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*Review*

# Recent Approaches to Chiral 1,4-Dihydropyridines and their Fused Analogues

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**Abstract:** The purpose of this review is to highlight recent developments in the synthesis of chiral 1,4-dihydropyridines and their fused analogues. 1,4-Dihydropyridines are among the most active calcium antagonists that are used for the treatment of hypertension. Enantiomers of unsymmetrical 1,4-dihydropyridines often show different biological activities and may have even an opposite action profile. Hantzsch synthesis usually produces racemic mixtures of unsymmetrical 1,4-dihydropyridines. Therefore, the development of stereoselective synthesis of 1,4-dihydropyridines is one of the priorities of medicinal chemistry. Over the years, numerous methodologies have been developed for the production of enantiopure 1,4-dihydropyridines, such as stereoselective synthesis using chiral auxiliaries and chiral cyclocondensation partners, chromatographical methods, resolution of diastereomeric 1,4-dihydropyridine salts, enzyme catalysed kinetic resolution, or asymmetrisation of ester groups of 1,4-dihydropyridines. These approaches have been studied in detail and are relatively well established. The catalytic asymmetric approach holds the greatest promise in delivering the most practical and widely applicable methods. Substantial progress has been made toward the development of enantioselective organocatalytic methods for the construction of the chiral dihydropyridines. However, most of them do not provide a convenient way to pharmacologically important 1,4-dihydropyridine-3,5-dicarboxylates. Organocatalytic enantioselective desymmetrisation of prochiral 1,4-dihydropyridine-3,5-dicarbaldehydes also has great promise in the synthesis of pharmacologically important 1,4-dihydropyridine-3,5-dicarboxylates.

**Keywords:** six-membered N-heterocycles; 1,4-dihydropyridines; calcium channel antagonists; chirality; enzyme-catalysed hydrolysis; resolution of diastereomeric salts; separation; multicomponent reactions; asymmetric synthesis; organocatalysis

## 1. Introduction

1,4-Dihydropyridines (1,4-DHP) belong to the most beneficial scaffolds with unprecedented biological properties that are investigated by pharmaceutical research providing medicines for the treatment of various diseases [1,2]. It is worth underlining that, according to Triggle, 1,4-DHP is a privileged structure that can interact at diverse receptors and ion channels and receptors of the G-protein class, when scaffold is properly substituted [3]. 4-Aryl-1,4-DHP derivatives are among the most active calcium antagonists [4]. The intensive investigations of 1,4-DHPs encouraged by successful introduction of nifedipine in early 1970s [5] by Bayer AG led to the development of several generations of calcium antagonists, possessing longer lasting antihypertensive activity, better tissue selectivity,

and gradual onset of activity. Some representatives of the class are felodipine, isradipine, nicardipine (second generation), amlodipine, barnidipine, and lercanidipine (third generation), and cilnidipine (fourth generation) (Figure 1) [6–8].

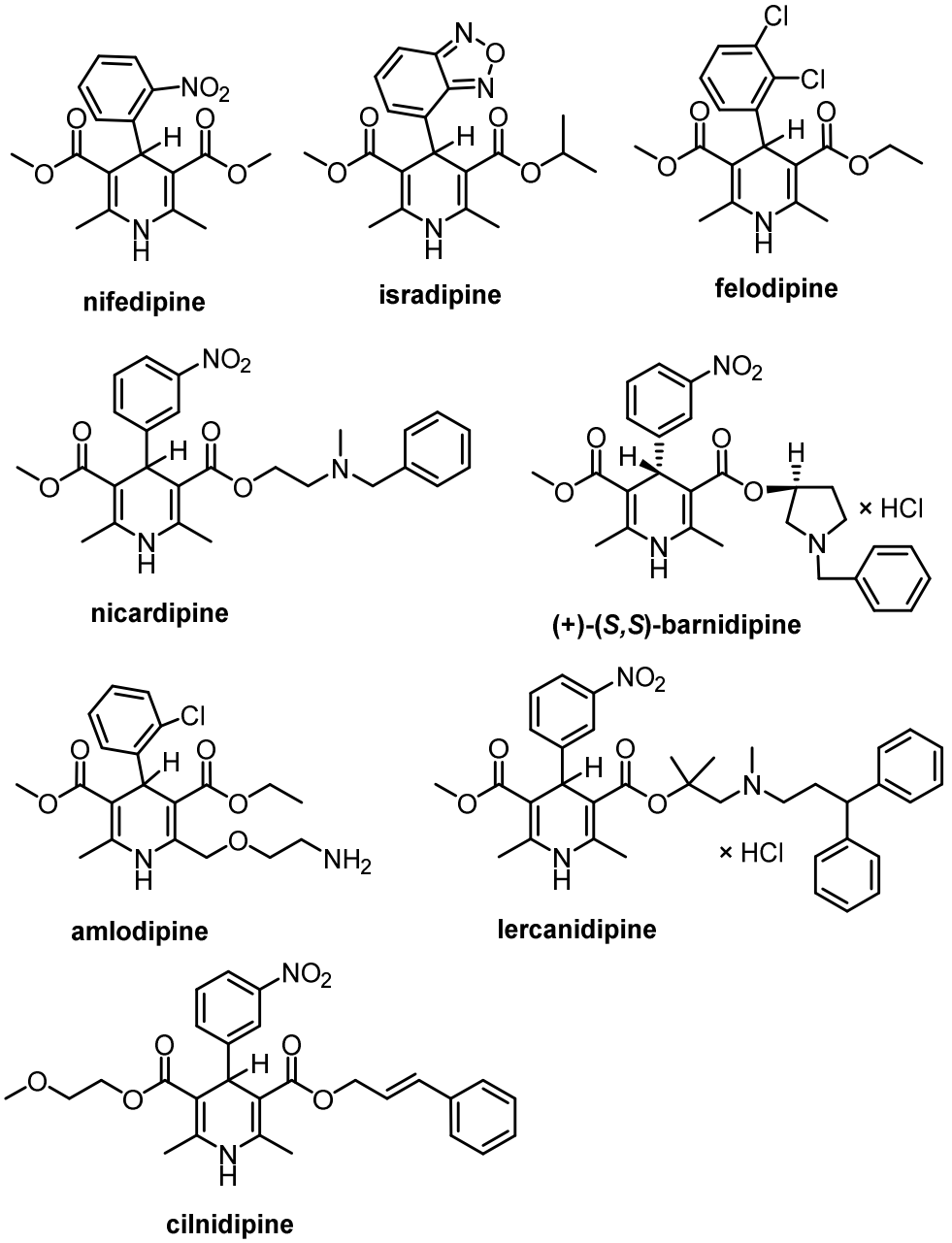



**Figure 1.** Representatives of 1,4-dihydropyridine calcium channel blockers.

The analysis of the structures shows that most of them are the unsymmetrical ones. When substituents on the left side differ from those on the right side of a 1,4-DHP, the molecule becomes chiral, with C4 being the stereogenic centre [9]. Enantiomers of unsymmetrical 1,4-DHP often show different biological activities and they could have even an opposite action profile. For example, it was established that (−)-*S*-amlodipine [10], (+)-*S*-manidipine, and [11] (−)-*S*-nitrendipine [11,12] were more potent calcium channel blockers than the respective opposite enantiomers (Figure 2). The same occurrence was described for barnidipine, where the most active was (+)-*S*,*S*-isomer (Figure 1) [13].

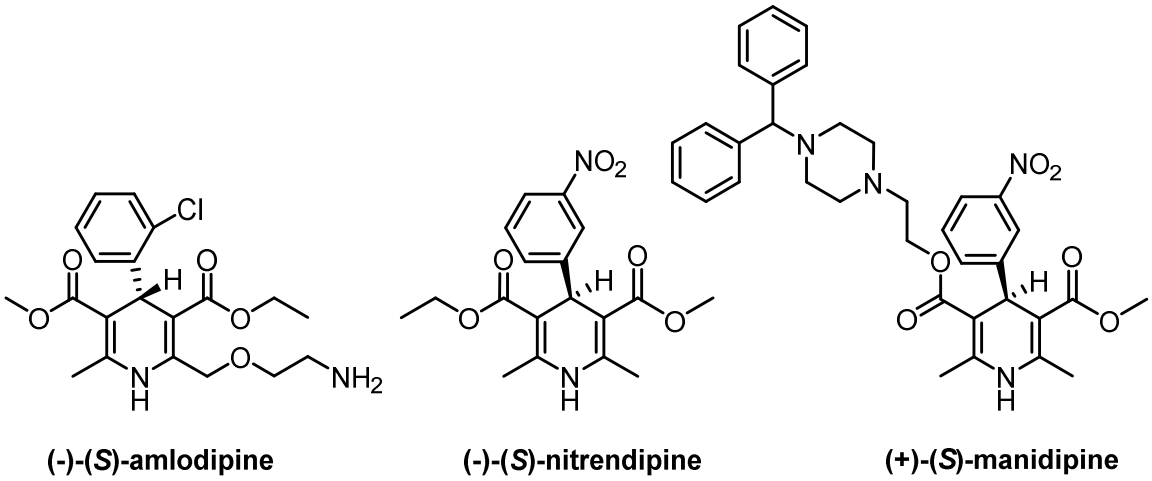



**Figure 2.** Structures of (−)-(S)-amlodipine, (−)-(S)-nitrendipine and (+)-(S)-manidipine.

The opposite effects on function of *L*-type channels were reported, for example, for derivative PN 202-791 and BAYK8644, where (−)-*R*-enantiomers of PN 202-791 and (+)-*R*-BAYK8644 were calcium channel blockers, while the corresponding (+)-*S*-PN 202-791 and (−)-*S*-BAYK8644 enantiomers were calcium channel agonists (Figure 3) [14–16]. Currently (−)-(*S*)-amlodipine is marketed as levamlodipine and *S*,*S*-barnidipine is marketed in Japan under the trade name of Hypoca (Astellas Pharma Inc, Tokyo, Japan).

