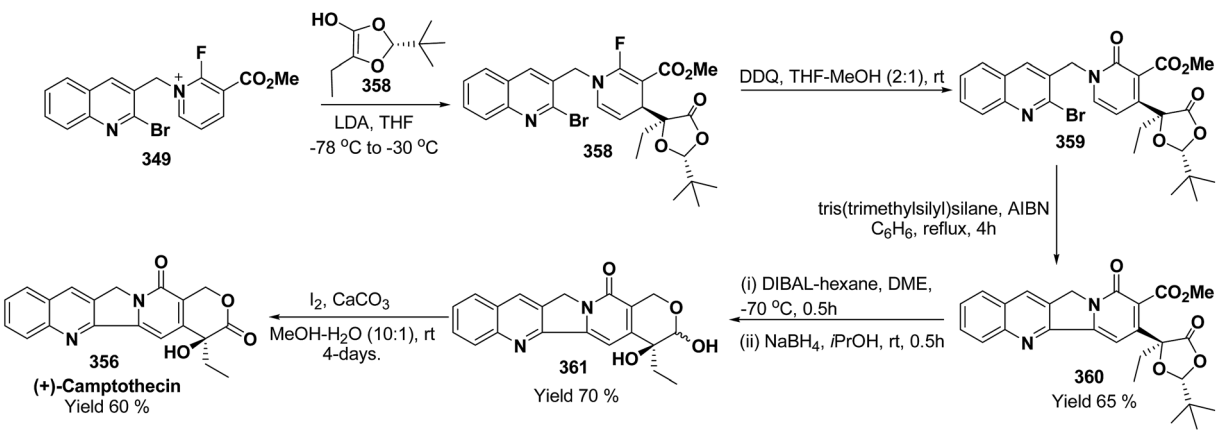
Scheme 92 Synthesis of geissoschizine **345**.

Formal synthesis of (±)-geissoschizine had been carried out using 1,4-dihydropyridine derivative **340**.[107] The 1,4-dihydropyridine derivative **340** was synthesized from nucleophilic attack of the *N*-acetyl indole **331** on pyridinium salt **339**. Compound **340** was converted into **341** using sulfonic acid in benzene, which on treatment with HCl followed by borohydride reduction yielded **342a**. Compound **342a** was first converted into sulfone **342b**, followed by treatment with sodium methoxide resulted into the formation of compound **343**, which on desulferisation using tributyltin hydride and AlBn give compound **344** (Scheme 92). Compound **344** has been converted into geissoschizine **345** by Yamada, *et al.*[108]

A concise total synthesis of (±)-camptothecin and natural (+)-camptothecin has been reported starting from 2-fluoro-1,4-dihydropyridine adduct **351**.[109] The 1,4-DHP adduct **351** was achieved from compound **346** in three steps. 2-Fluoro-1,4-dihydropyridine adduct **351** on oxidation with DDQ resulted into the formation of compound **352**, which on treatment with hydrogen atom donor tris(trimethylsilyl)silane-AIBN give compound **353** (Scheme 93). Formation of the pyran ring in compounds **354** and 20-dioxycamptothecin **355** takes place by the treatment of compound **353** with DIBAL and borohydride reduction. 20-Dioxycamptothecin **355** was further used for the synthesis of (±)-camptothecin and natural (+)-camptothecin *via* the literature procedure.[110]



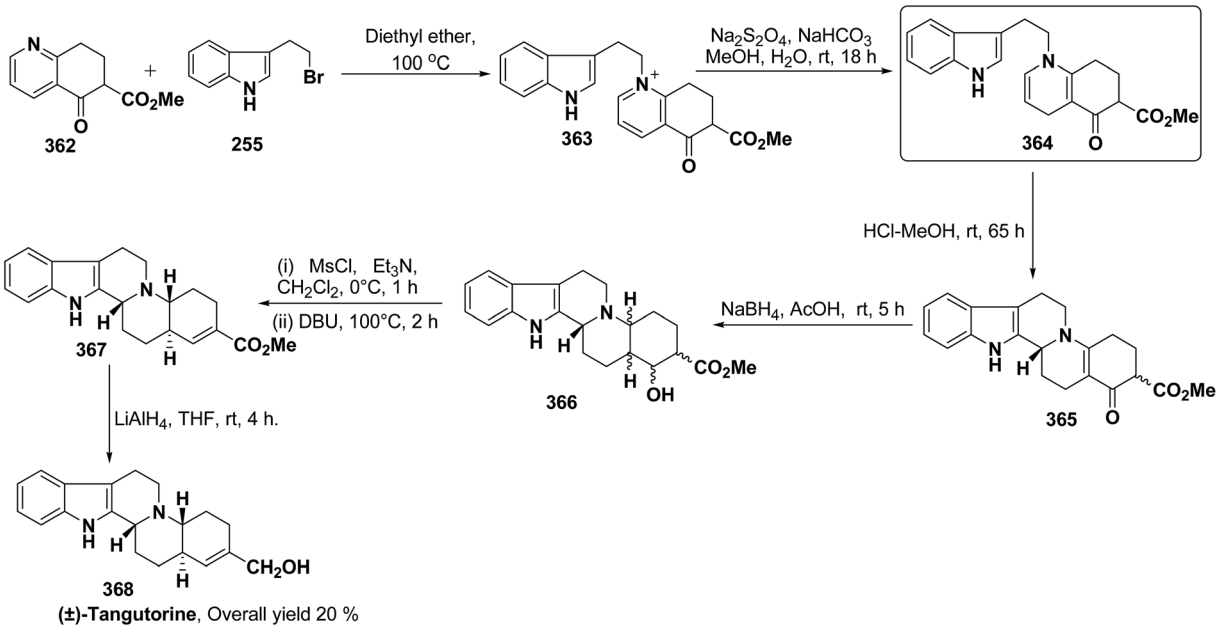
Scheme 93 Synthesis of (±)-camptothecin and natural (+)-camptothecin.



