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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 regioisomers 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 nicotinamide 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-azabicyclo[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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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}

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.



Scheme 1 Synthesis of 1,2- and 1,4-dihydropyridines 1 and 2 by reduction of pyridine using NaBH₄.



Scheme 2 Dihydropyridine 4 generated from precursor chromium complex 3.

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.



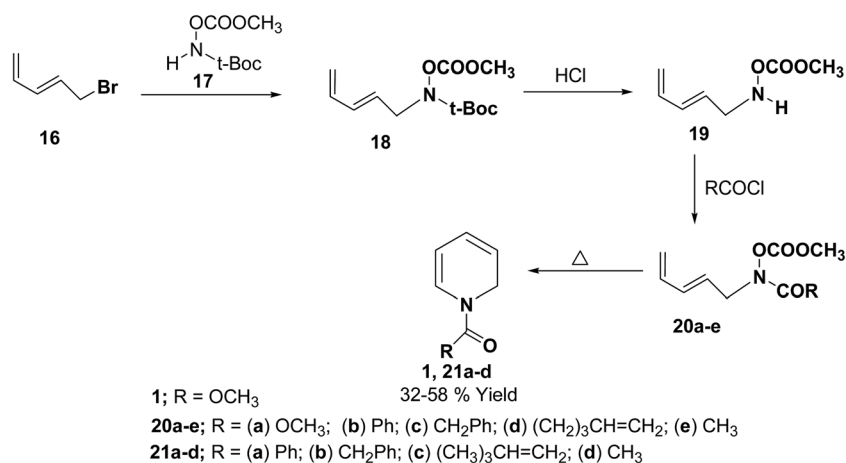
dihydropyridine. This metal carbonyl complex **3** has been used for the synthesis of essentially pure *N*-methyl-3-ethyl-1,2-dihydropyridine **4**, which can be used as a precursor to synthesize a number of useful heterocyclic compounds such as **5** and **6** (Scheme 2).

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 led 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 ClCOOCH₃ 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-dihydropyridines **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*-

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

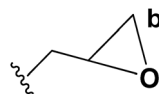
Entry	R*OCOCl	RMgX	Product	Yield%	de
1	23a	<i>n</i> -PrMgCl	25a	72	82
2	23b	<i>n</i> -PrMgCl	25b	81	78
3	23a	<i>n</i> -HexMgCl	25c	81	91
4	23a	PhCH ₂ MgCl	25d	58	76
5	23a	VinylMgBr	25e	71	90
6	23a	PhMgCl	25f	85	89
7	23b	PhMgCl	25g	87	84
8	23a	<i>p</i> -MePhMgBr	25h	86	92

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).



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) ₃ Cl	(CH ₂) ₃ Cl	A	96
9	I(CH ₂) ₃ Cl	(CH ₂) ₃ Cl	B	96
10	I(CH ₂) ₄ Cl	(CH ₂) ₄ Cl	A	99
11	I(CH ₂) ₄ Cl	(CH ₂) ₄ Cl	B	91
12	I(CH ₂) ₅ Cl	(CH ₂) ₅ Cl	A	97
13	I(CH ₂) ₅ Cl	(CH ₂) ₅ Cl	B	94

^a Method A: Na (3.5 equiv.), NH₃/THF, -78 °C, then R-X (3.5 equiv.), then NH₄Cl 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 NH₄Cl 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**.



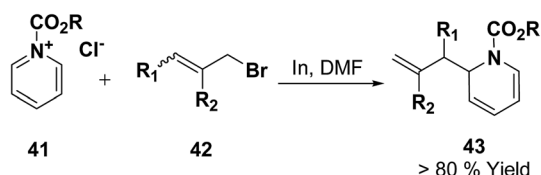
The presence of the chiral auxiliary in **25** may find application in the several transformations. Another asymmetric synthesis was developed for the synthesis of 1,2-dihydropyridines as shown in Scheme 7. The chiral salt **27** prepared *in situ* from 4-methoxy-3-



Scheme 9 Regioselective synthesis of 1,2-dihydropyridine.



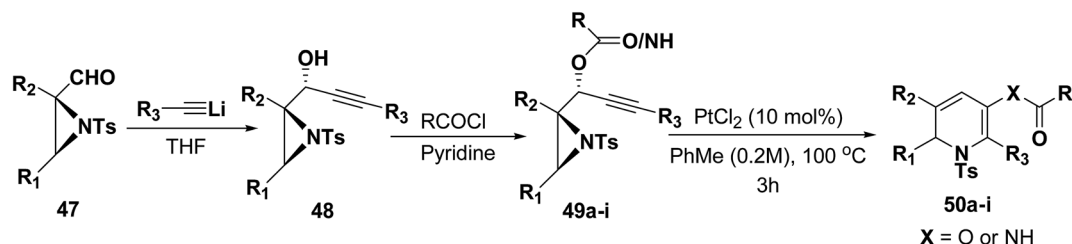
Scheme 10 1,2-Dihydropyridine via [3 + 3] cycloaddition reaction.



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



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



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

(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).

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 **35** and **36** under reflux in toluene form a broad variety of substituted dihydropyridines **37** in a regioselective 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 vinyloxirane **44** (1.5 equiv.) with benzhydryl protected aldimine **45** (1.0 equiv.) in the presence of catalytic amount of $\text{Sc}(\text{OTf})_3$ (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



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 alkyl lithium or Grignard reagent. The aziridinyl propargylic esters **49a–i** on cycloisomerisation using Pt(II) catalysis (10 mol% of PtCl₂, 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 Bu₃SnH (2.0 equiv.) gave the 1,2-dihydropyridines **54a–b** in 37 and 10% yields, respectively (Scheme 15).

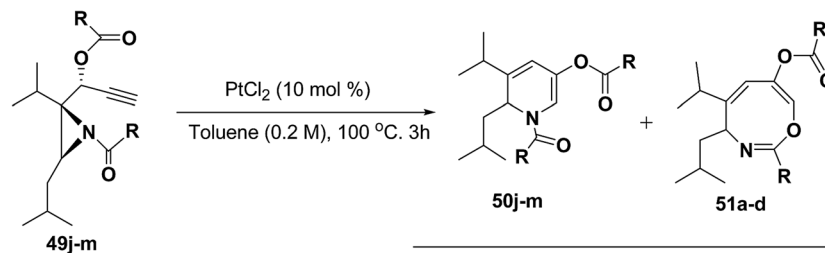
Wan, *et al.*¹⁶ have reported the three component sequential reaction enaminones **55**, α,β -unsaturated aldehydes **56a–b** and amines **57a–k** to afford 1,2-dihydropyridines **58** in highly regioselective manner. This novel regioselectivity has been

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

Entry	Substrate	Product	Yield ^b (%)
1	 <p>49a–d (a) R = Me (b) R = <i>p</i>-ClPh (c) R = <i>t</i>-Bu (d) R = Ph</p>	 <p>50a–d (a) R = Me (b) R = <i>p</i>-ClPh (c) R = <i>t</i>-Bu (d) R = Ph</p>	(50a) 76%, (50b) 72%, (50c) 76%, (50d) 76%
2	 <p>49e</p>	 <p>50e</p>	(50e) 56%
3	 <p>49f–h (f) R₃ = Cyclopropyl (g) R₃ = Ph (h) R₃ = H</p>	 <p>50f–h (f) R₃ = Cyclopropyl (g) R₃ = Ph (h) R₃ = H</p>	(50f) 62%, (50g) 69%, (50h) 70%
4	 <p>49i</p>	 <p>50i</p>	(50i) 76%

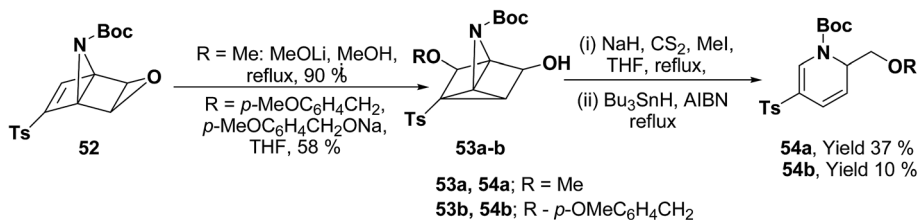
^a Standard conditions: 10 mol% of PtCl₂, 0.2 M in toluene at 100 °C over 3 h. ^b Isolated yields after column chromatography.





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

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

Scheme 15 Bu₃SnH 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) <i>p</i> -NO ₂	(58a) 63	nd
2	<i>p</i> -OCH ₃	H	(57a) <i>p</i> -NO ₂	(58b) 14	(59c) 53
3	H	H	(57b) <i>o</i> -F	(58c) nd ^c	(59c) 70
4	<i>p</i> -OCH ₃	H	(57b) <i>o</i> -F	(58d) nd	(59d) 52
5	H	H	(57c) <i>o</i> -Cl	(58e) 59	(59e) nd
6	<i>o</i> -Cl	<i>o</i> -Cl	(57d) H	(58f) 52	(59f) nd
7	<i>o</i> -Cl	H	(57c) <i>o</i> -Cl	(58g) 60	(59g) nd
8	H	H	(57e) <i>o</i> -Br	(58h) <10	(59h) 46
9	H	H	(57d) <i>o</i> -I	(58i) 27	(59i) 51
10	H	H	(57g) <i>o</i> -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 H₂O + 0.5 mL of DMF), stirred at 85 °C for 10 h. ^b Isolated yield based on the corresponding enaminone. ^c nd = not determined.



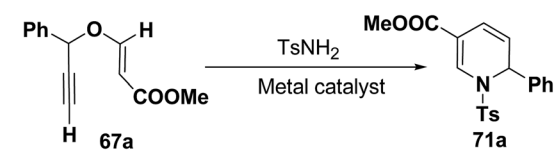
Table 5 Domino synthesis of 1,2-dihydropyridines **69a–q** from propargyl enol ethers **67** and primary amines^a



Entry	R ₁	R ₂	R ₃	67	R ₄ NH ₂	69	Yield (%)
1	H	Ph	H	a	<i>p</i> MeOC ₆ H ₄ (62h)	a	100
2	H	H	H	b	<i>p</i> MeOC ₆ H ₄ (62h)	b	51 ^b
3	H	Me	H	c	<i>p</i> MeOC ₆ H ₄ (62h)	c	87
4	h	<i>n</i> Pent	H	d	<i>p</i> MeOC ₆ H ₄ (62h)	d	71
5	Ph	Ph	H	e	<i>p</i> MeOC ₆ H ₄ (62h)	e	95
6	<i>c</i> Hex	Ph	H	f	<i>p</i> MeOC ₆ H ₄ (62h)	f	55
7	H	Ph	Me	g	<i>p</i> MeOC ₆ H ₄ (62h)	g	24 ^c
8	H	Me	Me	h	<i>p</i> MeOC ₆ H ₄ (62h)	h	17 ^c
9	H	Ph	H	i	<i>p</i> MeOC ₆ H 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	(<i>S</i>)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 ₆ H ₄ (70d)	p	88
17	H	Ph	H	a	<i>p</i> MeOC ₆ H ₄ (62h)	q	100 ^h

^a Propargyl vinyl ether **67** (1.0 equiv.), primary amine **62h** (1.1 equiv.) in toluene (5 mL). Z = CO₂CH₃. ^b 300 W, 150 °C, 2 h. ^c 300 W, 150 °C, 3 h, Z = CO₂CH₂CH₃. ^d Z = SO₂Tol. ^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

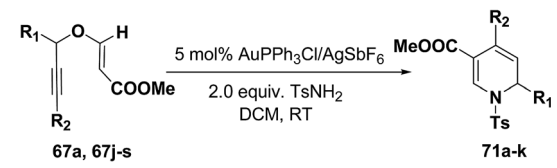


Entry	Catalyst (mol%)	Solution	TsNH ₂ (mol%)	Yield (%)
1	AuCl ₃	DCM	200	NR ^b
2	PPh ₃ AuCl/AgOTf	DCM	200	NR ^b
3	PPh ₃ AuCl/AgBF ₄	DCM	200	84
4	PPh ₃ AuCl/AgSbF ₆	DCM	200	92
5	PPh ₃ AuCl	DCM	200	NR ^b
6	AgSbF ₆	DCM	200	NR ^b
7	PdCl ₂ (CN) ₂	DCM	200	NR ^b
8	PtCl ₂	DCM	200	NR ^b
9	PPh ₃ AuCl/AgSbF ₆	Toluene	200	Trace ^c
10	PPh ₃ AuCl/AgSbF ₆	CH ₃ CN	200	NR ^b
11	PPh ₃ AuCl/AgSbF ₆	DCE	200	77
12	PPh ₃ AuCl/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.

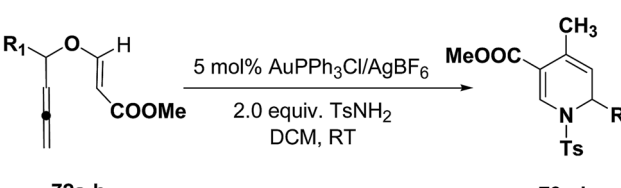
acetylenic esters **61a–b** and primary alkylamine (**62a–i**). The reaction of alkyl isocyanides **60a–b**, dimethyl acetylenedicarboxylate (**61a**), and primary amines **57a**, **62a–h**, proceeded smoothly in CH₂Cl₂ at room temperature and produced tetramethyl 4-(alkylamino)-1-alkyl(aryl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **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 CH₂Cl₂ at rt, produced 5,6-diethyl 2,3-

Table 7 Tandem synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and TsNH₂^a



Entry	R ₁	R ₂	67	Product	Yield ^b (%)
1	C ₆ H ₅	H	67a	71a	92
2	2-Me-C ₆ H ₄	H	67j	71b	90
3	4-Me-C ₆ H ₄	H	67k	71c	91
4	3-Me-C ₆ H ₄	H	67l	71d	80
5	3,4-Di-Me-C ₆ H ₃	H	67m	71e	78
6	2-MeO-C ₆ H ₄	H	67n	71f	89
7	4-Cl-C ₆ H ₄	H	67o	71g	85
8	2-Cl-C ₆ H ₄	H	67p	71h	84
9	2-Naphthyl	H	67q	71i	88
10	<i>n</i> -Hexyl	H	67r	71j	82
11	C ₆ H ₅	<i>n</i> -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 ₆ H ₅	73a	69
2-Me-C ₆ H ₄	73b	67
4-Me-C ₆ H ₄	73c	65
3-Me-C ₆ H ₄	73d	56
4-Cl-C ₆ H ₄	73e	55
4-Br-C ₆ H ₄	73f	48
2-naphthyl	73g	62
<i>n</i> -hexyl	73h	NR

Scheme 21 Tandem synthesis of 1,2-dihydropyridines **73a–h** from allenic vinyl ethers and TsNH₂.