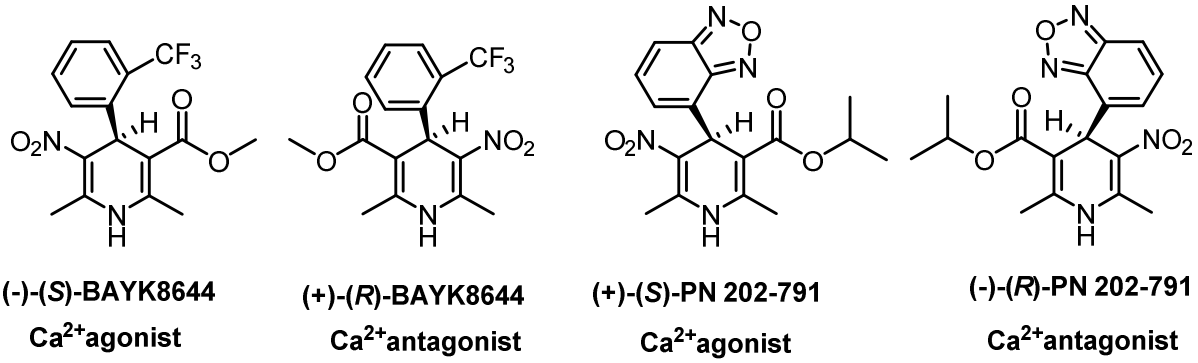



**Figure 3.** Opposite effects of 1,4-dihyropyridine derivatives on function of *L*-type channels.

*L*-type voltage operated calcium channels are well-known for their involvement in electrical current generation; therefore, predominantly found in "excitable" cells, such as cardiomyocytes, muscle cells or neurons. In addition to the well-known role of 1,4-DHPs on the treatment of cardiovascular system disorders, as efficient agents in the management of hypertension, their potential activity on the cells from other tissues and organs is increasingly being revealed. L-type voltage operated calcium channels are also abundantly expressed in a range of "non-excitable" cells, including mesenchymal stem cells, osteoblasts, and chondrocytes, and they seem to have a range of activities, including mechanotransduction [17,18]. Alterations in intracellular $Ca^{2+}$ concentrations may initiate the downstream response of chondrocytes to mechanical stress via mechanosensitive ion-channels [19]. Therefore, the potential in regulation of chondrogenesis processes through the regulation of ion channels increasingly gain attention for stimulation of cartilage regeneration [20]. Mechanical loads trigger anabolic and catabolic responses in chondrocytes [21]. Noteworthy, the analysis of downstream signalling effects and functions suggested that the activated mechanotransductive pathways are distinct in various loading modalities or electric stimuli [21,22]. Furthermore, the application of the same 1,4-DHP drug nifedipine generated different metabolic responses and inflammatory activity in different

cell types, namely mesenchymal stem cells and chondrocytes, while the effects of agonist BAYK8644 were also different, but not the opposite [18]. Those data further imply the diversity of regulatory mechanisms in VOCC L-type channels that emphasise the need of agents with different activities for each particular therapeutic application.

After synthesis, study and development of a class of calcium antagonists the interest is also growing towards other activities of 1,4-DHPs, such as neuroprotective [23], radioprotective [24], antimutagenic [25], antioxidative [26], anticancer [27], and antimicrobial [28–30]. Consequently, during the last decades, the development of new pyridinium moieties containing compounds based on a 1,4-DHP core has become an interesting area for medicinal chemistry research. Cationic 1,4-DHP amphiphiles having one or two cationic moieties and various length ester appendages, were found to be capable of transfecting pDNA into different cell lines in vitro [31,32], due to their self-assembling properties [33,34].

## 2. Stereoselective Synthesis of 1,4-Dihydropyridines

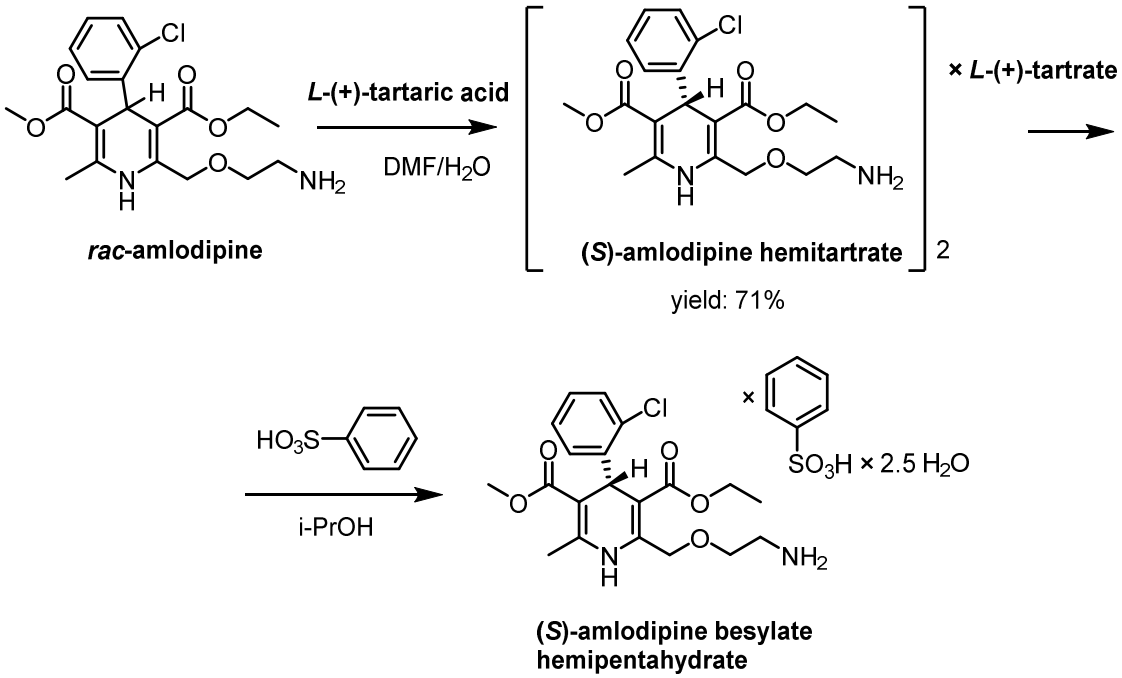
The synthesis of Hantzsch-type 1,4-DHPs remains to be an important field in organic chemistry. The most common way of synthesis of 1,4-DHPs is Hantzsch cyclisation and its modifications [35,36]. Information the scope and limitations of methods of synthesis and chemical properties of hydrogenated pyridine derivatives can be found in several good reviews and in citations therein [1,37–40]. However, classical Hantzsch synthesis usually produces only racemic mixtures of unsymmetrical 1,4-DHPs. Therefore, the development of stereoselective synthetic methods for obtaining of therapeutic agents is one of the main priorities of medicinal chemistry.

Over the years numerous methodologies have been developed for the production of enantiopure 1,4-DHP derivatives, such as stereoselective synthesis using chiral auxiliaries and chiral cyclocondensation partners [41], catalytic asymmetric synthesis [42], resolution of diastereomeric 1,4-DHP salts derived from chiral acids or bases [43], enzyme catalysed kinetic resolution, or asymmetrisation of enzymatically labile esters activated spacer groups [9,44–46].

### *2.1. Resolution of Racemic Basic 1,4-Dihydropyridine Derivatives*

Among all of the separation techniques, preparative chiral chromatography on stationary phases is the most widely used technique for the direct analysis of enantiomers and it remains to be important way for the obtaining of 1,4-DHP enantiomers in the analytical scale.

Initially, the state of art for the preparation of (−)-(*S*)-amlodipine was based on a procedure where the key-step was chromatographic separation of its and (+)-*S*-2-phenylethanol diastereoisomeric derivative [47], its (−)-(1*S*)-camphanic acid derivatives [10] and by the resolution of intermediate racemic azido acid cinchonidine salts [48]. In the last decade, resolution of racemic amlodipine base to (+)-*R* and (−)-*S* isomer was performed using tartaric acids in dimethylformamide (DMF)/water mixture. Thus, (+)-L-tartrate salt of the unwanted *R*-isomer of amlodipine was crystallised in DMF/water mixture, while the salt of the required *S*-form was provided in DMF/water. The addition of water (15%) to DMF, as shown in Scheme 1, significantly improved the efficiency of resolution (yield 71%, enantiomeric excess (ee) 99%) [49].

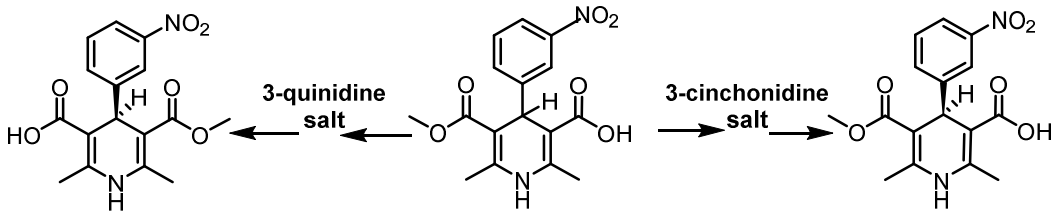



**Scheme 1.** Resolution of amlodipine with tartaric acid [49].

### 2.2. Resolution of Racemic 1,4-Dihydropyridinedicarboxylic Acid Derivatives

The resolution of racemic 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid was also achieved using commercially available Cinchona alkaloids (cinchonidine and quinidine) as the resolving agents. Under the optimum conditions, for both *R*- and *S*-enantiomers enantiomeric excess >99.5% was reached. The optimum conditions were approached by varying of the solvent, where the best results were found in the DMF/water mixture (8:5) (Table 1) [50].