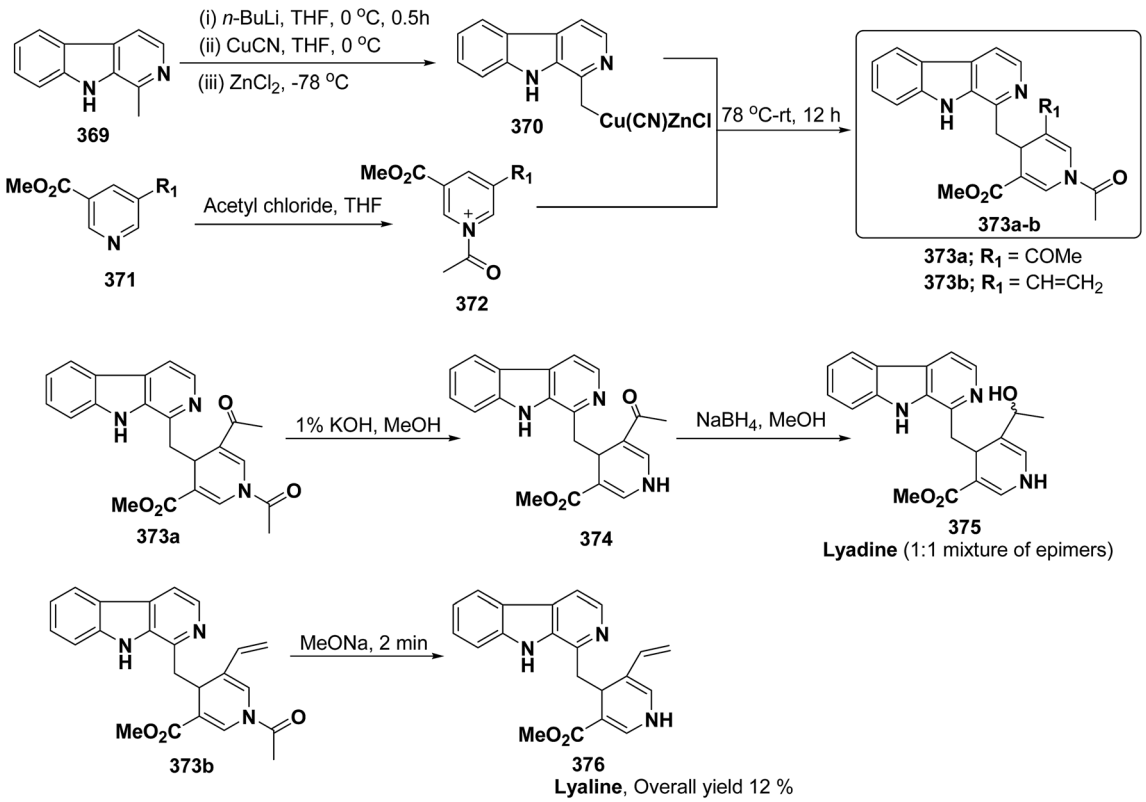
Scheme 94 Synthesis of (+)-camptothecin **356**.

The synthesis of natural (+)-camptothecin **356** has been reported by the nucleophilic addition of a chiral auxiliary **357** to the pyridinium salt **349** (Scheme 94). The remaining synthetic steps are similar as used in Scheme 93.[109]

Putkonen, *et al.*[111] has reported the total synthesis of (±)-tangutorine **368** and modified the first synthetic procedure reported by Berner, *et al.*[112] For the synthesis of (±)-tangutorine **368**, desired quinoline derivative **362** was reacted with



Scheme 95 Synthesis of (±)-tangutorine **368**.



Scheme 96 Synthesis of lyadine **375** and lyaline **376**.

tryptophyl bromide **255** to afford pyridinium salt **363**. Since the total yield of the tangutorine skeleton was relatively low due to the different stereoisomers formed in the Fry reaction.[112] The total synthesis of indole alkaloid (±)-tangutorine **368** has been carried out using dithionite reduction of pyridinium salt **363** to afford the 1,4-dihydropyridine intermediate **365**. Cyclization of compound **364** in HCl/MeOH to compound **365** and reduction with sodium borohydride in glacial acetic acid for overnight yielded a mixture of isomers of compound **366**. (±)-Tangutorine **368** was afforded after dehydration of compound **366** and finally reduction of the ester group in compound **367** (Scheme 95).

The harman-1,4-dihydropyridines **373a–b**, which constitutes the original proposed structures for the indole alkaloid lyadine **375** and lyaline **376** have been synthesized by Bennasar, *et al.*[113] (Scheme 96). The harman-1,4-dihydropyridines **373a–b** were synthesized starting from harman **369** and pyridine **371**. The nucleophilic addition reaction of Grignard reagent of harman **370** with pyridinium salt **372** prepared from pyridine **371**. The harman-1,4-dihydropyridine **373a** was converted into lyadine **375** in two synthetic steps first by *N*-deacetylation followed by borohydride reduction, whereas lyaline **376** was obtained from the *N*-deacetylation of compound **373b**.