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



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**.



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 AuCl₃ or AuPPh₃Cl/AgOTf (5 mol% each) in CH₂Cl₂ at room temperature (entries 1 and 2, Table 6). 1,2-Dihydropyridine was obtained in 84% yield when AuPPh₃Cl/AgBF₄ (5 mol%) was used (entry 3). It was interesting result that 92% yield was realized by using AuPPh₃Cl/AgSbF₆ (5 mol%) at room temperature (entry 4). Ag(i) could serve to abstract the chloride from AuPPh₃Cl to form a more electrophilic catalyst. On the contrary, when Au(PPh₃)Cl or AgSbF₆ 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 PtCl₂ or PdCl₂(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 CH₂Cl₂ (entries 9–11). However, the yield decreased when the amount of TsNH₂ was reduced from 2.0 to 1.2 equivalents (entry 12). Thus the use of 5 mol% of AuPPh₃Cl/AgSbF₆, with 2.0 equivalents of TsNH₂ in CH₂Cl₂ 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



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

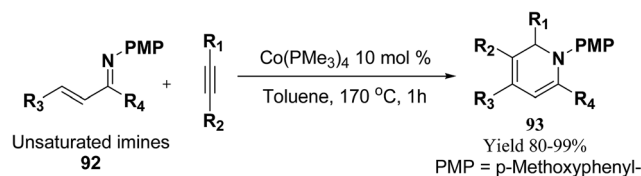


Scheme 27 Cascade synthesis of 1,2-dihydropyridine **91** by variation of aldehydes and amines.

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% AuPPh₃Cl/AgBF₄ in presence of 2.0 equiv. TsNH₂ 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



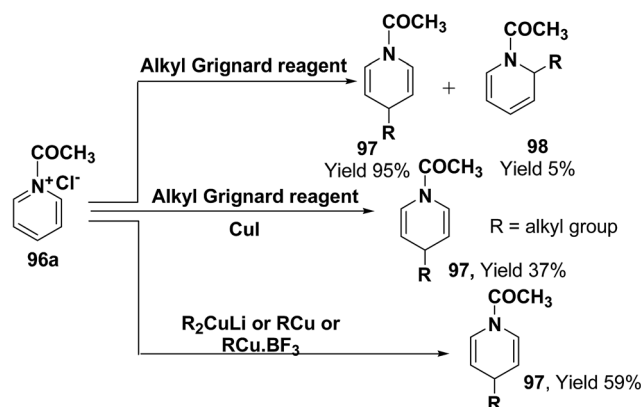
Scheme 28 Annulation reaction between unsaturated imines and alkynes for the formation of 1,2-dihydropyridines **93**.



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) R₃NH₂ (**57d**, **62a**, **62c**, **62h** and **75a–c**); (iii) *p*-TsOH (20 mol%), 40 °C, CH₂Cl₂] (Scheme 22). The formation of 1,2-dihydropyridines **76a–o** tolerated substitution of R₁ and R₂ with both aryl and alkyl groups (Scheme 22). Compound **76l** bearing no substituent in the 2-position (R₁ = H) was obtained in only moderate yield.



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

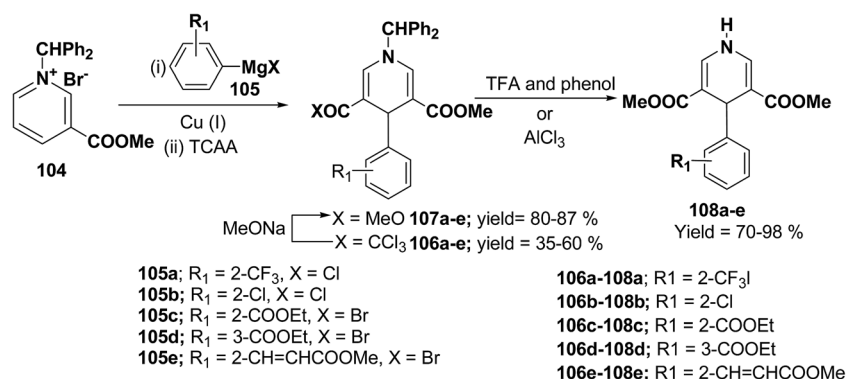
Further this one-pot procedure is extended by an additional step that is the formation of the propargyl vinyl ethers. When propargylic alcohols **77a–c** were reacted with 1.0 equiv. of ethyl propiolate **78a**/methyl propiolate **78b** and 5 mol% of P(*n*-Bu)₃, the Michael-addition remained an efficient process. Subsequent addition of both AuCl and AgSbF₆ (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**.

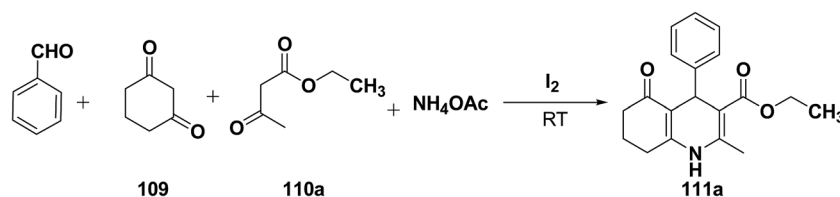


Tejedor, *et al.*²³ has developed a general and practical metal-free protocol for the synthesis of 1,2-dihydropyridines (Scheme 26) with variety of structural/functional diversity at the ring and featuring mono, double, or spiro substitution at the sp³ hybridized carbon position. The protocol contains 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 CF₃COOH in a one-pot cascade synthesis. The advantages associated with this transformation include conditions that are metal-free, room temperature,

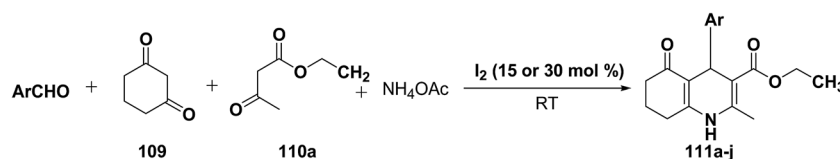
Table 8 Optimizing the reaction conditions^a



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



Entry	105	Ar	Iodine (mol%)	Time (h)	Yield ^a (%)
1	111a	C ₆ H ₅	30	2.5 h	99
2	111a		15	30 min	93
3	111b	<i>p</i> -Me-C ₆ H ₄	30	1.5 h	90
4	111b		15	35 min	99
5	111c	<i>p</i> -Me-C ₆ H ₄	30	4 h	97
6	111c		15	40 min	87
7	111d	<i>p</i> -F-C ₆ H ₄	30	3.5 h	91
8	111d		15	35 min	87
9	111e	<i>p</i> -Cl-C ₆ H ₄	30	6 h	99
10	111e		15	40 min	90
11	111f	<i>p</i> -OH-C ₆ H ₄	30	2.5 h	99
12	111f		15	45 min	92
13	111g	<i>o</i> -NO ₂ -C ₆ H ₄	30	1.5 h	94
14	111g		15	25 min	91
15	111h	<i>m</i> -NO ₂ -C ₆ H ₄	30	1.5 h	99
16	111h		15	25 min	92
17	111i	<i>p</i> -NO ₂ -C ₆ H 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.



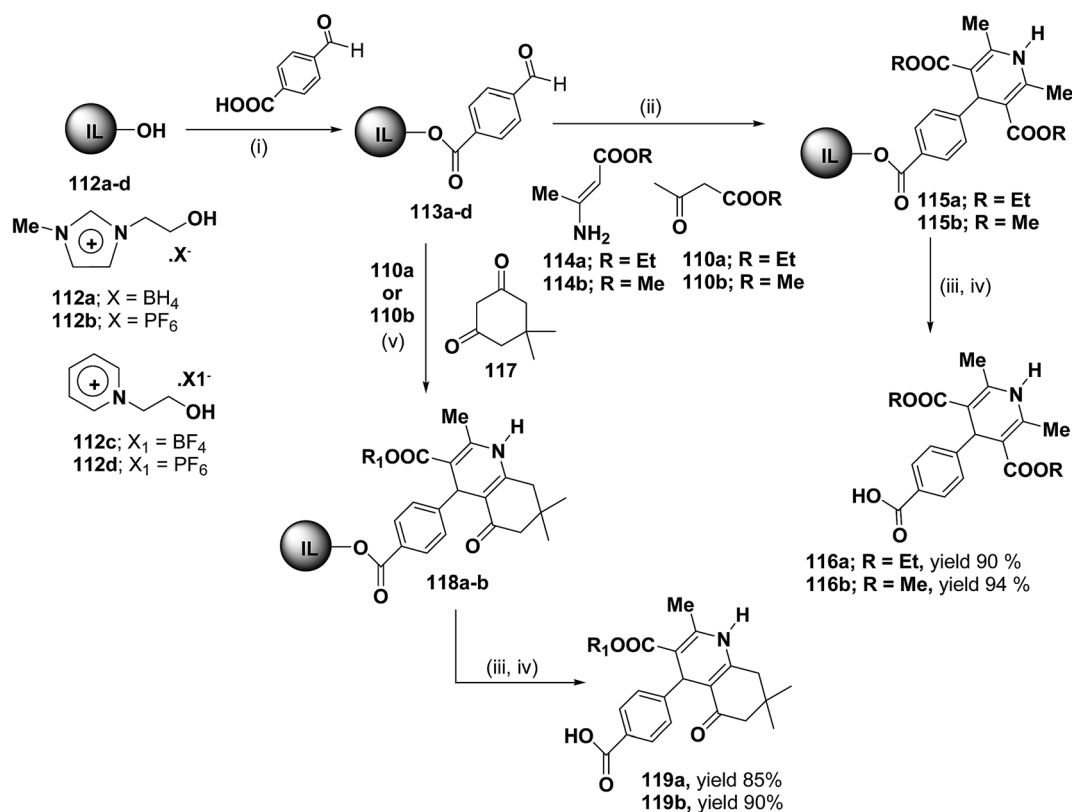
undistilled solvent, and expeditious in excellent yields. Out of the several acid catalyst used for the optimisation of the reaction condition trifluoroacetic acid was found to be excellent, which yield 1,2-dihydropyridine in excellent yield (Scheme 27). The substrate scope has been demonstrated with 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

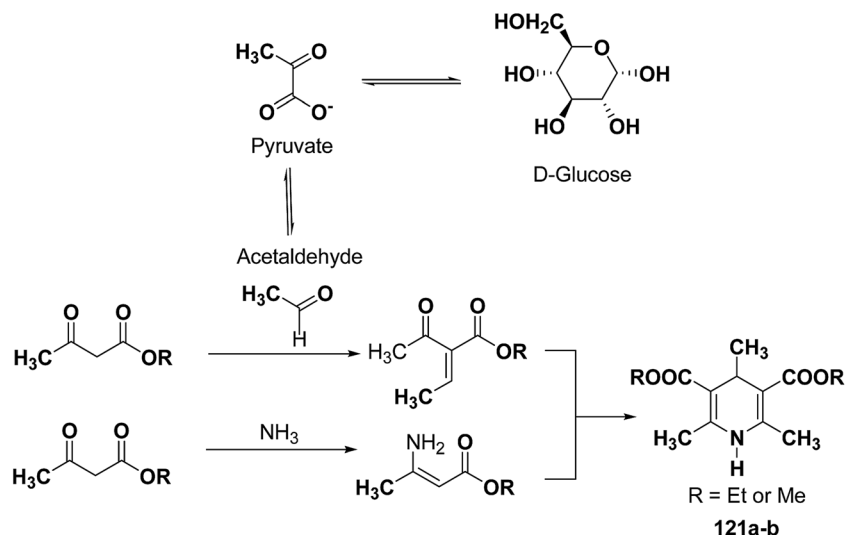


Scheme 35 Ionic liquid supported synthesis of 1,4-DHPs. Reagents and conditions (i) DCC (1.0 equiv.), DMAP (5%), dry MeCN, rt, 24 h; (ii) method A: **110** (1.0 equiv.), **114** (1.0 equiv.), mw: 120 °C (power level: 50%, 150 W), 10 min or method B: **110** (2.0 equiv.), NH_4OAc (2.0 equiv.), mw: 120 °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).

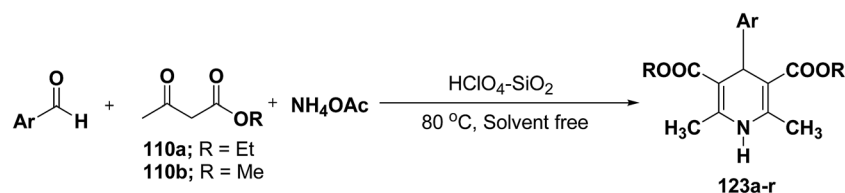


Scheme 36 Baker's yeast catalyzed synthesis of 1,4-DHPs **121** and **122**.