**Table 1.** Resolution of racemic 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid **1** with cinchonidine or quinidine [50].




| Entry | Resolving Agent | Solvent Ratio | Yield, (%) | ee, (%) | Abs. conf. * |
|---|---|---|---|---|---|
| 1 | cinchonidine | DMF-$H_2O$ (4:1) | 32 | 99.5 | S |
| 2 | cinchonidine | DMF-$H_2O$ (8:5) | 41 | >99.5 | S |
| 3 | cinchonidine | DMF-$H_2O$ (1:1) | 44 | 97.8 | S |
| 4 | quinidine | DMF-$H_2O$ (8:5) | 43 | >99.5 | R |
| 5 | quinidine | DMF-$H_2O$ (1:1) | 46 | 96.6 | R |

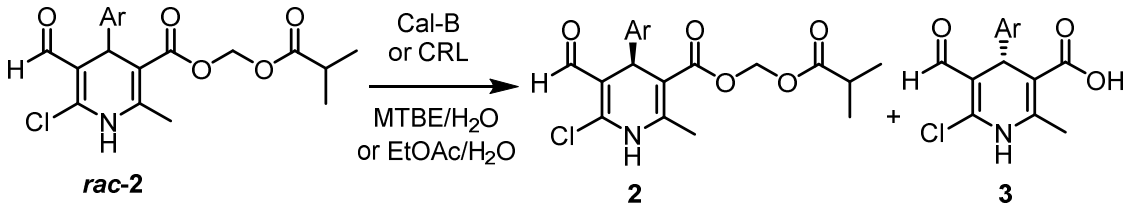
* absolute configuration.

### 2.3. Lipase-catalysed Kinetic Resolution of Racemic Activated Esters of 1,4-Dihydropyridinecarboxylic Acid

Enzyme-catalysed approach to enantiopure 1,4-DHPs was pioneered by groups of Sih and Achiwa in 1991. Since then, this methodology was widely used for asymmetrisation or kinetic resolution of enzymatically labile esters activated spacer groups [44–46]. In the last decade, this approach was successfully applied by Tores et al. to kinetic resolution of various 1,4-DHPs and dihydropyridone

derivatives (Table 2). Applying previously well-known [(2-methylpropanoyl) oxy]methyl ester as activating group [51–53] in the substrate and *Candida rugosa* (CRL) or *Candida antarctica* B (CAL-B) as enzyme good to excellent enantioselectivity was reached [54,55]. Interestingly, that besides frequently used as solvents wet ethers, CRL has been found very efficient in EtOAc, in spite of the fact that this solvent is also susceptible to be hydrolysed by the lipase. The best results of CRL catalysed kinetic resolutions in wet EtOAc were obtained when aryl substituent in the position four of 1,4-DHP *rac*-**2** ring was 2- or 3-$NO_2$-$C_6H_4$-, 2-Cl-5-$NO_2$-$C_6H_3$-, naphthyl- in short reaction times not exceeding 2.5 h, with high enantioselectivity (*E*-value) ranging from 50 to >200. CAL-B has been also shown enantioselectivity toward similar substrates in the range of 11–63 (*E*-value), where the advantage of the use of EtOAc as reaction media was also proven. CAL-B shows better enantioselectivity toward substrates *rac*-**2** having bromine or methoxy group in 4-aryl substituent in comparison with CRL. Thus, hydrolysis of 4-Br-$C_6H_4$- substituted 1,4-DHP *rac*-**2** in methyl tert-butyl ether (MTBE)/water occluded with *E* 24–27, while in EtOAc *E* 34 was reached. The same occurrence was described for 3-$CH_3O$-$C_6H_4$-substituted 1,4-DHP *rac*-**2** where *E* 29-31 was in MTBE/water and *E* 63 was in EtOAc.

**Table 2.** Lipase-catalysed kinetic resolution of racemic [(2-methylpropanoyl)oxy]methyl ester 1,4-DHP-3-carboxylates *rac*-**2** [54,55].



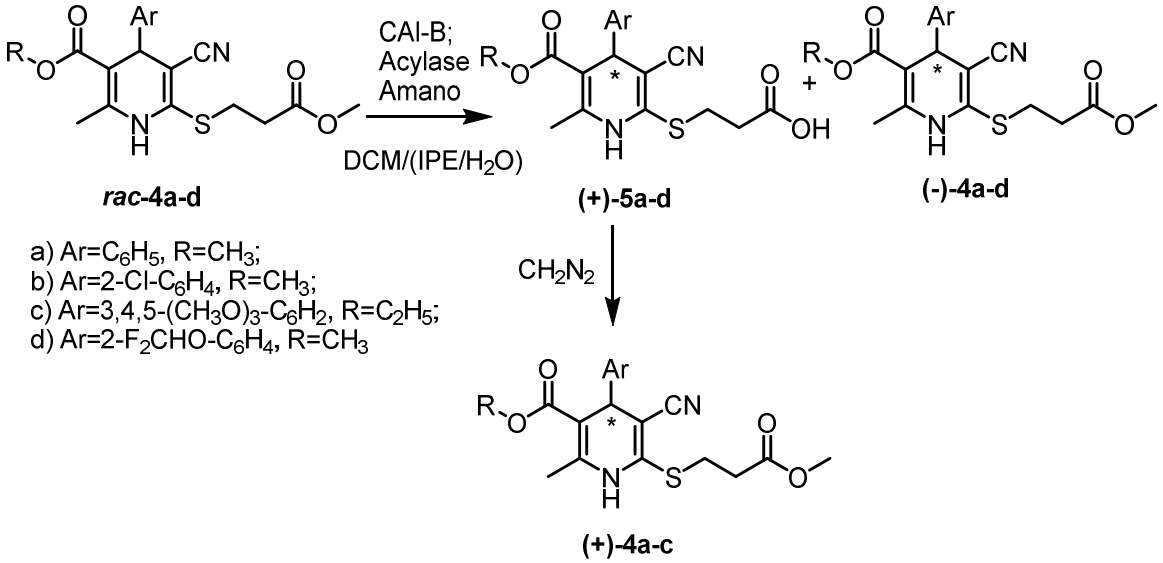

*rac*-**2** **2** **3**

| Entry | Ar | Lipase | Solvent | t *, h | Conv. †, (%) | 2 Abs. conf. /$ee_s$, (%) | 3 Abs. conf. /$ee_p$, (%) | *E*-Value ‡ |
|---|---|---|---|---|---|---|---|---|
| 1 | 2-$NO_2$-$C_6H_4$ | CRL | EtOAc | 0.7 | 47 | *S*/84 | *R*/95 | 103 |
| 2 | 3-$NO_2$-$C_6H_4$ | CRL | EtOAc | 1.5 | 50 | *S*/89 | *R*/88 | 46 |
| 3 | 2-Cl-$NO_2$-$C_6H_3$ | CRL | EtOAc | 0.8 | 49 | *R*/95 | *S*/98 | >200 |
| 4 | Naphthyl | CRL | EtOAc | 2.5 | 46 | *S*/84 | *R*/97 | 175 |
| 5 | 4-Br-$C_6H_4$ | CRL | EtOAc | 23 | 51 | *S*/60 | *R*/58 | 7 |
| 6 | 3-$CH_3O$-$C_6H_4$ | CRL | EtOAc | 10 | 39 | *S*/40 | *R*/62 | 6 |
| 7 | 4-Br-$C_6H_4$ | Cal-B | MTBE | 6 | 47 | *S*/75 | *R*/85 | 27 |
| 8 | 4-Br-$C_6H_4$ | Cal-B | EtOAc | 25 | 43 | *S*/67 | *R*/89 | 34 |
| 9 | 3-$CH_3O$-$C_6H_4$ | Cal-B | MTBE | 9 | 41 | *S*/62 | *R*/88 | 29 |
| 10 | 3-$CH_3O$-$C_6H_4$ | Cal-B | EtOAc | 21 | 34 | *S*/49 | *R*/95 | 63 |

* time; † conversion; ‡ enantiomeric ratio.

Enzyme-catalysed kinetic resolution of 6-methoxycarbonylethylsulfanyl-1,4-dihydropyridines *rac*-**4** has been performed by Krauze group using Amano Acylase (*Aspergillus mellus*) and *Candida antarctica* lipase B (CAL-B, Novozyme 435®) in wet diisopropyl ether (IPE) with dichloromethane (DCM) as an additive to improve the solubility of the substrate *rac*-**4** [56]. Table 3 shows the most enantioselective examples. The enantioselectivity of CAL-B increased together with an increase of the temperature. Thus the best enantioselectivities of CAL-B were achieved at 45°C when the substituent at the position 4 of 1,4-DHP was substituted aryl (Table 3, entries 5–7). While Amano Acylase was less enantioselective toward the same substrate *rac*-**4** showing no enantioselectivity at elevated temperatures (Table 3, entries 9–12).

**Table 3.** Enzyme-catalysed kinetic resolution of 6-methoxycarbonylethylsulfanyl-1,4-dihydropyridines *rac*-**4** [56].