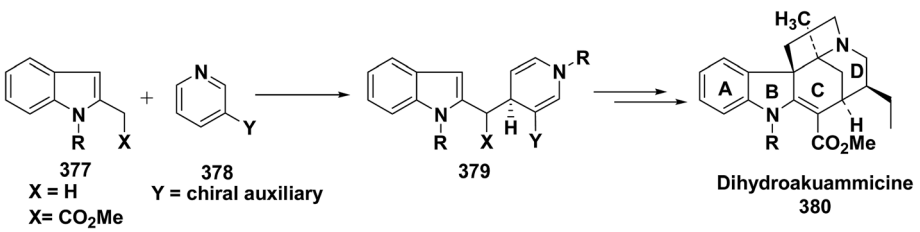
Amat, *et al.*[114] has proposed a model for the synthesis of *Strychnos* alkaloid *e.g.* dihydroakuammicine **380** could be obtained starting from a suitable functionalized enantiopure 2-(1,4-dihydro-4-pyridylmethyl)indole **377** (Scheme 97).

The nucleophilic addition of indole acetic ester **381** and *N*-alkyl pyridinium salt **382a–b** followed by acid cyclization gave a mixture of expected tetracyclic compound **383a–b** along with regioisomer **384a–b** (Scheme 98). It is probably the bulkiness of chiral auxiliary hinders the approach of the nucleophile to the adjacent 4-position of pyridine ring.

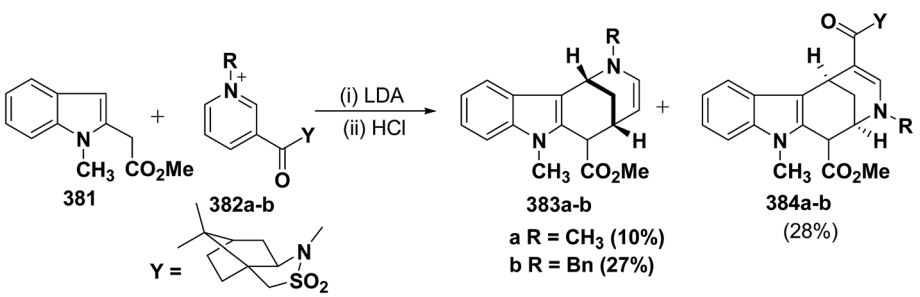
The strategy for the synthesis of tetracyclic precursors ABCD of dihydroakuammicine using chiral auxiliary suffers two major drawbacks (i) low facial stereoselectivity due to inefficient coordination of nucleophile with the chiral auxiliary and (ii) low regioselectivity due to bulkiness of chiral auxiliary.[114]

4. Medicinal importance of dihydropyridines

The first synthesis of 1,4-dihydropyridine (1,4-DHP) nucleus was reported in 1881 by A. Hantzsch.[26a] It took 80 years to test these compounds for their biological activity, and finally Bossert and Vater at Bayer AG got the Hantzsch type 1,4-DHP possessing outstanding coronary vasodilator activity.[115] Nifedipine, the 2-nitrophenyl derivative (Table 17) was then introduced for the treatment of coronary diseases.[116] Due to the resemblance with NADH and also interesting biological activities, subsequently several other 1,4-DHPs (Table 17) have been introduced for clinical use as hypertensive agents that have a worldwide market of several billion dollars.[117] Amlodipine (Norvasc), with sales of more than $ 5 billion in recent years is among the top-five best selling drugs. DHP's have also been explored as anti-inflammatory,[118] anti-tumor,[119] anti-tubercular,[120] anti-convulsant activity[121] *etc.* 1,4-DHP drugs can be divided into three generations depending on their pharmacologic and pharmacokinetic profiles.[122] Because of the short duration and rapid onset of vasodilator action, nifedipine activated sympathetic tone.[123] Therefore, in the quest of better therapeutic standard, the first-generation drug, nifedipine has been extensively modified. The second generation drugs exert less sympathetic reflex by designing slow-release formulations of preparations of the short-acting drugs.[124]



Scheme 97 Proposed procedure for the synthesis of dihydroakuammicine **380**.



Scheme 98 Synthesis of tetracyclic precursors **383** and **384** of dihydroakuammicine.

Table 17 Commercially important 1,4-DHP's

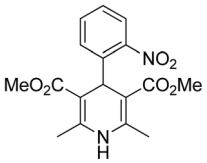
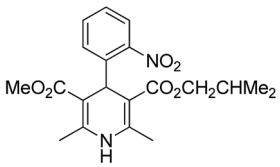
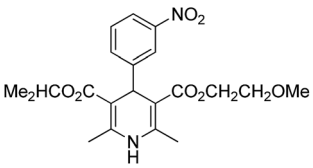
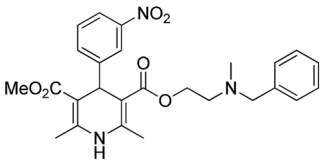
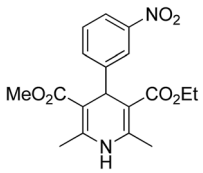
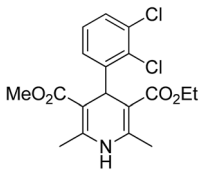
DHP Drug	Brand name	X	R^1	R^2	Y
1st generation					
 **Nifedipine**	Procardia, Adalat	2-NO_2	–Me	–Me	Me
2nd generation					
 **Nisoldipine**	Baymycard, Sular, Syscor	2-NO_2	–Me	$-CH_2CHMe_2$	Me
 **Nimodipine**	Nimotop	3-NO_2	$-CHMe_2$	$-CH_2CH_2OMe$	Me
 **Nicardipine**	Cardene, Carden SR	3-NO_2	–Me	$-CH_2CH_2N(Me)CH_2Ph$	Me
 **Nitrendipine**	Cardif, Nitrepin, Baylotensin	3-NO_2	–Me	–Et	Me
 **Felodipine**	Plendil	2,3-Di-Cl	–Me	–Et	Me

Table 17 (*Contd.*)

