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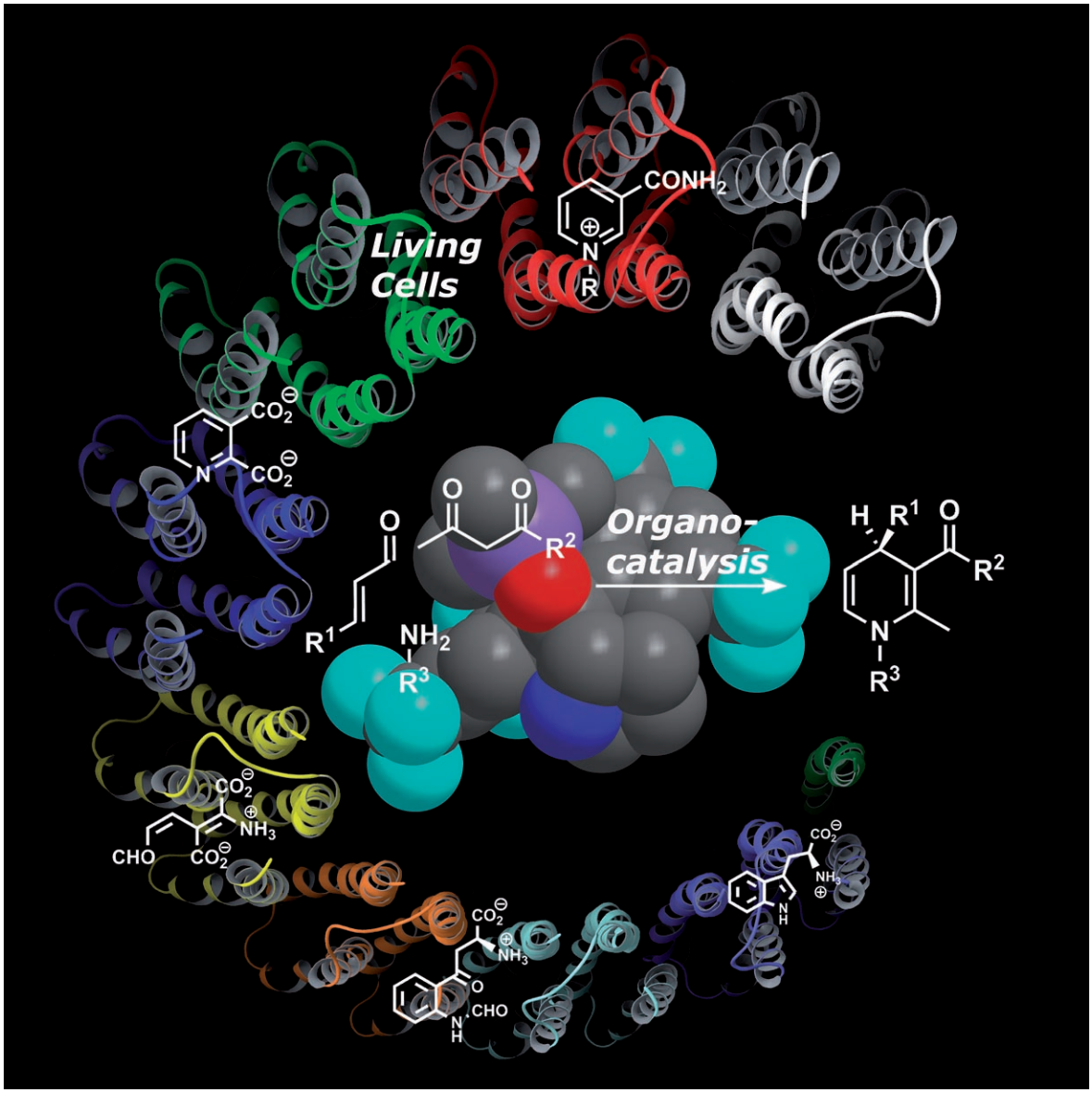
Organocatalytic Enantioselective One-Pot Synthesis and Application of Substituted 1,4-Dihydropyridines—Hantzsch Ester Analogues