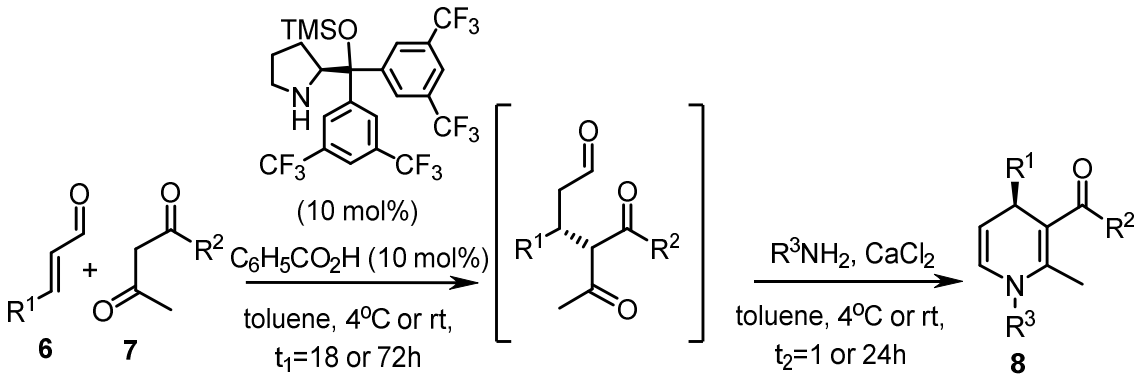

| Entry | Compound | Enzyme | Temp *, °C | t, h | (-)-4 Yield, (%) | (-)-4 $ee_s$, (%) | (-)-3 Yield, (%) | $E_s$-Value † | Abs. conf. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | a | Cal-B | 25 | 48 | 49 | 82 | 47 | 22 | Not known |
| 2 | b | Cal-B | 25 | 165 | 46 | 80 | 48 | 20 | |
| 3 | c | Cal-B | 25 | 51 | 46 | 77 | 47 | 16 | |
| 4 | d | Cal-B | 25 | 264 | 46 | 65 | 46 | 8 | |
| 5 | a | Cal-B | 45 | 18 | 49 | 95 | 47 | 104 | |
| 6 | b | Cal-B | 45 | 48 | 46 | 92 | 48 | 65 | |
| 7 | c | Cal-B | 45 | 26 | 46 | 99 | 46 | >200 | |
| 8 | d | Cal-B | 45 | 168 | 46 | 86 | 46 | 29 | |
| 9 | a | Acylase | 25 | 96 | 47 | 52 | 48 | 5 | |
| 10 | b | Acylase | 25 | 310 | 45 | 89 | 48 | 44 | |
| 11 | c | Acylase | 25 | 100 | 48 | 38 | 47 | 3 | |
| 12 | d | Acylase | 25 | 336 | 45 | 48 | 48 | 4 | |

* temperature; † enantiomeric ratio ($E_s$-value) calculated according to Chen [57].

### *2.4. Organocatalytic Enantioselective Synthesis of 1,4-Dihydropyridines*

The above-mentioned approaches have been studied in the detail and they are relatively well established. The catalytic asymmetric approach holds the greatest promise in delivering the most practical and widely applicable methods. During the last decade, substantial progress has been made in this field toward development of enantioselective organocatalytic methods for the direct construction of the chiral DHPs. However, most of them do not provide a convenient way to pharmacologically important 1,4-DHP-3,5-dicarboxylates. On the other hand, recently reported organocatalytic enantioselective desymmetrisation of prochiral 1,4-dihydropyridine-3,5-dicarbaldehydes also has great promise in the synthesis of pharmacologically important 1,4-dihydropyridine-3,5-dicarboxylates.

In 2008, the Jorgensen group reported the first examples of catalytic asymmetric four substituted 1,4-DHPs **8** synthesis using TMS-prolinol enabled iminium catalysis (Scheme 2) [58]. In this methodology, only non-aromatic α,β-unsaturated aldehydes **6** are able to give products **8** with high levels of stereoinduction ($R^1$ = aryl, led to a low stereoselectivity).




**Scheme 2.** Iminium catalysed synthesis of 1,4-DHPs **8** [58].

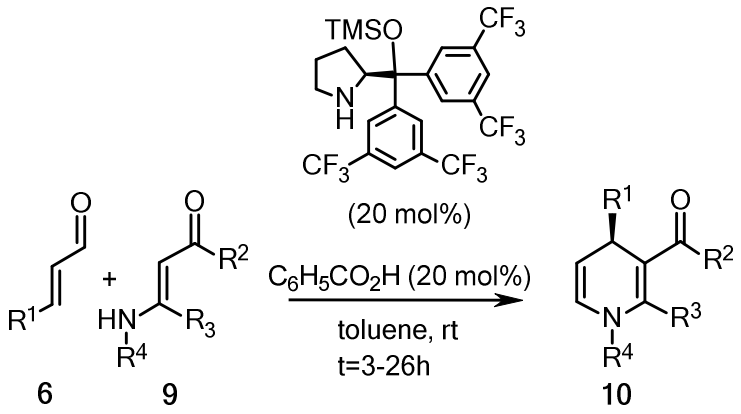
With this method, it was possible to vary the substituents in the positions 1, 3, and 4 in the 1,4-dihydropyridine ring. In the cases of use of non-aromatic α,β-unsaturated aldehydes **6**, moderate yields and high enantioselectivities of 1,4-DHPs **8** (88–95% ee) were achieved (Table 4, entries 1–4,6). Low to moderate enantioselectivities of catalysis were reached with aromatic aldehydes at 4 °C (Table 4, entries 5,9). High enantioselectivities of iminium catalysis were achieved for both kinds of α,β-unsaturated aldehydes **6**: diketones (Table 4, entries 1–6,9–11) and β–ketoesters (Table 4, entries 7,8) [58]. From the tested catalysts, 2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilanyloxymethyl] pyrrolidine was identified as the most enantioselective.

**Table 4.** Some characteristic examples of iminium catalysed 1,4-DHPs **8** synthesis [58].

| Entry | $R^1$ | $R^2$ | $R^3$ | Temp, °C | $t_1$, h | $t_2$, h | **8** | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Yield, (%) | ee, (%) |
| 1 | $C_2H_5$ | $CH_3$ | $C_6H_5$ | rt | 18 | 1 | 55 | 90 |
| 2 | Hex-3-en-yl | $CH_3$ | $C_6H_5$ | rt | 18 | 1 | 45 | 92 |
| 3 | $COOC_2H_5$ | $CH_3$ | $C_6H_5$ | rt | 18 | 24 | 31 | 88 |
| 4 | $(CH_2)_2OTBDMS$ | $CH_3$ | $C_6H_5$ | rt | 18 | 1 | 33 | 95 |
| 5 | Furyl | $CH_3$ | $C_6H_5$ | 4 | 18 | 24 | 35 | 64 |
| 6 | $CH(CH_3)_2$ | $CH_3$ | $C_6H_5$ | rt | 18 | 1 | 33 | 92 |
| 7 | $C_2H_5$ | $OCH_3$ | $C_6H_5$ | rt | 18 | 1 | 41 | 91 |
| 8 | $CH_3$ | $OCH_3$ | $C_6H_5$ | 4 | 18 | 24 | 39 | 82 |
| 9 | $C_6H_5$ | $CH_3$ | $C_6H_5$ | 4 | 72 | 1 | 60 | 38 |
| 10 | $C_2H_5$ | $CH_3$ | $CH(CH_3)_2$ | rt | 18 | 1 | 39 | 90 |
| 11 | $C_2H_5$ | $CH_3$ | 4-Br-$C_6H_4$ | rt | 18 | 1 | 48 | 92 |

In 2011, the Kanger group reported [59] the approach to enantiomerically enriched four substituted 1,4-DHPs **10** based on the use of diarylprolinol-TMS ether and benzoic acid as catalytic system previously developed by Jorgensen group [58]. In this via TMS-prolinol organocatalytic approach β-enaminones and β-enamino esters **9** were preformed prior to the aza-ene-type reaction with α,β-unsaturated aldehydes **6**. With this method moderate to high enantioselectivities (71–96% ee) and yields (45–96%) of 1,4-DHPs **10** were approached. The method also allowed to vary substituents in the positions 1, 3, and 4 in the ring to afford three or four substituted 1,4-DHPs **10**. Table 5 summarizes some characteristic examples.

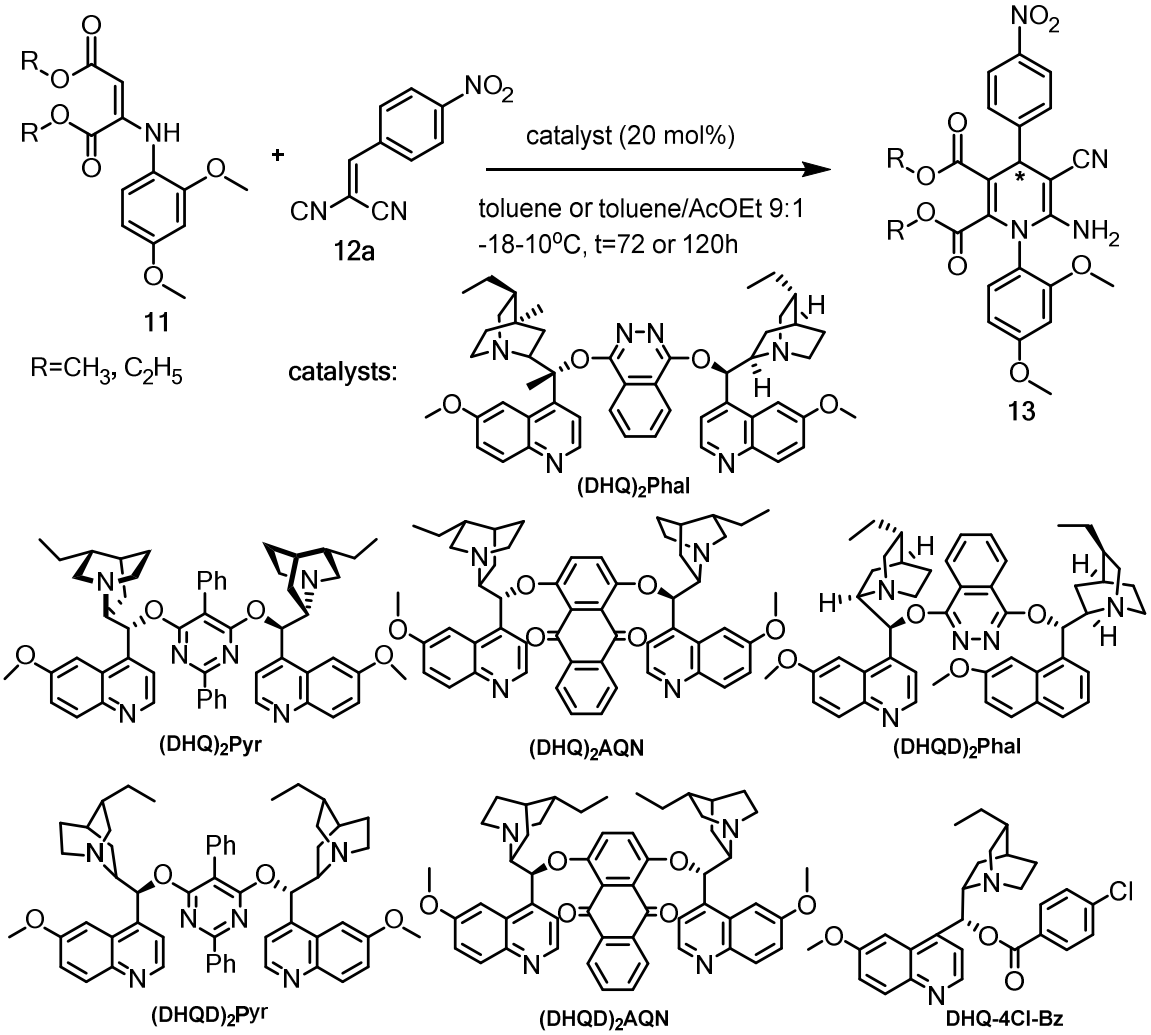
**Table 5.** Organocatalytic reaction β-enaminones and β-enamino esters **9** with α,β-unsaturated aldehydes **6** [59].




