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# Enantioselective Desymmetrization of 1,4-Dihydropyridines by Oxidative NHC Catalysis**

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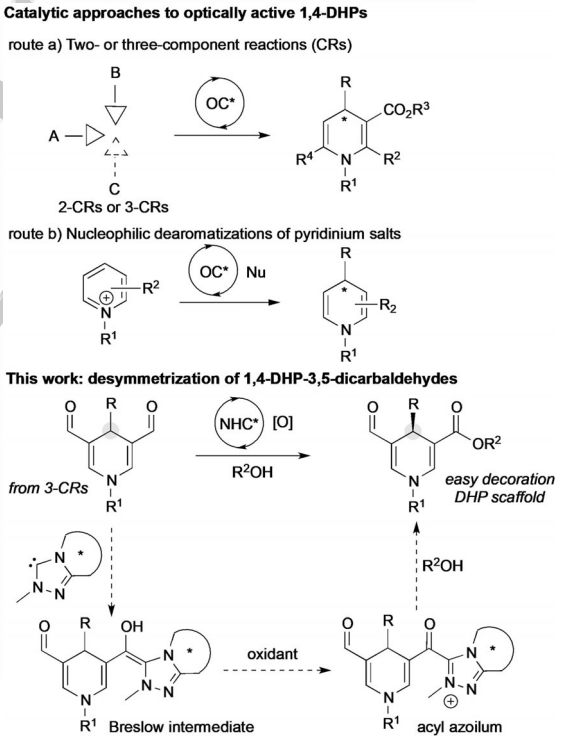
**Abstract:** The unprecedented desymmetrization of prochiral dialdehydes catalyzed by N-heterocyclic carbenes under oxidative conditions was applied to the highly enantioselective synthesis of 1,4-dihydropyridines (DHPs) starting from 3,5-dicarbaldehyde substrates. Synthetic elaboration of the resulting 5-formyl-1,4-DHP-3-carboxylates allowed for access to the class of pharmaceutically relevant 1,4-DHP-3,5-dicarboxylates (Hantzsch esters). DFT calculations suggested that the enantioselectivity of the process is determined by the transition state involving the oxidation of the Breslow intermediate by the external quinone oxidant.

According to Evans' definition,[1] 1,4-dihydropyridines (1,4-DHPs) are privileged structures endowed with a plethora of different biological activities depending on substitution of the heterocyclic scaffold. 1,4-DHPs are primarily used as calcium channel blockers for the treatment of vascular disorders,[2] but also as antitumor[3] and antidiabetic agents,[4] and drugs to cure many other diseases.[5] As with other pharmaceuticals, the role of C4 stereochemistry in chiral 1,4-DHPs is fundamental to modulate the biological activity and prevent adverse effects of these molecules.[6] Additionally, optically pure DHPs are precious precursors of different chiral N-heterocycles[7] and may serve as reduced nicotinamide adenine dinucleotide■■ok?■■ (NADH) mimetics in asymmetric reductions.[8] Racemic, unsymmetrically substituted 1,4-DHPs are easily accessible through the three-component variant of the Hantzsch synthesis[7,9] comprising the aldehyde-ketoester-enamino ester system. The preparation of enantiomerically enriched 4-substituted 1,4-DHPs is well-documented by using chiral auxiliaries[10] or by resolution of racemates.[11] Surprisingly, metal-catalyzed enantioselective methods are missing in the literature. Only a few organocatalytic approaches have been developed for the direct construction of the chiral DHP nucleus,[12] but none of them is adequate to access the biologically active 3,5-dicarboxylate series (Hantzsch esters; Scheme 1, route a). Lately, the regioselective nucleophilic dearomatization of pyridinium salts has also been described to access 1,4-DHPs by conventional (anion-binding, hydrogen-bonding, amino catalysis)[13] and unconventional (umpolung catalysis) strategies (route b).[14] Within the field of catalysis mediated by chiral N-heterocyclic carbenes (NHCs),[15] the implementation of oxidative reaction




**Scheme 1.** Reported enantioselective syntheses of 1,4-dihydropyridines (DHPs) with organocatalysts (OCs) and desymmetrization of 1,4-DHP-3,5-dicarbaldehydes by oxidative NHC catalysis.