Patrick T. Franke, Rasmus L. Johansen, Søren Bertelsen, and Karl Anker Jørgensen*[a]

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday



Abstract: An easy and simple one-pot approach for the formation of optically active substituted 1,4-dihydropyridines by using asymmetric organocatalysis is presented. The one-pot reaction of α,β-unsaturated aldehydes with β-diketones or β-ketoesters and primary amines gives optically active 2,3-substituted 1,4-dihydropyridines in moderate yields and with enantioselectivities up to 95% *ee*. It is also demonstrated that the optically active 1,4-dihydropyridines can be used in situ for the direct enantioselective reduction of, for example, α-ketoesters with high enantioselectivity.

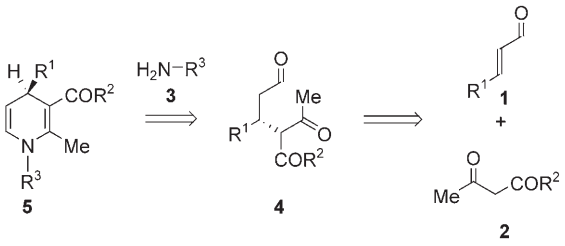
Keywords: asymmetric synthesis · multicomponent reactions · nitrogen heterocycles · organocatalysis · reduction

Introduction

Organocatalysis has in the past few years proved to be a powerful tool in the development of a large number of enantioselective reactions.[1] Among the organocatalysts used, chiral secondary amines have shown the potential to catalyze a large number of highly stereoselective transformations of carbonyl compounds, for example, the enantioselective α-,[2] β-,[3] and γ-functionalizations[4] of aldehydes. Organocatalysis has also demonstrated its potential for the construction of multiple bonds and stereocenters in terms of enantioselective domino, one-pot, and multicomponent reactions.[5] These latter strategies allow a fast, environmentally friendly, and easy approach to the formation of complex molecules with a minimum of manual operations and purification steps, and therefore methodologies that adopt these strategies are highly desirable.

One example of a multicomponent reaction is the classical synthesis of Hantzsch esters,[6] which are derivatives of 1,4-dihydropyridines (DHPs).[7] These compounds are closely related to the NADH system—a biological system of utmost importance.[8] DHPs are important drugs in virtue of their pharmacological activities, and they are used in the treatment of a number of diseases,[9] such as cardiovascular diseases[10] and Alzheimer's disease.[11]

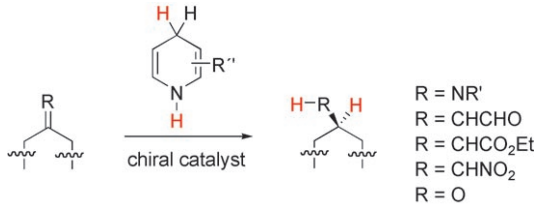
We envisioned that it might be possible to develop a closely related reaction in an organocatalytic fashion for the formation of enantiomerically enriched DHPs by an enantioselective one-pot multicomponent reaction as outlined in Scheme 1. The strategy for the formation of the DHPs **5** in



Scheme 1. Retrosynthetic approach for the organocatalytic enantioselective one-pot multicomponent reaction leading to enantiomerically enriched 1,4-dihydropyridines.

Scheme 1 is based on the initial reaction of an α,β-unsaturated aldehyde **1** with a dicarbonyl compound or β-ketoester **2** in the presence of an organocatalyst, followed by the addition of a primary amine **3** under one-pot reaction conditions.