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | t, h | 10 | |
|---|---|---|---|---|---|---|---|
| | | | | | | Yield, (%) | Abs. conf. /ee, (%) |
| 1 | $C_6H_5$ | n-$C_4H_9$ | H | $C_6H_5$ | 19 | 79 | *S*/76 |
| 2 | $C_6H_5$ | n-$C_4H_9$ | H | $CH_2C_6H_5$ | 24 | 54 | *S*/87 |
| 3 | $C_6H_5$ | n-$C_4H_9$ | H | $C(CH_3)_3$ | 26 | 72 | *S*/89 |
| 4 | $C_6H_5$ | n-$C_4H_9$ | H | $CH(CH_3)_2$ | 20 | 75 | *S*/93 |
| 5 | 4-$NO_2$-$C_6H_4$ | n-$C_4H_9$ | H | $CH(CH_3)_2$ | 3 | 83 | *S*/89 |
| 6 | 4-$NO_2$-$C_6H_4$ | $OC_2H_5$ | $CH_3$ | $CH(CH_3)_2$ | 4 | 45 | *S*/84 |
| 7 | 4-$NO_2$-$C_6H_4$ | $OC_2H_5$ | $CH_3$ | $CH_2C_6H_5$ | 4 | 70 | *S*/89 |
| 8 | $C_2H_5$ | n-$C_4H_9$ | H | $CH(CH_3)_2$ | 18 | 69 | *R*/93 |
| 9 | n-$C_4H_9$ | n-$C_4H_9$ | H | $CH(CH_3)_2$ | 17 | 96 | *R*/96 |
| 10 | n-$C_4H_9$ | $OC_2H_5$ | $CH_3$ | $CH_2C_6H_5$ | 4 | 62 | *R*/71 |

From the recent achievements, the synthesis of fully substituted 1,4-DHP 13 was performed by Herrera's group in 2017 (Table 6) [60]. Bis-cinchona catalyst activates the Michael addition reaction between malononitrile derivatives **12** and enamines **11**, affording 4-aryl-6-amino-5-cyano-1,4-dihydropyridine-2,3-dicarboxylates **13** with moderate enantioselectivity. At the beginning hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2$Phal), hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2$Pyr), hydroquinine anthraquinone-1,4-diyl diether ($(DHQ)_2$AQN), hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2$Phal), hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2$Pyr), hydroquinidine (anthraquinone-1,4-diyl), diether ($(DHQD)_2$AQN), and hydroquinine 4-chlorobenzoate (DHQ-4Cl-Bz) were studied as catalysts for the reaction of enamine **11** (R = $CH_3$) and malononitrile **12a** in toluene/EtOAc (9:1) as solvent for 72 h at 10 °C. Table 6 summarises the best results (Table 6, entries 1–5). The enantioselectivity appeared to be the highest for $(DHQ)_2$Pyr where 80% of ee (Table 6, entry 6) was achieved. Further fine tuning of reaction conditions allowed to approach a slightly better enantioselectivity albeit to the reaction rate (Table 6, entries 9,11).

**Table 6.** Cinchona-alkaloid catalysed synthesis of enantiomerically enriched 1,4-DHPs **13** [60].

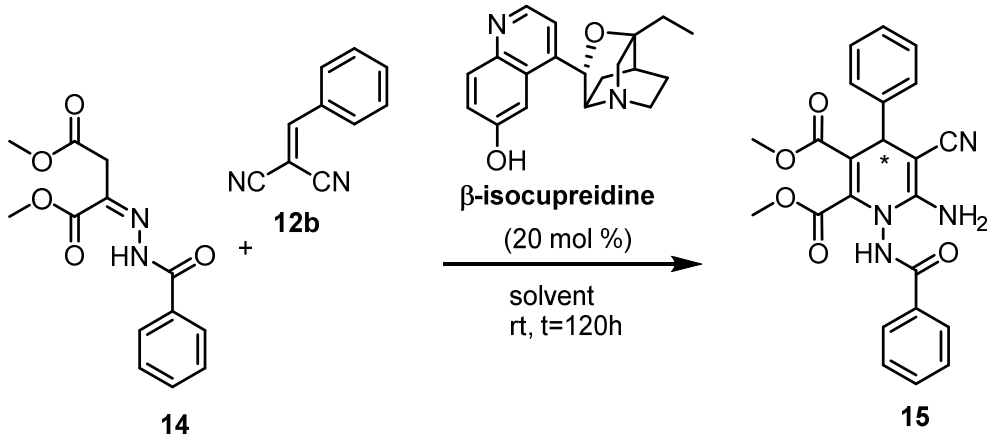



| Entry | Catalyst | R | Solvent | Temp, °C | t, h | 13 | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Yield, (%) | $ee_p$, (%) | Abs. conf. |
| 1 | $(DHQ)_2Phal$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 91 | 66 | |
| 2 | $(DHQ)_2AQN$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 22 | 54 | |
| 3 | $(DHQD)_2Phal$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 47 | 64 | |
| 4 | $(DHQD)_2Pyr$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 13 | 54 | |
| 5 | $(DHQD)_2AQN$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 23 | 68 | |
| 6 | $(DHQ)_2Pyr$ | $CH_3$ | toluene/AcOEt (9:1) | 10 | 72 | 81 | 80 | Not known |
| 7 | $(DHQ)_2Pyr$ | $CH_3$ | toluene | 10 | 72 | 88 | 82 | |
| 8 | $(DHQ)_2Pyr$ | $CH_3$ | toluene/AcOEt (9:1) | 0 | 72 | 32 | 80 | |
| 9 | $(DHQ)_2Pyr$ | $CH_3$ | toluene/AcOEt (9:1) | −18 | 120 | <5 | 85 | |
| 10 | $(DHQ)_2Pyr$ | $C_2H_5$ | toluene/AcOEt (9:1) | 10 | 72 | 97 | 76 | |
| 11 | $(DHQ)_2Pyr$ | $C_2H_5$ | toluene/AcOEt (9:1) | −18 | 72 | <5 | 90 | |

Recently, the synthesis of highly functionalised 1-benzamido-1,4-dihydropyridine derivatives **15** from hydrazones **14** and alkylidenemalononitrile **12b** in the presence of β-isocupreidine as organocatalyst was reported with rather low enantioselectivity (up to 10–52% ee) by Herrera's group [61]. From ten different chiral organocatalysts, β–isocupreidine was chosen as the most enantioselective. Table 7 summarizes some characteristic examples.

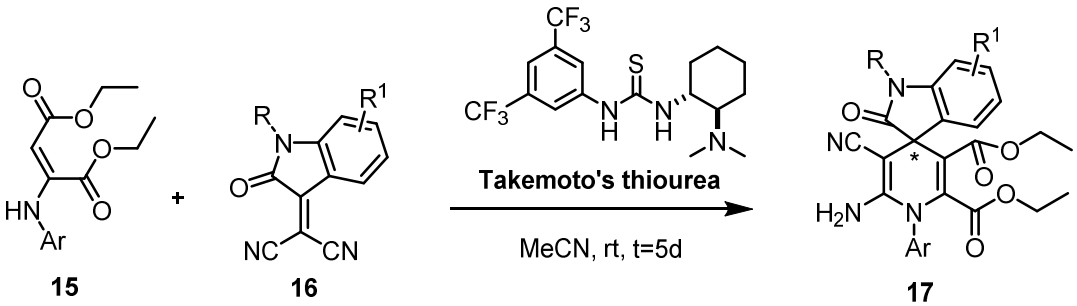
In 2015, Herrera's group reported the synthesis of enantioenriched 2-oxospiro-[indole-3, 4′-(1′,4′-dihydropyridine)] derivatives—spirocyclic 1,4-DHPs **17** having highly substituted DHP ring. Table 8 summarizes several characteristic examples [62].