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

Scheme 38 Heterogeneous catalyst ($\text{HClO}_4\text{-SiO}_2$) 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 $\text{HClO}_4\text{-SiO}_2^a$

Entry	(Ar) 123	110	Reaction time (min.)	% yield
1	C_6H_5 (123a)	110b	20	95
2	<i>p</i> - $\text{CH}_3\text{-C}_6\text{H}_4$ (123b)	110b	25	90
3	<i>p</i> - $\text{CH}_3\text{O-C}_6\text{H}_4$ (123c)	110b	28	92
4	<i>p</i> - $\text{Cl-C}_6\text{H}_4$ (123d)	110b	20	89
5	<i>p</i> - $\text{OH-C}_6\text{H}_4$ (123e)	110b	26	90
6	<i>o</i> - $\text{NO}_2\text{-C}_6\text{H}_4$ (123f)	110b	35	92
7	<i>o</i> - $\text{Cl-C}_6\text{H}_4$ (123g)	110b	26	87
8	<i>p</i> - $\text{NO}_2\text{-C}_6\text{H}_4$ (123h)	110a	33	92
9	<i>o</i> - $\text{CH}_3\text{O-C}_6\text{H}_4$ (123i)	110a	42	90
10	<i>p</i> - $\text{Br-C}_6\text{H}_4$ (123j)	110a	40	92
11	<i>o</i> - $\text{Br-C}_6\text{H}_4$ (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	<i>p</i> - $\text{CH}_3\text{-C}_6\text{H}_4$ (123p)	110b	25	92
17	<i>o</i> - $\text{CH}_3\text{O-C}_6\text{H}_4$ (123q)	110b	25	90
18	<i>o</i> - $\text{NO}_2\text{-C}_6\text{H}_4$ (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 regioselective and resulted in the exclusive formation of 1,4-dihydropyridines 97. Stoichiometric organocopper reagent (*e.g.* R₂CuLi, RCu, RCu·BF₃) also give 1,4-addition product and resulted into the formation of 1,4-dihydropyridines 97 (Scheme 31).³⁶

Several hydride reagents *e.g.* NaBH₄,³ NaBH₃CN, (PPh₃)₂-CuBH₄,³⁷ (Ph₂MeP)₃CuBH₄,³⁸ Semmelhack's "NaCuH₂"³⁹ and Semmelhack's "LiCuH₂"³⁹ has been used for the regioselective synthesis of 1,4-dihydropyridines from 1-(phenoxy-carbonyl)pyridinium chloride 99a (generate *in situ* by the reaction between pyridine and phenyl chloroformate), but none of these procedure resulted into the regioselective formation of 1,4-DHP. Comins, *et al.*⁴⁰ has used a copper hydride 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-(phenoxy-carbonyl)pyridinium chloride 96a in almost quantitative yield (Scheme 32). Further this procedure has been extended to the variety of the 1-(alkoxy/

aryloxy/acyloxycarbonyl)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

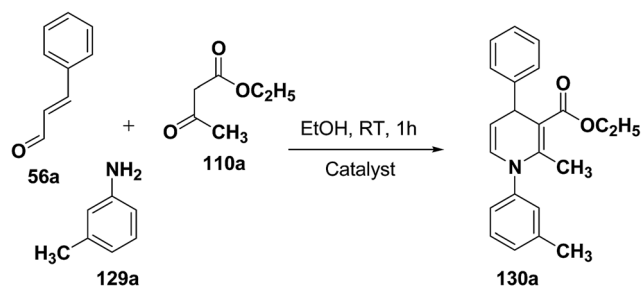
De Lucas, *et al.*⁴¹ have developed a novel methodology for the synthesis of *N*-substituted 1,4-dihydropyridines 103a–d by the reaction of 2-amino-5-formyl-4*H*-pyran 101 with primary amines 57d, 62a, 70d and 102 in moderate yield (Scheme 33). The formation of 1,4-dihydropyridines involves cleavage 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*-benzhydrylpyridinium salt 104,

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

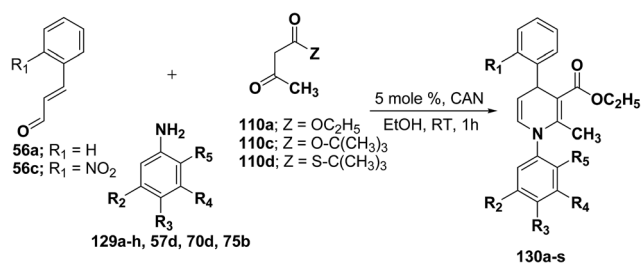
Entry	125	R ₂ Mg (128) ^a	Product	% yield ^b	Product ratio 126/127/125 (%) ^c
1	125a	Et ₂ Mg	126a, 127a	78	90/4/6
2	125a	<i>n</i> Bu ₂ Mg	126b, 127b	82	100/0/0
3	125a	Bn ₂ Mg	126c, 127c	92	95/2/3
4	125a	Ph ₂ Mg	126d, 127d	0	5/95 ^d /0
5	125a	Me ₂ Mg	126e, 127e	0	0/59/41
6	125a	<i>i</i> Pr ₂ Mg	126f, 127f	91	99/0/1
7	125a	<i>t</i> Bu ₂ Mg	126g, 127g	56	80/3/17 ^e
8	125a	Allyl ₂ Mg	126h, 127h	20	20/78 ^d /2
9	125b	Et ₂ Mg	126i, 127i	73	86/2/12
10	125b	<i>n</i> Bu ₂ Mg	126j, 127j	54	54/6/40
11	125b	Bn ₂ Mg	126k, 127k	85	95/0/5
12	125b	<i>i</i> Pr ₂ Mg	126l, 127l	78	100/0/0
13	125b	<i>t</i> Bu ₂ Mg	126m, 127m	5	6/0/94 ^f
14	125b	Allyl ₂ Mg	126n, 127n	12	21/70/9

^a After addition of the organomagnesium compound R₂Mg 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.

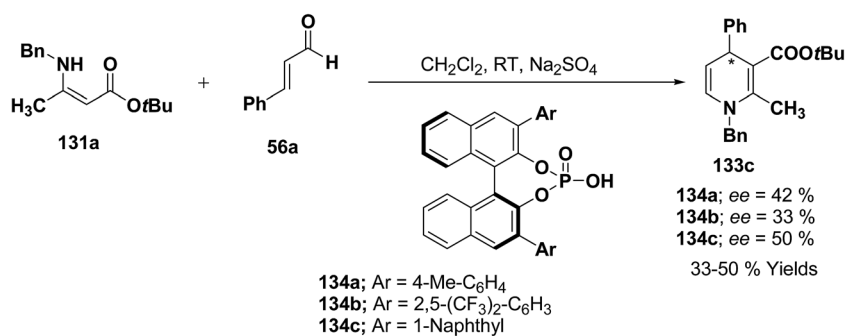


131a; R₁ = CH₃, R₂ = Bn, R₃ = *t*-Bu
 131b; R₁ = CH₃, R₂ = Bn, R₃ = Et
 131c; R₁ = Ph, R₂ = Bn, R₃ = Et
 131d; R₁ = CH₃, R₂ = Ph, R₃ = *t*-Bu

56d; R₄ = R₅ = CH₃, R₆ = H
 56e; R₄ = R₆ = CH₃, R₅ = H
 56f; R₄ = *p*-NO₂-C₆H₄, R₅ = R₆ = H
 56g; R₄ = *p*-OCH₂Ph-C₆H₄, R₅ = R₆ = H
 56h; R₄ = *p*-N(CH₃)₂-C₆H₄, R₅ = R₆ = H

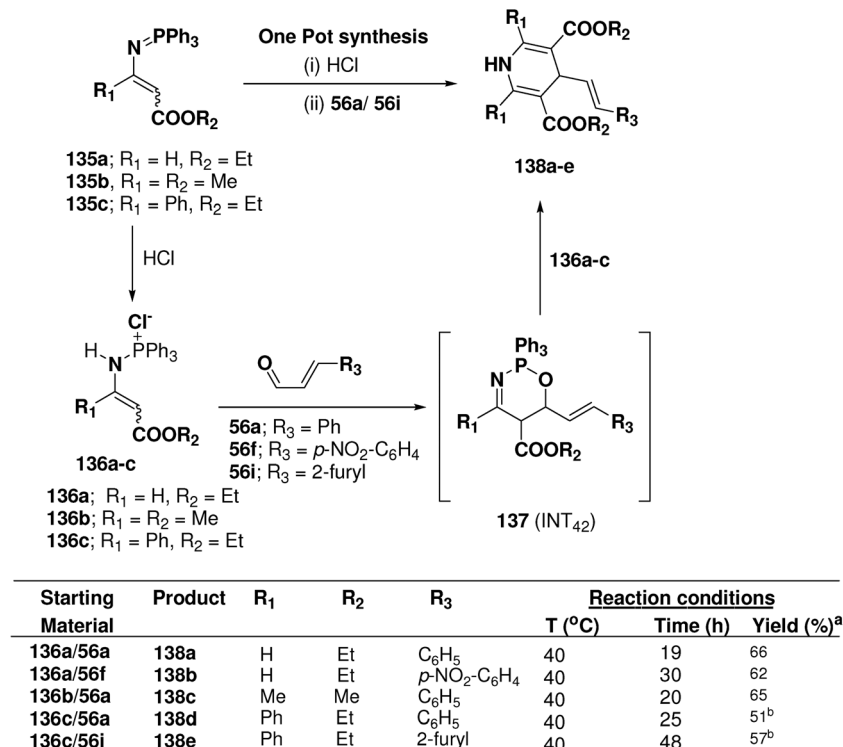
	131	56	133	(%) Yield
131a	56d	133a	89	
131a	56e	133b	70	
131a	56a	133c	89	
131a	56f	133d	79	
131a	56g	133e	39	
131a	56h	133f	66	
131a	56c	133g	84	
131b	56a	133h	54	
131c	56a	133i	71	
131c	56f	133j	71	
131c	56a	133k	77	
131d	56d	133l	31	
131d	56e	133m	32	

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



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





^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**.

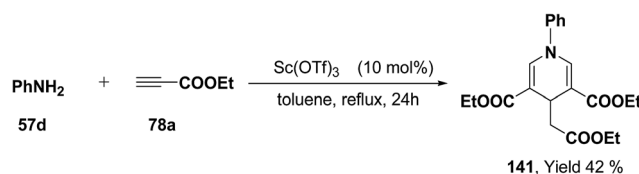
followed by acylation with trichloroacetic anhydride. The subsequent haloform reaction on **106a–e** yields **107a–e**, which on *N*-deprotection gives **108a–e** (Scheme 34).

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

Entry	Imine	R ₁	R ₂	Product 140	Yield ^b (%)
1	139a	<i>c</i> -Hex	Ph	140a	22 ^c
2	139b	<i>t</i> -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	<i>p</i> -MeOC ₆ H ₄	Ph	140f	75 ^c
7 ^d	139g	<i>p</i> -MeC ₆ H ₄	Ph	140g	62 ^c
8 ^d	139h	2,6-MeC ₆ H ₃	Ph	140h	77
9	139i	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	140i	78
10	139j	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	140j	54
11	139k	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -FC ₆ H ₄	140k	47
12	139l	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -NO ₂ C ₆ H ₄	140l	34
13	139m	<i>p</i> -MeOC ₆ H ₄	PhCH ₂ CH 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).

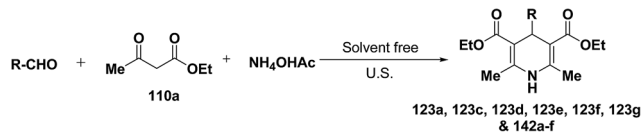


Scheme 45 Sc(OTf)₃ catalyzed reaction of aniline **57d** and **78a**: preparation of 1,4-DHP **141**.



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.

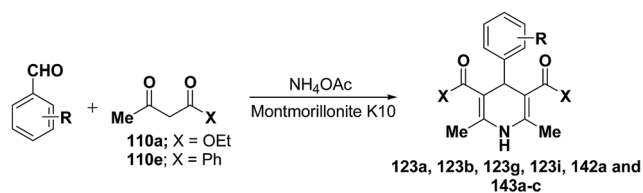
Bazureau, *et al.*⁴⁴ have developed a three component one pot microwave dielectric heating assisted liquid phase synthesis of 1,4-dihydropyridines using task specific ionic liquid as a soluble solid support. They synthesized the ILP bound aldehydes **113a–d** in high yields by the esterification of PEG-ILPs



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 ₃ O- C_6H_4 (123c)	No	60	90
8	2-Cl- C_6H_4 (123g)	No	60	82
9	$\text{C}_6\text{H}_5\text{-CH=CH}$ (142b)	No	70	90
10	3,4-(OCH ₂ O)- C_6H_3 (142c)	No	35	97
11	3-Cl- C_6H_4 (142d)	No	30	87
12	4-OH- $\text{C}_6\text{H}_3\text{-C}_6\text{H}_3$ (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.



Entry	Product (R)	Time (min)	Isolated yield (%)
1	H (123a)	30	65
2	<i>o</i> -OMe (123i)	40	83
3	<i>m</i> -NO ₂ (142a)	30	75
4	<i>o</i> -Cl (123g)	70	60
5	<i>p</i> -Me (123b)	60	60
6	<i>m</i> -NO ₂ (143a)	60	40
7	<i>o</i> -Cl (143b)	50	35
8	H (143c)	40	40

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

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

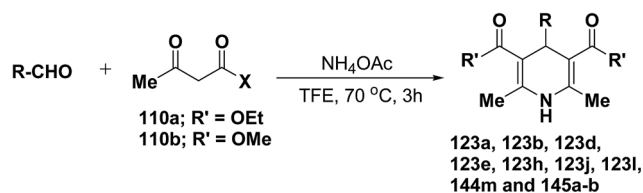
112a–d with 4-formylbenzoic acid in dry MeCN with dicyclohexylcarbodiimide (DCC) and 5% of dimethylamino pyridine (DMAP) as catalyst. The ILP bound 1,4-dihydropyridines **115** has been synthesized in an excellent yields *via* two methods. Method A involves the condensation of aldehydes **113a–d** and 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



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 ₂ N- C_6H_4 (144d)	110b	25	93
6	Me ₂ N- 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 (123i)	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 ₃ CH=CH (144k)	110b	15	93
16	CH ₃ CH=CH (144l)	110a	15	94
17	$\text{C}_6\text{H}_4\text{CH=CH}$ (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.



Entry	Product (R) ^a	R'	yield (%) ^b
1	C_6H_5 (123a)	OEt	97
2	<i>p</i> -Cl- C_6H_4 (123d)	OEt	96
3	$\text{C}_6\text{H}_5\text{CH=CH}$ (144m)	Me	95
4	cyclohexane (145a)	OEt	96
5	2-Furyl (123i)	OEt	98
6	<i>p</i> -Me- C_6H_4 (123b)	OEt	98
7	<i>p</i> -Br- C_6H_4 (123j)	OEt	97
8	<i>p</i> -OH- C_6H_4 (123e)	OEt	95
9	<i>p</i> -NO ₂ - C_6H_4 (123d)	OEt	96
10	<i>n</i> -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.