DHPs are also well-known reductants for imines, electrophilic alkenes, nitro- and carbonyl-substituted alkenes, and α- and β-ketoesters, as outlined in a general manner in Scheme 2. Recent examples of the use of Hantzsch esters are the enantioselective organocatalytic transfer hydrogenations as developed by the groups of MacMillan, List, Rueping, and Córdova.[12] Different types of catalysts are able to induce stereoselectivity in transfer hydrogenation, for example, imidazolodinones,[12c,d] pyrrolidines,[12e] ammonium phosphates,[12f] phosphoric acids,[12i] or thioureas.[12r] Such metal-



Scheme 2. Organocatalytic enantioselective transfer hydrogenations.

[a] P. T. Franke, R. L. Johansen, S. Bertelsen, Prof. Dr. K. A. Jørgensen
Danish National Research Foundation Center for Catalysis
Department of Chemistry
Aarhus University
DK-8000 Aarhus C (Denmark)
Fax: (+45) 89-19-6199
E-mail: kaj@chem.au.dk

free hydrogenations are receiving an increased amount of interest owing to the general importance of reductions in both laboratory and industrial scales.[13]

Normally, DHPs are obtained as racemates from a one-pot procedure involving primary amines, dicarbonyls, and α,β-unsaturated aldehydes, although the reaction sequence between these is not fully established.[7] To obtain enantioenriched DHPs, the racemate has to be separated by resolution techniques, and such resolution steps are often time-consuming and expensive. Keeping these precedents in mind, we have now developed the first organocatalytic enantioselective one-pot synthesis of optically active DHPs. We also demonstrate the combination of the one-pot synthesis of DHPs and the enantioselective reduction of an α-ketoester in highly enantioselective reduction reactions.

Results and Discussion

The organocatalytic one-pot reaction between α,β-unsaturated aldehydes and dicarbonyl compounds or β-ketoesters occurs in the presence of chiral secondary amines as organocatalysts with benzoic acid as additive in toluene as the solvent. The reaction is then treated—in a one-pot procedure—with a primary amine to form the desired DHPs.

A screening was performed to find the optimal reaction conditions. *trans*-2-Pentenal (**1a**), 2,4-pentadione (**2a**), and aniline (**3a**) were chosen as the constant parameters, while organocatalysts **6**, additives, solvents, and reaction temperatures were varied. A selection of the results is presented in Table 1.

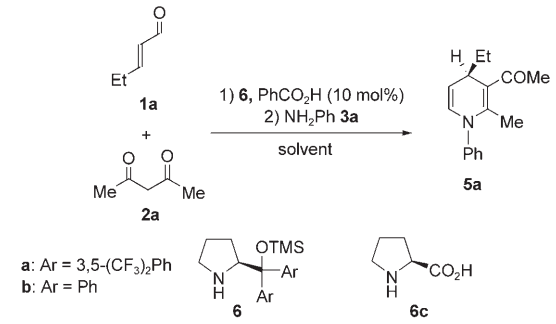
The screening of the different solvents showed that DHP **5a** was always formed with high enantioselectivity. The highest enantioselectivity, 91% *ee*, was obtained in CH_2Cl_2 with 2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (**6a**) as the catalyst (Table 1, entry 2). However, the yield in CH_2Cl_2 was lower than that in toluene (Table 1, entry 1). Other solvents gave full conversion into **5a**, although the yield of isolated **5a** was still only moderate at best. Several different secondary amines were also tested as the catalyst for the reaction, for example, 2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine (**6b**) and proline (**6c**). The latter catalyst showed very low activity with <10% conversion (Table 1, entry 6). Catalyst **6b** also gave lower yield and selectivity than **6a** (Table 1, entries 1 and 5).[14] Neither the yield nor the enantioselectivity improved when the reaction was performed at lower (4°C) or higher (40°C) temperatures. Different additives, such as CAN, *p*-nitrobenzoic acid, or various dehydrating agents led to slightly faster reactions, but with no improvement in the yield (Table 1, entries 9 and 10). However, in the case of $CaCl_2$, the yield of **5a** was improved to 55%, and the enantioselectivity was maintained at 90% *ee* (Table 1, entry 11). The catalyst loading could be lowered to 5 mol% without a significant decrease in yield or enantioselectivity (Table 1, entry 12).