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[**] *NHC = N-heterocyclic carbene.*

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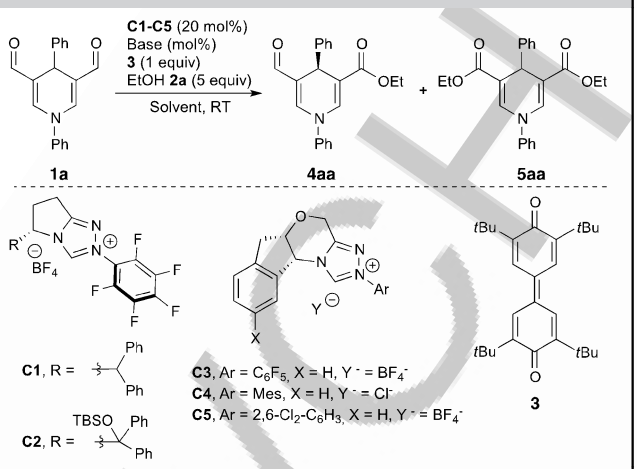
pathways (oxidative NHC catalysis)[16] has permitted to further expand the synthetic opportunities given by this class of organocatalysts, including the desymmetrization and resolution of alcohols and amines.[17] Mechanistically, in the oxidative activation of aldehydes catalyzed by chiral NHCs, the Breslow intermediate is oxidized by either an internal or external oxidant to form the acyl azolium, which then undergoes nucleophilic attack with stereodiscrimination.[16]

The development of highly enantioselective syntheses of 1,4-DHPs still remains an important challenge in medicinal and organic chemistry; therefore, we herein report the desymmetrization of prochiral 1,4-dihydropyridine-3,5-dicarbaldehydes in the presence of a chiral NHC catalyst, an external oxidant and an alcohol nucleophile to yield a small collection of 5-formyl-1,4-DHP-3-carboxylates with excellent enantioselectivities and capability of further diversification (Scheme 1).

At the beginning of this research we were not aware of previous studies on the desymmetrization of dialdehyde substrates by NHC catalysis.[17] Moreover, main challenges to be faced were the expected poor attitude of the aza-unsaturated aldehyde carbonyl group towards nucleophilic attack by carbenes and the possible aromatization of the 1,4-DHP ring under oxidative conditions. The starting 1,4-dihydropyridine-3,5-dicarbaldehydes **1** were readily prepared in satisfactory yields and preparative scale by adapting a known three-component procedure involving the cyclocondensation of an aromatic/aliphatic aldehyde, a primary amine, and a protected malondialdehyde derivative under microwave irradiation (see the Supporting Information).[18] A preliminary investigation by cyclic voltammetry (CV) revealed that the model DHP **1a** (Table 1) was irreversibly oxidized in a multielectron process at room temperature (0.1 M solution of $NBu_4PF_6$ in $CHCl_3$) with an estimated redox potential ($E$) of about +1.1 V (vs. SCE at 100 mV $s^{-1}$; SCE = saturated calomel electrode; Figure S1, Supporting Information). This experiment demonstrated the existence of a reaction window for the selective oxidation of the Breslow intermediate to the key acyl azolium employing the quinone **3** ($E = -0.52$, $-0.89$ V vs. SCE),[19] which is the most frequently used oxidant in NHC catalysis.[20] Hence, desymmetrization of **1a** was initially attempted with this oxidant (1 equiv) in dichloromethane at room temperature in the presence of the pyrrole-derived triazolium salt **C1** (20 mol%), *N*,*N*-diisopropylethylamine■■ok?■■ (DIPEA; 25 mol%), and ethanol **2a** (5 equiv) as the nucleophile (Table 1, entry 1). The target monoester **4aa** was formed smoothly after 72 hours in 48% isolated yield and with an encouraging enantiomeric excess (50% *ee*), together with unreacted **1a** (35%) and the diester **5aa** (12%) resulting from the overoxidation of **4aa**. Importantly, no evidence of DHP ring oxidation was observed under these conditions. The catalyst substituent effect was next investigated (entries 2–5) and a better enantioselectivity was detected with the amino-indanol-derived pre-catalyst **C5**, which afforded **4aa** in 82% *ee* but modest yield (36%, entry 5). A progressive increase of reactivity was detected using an equimolar amount of DIPEA (entry 6) and working at higher substrate concentration (0.16 M, entry 7). The solvent screening with **C5** (entries 8–11) indicated chloroform as the optimal reaction medium furnishing **4aa** in 67% yield and 90% *ee* (entry 11). The addition of 4 Å molecular sieves left almost un-