**Table 7.** β-isocupreidine catalysed synthesis of highly functionalised 1-benzamido1,4-dihydropyridine derivatives **15** [61].




| Entry | Solvent | 15 | |
|---|---|---|---|
| | | Yield, (%) | $ee_p$, (%) |
| 1 | MeCN | 56 | 10 |
| 2 | AcOEt | 54 | 40 |
| 3 | DCM | 35 | Rac. |
| 4 | $CHCl_3$ | 49 | 33 |
| 5 | $Et_2O$ | 39 | 40 |
| 6 | MeOH | 77 | Rac |
| 7 | THF | 48 | 52 |

**Table 8.** Takemoto's thiourea catalysed synthesis of spirocyclic1,4-DHPs **17** [62].




Ar=2,4-$(CH_3O)_2$-$C_6H_3$; 2,4-$(CF_3)_2C_6H_3$; 4-$CH_3O$-$C_6H_4$, 4-$((CH_3)_3C)$-$C_6H_4$, 4-$CF_3$-$C_6H_4$

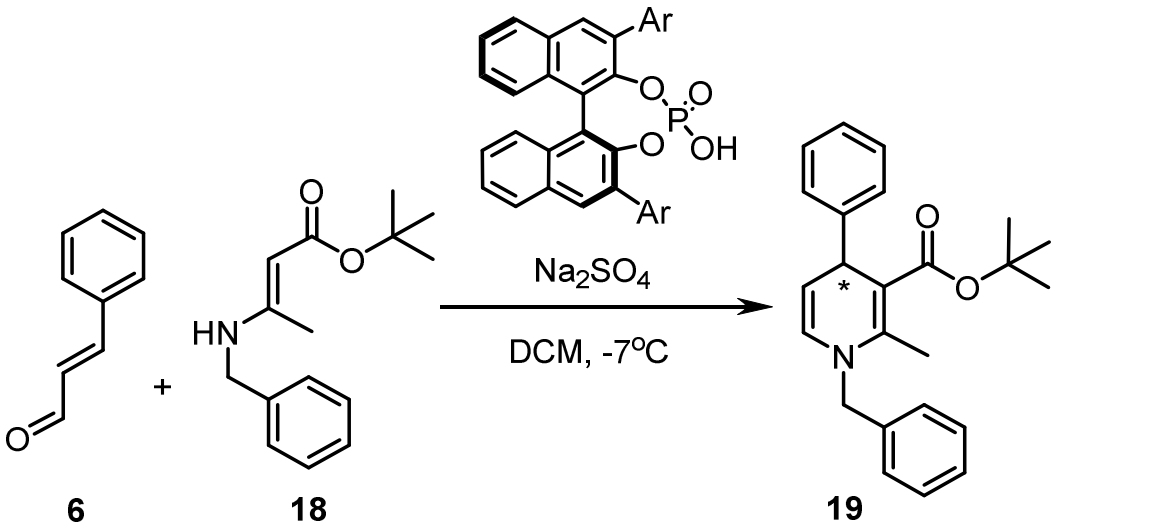
R=$CH_2C_6H_5$, Allyl, $C_2H_5$;

$R^1$=H, 5-Br, 5,7-di$CH_3$, 5-Cl, 5-$NO_2$

| Entry | Catalyst Loading (mol %) | R | Ar | $R^1$ | 17 Yield, (%) | 17 $ee_p$, (%) |
|---|---|---|---|---|---|---|
| 1 | 30 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | H | 30 | 42 |
| 2 | 20 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | H | 25 | 23 |
| 3 | 10 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | H | 29 | 11 |
| 4 | 30 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | 5-Br | 82 | 48 |
| 5 | 30 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | 5,7-di$CH_3$ | 40 | 30 |
| 6 | 30 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | 5-Cl | 71 | 30 |
| 7 | 30 | $CH_2C_6H_5$ | 2,4-$(H_3CO)_2$-$C_6H_3$ | 5-$NO_2$ | 65 | 58 |
| 8 | 30 | $CH_2C_6H_5$ | 3-$H_3CO$-$C_6H_4$ | H | 65 | 30 |
| 9 | 30 | Allyl | 3-$H_3CO$-$C_6H_4$ | H | 61 | 30 |
| 10 | 30 | $C_2H_5$ | 3-$H_3CO$-$C_6H_4$ | H | 49 | 32 |

The reaction of an enamines **15** with isatylidene malononitrile derivatives **16** was studied in the presence of various organocatalysts. It was found that only Takemoto's thiourea [63] catalysed the reaction with low degree of enantioselectivity. Additional screening of the catalyst loading, the variation of the substituents of starting enamine **15** and isatylidene malononitrile **16**, and the reaction conditions led to some improvement of enantioselectivity of the reaction from 44% to 58% ee. Not looking at low enantioselectivity, this is one of very few examples of synthesis of fully substituted 1,4-DHP derivatives.

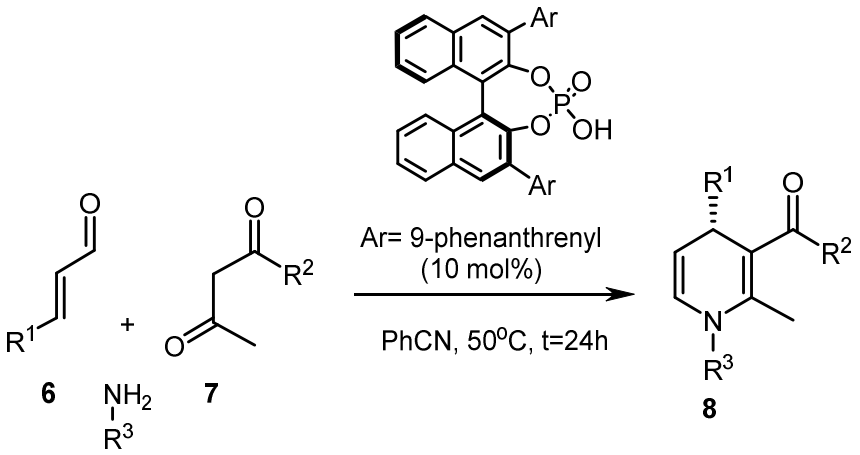
In 2007, by Renaud group was reported mechanistically different chiral Brønsted acids catalysed enantioselective synthesis of four substituted 1,4-DHPs **19** [64]. Primary screening of two component reaction of N-benzyl β-aminobutenoate **18** with cinnamaldehyde **6** have shown that BINOL-derived phosphoric acid derivatives proved to be capable of catalysing the reaction in up to 50% enantiomeric excess at −7 °C in DCM (Scheme 3).




**Scheme 3.** Brønsted acids catalysed enantioselective synthesis of 1,2,3,4 substituted 1,4-DHPs **19** [64].

The extension of the above method to the three-component reaction was performed by Gong group in 2008 utilising chiral Brønsted acid catalysis (Scheme 4) [65] The ability to alter the substituents at the positions 1, 3, and 4 of 1,4-DHP ring was also demonstrated.

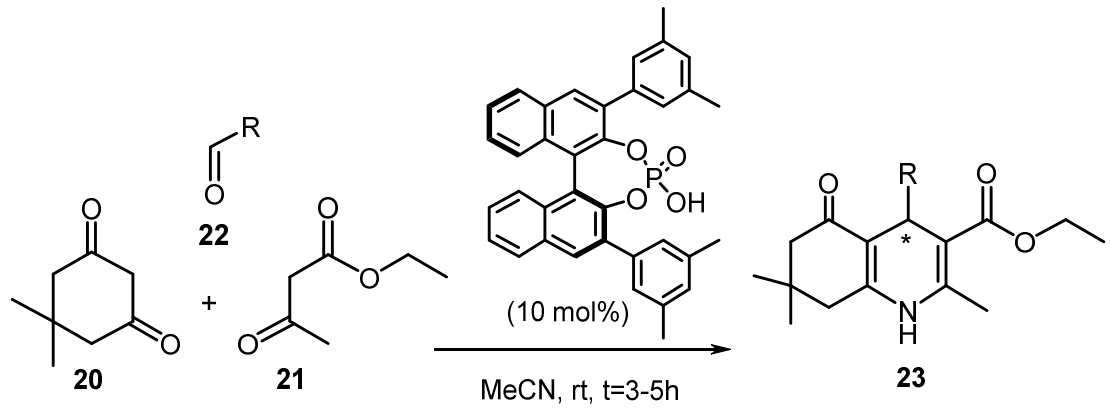
The mechanism of the reaction involves the formation of an α,β-unsaturated imine that is activated through hydrogen bonding interaction with the hydroxyl group of the organocatalyst and undergoes nucleophilic addition of β-ketoester. A wide range of cinnamaldehydes was employed, but contrary to the Jorgensen method the use of 2-hexenal led to a low enantioinduction. A serious limitation of these methods is the inability to introduce the substituents at 5- and 6- position of 1,4-DHP **8** ring.




when $R^1$=various aryls, $R^2$=$CH_3$, $OCH_3$, $OC_2H_5$,
O-$CH(CH_3)_2$, O-allyl, $R^3$= 4- or 3-$CH_3$-$C_6H_4$ - 37-93% yield, 73-98% ee (29 examples)
when $R^1$=n-$C_3H_7$ - only 66% ee (1 example)

**Scheme 4.** Chiral BINOL-derived phosphoric acid catalysed synthesis of 1,4-DHPs **8** [65].

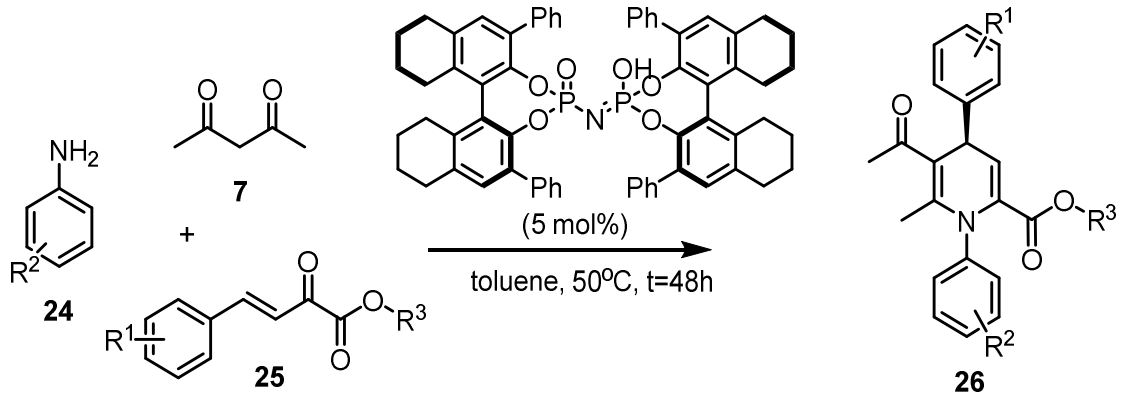
In 2009, Gestwicki demonstrated the first examples of fully substituted bicyclic DHP **23** synthesis [66]. A good substrate scope was demonstrated for aromatic aldehydes (Scheme 5). On the other hand, the reactions are limited to the use as β-dicarbonyl components dimedone **20** and ethyl acetoacetate **21**. When R of aldehyde component **22** is $C_6H_5$, 2,4-$Cl_2$-$C_6H_3$, 4-Br-$C_6H_4$, 3,5-$(CH_3O)_2$-$C_6H_3$, 2-$CF_3$-$C_6H_4$, 2,5-$F_2$-$C_6H_3$, 4-$C(CH_3)_3$-$C_6H_4$, 2-naphthyl, 2-CN-$C_6H_4$, 3,4-$(OH)_2$-$C_6H_3$, 2-Cl-$C_6H_4$, 4-$C_6H_5$-$C_6H_4$ high enantioselectivity of organocatalytic reaction ee > 95% can be reached.