With the reaction conditions developed, we investigated the scope of the reaction for the addition of diketones or β-ketoesters **2** and primary amines **3** to a number of different α,β-unsaturated aldehydes **1** to give the DHP products **5**. The results are presented in Table 2. It is important to emphasize the scope and potential of the reaction, as it is possible to vary the substituents in positions 1, 3, and 4 in the 1,4-dihydropyridine ring, which can give access to a great variety of optically active DHPs.

It appears from the results in Table 2 that substituents such as aliphatic, esters, heteroaromatic groups, aromatic groups, heteroatoms, and double bonds are tolerated in the α,β-unsaturated aldehydes. For all the non-aromatic α,β-unsaturated aldehydes, moderate yields (see below) and high enantioselectivities (88–95% *ee*) were obtained for the reaction with 2,4-pentadione (**2a**) and aniline (**3a**) as the primary amine (Table 2, entries 1–4, 6). However, only low to moderate stereoselectivities were observed when aromatic aldehydes were used, and, unfortunately, a lowering of the reaction temperature from 21°C to 4°C did not raise the selectivities above modest levels (Table 2, entries 5, 9), although the yield of the reaction with cinnamaldehyde was good (Table 2, entry 9).

The nucleophiles applied for the addition to the α,β-unsaturated aldehydes can be both diketones or β-ketoesters. Table 2 shows the results for 2,4-pentadione **2a** and β-ke-

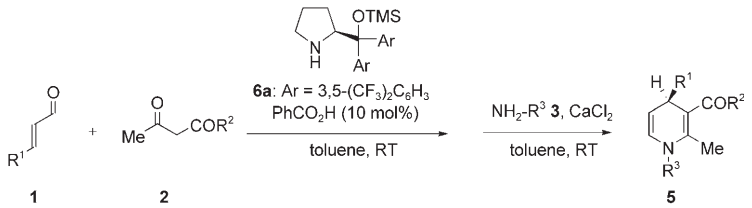
Table 1. Screening of various reaction conditions for the addition of **2a** to **1a** and subsequent cyclization with **3a** in the presence of catalysts **6a–c**.[a]



Entry	Solvent	Cat.	Additive	Conversion (yield) [%]	*ee*[b] [%]
1	toluene	**6a**	-	>95 (40)	90
2	CH_2Cl_2	**6a**	-	>95 (35)	91
3	EtOH	**6a**	-	>95 (35)	86
4	Et_2O	**6a**	-	>95 (30)	89
5	toluene	**6b**	-	>95 (20)	80
6	toluene	**6c**	-	<10 (n.r.)	n.r.
7[c]	toluene	**6a**	-	>95 (39)	91
8[d]	toluene	**6a**	-	>95 (39)	91
9	toluene	**6a**	CAN	>95 (40)	89
10	toluene	**6a**	*p*-NO_2PhCO_2H	>95 (37)	91
11	toluene	**6a**	$CaCl_2$	>95 (55)	90
12[e]	toluene	**6a**	$CaCl_2$	>95 (52)	90

[a] Performed with **1a** (0.25 mmol), **2a** (0.38 mmol), **6** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene (0.5 mL); after complete conversion of **1a**, compound **3a** and additional additives were added. [b] Determined by chiral-stationary-phase HPLC. [c] Performed at 4°C. [d] Performed at 40°C. [e] Performed with 5 mol% of **6a**. CAN = cerium ammonium nitrate.