**Table 1.** Optimization of the reaction conditions with quinone **3** as the oxidant.[a]




| Entry | NHC·HX | Solvent [M] | Base [mol%] | 4aa [%][b] | 5aa [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **C1** | $CH_2Cl_2$ (0.04) | DIPEA (25) | 43 | 12 | 50 |
| 2 | **C2** | $CH_2Cl_2$ (0.04) | DIPEA (25) | 20 | – | 40 |
| 3 | **C3** | $CH_2Cl_2$ (0.04) | DIPEA (25) | – | – | nd |
| 4 | **C4** | $CH_2Cl_2$ (0.04) | DIPEA (25) | – | – | nd |
| 5 | **C5** | $CH_2Cl_2$ (0.04) | DIPEA (25) | 29 | – | 82 |
| 6 | **C5** | $CH_2Cl_2$ (0.04) | DIPEA (100) | 36 | – | 82 |
| 7 | **C5** | $CH_2Cl_2$ (0.16) | DIPEA (100) | 51 | 8 | 82 |
| 8 | **C5** | THF (0.16) | DIPEA (100) | 31 | 12 | 3 |
| 9 | **C5** | $CH_3CN$ (0.16) | DIPEA (100) | 49 | 18 | 84 |
| 10 | **C5** | DCE (0.08) | DIPEA (100) | 65 | 10 | 84 |
| 11 | **C5** | $CHCl_3$ (0.16) | DIPEA (100) | 67 | 13 | 90 |
| 12[d] | **C5** | $CHCl_3$ (0.16) | DIPEA (100) | 66 | 12 | 88 |
| 13 | **C5** | $CHCl_3$ (0.16) | DBU (100) | – | – | – |
| 14[e] | **C5** | $CHCl_3$ (0.16) | KHMDS[f] (25) | 53 | 13 | 71 |
| 15[e,g] | **C5** | $CHCl_3$ (0.16) | $K_3PO_4$ (25) | 74 | 11 | 82 |
| 16 | **C5** | $CHCl_3$ (0.16) | TEA (100) | 52 | 10 | 88 |
| 17[h,i] | **C5** | $CHCl_3$ (0.40) | DIPEA (100) | 70 | 7 | 91 |
| 18[i,j] | **C5** | $CHCl_3$ (0.40) | DIPEA (100) | 25 | 2 | 91 |

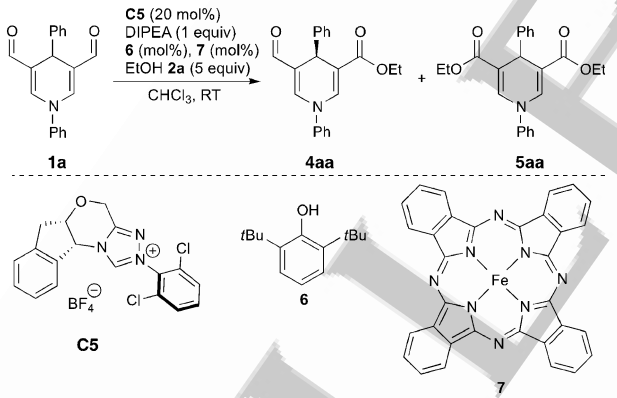
[a] Reactions performed with 0.04 mmol of **1a** for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction performed with 4 Å MS. [e] Reaction time: 7 h. [f] 1 M in Toluene. [g] Reaction performed at 0 °C. [h] Reaction time: 16 h. [i] Reaction performed at 40 °C. [j] **C5**: 10 mol%. TBS = *tert*-butyldimethylsilyl; DCE = 1,2-dichloroethane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TEA = Triethylamine.■■ok?■■