**Scheme 5.** Chiral BINOL-derived phosphoric acid catalysed synthesis of bicyclic 1,4-DHP **23** [66].

In 2015, Zhang et al. reported H8-BINOL-type chiral imidodiphosphoric acid promoted enantioselective cyclisation of β,γ-unsaturated α-ketoesters **25**, arylamines **24**, and acetylacetone **7** (Table 9). The change of BINOL scaffold to H8-BINOL gave better yields and enantioselectivities. Among the H8-BINOL-based imidodiphosphoric acids, the derivative that was substituted with four phenyl groups was found to be the best catalyst for the reaction. Under the optimised conditions penta substituted 1,4-DHPs **26** were obtained with moderate yields (34–61%) and good to excellent selectivities (75–97% ee) [67]. Table 9 provides some representative examples.

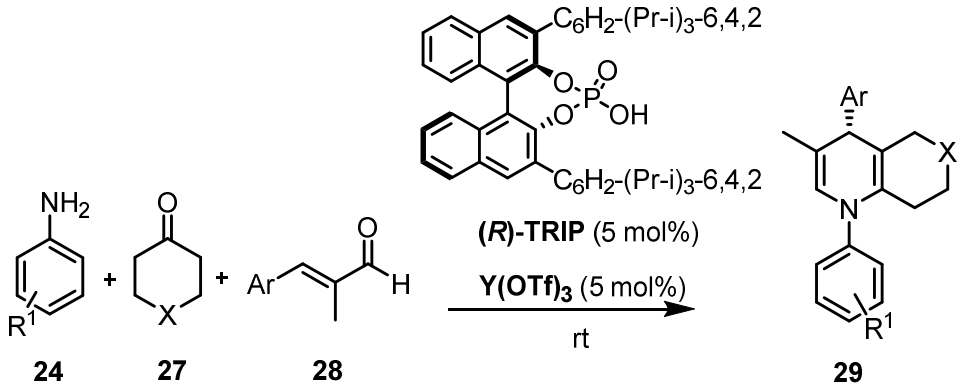
**Table 9.** Chiral imidodiphosphoric acid catalysed synthesis of 1,4-DHP **26** [67].




| Entry | $R^1$ | $R^2$ | $R^3$ | 26 | |
|---|---|---|---|---|---|
| | | | | Yield, (%) | ee, (%) |
| 1 | 4-$NO_2$ | 3-$OCH_3$ | $CH_3$ | 54 | 88 |
| 2 | 4-$NO_2$ | 3-$OCH_3$ | $C_2H_5$ | 61 | 85 |
| 3 | 4-$NO_2$ | 3-$OCH_3$ | $CH(CH_3)_2$ | 54 | 90 |
| 4 | 4-$NO_2$ | 3-$OCH_3$ | $CH_2C_6H_5$ | 51 | 89 |
| 5 | 4-$NO_2$ | 3-Cl | $CH(CH_3)_2$ | 53 | 91 |
| 6 | 4-$NO_2$ | 3-Br | $CH(CH_3)_2$ | 54 | 88 |
| 7 | 4-$NO_2$ | 3-F | $CH(CH_3)_2$ | 53 | 87 |
| 8 | 4-$NO_2$ | 3-$CH_3$ | $CH(CH_3)_2$ | 55 | 83 |
| 9 | 4-Br | 3-Cl | $CH(CH_3)_2$ | 54 | 92 |
| 10 | 4-CN | 3-Cl | $CH(CH_3)_2$ | 41 | 93 |
| 11 | 4-F | 3-Br | $C_2H_5$ | 51 | 94 |
| 12 | 2,3,4-triCl | 3-Cl | $CH_3$ | 55 | 95 |

In 2015, Wang's group has developed a trio catalytic system comprised of arylamine **24**, BINOL-derived phosphoric acid and hard metal Lewis acid (yttrium(III) trifluoromethanesulfonate, $Y(OTf)_3$) (Table 10) [68]. The combined catalyst was capable of promoting an aza-Diels-Alder reaction of various substituted cinnamaldehydes **28**, cyclic ketones **27**, and arylamines **24**. Binary acid (*R*)-TRIP/$Y(OTf)_3$ catalysed reaction allowed the formation of fused DHPs **26** in 59–84% yields and good to excellent enantioselectivities in most of the cases (91–99% ee). Table 10 provides some representative examples.

**Table 10.** Chiral BINOL-derived phosphoric acid, hard metal Lewis acid, and amine catalysed synthesis of 1,4-DHP **29** [68].



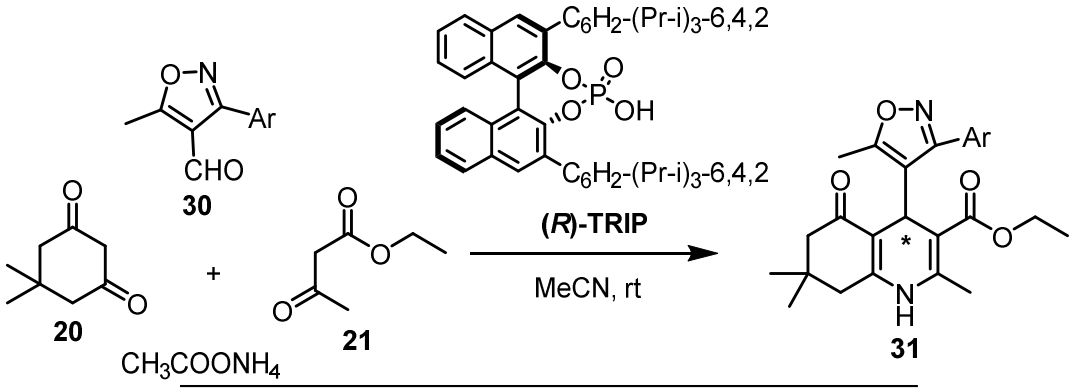

(1.3 equivalent)

| Entry | Solvent | $R^1$ | Ar | X | t, h | 29 | |
|---|---|---|---|---|---|---|---|
| | | | | | | Yield, (%) | $ee_p$, (%) |
| 1 | toluene | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 38 | 92 |
| 2 | MeCN | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 70 | 35 |
| 3 | Neat | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 15 | 80 |
| 4 | MeOH | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 67 | 93 |
| 5 | 1,4-dioxane | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 44 | 43 |
| 6 | $H_2O$ | 4-Cl | $C_6H_5$ | $CH_2$ | 48 | 50 | 99 |
| 7 | $CHCl_3$ | 4-Cl | $C_6H_5$ | $CH_2$ | 24 | 87 | 69 |
| 8 | acetone | 4-Cl | $C_6H_5$ | $CH_2$ | 24 | 78 | 88 |
| 9 | DCM | 4-Cl | $C_6H_5$ | $CH_2$ | 24 | 81 | 98 |
| 10 | DCE * | 4-Cl | $C_6H_5$ | $CH_2$ | 24 | 78 | 98 |
| 11 | DCE | 4-$CH_3O$ | $C_6H_5$ | $CH_2$ | 18 | 79 | 99 |
| 12 | DCE | H | $C_6H_5$ | $CH_2$ | 24 | 72 | 94 |
| 13 | DCE | 4-Br | $C_6H_5$ | $CH_2$ | 24 | 71 | 92 |
| 14 | DCE | 3-Cl | $C_6H_5$ | $CH_2$ | 30 | 66 | 99 |
| 15 | DCE | 4-Cl | 4-$CH_3O$-$C_6H_4$ | $CH_2$ | 24 | 73 | 98 |
| 16 | DCE | 4-Cl | 4-Cl-$C_6H_4$ | $CH_2$ | 24 | 71 | 99 |
| 17 | DCE | 4-Cl | 4-Br-$C_6H_4$ | $CH_2$ | 24 | 67 | 94 |
| 18 | DCE | 4-Cl | Naphthyl | $CH_2$ | 40 | 59 | 94 |
| 19 | DCE | 4-Cl | 4-$NO_2$-$C_6H_4$ | $CH_2$ | 16 | 84 | 98 |
| 20 | DCE | 4-$CH_3O$ | $C_6H_5$ | - | 20 | 68 | 91 |
| 21 | DCE | 4-Cl | $C_6H_5$ | - | 24 | 60 | 94 |
| 22 | DCE | 4-Cl | 4-$NO_2$-$C_6H_4$ | - | 24 | 63 | 98 |
| 23 | DCE | 4-Cl | 4-$CH_3O$-$C_6H_4$ | - | 24 | 68 | 98 |
| 24 | DCE | 4-$CH_3O$ | 4-$NO_2$-$C_6H_4$ | S | 30 | 73 | 98 |
| 25 | DCE | 4-$CH_3O$ | 4-$NO_2$-$C_6H_4$ | O | 30 | 70 | 95 |

* 1,2-dichloroethane (DCE).