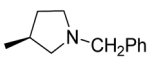
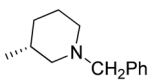
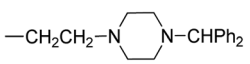
DHP Drug	Brand name	X	R^1	R^2	Y
Isradipine	DynaCirc, DynaCirc CR		–Me	$-CHMe_2$	Me
3rd generation					
Pranidipine	Acalas	3-NO_2	–Me	$-CH_2CH{=}CHPh$	Me
Lercanidipine	Zanidip	3-NO_2	–Me	$-C(Me)_2CH_2N(Me)CH_2CH_2CHPh_2$	Me
Barnidipine	HypoCa	3-NO_2	–Me		Me
Barnidipine	Coniel	3-NO_2	–Me		Me
Manidipine	Calslot, Madipine	3-NO_2	–Me		Me

Table 17 (*Contd.*)

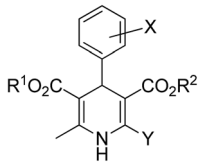
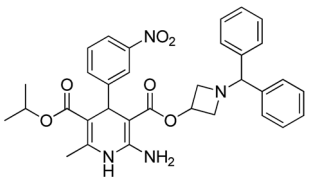
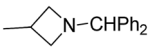
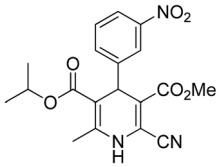
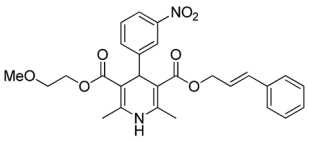
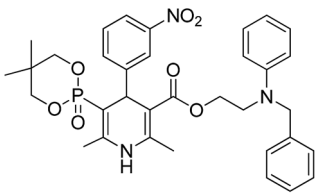
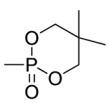
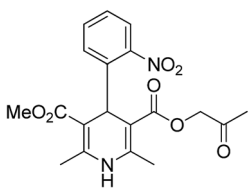
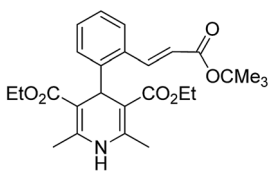
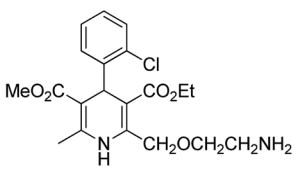
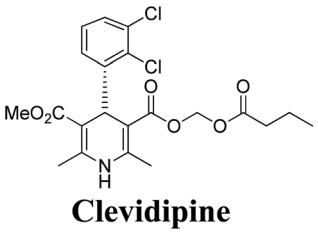
 DHP Drug	Brand name	X	R^1	R^2	Y
 **Azelnidipine**	Calblock	3-NO_2	–$CHMe_2$		NH_2
 **Nilvadipine**	Nilvadil	3-NO_2	–$CHMe_2$	–Me	CN
 **Cilnidipine**	Atelec, Cinalong, Siscard	3-NO_2	–CH_2CH_2OMe	–CH_2CH=$CHPh$	Me
 **Efonidipine**	Landel	3-NO_2		–$CH_2CH_2N(Ph)CH_2Ph$	Me
 **Aranidipine**	Sapresta	2-NO_2	–Me	–CH_2COCH_3	Me
 **Lacidipine**	Motens, Lacipil	2-CH= $CHCOOCMe_3$	–Et	–Et	Me
 **Amlodipine**	Norvasc, Amlodin	2-Cl	–Me	–Et	$CH_2OCH_2CH_2NH_2$

Table 17 (*Contd.*)

DHP Drug	Brand name	X	R^1	R^2	Y
 Clevidipine	Cleviprex	2,3-Di-Cl	–Me	$-CH_2OCOnPr$	Me

The third generation drugs exhibit more stable pharmacokinetics than the second-generation. These are less cardioselective and, hence well tolerated in patients with heart failure.[125] Now second and third generation 1,4-DHPs are being explored for the treatment of hypertension, angina, hypertrophic cardiomyopathy,[126] post-hemorrhagic cerebral vasospasm[127] and pulmonary hypertension, Raynaud's phenomenon.[128]

5. Conclusion

Dihydropyridine (DHP) scaffold has certainly revolutionalised the pharmaceutical research with its unprecedented biological properties. We have reviewed various methods for the synthesis of 1,2- and 1,4-dihydropyridine including the strategies which can furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. DHPs accept wide range of reactions that has triggered the synthesis of different class of compounds of great medicinal value, including natural products. Alkaloids deplancheine, tangutorine, dihydroakummicine, olivacine, (±)-guatambuine, L-pipecolic acid, (±)-geissoschizine, (±)-akagerine, lyaline, lyadine, harman-dihydropyrimidine, camptothecin, 20-deoxycamptothecin, akuammiline alkaloids precursor, silicine–methuenine alkaloids, vinoxine, (±)-2,7-dihydropleiocarpamine, tubifoline & tubifolidine, ervitsine and several other alkaloids have been synthesized following two simple reaction methodologies of DHPs. First, both 1,2 and 1,4-dihydropyridines give 1,3-dipolar addition reaction and readily undergo [2 + 2] cycloaddition reactions with dienophiles. Second, reaction of enamine functional group in dihydropyridines with electrophile (x^+) to form iminium salt, which undergoes α-attack of nucleophiles in a regio- and stereoselective manner (non-biomimetic oxidation) to give substituted tetrahydropyridine derivatives.

We have collated vast amount of literature regarding the strategies for the synthesis of DHPs. However, the continuously growing field of DHPs demands more diversity, tethering/merging of new moieties with DHP scaffold. Therefore this is still a vibrant and challenging area for medicinal chemists to explore new synthetic methodologies or sync different methodologies together to develop new DHP-drugs. Many DHP-based drugs have been blockbuster of their time; therefore, we have also highlighted commercial value of previously approved DHP-based drugs in brief.