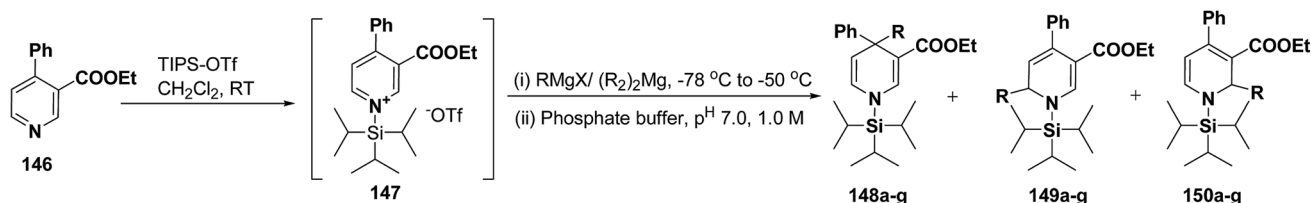


microwave reaction conditions (120 °C, 10 min) (Scheme 35). IL-phase, the bound products **115a–b** were subjected to cleavage by: (i) transesterification with 30% of MeONa in refluxed MeOH during 18 h, (ii) saponification with 60% of LiOH in THF at room temperature, followed by controlled acidification 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 NH₄OAc (2.0 equiv.) under the same microwave radiation condition. **118a–b** on transesterification followed by saponification yielded **119a–b**.

J. H. Lee⁴⁵ 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 ₂ Mg) ^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 ₂ Mg	-	- ^d	-	148a	e
3	EtMgCl	-	61/35/4	58/42	148b	20
4	Et ₂ Mg	-	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 ₂ Mg	CuBr.SMe ₂	76/14/1	44/55	148b	23
8	<i>i</i> PrMgCl	-	99/1/0	70/30	148c	63
9	<i>i</i> Pr ₂ Mg	-	100/0/0	97/3	148c	91
10	<i>t</i> BuMgCl	-	94/6/0	40/60	148d	47
11	<i>t</i> Bu ₂ Mg	-	86/14/0	89/11	148d/149d	56/5 ^f
12	AllMgCl	-	- ^d	-	148e	e
13	All ₂ Mg	-	- ^d	-	148e	e
14	BnMgCl	-	72/28/0	69/31	148f/149f	38/7
15	Bn ₂ Mg	-	50/49/1	98/2	148f/149f	45/24
16	BnMgCl	CuBe.SMe ₂	95/5/0	95/5	148f	41
17	BnMgCl	Me ₂ S ^g	85/15/0	46/54	148f	40
18	Bn ₂ Mg	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	38
21	BnMgCl	Bu ₄ N ⁺ I ⁻	90/1/-0	60/40	148f/149f	39
22	BnMgCl	Bu ₄ N ⁺ Br ⁻	92/8/0	46/54	148f	44
23	BnMgCl	Bu ₄ N ⁺ Cl ⁻	85/15/0	43/57	148f	7
24	PhMgCl	-	90/10/0	13/87	148f/149g	46
25	Ph ₂ Mg	-	98/2/0	63/37	148g	

^a Compound **146** was dissolved in CH₂Cl₂ 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 CH₂Cl₂.

^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 ($\text{HClO}_4\text{-SiO}_2$) 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 ($\text{HClO}_4\text{-SiO}_2$). 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 enamino-phosphonium salts **136a-c** derived from phosphazenes **135a-c** with α,β -unsaturated aldehydes **56a**, **56f** and **56i** (Scheme 44). The reaction of enamino-phosphonium 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 enamino-phosphonium salt **136a** to the carbonyl group of the aldehydes **56a** to give the cycloadduct intermediate 1,2,5-oxazaphosphoranes **137** (INT₄₂) 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 $\text{Sc}(\text{OTf})_3$ 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**/



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 ₂ O ₃ (0.2g)	20	90
8	40 wt% SiW/g-Al ₂ O 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% PMo/SiO ₂ (0.2g)	5	85
15	40 wt% PW/SiO ₂ (0.2g)	5	90
16	20 wt% PW/SiO ₂ (0.2g)	9	35
17	60 wt% PW/SiO ₂ (0.2g)	9	50
18	40 wt% PW/SiO ₂ (0.14g)	5	40
19	40 wt% PW/SiO ₂ (0.4g)	5	30

^aIsolated yield, based on benzaldehyde

H₃PW₁₂O₄₀ (PW), H₄SiW₁₂O₄₀ (SiW), and H₃PMo₁₂O₄₀ (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/SiO₂ as catalyst

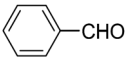
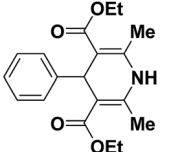
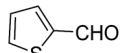
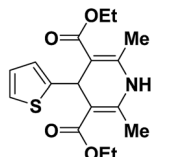
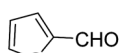
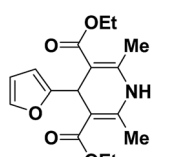
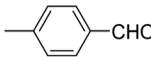
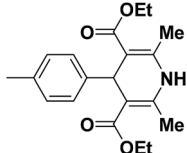
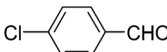
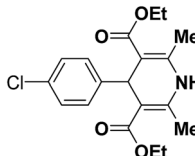
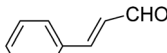
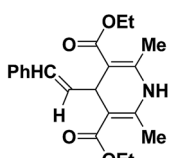
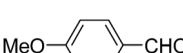
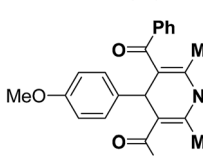

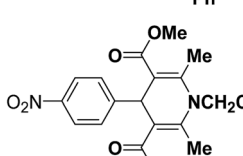
Entry	Aldehyde	X	Amine	Product	Product no.	Time (min)/% yield ^a (%)
1		OEt	NH ₄ OAc		123a	5/190
2		OEt	NH ₄ OAc		123m	13/94
3		OEt	NH ₄ OAc		123l	4/98
4		OEt	NH ₄ OAc		123b	35/96
5		OEt	NH ₄ OAc		123d	8/92
6		OMe	NH ₄ OAc		142b	20/91
7		Ph	NH ₄ OAc		151a	32/55
8		OMe	OH(CH ₂) ₂ NH ₂		151b	15/86



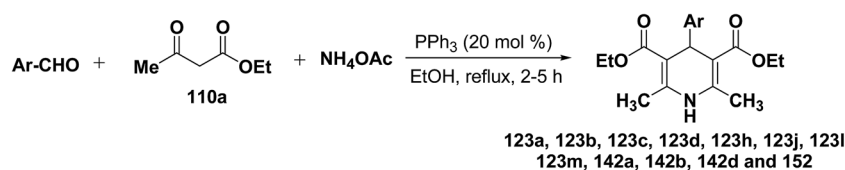
Table 14 (Contd.)

Entry	Aldehyde	X	Amine	Product	Product no.	Time (min)/% yield ^a (%)
9		OMe	OH(CH ₂) ₂ NH ₂		151c	20/84
10 ^b		OMe	OH(CH ₂) ₂ NH 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 NH₄OAc 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 NH₄OAc using barium nitrate as a efficient catalyst to afford 1,4-dihydropyridines **123n**, **123f**, **123l**, **142a** and **144a–q** (Scheme 48).



Entry	Product (Ar)	Time (h)	Yield ^a (%)
1	C ₆ H ₅ (123a)	3	72
2	4-Me-C ₆ H ₄ (123b)	3.5	90
3	4-MeO-C ₆ H ₄ (123c)	3	75
4	3-Cl-C ₆ H ₄ (142d)	3	85
5	4-Cl-C ₆ H ₄ (123d)	2	81
6	3-NO ₂ -C ₆ H ₄ (142a)	4.5	94
7	4-NO ₂ -C ₆ H ₄ (123h)	2	92
8	4-Br-C ₆ H ₄ (123j)	3.5	93
9	3,5-Cl ₂ -C ₆ H 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.



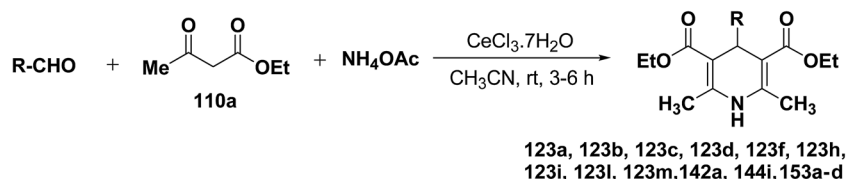
Heydari, *et al.*⁵⁸ has synthesized 1,4-dihydropyridines **123a**, **123b**, **123d**, **123e**, **123h**, **123j**, **123l**, **144m** and **145a–b** in excellent yields by the reaction of aldehydes, alkyl acetoacetate **110a–b**, and ammonium acetate (Scheme 49) at 70 °C in trifluoroethanol (TFE). 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-dihydropyridines **148a–g** by the regioselective addition of Grignard reagents RMgX or R₂Mg 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 SiO₂ (0.2 g) under solvent-free condition has been found to be the best catalyst for the synthesis of 1,4-dihydropyridines.

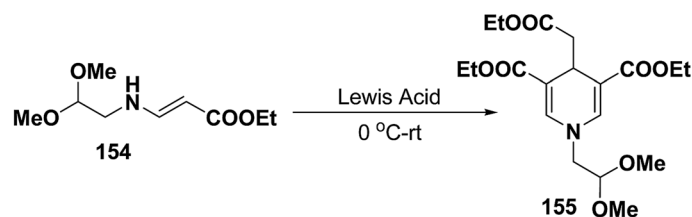
A series of 4-aryl, *N*-alkyl, and *N*-aryl substituted 1,4-dihydropyridines **123a**, **123b**, **123m**, **123l**, **123d**, **142b** and **151a–f** have been synthesized using different aldehydes in good to excellent yield in short reaction times (Table 14).



Entry	Product (R)	Time (h)	Yield ^a (%)
1	C ₆ H ₅ (123a)	3	80
2	4-OMe-C ₆ H ₄ (123c)	4	82
3	4-F-C ₆ H ₄ (153d)	3.5	86
4	4-Cl-C ₆ H ₄ (123d)	4	91
5	4-CH(CH ₃) ₂ -C ₆ H ₄ (153a)	5	81
6	4-C(CH ₃) ₃ -C ₆ H ₄ (153b)	5	86
7	4-NO ₂ -C ₆ H ₄ (123h)	3.5	82
8	2-NO ₂ -C ₆ H ₄ (123f)	5.6	65
9	3-NO ₂ -C ₆ H ₄ (142a)	5	71
10	β-Naphthyl (144i)	5	72
11	4-Me-C ₆ H ₄ (123b)	3	82
12	2-OMe-C ₆ H 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 CeCl₃·7H₂O-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 ₂ AlCl	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 $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ -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 $\text{BF}_3 \cdot \text{OEt}_2$, 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 $\text{TsOH} \cdot \text{H}_2\text{O}$, TFA or $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ 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 $\text{TsOH} \cdot \text{H}_2\text{O}$ as a catalyst (85–87%; Table 15, entries 6 and 7).



Entry	Acrylate	R	TiCl_4 (equiv)	Product	Yield (%)
1	156a	<i>n</i> -Bu	0.2	157a	81
2	156b	<i>n</i> -C ₁₈ H ₃₇	0.2	157b	83
3	156c	Bn	0.2	157c	79
4	156d	HOCH ₂ CH ₂	0.2	157d	81
5	156e	Ph	0.5	141	82
6	156f	<i>p</i> -MeO-C ₆ H ₄	0.2	157e	52
7	156f	<i>p</i> -MeO-C ₆ H ₄	0.5	157e	76
8	156g	<i>p</i> -I-C ₆ H ₄	0.2	157f	58
9	156g	<i>p</i> -I-C ₆ H ₄	0.5	157f	79
10	156h	<i>p</i> -F-C ₆ H ₄	0.5	157g	70
11	156i	<i>m</i> -Cl-C ₆ H ₄	0.5	157h	76

Scheme 55 TiCl_4 catalyzed 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 $\text{Yb}(\text{OTf})_3$ -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.

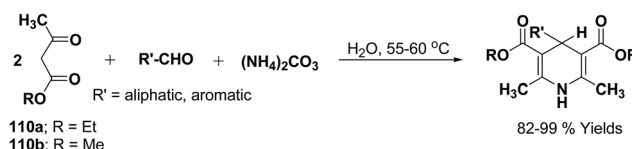
2.3. Synthesis of enantiopure 1,4-dihydropyridines

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**

Entry	<i>p</i> -NO ₂ -C ₆ H ₄ -CHO (eq.)	Catalyst (mol%)	Time (h)	% yield of 159a ^a
1	0.75	$\text{Sc}(\text{OTf})_3$ (5)	12	34
2	0.75	$\text{TsOH} \cdot \text{H}_2\text{O}$ (10)	3	75
3	0.75	TFA (10)	5	71
4	1.0	$\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ (5)	1	79
5	1.0	TFA (5)	20	91
6	1.0	$\text{TsOH} \cdot \text{H}_2\text{O}$ (10)	1	85
7	1.0	$\text{TsOH} \cdot \text{H}_2\text{O}$ (5)	1	87
8	1.0	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10)	3	48
9	1.0	—	10	NR ^b

^a Isolated yields. ^b NR = no reaction.