Table 2. Scope and yield of the TMS-prolinol-protected catalyzed synthesis of 1,4-dihydropyridines.[a]



Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**3**)	*t* [h]	Product (Yield [%])	*ee* [%][b]
1	Et (**1a**)	Me (**2a**)	Ph (**3a**)	18+1	**5a** (55)	90
2	Hex-3-en-1-yl (**1b**)	Me (**2a**)	Ph (**3a**)	18+1	**5b** (45)	92
3	CO_2Et (**1c**)	Me (**2a**)	Ph (**3a**)	18+24	**5c** (31)	88
4	$(CH_2)_2OTBDMS$ (**1d**)	Me (**2a**)	Ph (**3a**)	18+1	**5d** (33)	95
5[c]	2-Furyl (**1e**)	Me (**2a**)	Ph (**3a**)	18+24	**5e** (35)	64
6	*i*Pr (**1f**)	Me (**2a**)	Ph (**3a**)	18+1	**5f** (33)	92
7	Et (**1a**)	OMe (**2b**)	Ph (**3a**)	18+1	**5g** (41)	91
8[c]	Me (**1g**)	OMe (**2b**)	Ph (**3a**)	18+24	**5h** (39)	82
9[c]	Ph (**1h**)	Me (**2a**)	Ph (**3a**)	72+1	**5i** (60)	38
10	Et (**1a**)	Me (**2a**)	*i*Pr (**3b**)	18+1	**5j** (39)	90
11	Et (**1a**)	Me (**2a**)	*p*-BrPh (**3c**)	18+1	**5k** (48)	92

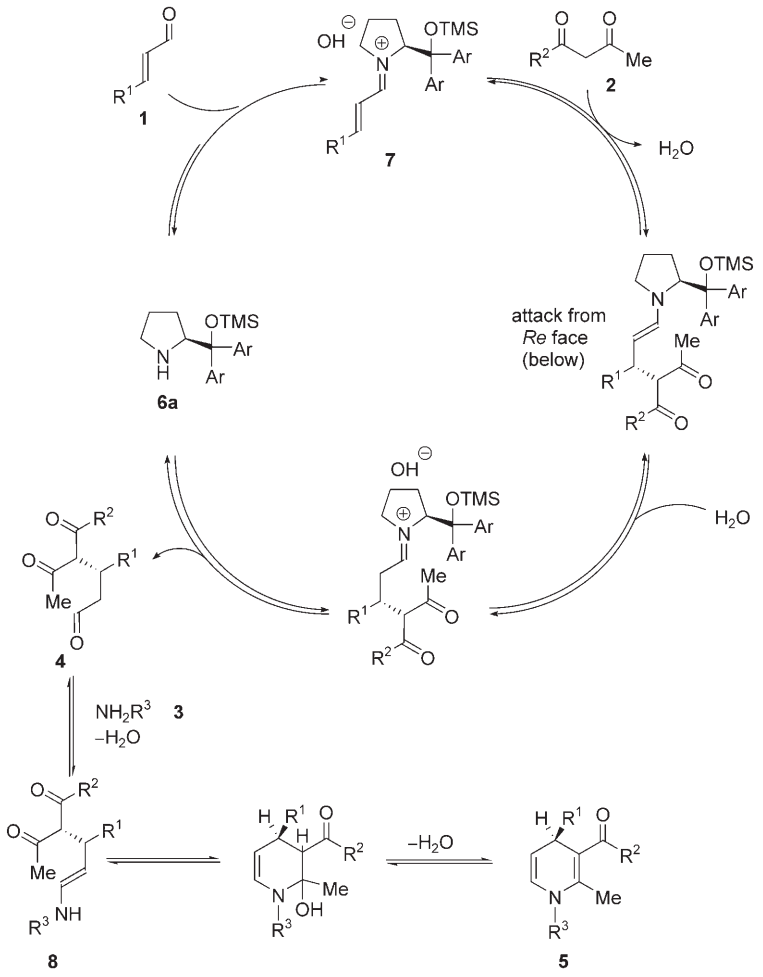
[a] Performed with **1** (0.25 mmol), **2** (0.38 mmol), **6** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene (0.5 mL). [b] Determined by chiral-stationary-phase HPLC. [c] Performed at 4 °C.

toester **2b**, and consistently high enantioselectivities were observed for both kinds of nucleophiles.