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References

1 Q. Huang, Y. Li, C. Sheng, Y. Dou, M. Zheng, Z. Zhu and J. Wang, *J. Hypertens.*, 2015, **33**(1), e94.
2 H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano and Y. Kohari, *Chem. Commun.*, 2010, **46**, 4827–4829.
3 (*a*) S. K. Singh and V. K. Sharma, *Curr. Org. Chem.*, 2014, **18**, 1159–1207; (*b*) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141–1156; (*c*) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1–43; (*d*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223–243; (*e*) E. M. P. Silva, P. A. M. M. Varandas and A. M. S. Silva, *Synthesis*, 2013, **45**, 3053–3089.
4 F. W. Fowler, *J. Org. Chem.*, 1972, **37**, 1321–1323.
5 (*a*) C. A. Bear, W. R. Cullen, J. P. Kutney, V. E. Ridaura, J. Trotter and A. Zanarotti, *J. Am. Chem. Soc.*, 1973, **95**, 3058–3060; (*b*) J. P. Kutney, R. Greenhouse and V. E. Riduara, *J. Am. Chem. Soc.*, 1974, **96**, 7364–7365.
6 P. Beeken, J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, K. A. Zoo and F. W. Fowler, *J. Am. Chem. Soc.*, 1979, **101**, 6677–6682.