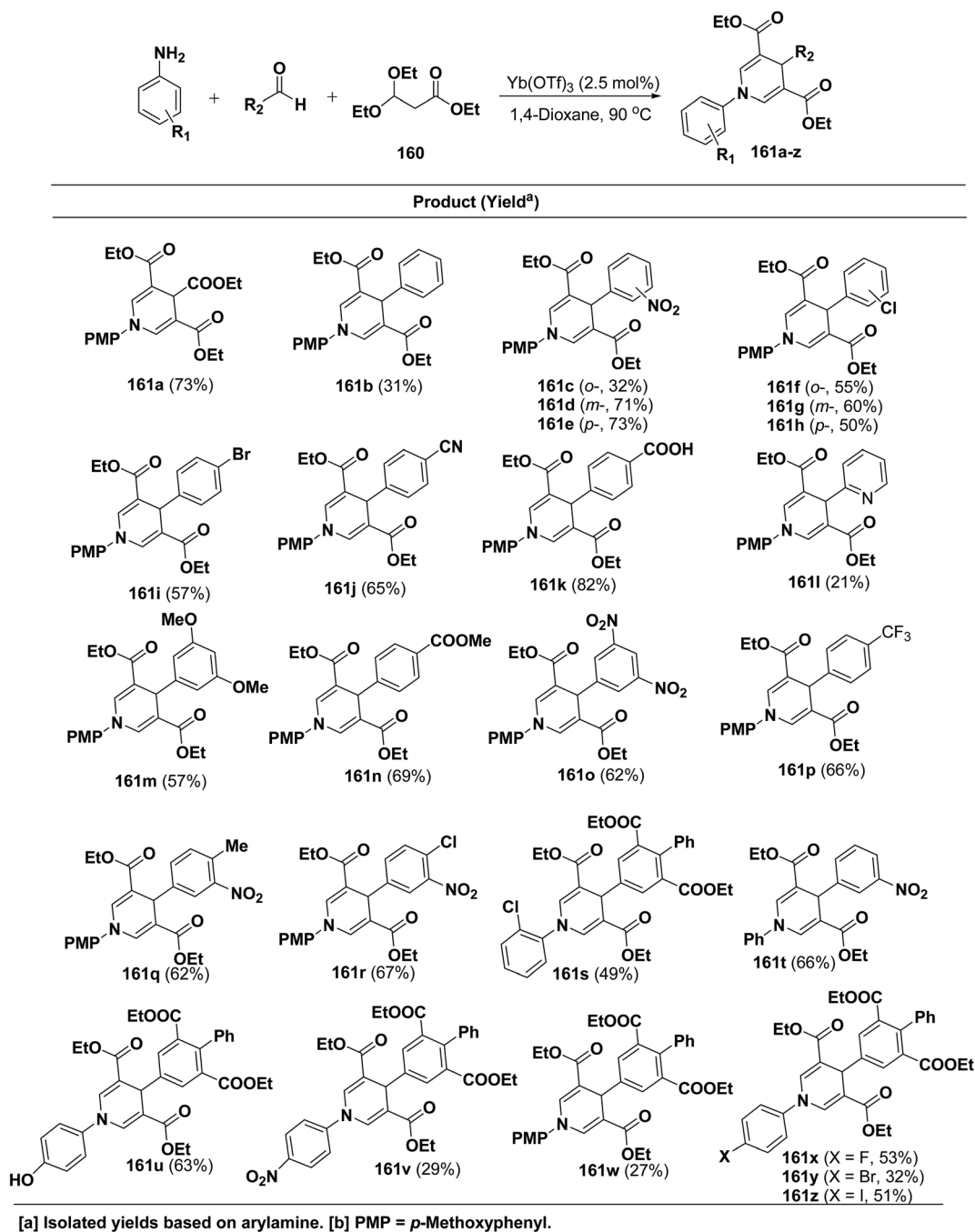


Scheme 56 Synthesis of 1,4-dihydropyridines using ammonium carbonate in water.

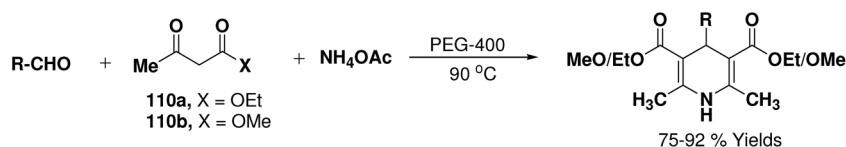


with the use of resolving agents to form diastereomeric salts is a widely used technique for resolving chiral compounds. Cinchonidine, cinchonine and quinidine are the most commonly

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 7 Yb(OTf)₃ catalyzed one-pot synthesis of 1,4-DHPs 161a–z.



Scheme 8 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 Shibamura, *et al.*⁶⁸ to synthesize nicardipine from 1-ethoxymethyl-5-methoxycarbonyl-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (\pm)-**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

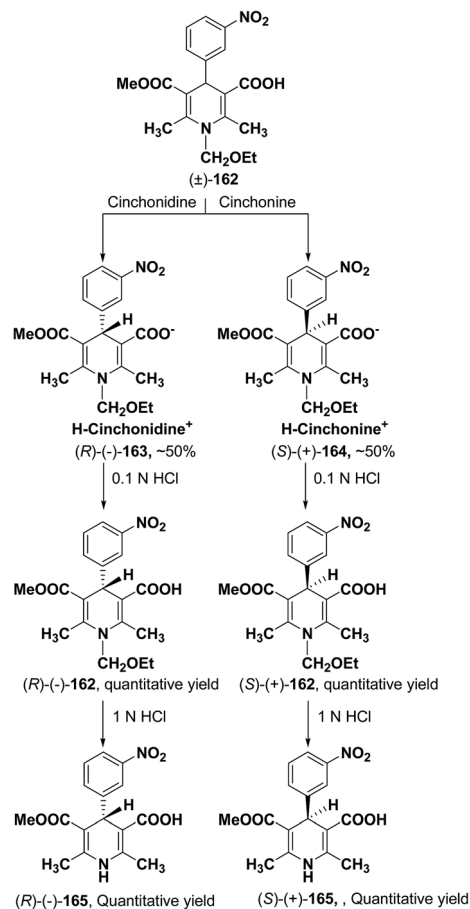
Synthesis of optically-active 1,4-dihydropyridine derivatives from 1-ethoxymethylated carboxylic acid **162** involves protection and deprotection approach for NH group in 1,4-DHP ring. Use of unprotected racemic acid for direct resolution has also been investigated in detail. Zhang, *et al.*⁷⁰ treated racemic acid (\pm)-**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

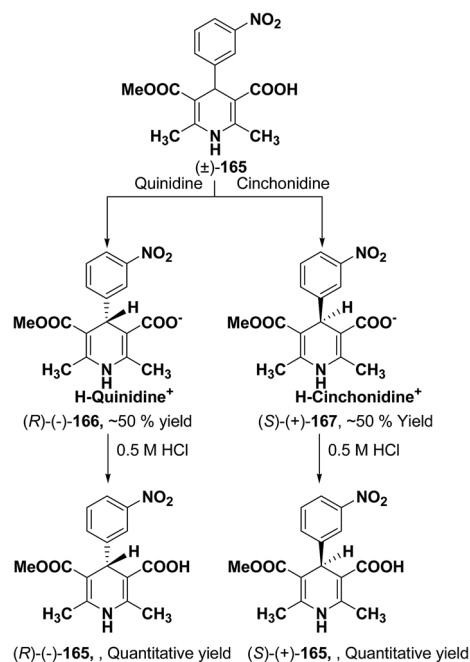
Various chiral acids have been used for the separation of racemic basic dihydropyridines. Racemic amlodipine **170** has been resolved using (1*S*)-(-)-camphanic acid chloride (Scheme 62) by Goldmann, *et al.*⁷² The diastereomeric amides **171** obtained were easily separated chromatographically on Chiralcel 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/H₂O (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.

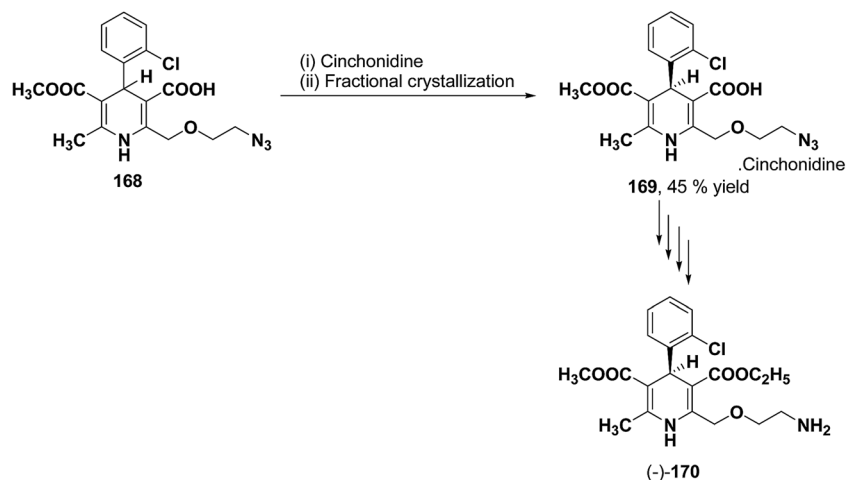


pyridines have been achieved by Taylor, *et al.*⁷⁵ The monoester derivative **174** was reacted with nitrile oxide to produce isoxazolo[5,4-*b*]pyridine **175** in 74% yield (Scheme 64). Its saponification formed an acid which was then re-esterified with (–)-menthol. The resulting diastereomeric esters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

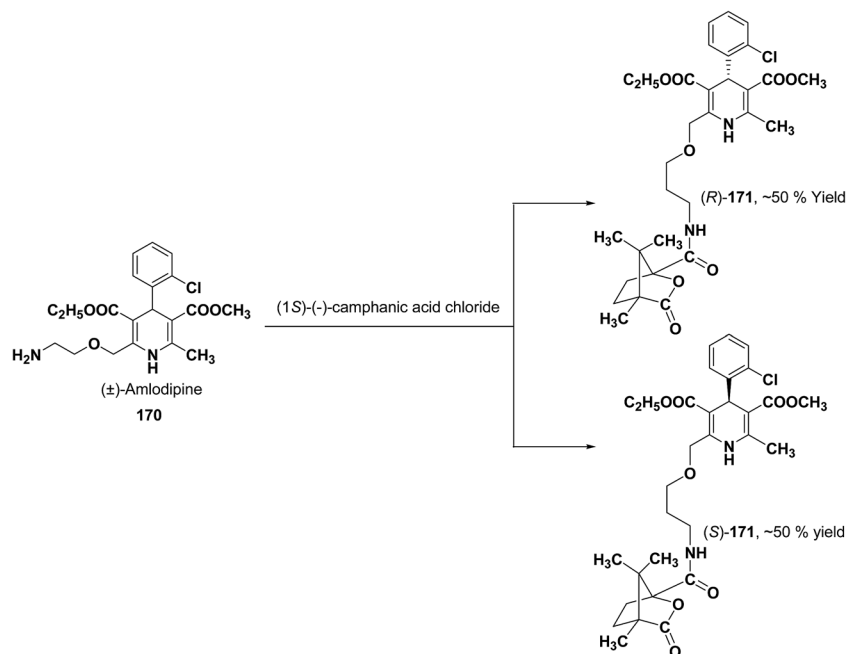
Arrowsmith, *et al.*⁷⁶ esterified (±)-**178** using optically pure (*S*)-(+)-2-phenylethanol to give diastereomeric mixture **179**. It was chromatographically separated on silica gel to form pure diastereomers and further treatment with sodium ethoxide and finally reduction of azide group by palladium 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.



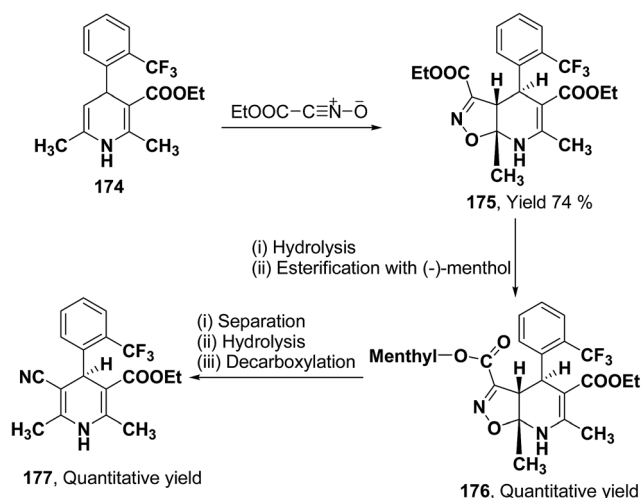
Hantzsch condensation afforded the mixture of 1,4-DHP diastereomers **188** separable by silica gel column chromatography. This was followed by removal of chiral auxiliary using DBU to yield **189** and desired enantiopure (–)-**190** and (+)-**190** were synthesized using isopropyl bromide and potassium 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-carboxylate⁷⁹ **192** exhibiting dual cardioselective agonist/smooth muscle selective antagonist activity⁸⁰ 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*-isopropylidene-*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*-isopropylidene-*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**.