changed the reaction outcome (entry 12). The use of stronger organic and inorganic bases produced unsatisfactory results (entries 13–15). Notably, potassium bis(trimethylsilyl)amide■■ok?■■ (KHMDS) and $K_3PO_4$ significantly increased the reaction rate at the expense, however, of the enantioselectivity of the process (see the Supporting Information for the full set of experiments of the optimization study, including those with the use of additives). Gratifyingly, a further increase of **1a** concentration (0.4 M) and raising the temperature to 40 °C led to a marked decrease of the reaction time (16 h vs. 72 h) accompanied by a slight improvement of enantioselectivity (91% *ee*; entry 17).

Disappointingly, the reduction of catalyst loading to 10 mol% determined a significant reduction of **3aa** yield (25%, entry 18). In a control experiment, an authentic sample of **3aa** (91% *ee*) was subjected to a second catalytic oxidation under the optimized conditions of entry 17. The reaction was quenched at approximately 50% conversion giving the diester **4aa** (39%) and unreacted monoester **3aa** (41%) with unmodified enantiomeric excess (91% *ee*). This result seemed to exclude the contribution of **3aa** resolution to the stereochemical outcome of the desymmetrization process of **1a**.

The use of oxygen as the terminal oxidant was next attempted in our model reaction by applying the system of electron transfer mediators (ETMs) developed by Bäckvall[21] and Sundén[22] groups (Table 2). Accordingly, catalytic **3** formed and regenerated in situ from the inexpensive alcohol **6** (20 mol%), iron(II)phthalocyanine **7** (5 mol%), and atmospheric oxygen under basic conditions. With this oxidation system, the optimal

**Table 2.** Optimization of the reaction conditions with oxygen as the terminal oxidant.[a]




| Entry | 6 [mol%] | 7 [mol%] | 4aa [%][b] | 5aa [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | 20 | 5 | 46 | 5 | 86 |
| 2 | 40 | 10 | 53 | 7 | 90 |
| 3[d] | 40 | 10 | 55 | 8 | 87 |
| 4[e] | 40 | 10 | 54 | 7 | 86 |

[a] Reactions performed with 0.04 mmol of **1a** (0.16 M) and atmospheric air (balloon technique) for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction performed at 40 °C. [e] Reaction performed with oxygen (balloon technique).

**C5**/DIPEA couple promoted the formation of **3aa** ($CHCl_3$, RT, 24 h) in 46% yield and 86% *ee* without evidences of DHP ring oxidation (Table 2, entry 1). Increasing the loading of **6** (10 mol%) and **7** (40 mol%) resulted in a slight improvement of yield (53%) and enantioselectivity (90% *ee*) of **3aa** (entry 2), whereas raising the temperature to 40 °C or replacing air with oxygen had no significant effects on the reaction efficiency (entries 3–4).

On the basis of the above results, the scope of the disclosed desymmetrization process of 1,4-DHP-3,5-dicarbaldehydes **1** was next investigated with the best performing Kharasch oxidant **3**, which could be easily regenerated (Supporting Information) and re-used in different runs (Figure 1).■■Table 3 changed to Figure 1■■

Variation of the alcohol nucleophile (NuX = $R^3OH$) in the **1a**/**2** combination gave DHPs **4aa–4ad** with high enantioselectivities (91–98% *ee*), although the utilization of *i*PrOH produced a significant drop of yield (**4ac**: 25%). The presence of either electron-withdrawing or electron-donating groups in the *ortho*-, *meta*-, and *para* position of the C4 phenyl substituent had little effect on the yield of DHPs **4ba–4ha** (48–70%), whereas higher enantioselectivities were registered with the *ortho*-phenyl substituted derivatives **4ga** (98% *ee*) and **4ha** (96% *ee*). Best results in terms of chemical yield were detected for DHPs **4ia**, **4ie**, and **4ja** (70–75%) displaying an alkyl group at C4 position. The effect of the N-substituent was also investigated and no appreciable modification of reaction efficiency was observed in the formation of DHPs **4ka** and **4la** bearing an electron-withdrawing and electron-donating group, respectively, on the N1 phenyl ring. On the contrary, the presence of a N-alkyl substituent caused a marked decrease of yield (**4ma**: 20%) with maintenance of selectivity (98% *ee*).