7 (*a*) Y.-S. Cheng, A. Lupo and F. W. Fowler, *J. Am. Chem. Soc.*, 1983, **105**, 7696–7703; (*b*) M. J. Wyle and F. W. Fowler, *J. Org. Chem.*, 1984, **49**, 4025–4029.
8 D. L. Comins, H. Hong and J. M. Salvador, *J. Org. Chem.*, 1991, **56**, 7197–7199.
9 T. J. Donohoe, A. J. McRiner and P. Sheldrake, *Org. Lett.*, 2000, **2**, 3861–3863.
10 (*a*) F. Palacios, C. Alonso, G. Rubiales and J. M. Ezpeleta, *Eur. J. Org. Chem.*, 2001, 2115–2122; (*b*) F. Palacios, E. Herrán and G. Rubiales, *J. Org. Chem.*, 1999, **64**, 6239–6246.
11 (*a*) H. M. Sklenicka, R. P. Hsung, L.-L. Wei, M. J. McLaughlin, A. I. Gerasyuto and S. J. Degen, *Org. Lett.*, 2000, **2**, 1161–1164; (*b*) L.-L. Wei, R. P. Hsung, H. M. Sklenicka and A. I. Gerasyuto, *Angew. Chem., Int. Ed.*, 2001, **40**, 1516–1518; (*c*) J. K. F. Geirsson and J. F. Johannesdottir, *J. Org. Chem.*, 1996, **61**, 7320–7325.
12 T.-P. Loh, P.-L. Lye, R.-B. Wang and K.-Y. Sim, *Tetrahedron Lett.*, 2000, **41**, 7779–7783.
13 B. Brunner, N. Stogaitis and M. Lautens, *Org. Lett.*, 2006, **8**, 3473–3476.
14 M. Motamed, E. M. Bunnelle, S. W. Singaram and R. Sarpong, *Org. Lett.*, 2007, **9**, 2167–2170.
15 D. M. Hodgson, M. L. Jones, C. R. Maxwell, A. R. Cowely, A. L. Thompson, O. Ichihara and I. R. Matthews, *Tetrahedron*, 2009, **65**, 7825–7836.
16 J.-P. Wan, S.-F. Gan, G.-L. Sun and Y.-J. Pan, *J. Org. Chem.*, 2009, **74**, 2862–2865.
17 I. Yavari, M. J. Bayat, M. Sirouspour and S. Souri, *Tetrahedron*, 2010, **66**, 7995–7999.
18 J. T. Binder and S. F. Kirsch, *Org. Lett.*, 2006, **8**, 2151–2153.
19 D. Tejedor, G. Méndez-Abt and F. García-Tellado, *Chem.–Eur. J.*, 2010, **16**, 428–431.
20 H. Wei, Y. Wang, B. Yue and P.-F. Xu, *Adv. Synth. Catal.*, 2010, **352**, 2450–2454.
21 T. Harschneck and S. F. Kirsch, *J. Org. Chem.*, 2011, **76**, 2145–2156.
22 T. Shono, Y. Matsumara, O. Onomura and Y. Yamada, *Tetrahedron Lett.*, 1987, **28**, 4073–4074.
23 (*a*) D. Tejedor, L. Cotos, G. Méndez-Abt and F. García-Tellado, *J. Org. Chem.*, 2014, **79**, 10655–10661; (*b*) D. Tejedor, M. C. Prieto-Ramírez, M. Ingold, M. Chicón and F. García-Tellado, *Org. Lett.*, 2016, **18**, 2770–2773.
24 C. Challa, M. John and R. S. Lankalapalli, *Tetrahedron Lett.*, 2013, **54**, 3810–3812.
25 B. J. Fallon, J. B. Garsi, E. Derat, M. Amatore, C. Aubert and M. Petit, *ACS Catal.*, 2015, **5**, 7493–7497.
26 (*a*) A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 1637–1638; (*b*) A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **1**, 215–219.
27 M.-L. Bennasar, R. Lavilla, M. Alvarez and J. Bosch, *Heterocycles*, 1988, **27**, 789–824.
28 F. Kröhnke, *Angew. Chem.*, 1953, **65**, 605–628.
29 F. Kröhnke, K. Ellgast and E. Bertram, *Liebigs Ann. Chem.*, 1956, **600**, 176–210.
30 H. Ahlbrecht and F. Kröhnke, *Liebigs Ann. Chem.*, 1967, **704**, 133–139.
31 D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, 1955, **77**, 2261–2264.
32 R. F. Hutton and F. H. Westheimer, *Tetrahedron*, 1958, **3**, 73–77.
33 H. Minato, S. Fujie, K. Okuma and M. Kobayashi, *Chem. Lett.*, 1977, 1091–1094.
34 (*a*) D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, 1982, **47**, 4315–4319; (*b*) D. L. Comins and N. B. Mantlo, *J. Heterocycl. Chem.*, 1983, **20**, 1239–1243; (*c*) D. L. Comins, A. H. Abdullah and R. K. Smith, *Tetrahedron Lett.*, 1983, **24**, 2711–2714; (*d*) D. L. Comins, *Tetrahedron Lett.*, 1983, **24**, 2807–2810; (*e*) D. L. Comins and N. B. Mantlo, *Tetrahedron Lett.*, 1983, **24**, 3683–3686; (*f*) D. L. Comins, E. D. Stroud and J. J. Herrick, *Heterocycles*, 1984, **22**, 151–157.
35 R. Yamaguchi, Y. Nakazono and M. Kawanisi, *Tetrahedron Lett.*, 1983, **24**, 1801–1804.
36 (*a*) E. Piers and M. Soucy, *Can. J. Chem.*, 1974, **52**, 3563–3564; (*b*) K. Akiba, Y. Iseki and M. Wada, *Tetrahedron Lett.*, 1982, **23**, 429–432; (*c*) D. D. Weller, G. R. Luellen and D. L. Weller, *J. Org. Chem.*, 1983, **48**, 3061–3067; (*d*) D. D. Weller, E. P. Stirchak and D. L. Weller, *J. Org. Chem.*, 1983, **48**, 4597–4605.
37 G. W. J. Fleet, C. J. Fuller and P. J. C. Harding, *Tetrahedron Lett.*, 1978, **19**, 1437–1440.
38 (*a*) J. C. Bommer and K. W. Morse, *J. Chem. Soc., Chem. Commun.*, 1977, 137–138; (*b*) J. C. Bommer and K. W. Morse, *Inorg. Chem.*, 1980, **19**, 587–593.
39 M. F. Semmelhack, R. D. Stauffer and A. Yamashita, *J. Org. Chem.*, 1977, **42**, 3180–3188.
40 D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, 1984, **49**, 3392–3394.
41 A. I. De Lucas, J. Fernández-Gadea, N. Martín and C. Seoane, *Tetrahedron*, 2001, **57**, 5591–5595.
42 M.-L. Bennasar, T. Roca, M. Monerris, C. Juan and J. Bosch, *Tetrahedron*, 2002, **58**, 8099–8106.
43 S. Ko, M. N. V. Sastry, C. Lin and C.-F. Yao, *Tetrahedron Lett.*, 2005, **46**, 5771–5774.
44 J.-C. Legeay, J. J. V. Eynde and J. P. Bazureaua, *Tetrahedron*, 2005, **61**, 12386–12397.
45 J. H. Lee, *Tetrahedron Lett.*, 2005, **46**, 7329–7330.
46 M. Meheswara, V. Siddaiah, Y. K. Rao, Y.-M. Tzeng and C. Sridhar, *J. Mol. Catal. A: Chem.*, 2006, **260**, 179–180.
47 J. Bräckow and K. T. Wanner, *Tetrahedron*, 2006, **62**, 2395–2404.
48 G. Babu and P. T. Perumal, *Aldrichimica Acta*, 2000, **33**, 16–22.
49 (*a*) R. Nagarajan, S. Chitra and P. T. Perumal, *Tetrahedron*, 2001, **57**, 3419–3423; (*b*) M. Anniyappan, D. Muralidharan and P. T. Perumal, *Tetrahedron Lett.*, 2003, **44**, 3653–3657.
50 R. S. Kumar, R. Nagarajan and P. T. Perumal, *Synthesis*, 2004, 949–959.
51 V. Sridharan, P. T. Perumal, C. Avendano and J. C. Menendez, *Tetrahedron*, 2007, **63**, 4407–4413.
52 J. Moreau, A. Duboc, C. Hubert, J.-P. Hurvois and J.-L. Renaud, *Tetrahedron Lett.*, 2007, **48**, 8647–8650.
53 F. Palacios, E. Herrán, C. Alonso and G. Rubiales, *ARKIVOC*, 2007, **iv**, 397–407.