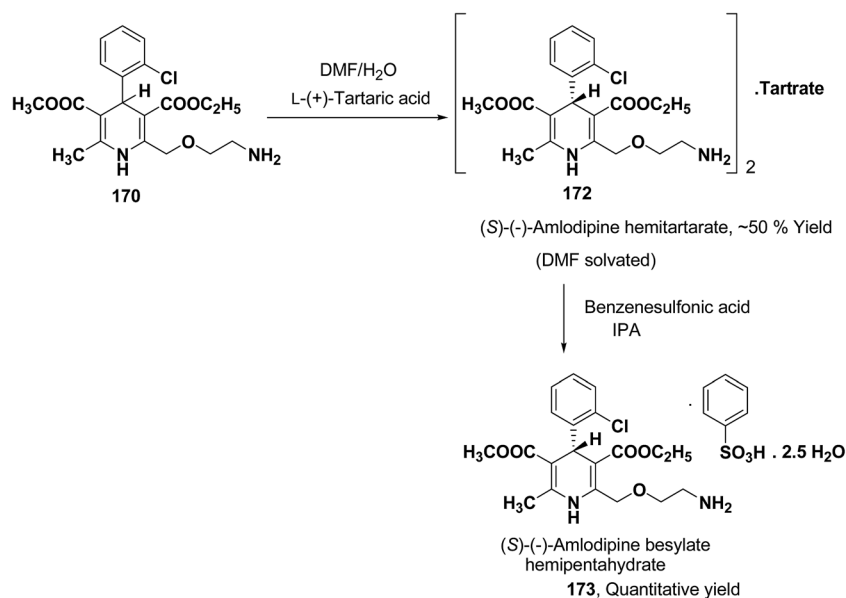
2.3.3. Synthesis of enantiomerically pure 1,4-DHPs using chiral aldehydes. Synthetic methodology to synthesize 4-alkyl-3,5-dialkoxy carbonyl-2,6-dimethyl-1,4-dihydropyridines **200a–c** has been developed by utilizing chiral aldehydes **198a–c** (Scheme 69).⁸² Enantiomerically pure 1,4-DHPs **200a–c** 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



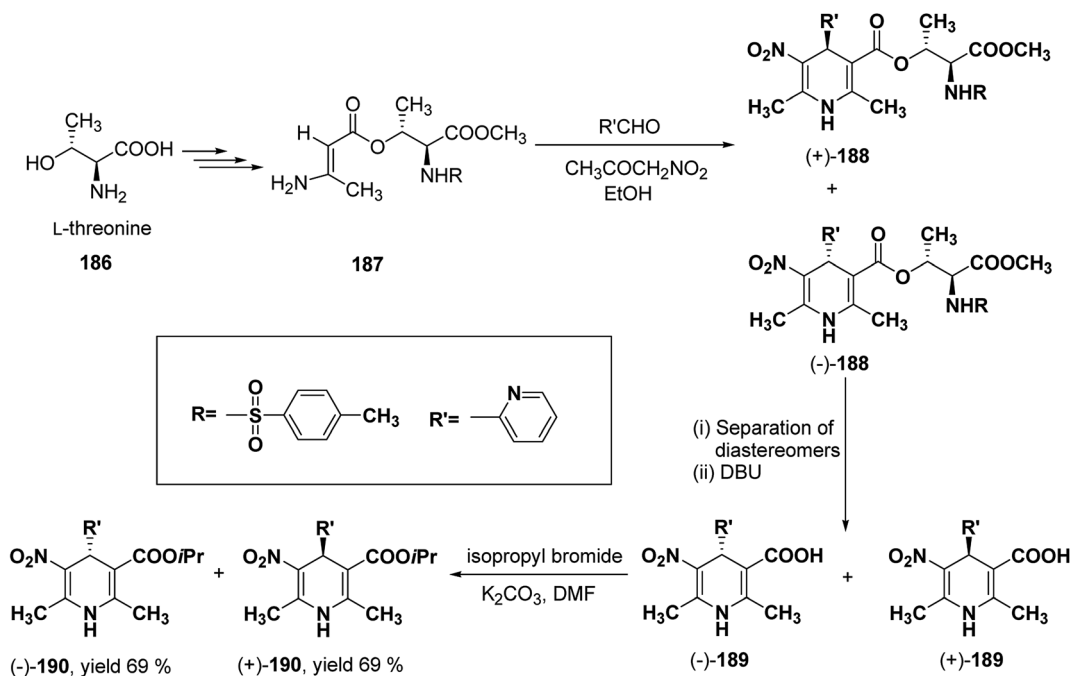
Scheme 64 Separation of **174** using nitrile oxide as a chiral auxiliary.

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





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

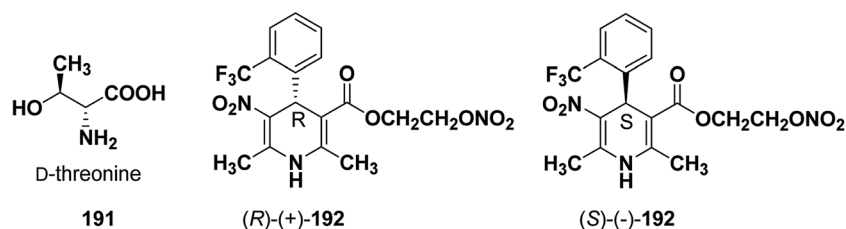


Fig. 2 Structures of D-threonine 191 and 2-nitroxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate 192.

The synthesis of (\pm)-elaekanine 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 (\pm)-elaekanine 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

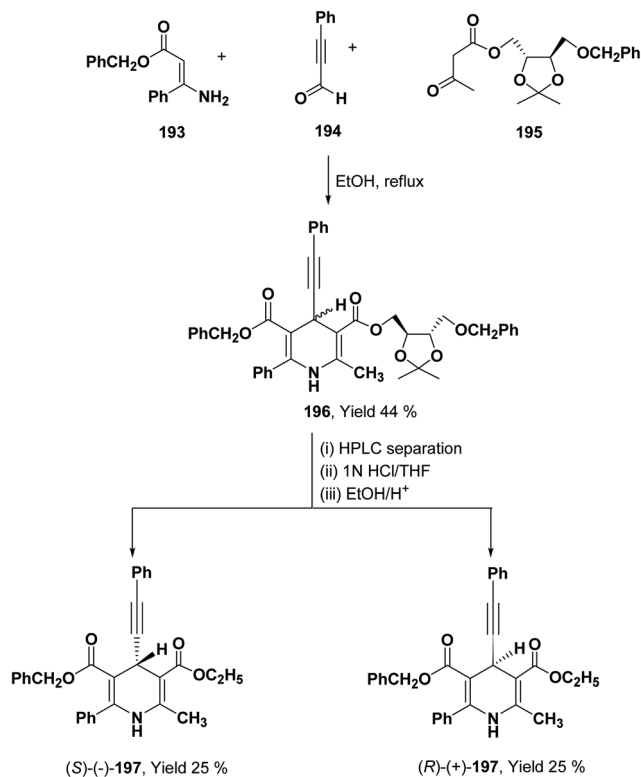
2,3-Disubstituted-1,2-dihydropyridines **224** and **225** have been synthesized from the 3-substituted pyridinium salts **222** and **223**, respectively (Scheme 75). This methodology has been applied for the synthesis of (-)-L-733 061 (**226**) and (-)-CP-

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 C₆N₄ 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



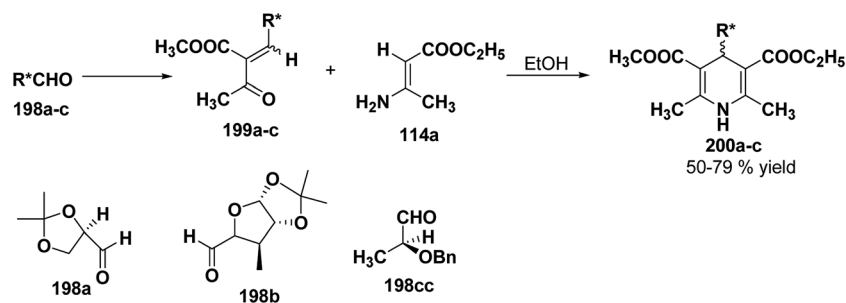


Scheme 68 Use of (4*R*,5*R*)-(-)-2,3-*O*-isopropylidene-D-threitol was used as chiral auxiliary in the separation of 1,4-DHP.

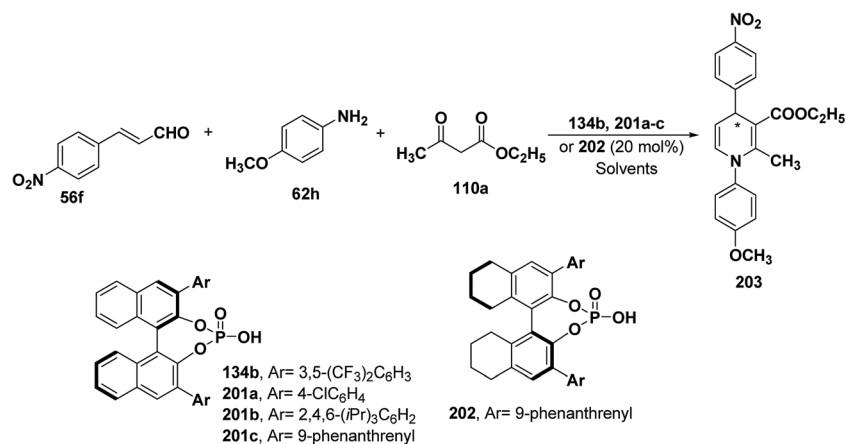
Table 16 Effect of phosphonic acids 134b, 201a–c and 202 and increase in the reaction temperature on the enantioselectivity of 203

Catalyst	Solvent	Temperature (°C)	Yield (%)	ee (%)	Product
201a	CHCl ₃	25	72	19	(<i>S</i>)-203
134b	CHCl ₃	25	85	19	(<i>S</i>)-203
201b	CHCl ₃	25	62	31	(<i>S</i>)-203
201c	CHCl ₃	25	67	73	(<i>S</i>)-203
201c	CHCl ₃	40	80	80	(<i>S</i>)-203
201c	CHCl ₃	50	85	82	(<i>S</i>)-203
201c	PhCN	50	82	89	(<i>S</i>)-203
202	CHCl ₃	25	69	64	(<i>R</i>)-203
202	CHCl ₃	50	86	72	(<i>R</i>)-203
202	PhCN	50	83	90	(<i>R</i>)-203
202 (10 mol%)	PhCN	50	82	92	(<i>R</i>)-203

Marine metabolites pyrrole-2-aminoimidazole oridine, 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

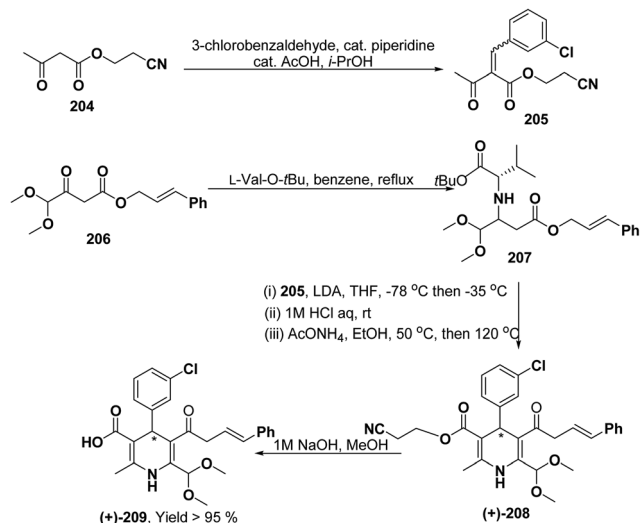


Scheme 69 Synthesis of chiral 1,4-DHPs 200a–c using chiral aldehydes.



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

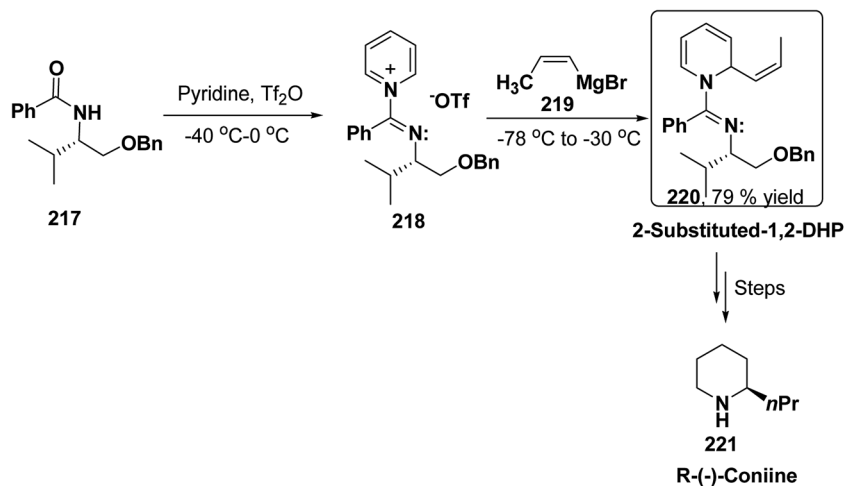
Stereoselective synthesis of *L*-picolic acid and (2*S*,3*S*)-3-hydroxypipercolic acid were achieved from a chiral 1,2-dihydropyridine intermediate **244**. *L*-Picolic acid **248** has been obtained *via* reduction of **244** to **245**, removal of chiral auxiliary yields **246**, oxidation yields **247** and basic hydrolysis of **247** yields *L*-picolic acid **248**. (2*S*,3*S*)-3-Hydroxypipercolic 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-Hydroxypipercolic acid is found in febrifugine a potent antimalarial agent. Both *L*-picolic acid and (2*S*,3*S*)-3-hydroxypipercolic 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·H₂O 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 dihydropyridine–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-picolinic acid and (2S,3S)-3-hydroxypicolinic 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 desulfurisation 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 $\text{Me}_2\text{N}^+=\text{CH}_2\text{I}^-$. 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 $\text{C}_6\text{H}_5\text{SeBr}$ -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 $\text{Me}_2\text{N}^+=\text{CH}_2\text{I}^-$ promoted cyclization has been further reported by Bennasar, *et al.*⁹⁹

The first total synthesis of (\pm)-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 debenzoylation 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.