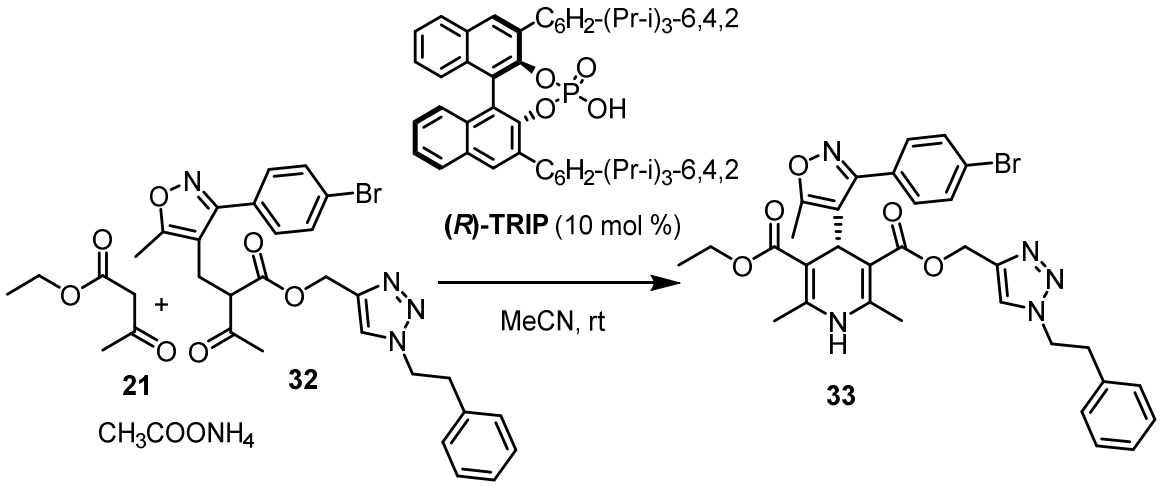
The asymmetric synthesis of fused derivatives—chiral N-unsubstituted 4-isoxazolyl-quinolones **31**—was performed applying the methodology elaborated by Gestwicki, from the isoxazole aldehydes **30**, dimedone **20**, and ethyl acetoacetate **21** using BINOL phosphate (*R*)-TRIP, as pioneered by Gong in moderate yields (Table 11) [69]. According to the provided chromatograms, the authors proposed that enantiomeric excess for obtained compounds was more than 90%.

**Table 11.** (*R*)-TRIP catalysed synthesis of fused 1,4-DHPs **31** [69].




| Entry | Ar | 31 Yield, (%) |
|---|---|---|
| 1 | $C_6H_5$ | 26 |
| 2 | 2-Br-$C_6H_4$ | 64 |
| 3 | 3-Br-$C_6H_4$ | 60 |
| 4 | 4-Br-$C_6H_4$ | 65 |

Natale group in supplementing materials of the article [69] also provided BINOL phosphate (*R*)-TRIP catalysed synthesis of 1,4-DHP-3,5-dicarboxylate **33** with (*S*)-absolute configuration in 21% of yield from pre-formed isoxazolylidene acetoacetate **32**, ethyl acetoacetate **21,** and a source of ammonia. This is the first reported example of enantioselective organocatalytic synthesis of the scaffold of many pharmaceutically relevant 1,4-DHPs: 4-substituted 2,6-dimethyl-1,4-DHP-3,5-dicarboxylate **33**. The authors proposed that the enantiomeric excess of the obtained compound was more than 90%, as in the above cases (Scheme 6).



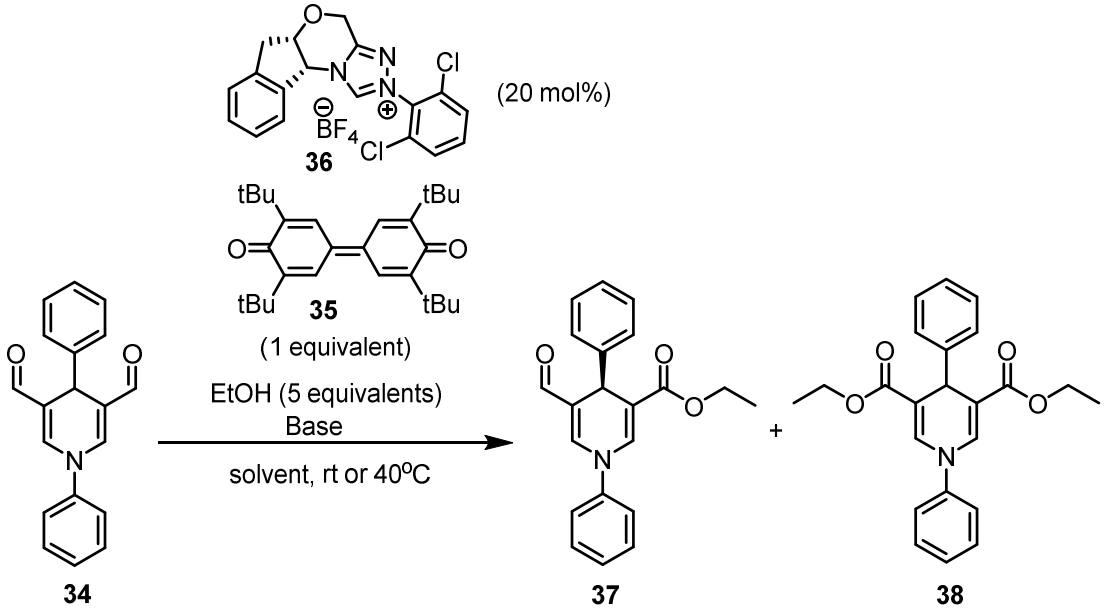

**Scheme 6.** (*R*)-TRIP catalysed synthesis of 1,4-DHP-3,5-dicarboxylate **33** [69].

*2.5. Organocatalytic Desymmetrisation of Prochiral 1,4-Dihydropyridine-3,5-dicarbaldehydes*

In 2019, enantioselective desymmetrisation of prochiral 1,4-dihydropyridine3,5-dicarbaldehydes **34** catalysed by chiral N-heterocyclic carbenes (NHC catalyst), an external oxidant, and an alcohol nucleophile leading to the highly enantioselective formation of 5-formyl-1,4-DHP-3-carboxylates **37** has been reported [70]. This approach is based on organocatalytic enantioselective desymmetrisation of prochiral 1,4-dihydropyridine3,5-dicarbaldehydes **38** but not on the direct construction of the chiral DHP core. After the search for the best reaction conditions, the following system was selected as

an optimal: Desymmetrisation of 3,5-dicarbaldehydes was quinone **35** as oxidant (1 equiv) in the presence of aminoindanol derived pre-catalyst **36**, which showed a better enantioselectivity, and base (*N*,*N*-diisopropylethylamine, DIPEA), and ethanol as the nucleophile (Table 12, entry 10).

**Table 12.** NHC-catalysed desymmetrisation of prochiral 1,4-dihydropyridine-3,5-dicarbaldehydes **34** [70].




| Entry | Solvent | Base (mol %) | T, °C | t, h | 37 Yield (%) | 38 Yield (%) | 37 ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | DCM | DIPEA (25) | r.t. | 72 | 29 | - | 82 |
| 2 | DCM | DIPEA (100) | r.t. | 72 | 36 | - | 82 |
| 3 | THF | DIPEA (100) | r.t. | 72 | 31 | 12 | 3 |
| 4 | MeCN | DIPEA (100) | r.t. | 72 | 49 | 18 | 84 |
| 5 | DCE | DIPEA (100) | r.t. | 72 | 65 | 10 | 84 |
| 6 | $CHCl_3$ | DIPEA (100) | r.t. | 72 | 67 | 13 | 90 |
| 7 | $CHCl_3$ | KHDMS (25) | r.t. | 72 | 53 | 13 | 71 |
| 8 | $CHCl_3$ | $K_3PO_4$ (25) | r.t. | 72 | 74 | 11 | 82 |
| 9 | $CHCl_3$ | TEA (25) | r.t. | 72 | 52 | 10 | 88 |
| 10 | $CHCl_3$ | DIPEA (100) | 40 | 16 | 70 | 7 | 91 |

The use of other bases potassium triethylamine (TEA), bis(trimethylsilyl)amide (KHMDS) and $K_3PO_4$ led to lover enantioselectivity. Chloroform was selected as the best for these reactions and solvents such as dicholoromethane, dichloroethane and acetonitrile were found less suitable. DHP ring oxidation was not observed under these conditions. The resulting 5-formyl-1,4-DHP-3-carboxylate **37** allows access to the class of pharmaceutically relevant 1,4-DHP-3,5-dicarboxylates.

## 3. Conclusions

The resolution of diastereomeric 1,4-DHP salts derived from chiral acids or bases, enzyme catalysed kinetic resolution, or asymmetrisation of enzymatically labile esters activated spacer groups, separation techniques, such as preparative chiral chromatography on stationary phases are the most widely used techniques for the obtaining of 1,4-DHP enantiomers. These approaches have been studied well in detail and they are relatively well established. The catalytic asymmetric approach holds the greatest promise in delivering the most practical and widely applicable methods. Recently, substantial progress has been made in this field and several enantioselective organocatalytic methods were developed for the direct construction of the chiral DHP core. However, the major deficiency of the methods lies in their limited scope and generality. Thus, the reported organocatalytic methods provided a way to partially substituted, spiro, or fused

in most cases also N-substituted 1,4-DHPs. Organocatalytic approach to pharmacologically important enantiopure 1,4-DHP-3,5-dicarboxylates until recently remained quite unpractical. Subsequently, BINOL phosphate (*R*)-TRIP catalysed enantioselective synthesis of N-unsubstituted 4-isoxazolyl-2,6-dimethyl-1,4-DHP-3,5-dicarboxylate from isoxazolylidene acetoacetate and ethyl acetoacetate was reported. This can be considered as a substantial achievement in the synthesis of enantiopure 1,4-DHPs. On the other hand, recently reported organocatalytic enantioselective desymmetrisation of prochiral 1,4-dihydropyridine-3,5-dicarbaldehydes has great promise in the synthesis of pharmacologically important 1,4-dihydropyridine-3,5-dicarboxylates.

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