54 S. Kikuchi, M. Iwai, H. Murayama and S. Fukuzawa, *Tetrahedron Lett.*, 2008, **49**, 114–116.
55 S.-X. Wang, Z. Y. Li, J.-C. Zhang and J.-T. Li, *Ultrason. Sonochem.*, 2008, **15**, 677–680.
56 A. M. Zonouz and S. B. Hosseini, *Synth. Commun.*, 2008, **38**, 290–296.
57 M. Sharma, N. Aggarwal and D. S. Rawat, *J. Heterocycl. Chem.*, 2008, **45**, 737–739.
58 A. Heydari, S. Khaksar, M. Tajbakhsh and H. R. Bijanzadeh, *J. Fluorine Chem.*, 2009, **130**, 609–614.
59 C. A. Sperger and K. T. Wanner, *Tetrahedron*, 2009, **65**, 5824–5833.
60 E. Rafiee, S. Eavani, S. Rashidzadeh and M. Joshaghani, *Inorg. Chim. Acta*, 2009, **362**, 3555–3562.
61 A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati and B. Carboni, *Tetrahedron Lett.*, 2009, **50**, 5248–5250.
62 G. Sabitha, K. Arundhathi, K. Sudhakar, B. S. Sastry and J. S. Yadav, *Synth. Commun.*, 2009, **39**, 2843–2851.
63 T. Sirijindalert, K. Hansuthirakul, P. Rashatasakhon, M. Sukwattanasinitt and A. Ajavakom, *Tetrahedron*, 2010, **66**, 5161–5167.
64 J. Yang, C. Wang, X. Xie, H. Li and Y. Li, *Eur. J. Org. Chem.*, 2010, 4189–4193.
65 F. Tamaddon, Z. Razmi and A. A. Jafari, *Tetrahedron Lett.*, 2010, **51**, 1187–1189.
66 S. Sueki, R. Takei, J. Abe and I. Shimizu, *Tetrahedron Lett.*, 2011, **52**, 4473–4477.
67 X. Wang, H. Gong, Z. Quan, L. Li and H. Ye, *Synth. Commun.*, 2011, **41**, 3251–3258.
68 T. Shibanuma, M. Iwanani, K. Okuda, T. Takenaka and M. Murakami, *Chem. Pharm. Bull.*, 1980, **28**, 2809–2812.
69 T. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki and M. Terai, *J. Med. Chem.*, 1986, **29**, 2504–2511.
70 B.-L. Zhang, W. He, X. Shi, M.-L. Huan, Q.-J. Huang and S.-Y. Zhou, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 805–808.
71 J. W. Young, *US Pat.*, 2002, vol. 6, 448), pp. 275B2.
72 S. Goldmann, J. Stolefuss and L. Born, *J. Med. Chem.*, 1992, **35**, 3341–3344.
73 (*a*) Z. Xitian, *US Pat.*, 2003, vol. 6, 646), p. 131; (*b*) R. Joshi and M. Gurjar, *US Pat.*, 2005, vol. 7, 148), p. 358; (*c*) P. Spargo, *US Pat.*, 2000, vol. 6, 046), p. 338.
74 D. M. Gotrane, R. D. Deshmukh, P. V. Ranade, S. P. Sonawane, B. M. Bhawal, M. M. Gharpure and M. K. Gurjar, *Org. Process Res. Dev.*, 2010, **14**, 640–643.
75 M. D. Taylor, R. J. Himmelsbach, B. E. Kornberg, J. Quin, E. Lunney and A. Michel, *J. Org. Chem.*, 1989, **54**, 5585–5590.
76 J. E. Arrowsmith, S. F. Campbell, P. E. Cross, J. K. Stubbs, R. A. Burges, D. G. Gardiner and K. J. Blackburn, *J. Med. Chem.*, 1986, **29**, 1696–1702.
77 B. Lamm, R. Simonsson and S. Sundell, *Tetrahedron Lett.*, 1989, **30**, 6423–6426.
78 D. Vo, W. C. Matowe, M. Ramesh, N. Iqbal, M. W. Wolowyk, S. E. Howlett and E. E. Knaus, *J. Med. Chem.*, 1995, **38**, 2851–2859.
79 R. Shan, S. E. Howlett and E. E. Knaus, *J. Med. Chem.*, 2002, **45**, 955–961.
80 R. Shan and E. E. Knaus, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2613–2614.
81 J. Jiang, A.-H. Li, S.-Y. Jang, L. Chang, N. Melman, S. Moro, X. Ji, E. B. Lobkovsky, J. C. Clardy and K. A. Jacobson, *J. Med. Chem.*, 1999, **42**, 3055–3065.
82 N. Martín, A. Martinez-Grau, C. Seoane, J. L. Marco, A. Albert and F. H. Cano, *Tetrahedron: Asymmetry*, 1995, **6**, 877–880.
83 J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 2458–2462.
84 T. Yamamoto, S. Ohno, S. Niwa, M. Tokumasu, M. Hagihara, H. Koganei, S. Fujita, T. Takeda, Y. Saitou, S. Iwayama, A. Takahara, S. Iwata and M. Shoji, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3317–3319.
85 J. P. Kutney, M. Noda, N. G. Lewis, B. Monteiro, D. Mostowicz and B. R. Worth, *Can. J. Chem.*, 1982, **60**, 2426–2430.
86 D. L. Comins and Y. C. Myoung, *J. Org. Chem.*, 1990, **55**, 292–298.
87 A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf and J. Martel, *J. Am. Chem. Soc.*, 2001, **123**, 11829–11830.
88 A. Lemire, M. Grenon, M. Pourashraf and A. B. Charette, *Org. Lett.*, 2004, **6**, 3517–3520.
89 R. Abou-Jneid, S. Ghoulami, M.-T. Martin, E. T. H. Dau, N. Travert and A. Al-Mourabit, *Org. Lett.*, 2004, **6**, 3933–3936.
90 A. Lemire and A. B. Charette, *Org. Lett.*, 2005, **7**, 2747–2750.
91 C. Schroif-Gregoire, N. Travert, A. Zaparucha and A. Al-Mourabit, *Org. Lett.*, 2006, **8**, 2961–2964.
92 A. Lemire and A. B. Charette, *J. Org. Chem.*, 2010, **75**, 2077–2080.
93 E. Wenkert, T. D. J. Halls, G. Kunesch, K. Orito, R. L. Stephens, W. A. Temple and J. S. Yadav, *J. Am. Chem. Soc.*, 1979, **101**, 5370–5376.
94 R. Besselievre, B.-P. Cosson, B. C. Das and H.-P. Husson, *Tetrahedron Lett.*, 1980, **21**, 63–66.
95 J. Bosch, M.-L. Bennasar, E. Zulaica and M. Feliz, *Tetrahedron Lett.*, 1984, **25**, 3119–3122.
96 J. Bosch, M.-L. Bennasar and E. Zulaica, *J. Org. Chem.*, 1986, **51**, 2289–2297.
97 M. Alvarez, M. Salas, A. de Veciana, R. Lavilla and J. Bosch, *Tetrahedron Lett.*, 1990, **31**, 5089–5091.
98 M.-L. Bennasar, B. Vidal and J. Bosch, *J. Am. Chem. Soc.*, 1993, **115**, 5340–5341.
99 M.-L. Bennasar, B. Vidal and J. Bosch, *J. Chem. Soc., Chem. Commun.*, 1995, 125–126.
100 M.-L. Bennasar, E. Zulaica, J.-M. Jiménez and J. Bosch, *J. Org. Chem.*, 1993, **58**, 7756–7767.
101 (*a*) M.-L. Bennasar, B. Vidal and J. Bosch, *J. Org. Chem.*, 1996, **61**, 1916–1917; (*b*) M.-L. Bennasar, B. Vidal and J. Bosch, *J. Org. Chem.*, 1997, **62**, 3597–3609.
102 M.-L. Bennasar, B. Vidal, A. Lázaro, R. Kumar and J. Bosch, *Tetrahedron Lett.*, 1996, **37**, 3541–3544.
103 M.-L. Bennasar, B. Vidal and J. Bosch, *Chem. Commun.*, 1996, 2755–2756.