The organocatalytic enantioselective formation of optically active DHPs also shows the potential for varying the primary amine **3a**–**c**—the R^3 substituent in **5**. Both aliphatic and aromatic amines are tolerated, but aniline proved to have the highest reactivity and gave the products in up to 55% yield without diminishing the high enantioselectivities (Table 2, entries 1, 10, 11).

Mechanistic Model

The proposed mechanism for the chain of transformation is summarized in Scheme 3. The Michael addition follows the common path previously reported in the literature.[3f,p,5p,r,v] The α,β-unsaturated aldehyde **1** is transformed by catalyst **6a** and nucleophile **2** into the Michael adduct **4**. The stereocenter formed in the catalytic cycle is controlled by a *Re*-face attack of the nucleophile (dicar-

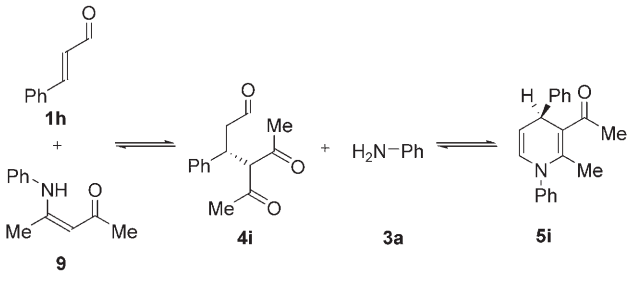


Scheme 3. Proposed mechanism for the organocatalytic one-pot Michael addition of α,β-unsaturated aldehydes **1** and β-dicarbonyls and β-ketoesters **2** followed by cyclization with primary amines **3** to chiral DHPs **5**. TMS = trimethylsilyl.

bonyl compound or β-ketoester) **2** on the planar iminium ion **7**. The *Re* face of the β carbon atom in the iminium-ion intermediate is favored for approach of the nucleophile owing to the bulk of the C2 substituent in the pyrrolidine ring of the catalyst **6a** which shields the *Si* face, as previously reported for the use of TMS-protected prolinols as organocatalysts.[3f,p,5p,r,v] After the formation of the stereocenter, the catalyst is released from the intermediate to give the Michael adduct **4**, which reacts with the primary amine **3** to form the enamine **8** in the next step. The amine moiety of the enamine attacks the keto functionality in a 6-*exo*-trig fashion to form the DHP **5** after elimination of water.

As can be seen in Table 2, the DHPs **5** are formed in moderate yields. Therefore, we performed a large number of experiments in an attempt to understand the moderate yields of the one-pot reaction. From a mechanistic point of view, we are faced with the challenge, that both a secondary amine (the catalyst) and a primary amine are present during the course of the reaction. These two amines might have the possibility to react with the two carbonyl compounds present in the reaction mixture, the α,β-unsaturated aldehyde and the diketone or β-ketoester, leading to the observed moderate yield in the one-pot reaction.

We believe that several of the steps in the proposed mechanism in Scheme 3 are reversible for the aromatic aldehydes. Evidence for this hypothesis was provided when the reaction was performed stepwise. The intermediate **4i** was isolated and purified by column chromatography and afterwards transformed into the DHP **5i**. The stepwise approach performed with the aromatic α,β-unsaturated aldehyde **1h** resulted in a mixture of the intended DHP **5i** and a by-product identified as **9** (Scheme 4). The side product **9** has previously been reported in the literature[15] and can only be formed by the reaction between 2,4-pentadione (**2a**) and aniline (**3a**). Hence, the Michael addition is probably reversible. Application of the same concept to the aliphatic α,β-unsaturated aldehyde **1a** yielded only the intended product **5a**. The reversibility of the reaction performed with aromatic substrates might explain the low enantioselectivity for these aldehydes. It should be noted that α,β-unsaturated aldehydes that bear an electron-rich aromatic substituent (*p*-MeOPh) gave an enantioselectivity of only 6% *ee*, indicating that an electron-rich aromatic substituent increases the reversibility. This hypothesis was tested by changing to a system with an electron-withdrawing substituent, as this should be expected to decrease the reversibility. To our great delight the experiment performed with *p*-NO_2Ph as substituent of the α,β-unsaturated aldehydes **1** led to an enantioselectivity of 60% *ee*.