The oxidative desymmetrization process was also extended to the synthesis of thioester **4af** and acyl azide **4ag** by using ethanethiol (NuX = EtSH) and trimethylsilyl azide (NuX = $TMSN_3$) as the nucleophile, respectively.[23] Compared to the acylation with alcohol nucleophiles, C–S and C–N bond formation in the oxidation of aldehyde **1a** proceeded with lower efficiency, especially in terms of enantioselectivity.

Being unfruitful any attempt to grow good single crystals, the absolute configuration of DHPs **4** was determined as (4*R*) by time-dependent (TD)-DFT-simulation of the electronic circular dichroism (ECD) spectra[24] by using **4da** as the model compound (Supporting Information).

To shed light on the origin of stereoselectivity, DFT calculations[25] were carried on the basis of some experimental evidences. We considered that strong and inorganic bases give lower enantiomeric excesses compared to DIPEA; furthermore, this organic base yields an acidic ammonium ion when it reacts with **C5**, whereas other bases produce neutral (HMDS) or anionic ($HPO_4^{2-}$) species. Hence, we propose the catalytic cycle depicted in Scheme 2. After the formation of NHC by deprotonation of **C5**, $[DIPEA-H]^+$ activates the carbonyl of **1** towards the addition of carbene (**TS1**). In the second step, the free DIPEA (1 equiv vs. **1**) deprotonates the intermediate alcohol (**TS2**) to yield the Breslow intermediate, which in turn is oxidized by **3** to the acyl azolium (**TS3**). The final nucleophilic