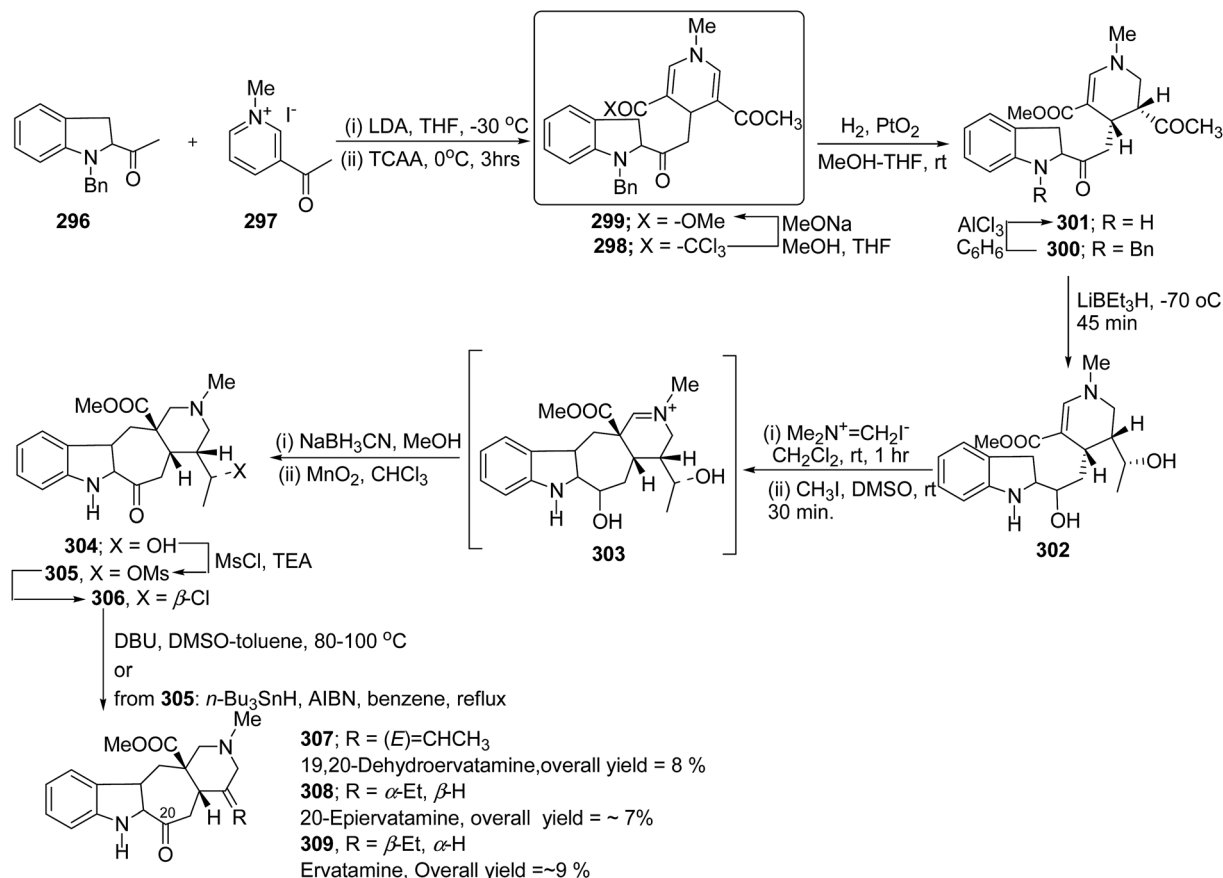


Scheme 86 Synthesis of (\pm)-2,7-dihydropleiocarpamine 295.

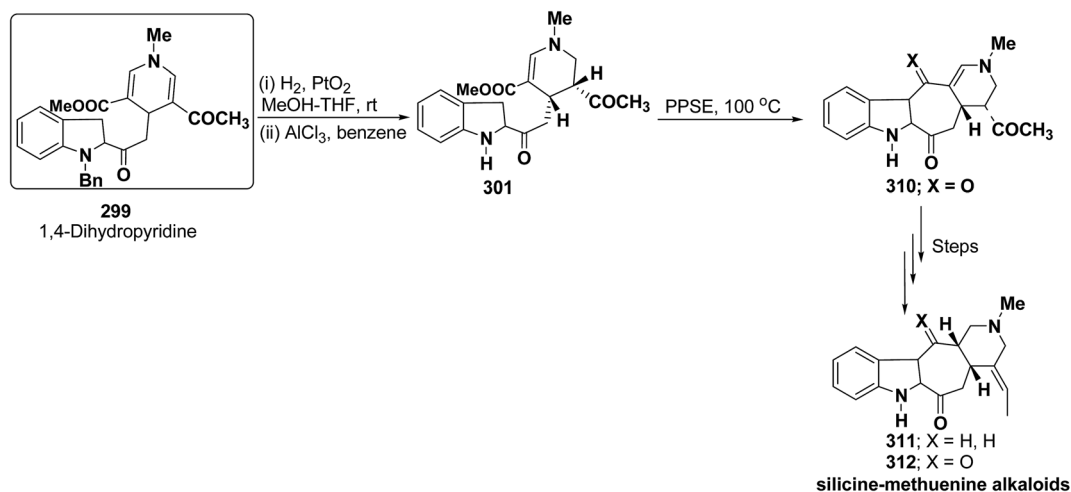


Bennasar, *et al.*¹⁰³ has reported a general route for the synthesis of 6-oxo-16-episilicine **320** (a silicine-methuenine alkaloid), involving the nucleophilic addition of an acetylindole enolate **296** to the pyridinium salt **284** to yield 1,4-dihydropyridine **313** as an intermediate. The 1,4-dihydropyridine **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·H₂O, 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 NaBH₃CN



Scheme 77 Synthesis of 19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**.



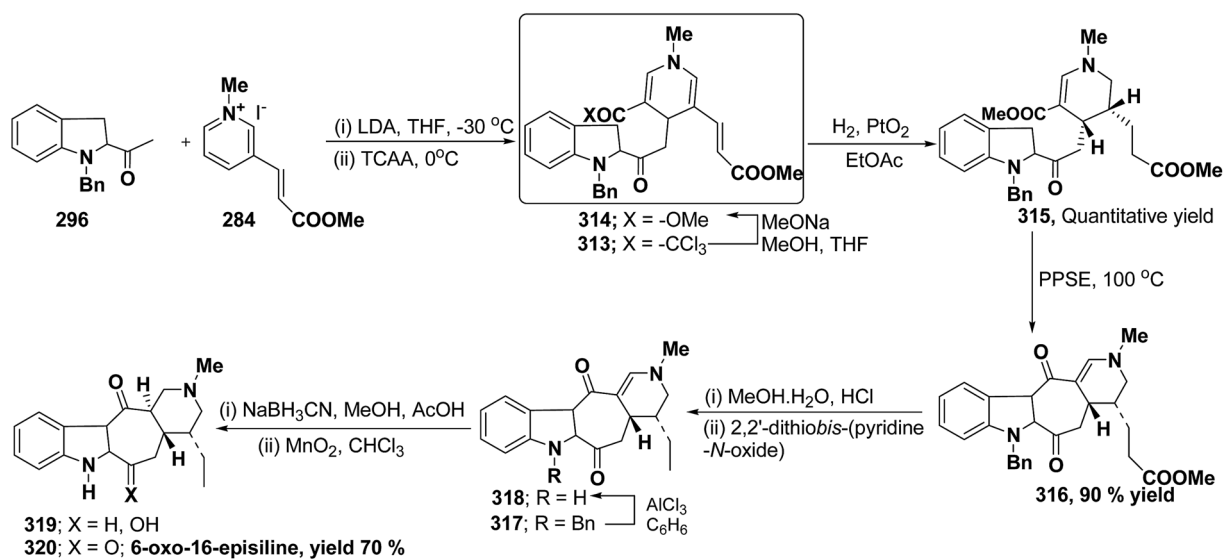
Scheme 78 Synthesis of silicine-methuenine alkaloids **311** and **312**.



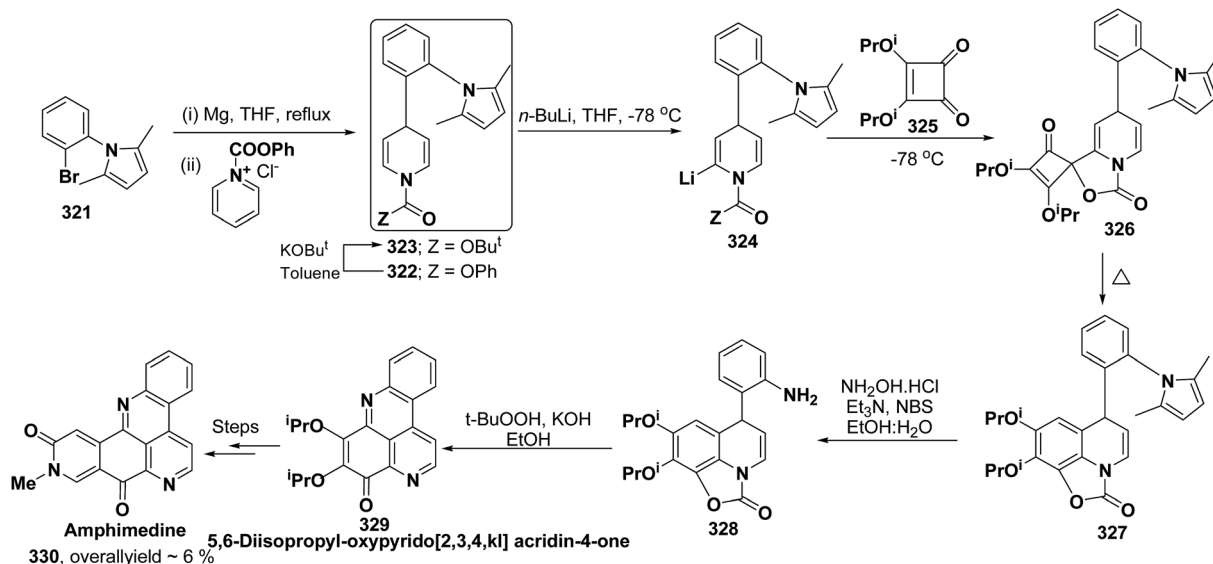
yields **319**, which on oxidation with MnO_2 yield 6-oxo-16-episilicine **320** (Scheme 89).

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 ^tbutyl-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*-carboxypyridinium 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

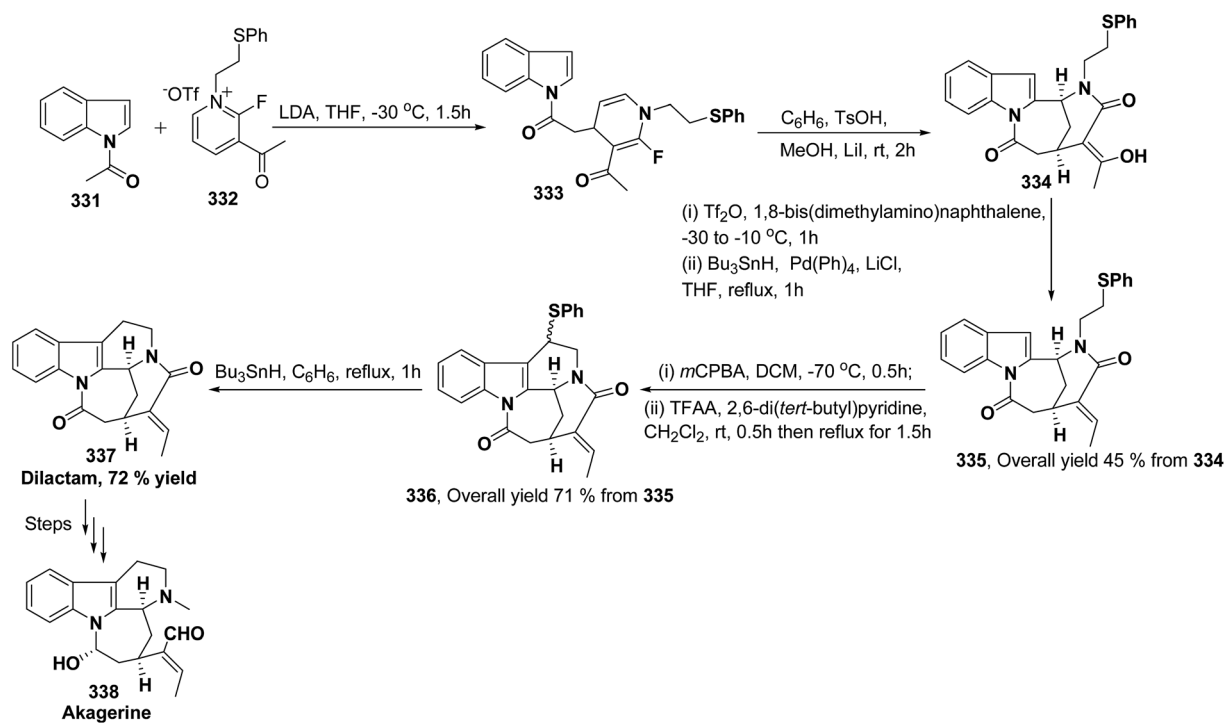


Scheme 89 Synthesis of 6-oxo-16-episilicine **320**.

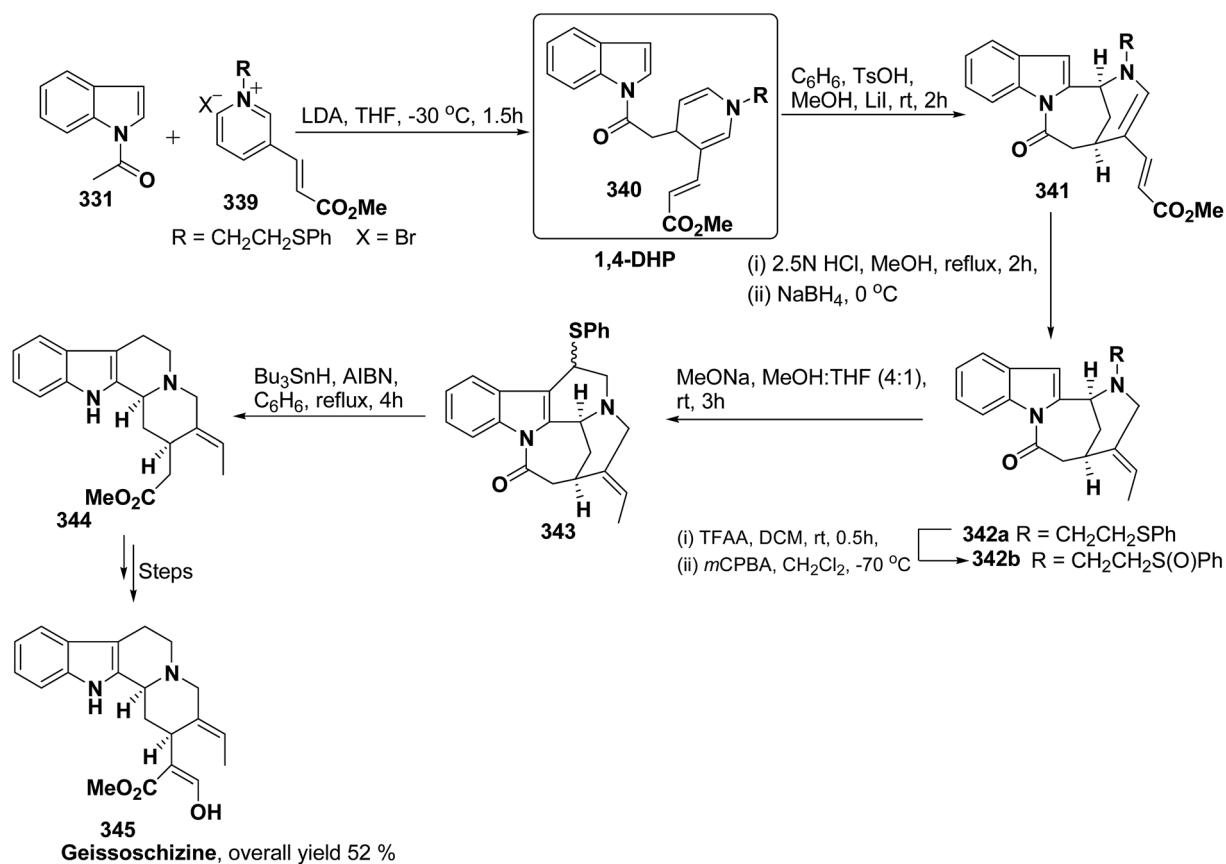


Scheme 90 Synthesis of 5,6-diisopropyl-oxy pyrido[2,3,4,kl]acridin-4-one **330**.