104 D. Zhang, I. Llorente and L. S. Liebesking, *J. Org. Chem.*, 1997, **62**, 4330–4338.
105 W. Benson and E. Winterfeldt, *Heterocycles*, 1981, **15**, 935–941.
106 M.-L. Bennasar, B. Vidal, B. A. Sufi and J. Bosch, *Chem. Commun.*, 1998, 2639–2640.
107 M.-L. Bennasar, J.-M. Jimenez, B. Vidal, B. A. Sufi and J. Bosch, *J. Org. Chem.*, 1999, **64**, 9605–9612.
108 K. Yamada, K. Aoki, T. Kato, D. Uemura and T. E. E. Van, *J. Chem. Soc., Chem. Commun.*, 1974, 908–909.
109 M.-L. Bennasar, E. Zulaica, C. Juan, Y. Alonso and J. Bosch, *J. Org. Chem.*, 2002, **67**, 7465–7474.
110 (*a*) R. T. Brown, L. Jianli and C. A. M. Santos, *Tetrahedron Lett.*, 2000, **41**, 859–862; (*b*) W. Shen, G. A. Coburn, W. G. Bornmann and S. J. Danishefsky, *J. Org. Chem.*, 1993, **58**, 611–617; (*c*) K. Tagami, N. Nakazawa, S. Sano and Y. Nagao, *Heterocycles*, 2000, **53**, 771–775.
111 T. Putkonen, A. Tolvanen and R. Jokela, *Tetrahedron Lett.*, 2001, **42**, 6593–6594.
112 M. Berner, A. Tolvanen and R. Jokela, *Tetrahedron Lett.*, 1999, **40**, 7119–7122.
113 M.-L. Bennasar, T. Roca and M. Monernis, *J. Org. Chem.*, 2004, **69**, 752–756.
114 M. Amat, M.-D. Coll, N. Llor, C. Escolano, E. Molins, C. Miravitlles and J. Bosch, *Tetrahedron: Asymmetry*, 2003, **14**, 1691–1699.
115 F. Bossert and W. Vater, *Med. Res. Rev.*, 1989, **9**, 291–324.
116 F. Bossert and W. Vater, *Naturwissenschaften*, 1971, **58**, 578.
117 (*a*) H. Nakayama and Y. Kanaoka, *Heterocycles*, 1996, **42**, 901–909; (*b*) F. Bossert, H. Meyer and E. Wehinger, *Angew. Chem., Int. Ed.*, 1981, **20**, 762–769.
118 H. Komoda, T. Inoue and K. Node, *Clin. Exp. Hypertens.*, 2010, **32**, 121–128.
119 R. Boer and R. Gekeler, *Drugs Future*, 1995, **20**, 499–509.
120 (*a*) G. A. Wächter, M. C. Davis, A. R. Martin and S. G. Franzblau, *J. Med. Chem.*, 1998, **41**, 2436–2438; (*b*) B. Desai, D. Sureja, Y. Naliapara, A. Shah and A. K. Saxena, *Bioorg. Med. Chem.*, 2001, **9**, 1993–1998.
121 J. M. Tusell, S. Barrón and J. Serratosa, *Brain Res.*, 1993, **622**, 99–104.
122 P. Ioan, E. Carosati, M. Micucci, G. Cruciani, F. Broccatelli, B. S. Zhorov, A. Chiarini and R. Budriesi, *Curr. Med. Chem.*, 2011, **18**, 4901–4922.
123 F. H. Leenen, *Am. J. Hypertens.*, 1996, **9**, 97S–104S.
124 D. D. Freedman and D. D. Waters, *Drugs*, 1987, **34**, 578–598.
125 T. F. Lüscher and F. Cosentino, *Drugs*, 1998, **55**, 509–517.
126 T. Tokushima, T. Utsunomiya, T. Ogawa, K. Kidoh, Y. Ohtsubo, T. Ryu, K. Yoshida, T. Ogata, S. Tsuji and S. Matsuo, *Basic Res. Cardiol.*, 1996, **91**, 329–336.
127 D. Tomassoni, A. Lanari, G. Silvestrelli, E. Traini and F. Amenta, *Clin. Exp. Hypertens.*, 2008, **30**, 744–766.
128 A. Herrick, *Curr. Treat. Options Cardiovasc. Med.*, 2008, **10**, 146–155.