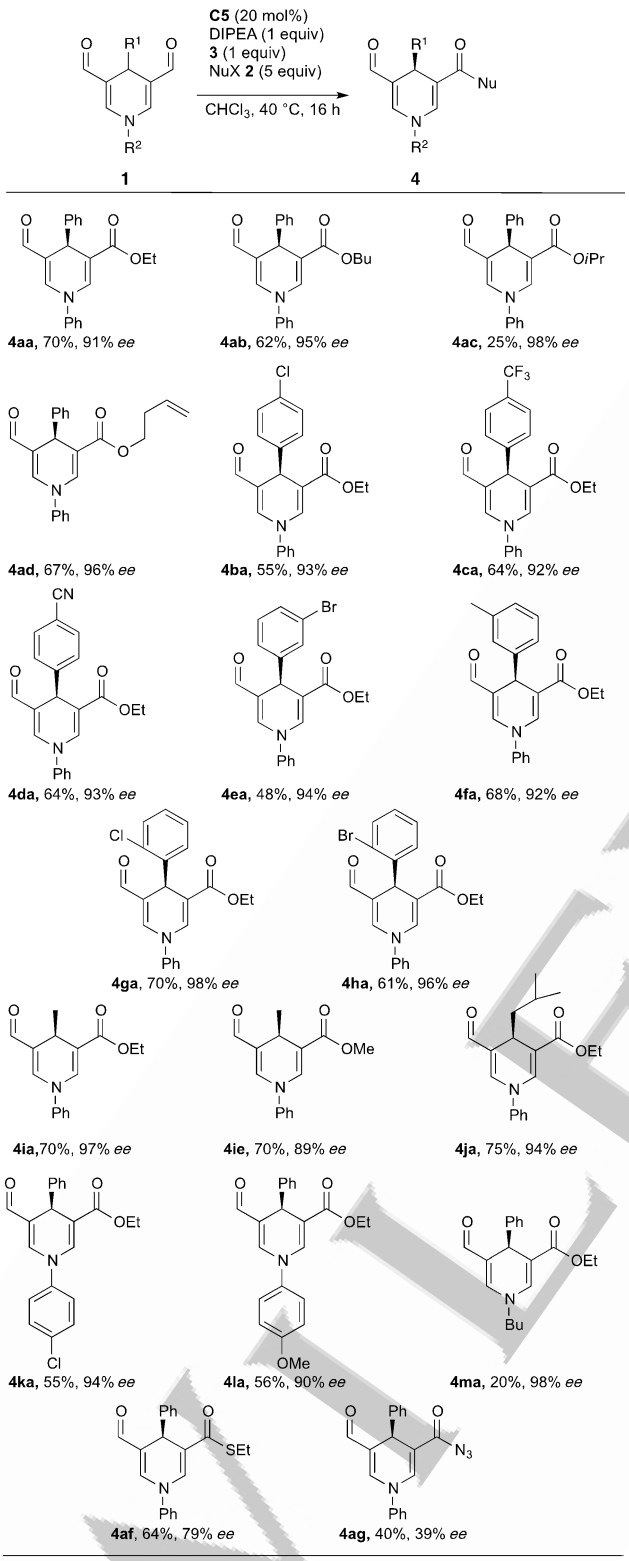
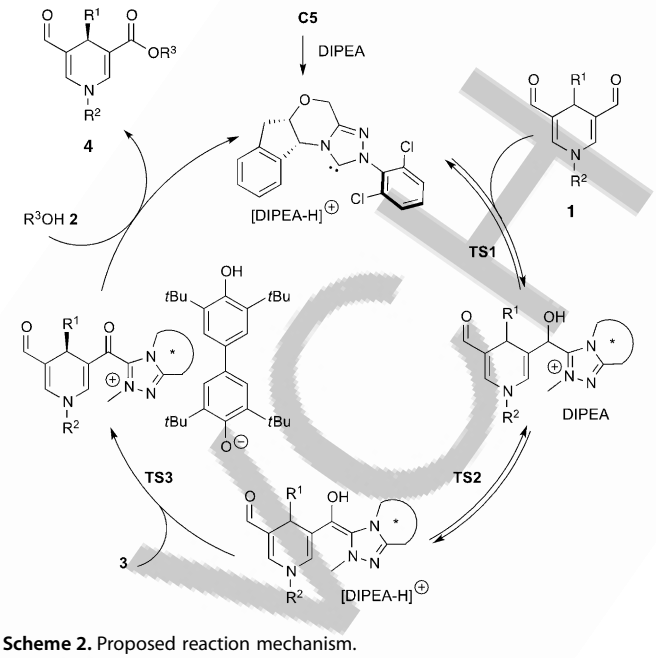


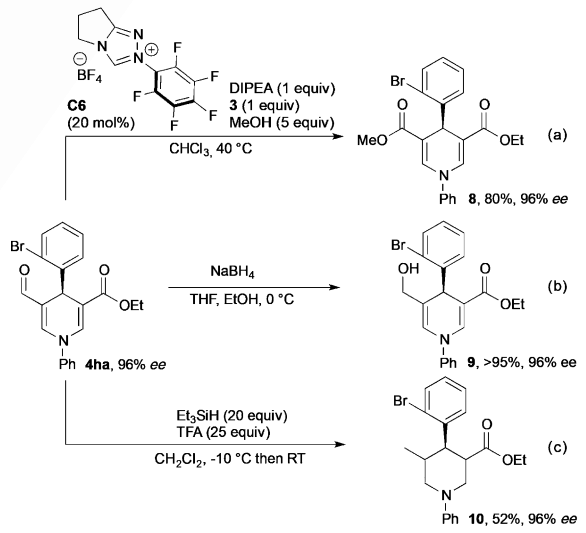

**Figure 1.** Optimization of the reaction conditions with quinone **3** as the oxidant. Conditions: **1** (0.16 mmol; 0.4 M).