Scheme 91 Synthesis of dilactam 337.

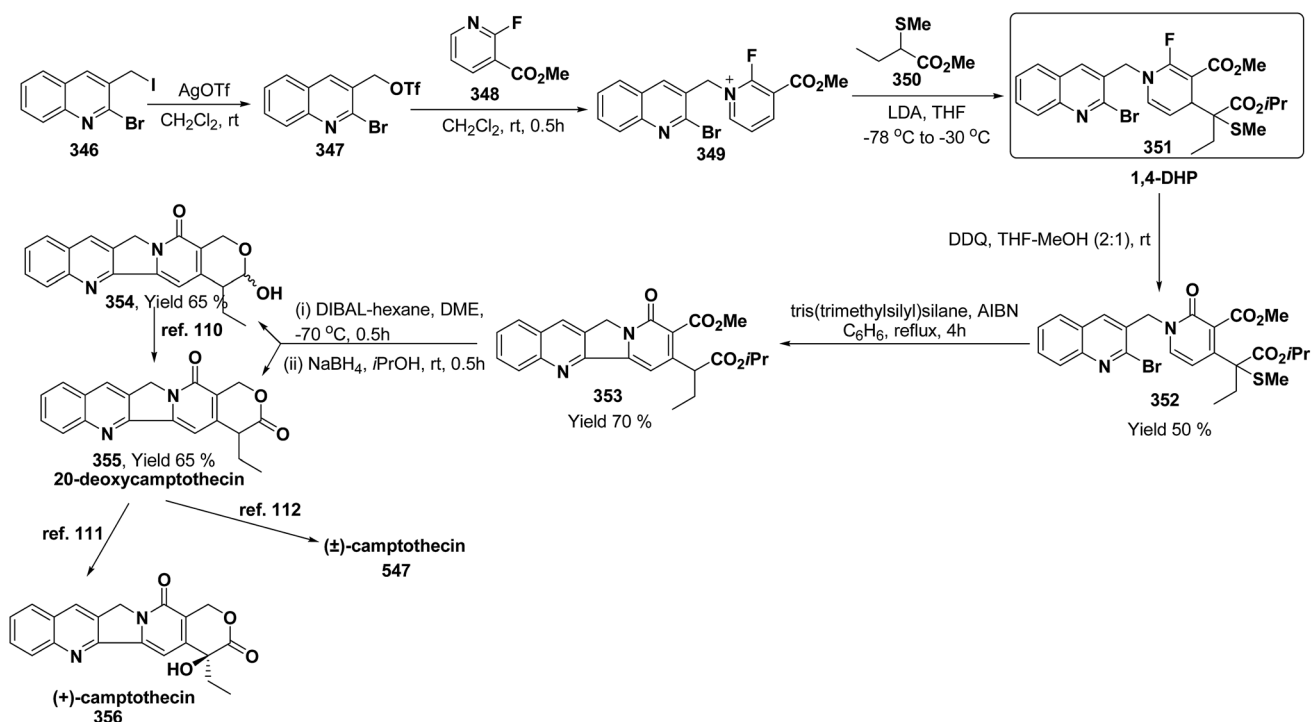


Scheme 92 Synthesis of geissoschizine 345.

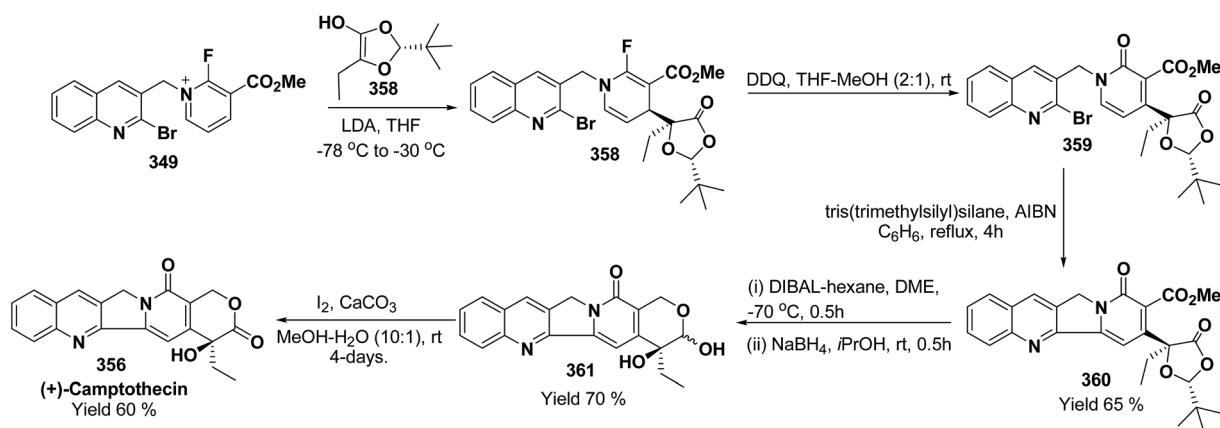


Formal synthesis of (\pm)-geissoschizine had been carried out using 1,4-dihydropyridine derivative **340**.¹⁰⁷ The 1,4-dihydropyridine derivative **340** was synthesized from nucleophilic attack of the *N*-acetyl indole **331** on pyridinium salt **339**. Compound **340** was converted into **341** using 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 desulfurisation 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 (\pm)-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 (\pm)-camptothecin and natural (+)-camptothecin *via* the literature procedure.¹¹⁰



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

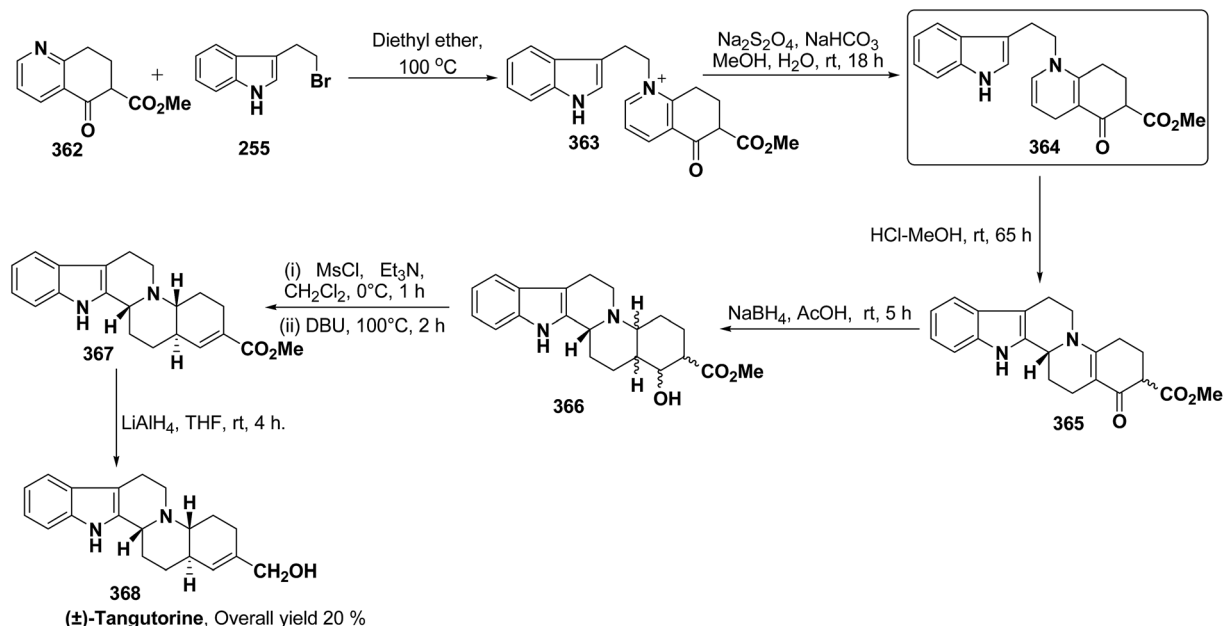


Scheme 94 Synthesis of (+)-camptothecin **356**.



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 (\pm)-tangutorine **368** and modified the first synthetic procedure reported by Berner, *et al.*¹¹² For the synthesis of (\pm)-tangutorine **368**, desired quinoline derivative **362** was reacted with



Scheme 95 Synthesis of (\pm)-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 (\pm)-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**. (\pm)-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 Bannasar, *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 activity¹²¹ *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

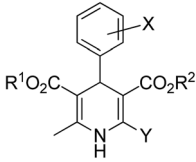
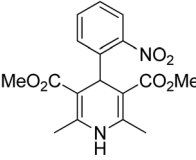
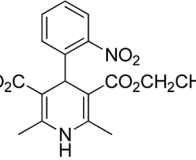
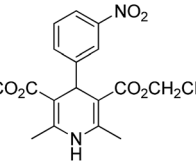
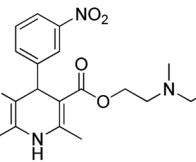
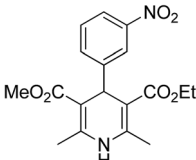
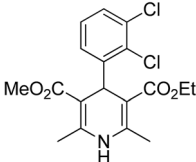
	DHP Drug	Brand name	X	R ¹	R ²	Y
1st generation						
	Nifedipine	Procardia, Adalat	2-NO ₂	-Me	-Me	Me
2nd generation						
	Nisoldipine	Baymycard, Sular, Syscor	2-NO ₂	-Me	-CH ₂ CHMe ₂	Me
	Nimodipine	Nimotop	3-NO ₂	-CHMe ₂	-CH ₂ CH ₂ OMe	Me
	Nicardipine	Cardene, Carden SR	3-NO ₂	-Me	-CH ₂ CH ₂ N(Me)CH ₂ Ph	Me
	Nitrendipine	Cardif, Nitrepin, Baylotensin	3-NO ₂	-Me	-Et	Me
	Felodipine	Plendil	2,3-Di-Cl	-Me	-Et	Me



Table 17 (Contd.)

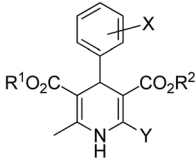
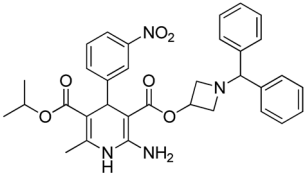
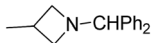
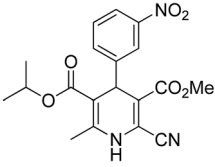
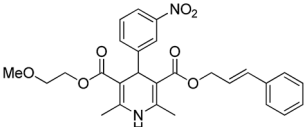
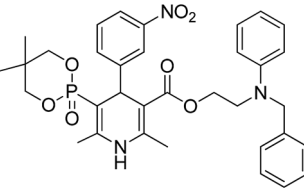
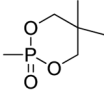
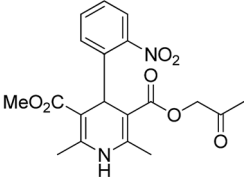
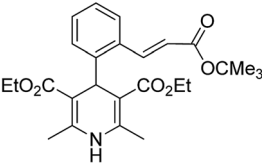
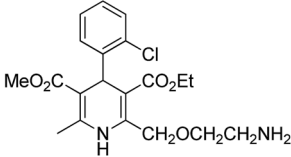
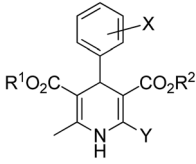
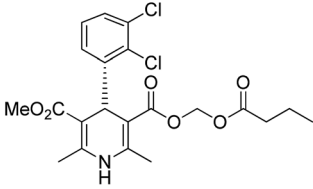
	Brand name	X	R ¹	R ²	Y
 Azelnidipine	Calblock	3-NO ₂	-CHMe ₂		NH ₂
 Nilvadipine	Nilvadil	3-NO ₂	-CHMe ₂	-Me	CN
 Cilnidipine	Atelec, Cinalong, Siscard	3-NO ₂	-CH ₂ CH ₂ OMe	-CH ₂ CH=CHPh	Me
 Efonidipine	Landel	3-NO ₂		-CH ₂ CH ₂ N(Ph)CH ₂ Ph	Me
 Aranidipine	Sapresta	2-NO ₂	-Me	-CH ₂ COCH ₃	Me
 Lacidipine	Motens, Lacipil	2-CH=CHCO ₂ Me ₃	-Et	-Et	Me
 Amlodipine	Norvasc, Amlodin	2-Cl	-Me	-Et	CH ₂ OCH ₂ CH ₂ NH ₂



Table 17 (Contd.)

	Brand name	X	R ¹	R ²	Y
	Cleviprex	2,3-Di-Cl	-Me	-CH ₂ OCO _n Pr	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 vasospasm¹²⁷ and pulmonary hypertension, Raynaud's phenomenon.¹²⁸

5. Conclusion

Dihydropyridine (DHP) scaffold has certainly revolutionised 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 stereo-selective 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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