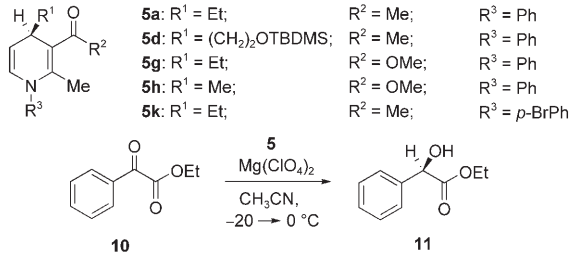
Scheme 4. Equilibria between the Michael adduct **4i** and aniline (**3a**) with the intended DHP **5i** and with by-product **9**.

The absolute stereochemistry of the intermediates **4**, and hence of the final products **5**, was assigned on the basis of earlier studies on the stereoselectivities of catalyst **6a** in the reaction between α,β-unsaturated aldehydes and β-dicarbonyl nucleophiles,[3f,5p,r,v] as well as computational studies on the conjugate addition of other nucleophiles.[3p]

Reduction Product Elaboration

The optically active DHPs **5a**,**d**,**g**,**h**,**k** were tested for their reductive abilities in asymmetric hydride-transfer reactions. Ethyl benzoylformate (**10**) was chosen as a model substrate as it has previously been reduced with related DHP compounds.[16] In Table 3 the results of the reductions under standard conditions are presented. The results show a great potential for highly stereoselective reductions.

Table 3. Results of the enantioselective transfer hydrogenation of **10** with **5**.[a]



Entry	DHP	*ee* DHP [%][b]	Conv.[c]	*ee* [%][b]
1	**5a**	90	full	81
2	**5d**	95	full	80
3	**5g**	91	full	82
4	**5h**	80	full	72
5	**5k**	92	full	82
6[d]	**5a**	n.d.	full	79

[a] Performed with **10** (0.15 mmol), $Mg(ClO_4)_2$ (0.15 mmol), and **5** (0.10 mmol) in CH_3CN (0.6 mL) overnight. [b] Determined by chiral-stationary-phase HPLC. [c] Determined by NMR spectroscopy. [d] Crude reaction mixture containing compound **5a** was used. TBDMS = *tert*-butyldimethylsilyl.

The DHPs **5** were added at −20 °C in MeCN to an equally cold solution of **10** and $Mg(ClO_4)_2$. Full conversion (^{1}H NMR spectroscopy) was observed for all DHPs, and in all cases high enantioselectivities of up to 82% *ee* were attained (Table 3). It was also found that changing the substituents R^1, R^2, and R^3 in the DHPs had only a minor effect on the enantioselectivity (Table 3, entries 1, 3, 4).

We also tried to perform the whole reaction sequence as a one-pot reaction starting from *trans*-2-pentenal (**1a**), 2,4-pentadione (**2a**), and aniline (**3a**), that is, the enantioselec-

tive organocatalytic formation of the DHP followed by reduction of ethyl benzoylformate. The crude reaction mixture containing compound **5a** was evaporated, and CH_3CN, **10**, and $Mg(ClO_4)_2$ were added. Full conversion and an enantioselectivity of 79% *ee* was observed (Table 3, entry 6). This shows that the new asymmetric organocatalytic reaction developed can easily provide a library of highly variable chiral DHPs, which can instantly be screened in enantioselective reduction reactions.