attack by alcohol **2** affords DHP **4** and the free NHC. The three transition states (**TS1**–**TS3**) were modelled and optimized by DFT[25] calculations at the PCM-M06-2X/6-31G(d,p) level of theory.[26] Free energies were then evaluated at the PCM-M06-2X/6-311++G(2df,2p) level with D3 correction.[27] We found that **TS1** and **TS2** have small activation energies, which are compatible with reversible steps at ambient temperature. The threshold TS resulted the oxidation of the Breslow intermediate, where the **TS3** geometry leading to the (*R*) product is stabilized by more than 3 kcal mol$^{-1}$ with respect to the pro-(*S*) pathway (Supporting Information).




**Scheme 2.** Proposed reaction mechanism.

As a proof of concept study, the enantiopure DHP **4ha** was readily converted into the biologically relevant 3,5-dicarboxylate **8** by application of the herein disclosed oxidative process in its racemic variant using the achiral pre-catalyst **C6** and methanol as the nucleophile [Scheme 3, reaction (a)]. Moreover, the same substrate **4ha** was quantitatively reduced with $NaBH_4$ to the alcohol **9** [reaction (b)], which belongs to the class of 1,4-DHP derivatives identified by the group of Meyers




**Scheme 3.** Derivatization of chiral DHP **4ha**.

as NADH mimetics for the enantioselective reduction of α-ketoesters.[28] Indeed, alcohol **9** was successfully utilized in the asymmetric reduction of methyl benzoylformate affording (*S*)-methyl mandelate in almost quantitative yield and 89% *ee* (Supporting Information).

Finally, treatment of **4ha** with an excess of $Et_3SiH$ and trifluoroacetic acid gave the piperidine **10** as single diastereoisomer with maintenance of enantiomeric excess [reaction (c)], thus further demonstrating the versatility of 5-formyl-1,4-DHP-3-carboxylates of type **4** in the synthesis of chiral heterocycles.

In conclusion, we have developed a highly efficient NHC-catalyzed desymmetrization of 1,4-DHP-3,5-dicarbaldehydes to access enantioenriched C4-substituted DHPs, which are versatile chiral scaffolds for applications in medicinal and organic chemistry. Additionally, formation of the acyl azolium intermediate as the enantiodetermining step of the reaction was supported by DFT calculations.

## Experimental Section

**General procedure:**■■ok?■■ A 1 mL vial equipped with a magnetic stirring bar was charged with 1,4-dihydropyridine-3,5-dicarbaldehyde **1** (0.16 mmol), pre-catalyst **C5** (0.032 mmol) and the oxidant **3** (0.16 mmol), then anhydrous $CHCl_3$ was added (0.4 mL) followed by the nucleophile (NuX) **2** (0.80 mmol) and DIPEA (0.16 mmol). The resulting solution was stirred at 40 °C for 16 hours, then cooled to RT and directly charged on a column of silica gel for chromatography to afford the target DHP **4**.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** carbenes · desymmetrization · DFT calculations · dihydropyridines · organocatalysis

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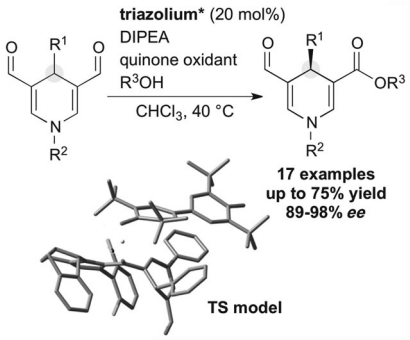
# COMMUNICATION

**Easy access** to pharmaceutically relevant dihydropyridines. A highly enantioselective synthesis of enantioenriched 1,4-dihydropyridines by desymmetrization of prochiral dialdehyde substrates promoted by N-heterocyclic carbenes under oxidative conditions is presented. New insights into the mechanism of Breslow intermediate formation and oxidation by a quinone have been gained by DFT calculations.




**Organocatalysis**

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■■ – ■■

**Enantioselective Desymmetrization of 1,4-Dihydropyridines by Oxidative NHC Catalysis**

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