The absolute stereochemistry assigned to **5** is further supported by the stereoinduction observed in the reduction of ethyl benzoylformate (**10**) to ethyl mandelate (**11**), as previously reported in the litterature.[16]

Conclusions

We have presented the first organocatalytic enantioselective one-pot synthesis of DHPs. This strategy gives access to a broad range of DHPs, variable at three different positions, with very good enantiomeric excesses using chiral aminocatalysis. The synthesized library of chiral DHPs could be used to screen enantioselective reductions. This was tested for the reduction of ethyl benzoylformate for which enantioselectivities of up to 82% *ee* were attained. We have also demonstrated that the combination of the one-pot synthesis of the DHPs and the enantioselective reduction of an α-ketoester were possible and lead to highly enantioselective reduction reactions.[18]

Experimental Section

General

NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^1H and ^{13}C NMR, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, $\delta = 7.26$ ppm for ^1H NMR and $\delta = 77.0$ ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired in broad-band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer by using electrospray (ES^+) ionization techniques. Analytical thin-layer chromatography (TLC) was performed on precoated aluminum-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation or $KMnO_4$ dip. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary-phase HPLC (Daicel Chiralpak AD or Daicel Chiralcel OD columns).

Materials

Analytical grade solvents, α,β-unsaturated aldehydes **1**, dicarbonyl compounds or β-ketoesters **2**, primary amines **3**, and benzoic acid are commercially available reagents and were used as received. Noncommercially available aldehydes were prepared according to literature. Flash chromatography was carried out by using Iatrobeads 6RS-8060 (spherical silica gel) or silica gel purchased from Fluka (silica gel 60, 230–400 mesh). Racemic samples were prepared by using a racemic mixture of the catalyst. Solvents and reagents were extensively flushed with argon when used for reductions in which 1,4-dihydropyridines were involved.

General Procedure for the One-pot Synthesis of 1,4-Dihydropyridines

The catalyst **6a** (10 mol%, 0.025 mmol), **1** (0.25 mmol, 1.0 equiv), **2** (0.375 mmol, 1.5 equiv), toluene (0.5 mL), and $PhCO_2H$ (10 mol%, 0.025 mmol) were added to a sample vial equipped with a magnetic stirring bar. The mixture was stirred overnight at ambient temperature, and then **3** (0.375 mmol, 1.5 equiv) and $CaCl_2$ (50.0 mg) were added. The reaction was completed after about 1 h (monitored by TLC or NMR spectroscopy). The reaction mixture was evaporated and loaded onto silica gel or Iatrobeads 6RS-8060, and the products **5a–k** was obtained by flash chromatography.

General Procedure for the Asymmetric Reduction of Ethyl Benzoylformate with 1,4-Dihydropyridines

The 1,4-dihydropyridines **5** (0.10 mmol) in MeCN (0.4 mL) were added to a sample vial equipped with a magnetic stirring bar and flushed with argon. The solution was cooled to −25 °C and then treated at once with an equally cold solution of $Mg(ClO_4)_2$ (0.133 mmol, 1.3 equiv) and methyl benzoylformate (0.133 mmol, 1.3 equiv) in MeCN (0.2 mL). The reaction mixture was allowed to reach 0 °C overnight, and ^1H NMR spectroscopy indicated completion of the reaction. The solution was evaporated, and the residue was diluted in water (3 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated after filtration, and the crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as eluent.

5a: 1-(4-Ethyl-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)ethanone (**5a**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2 as an oil (55% yield). $[\alpha]_D^{20} = -344.2$ ($c = 0.08$, CH_2Cl_2); ^1H NMR: $\delta = 7.41$–7.37 (m, 2H), 7.32–7.27 (m, 1H), 7.14–7.12 (m, 2H), 6.22 (d, $J = 7.4$ Hz, 1H), 5.02 (dd, $J = 6.1$, 7.4 Hz, 1H), 3.41 (dt, $J = 4.5$, 6.1 Hz, 1H), 2.78 (s, 3H), 2.02 (s, 3H), 1.48–1.34 (m, 2H), 0.93 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR: $\delta = 200.2$, 147.1, 143.6, 130.6, 129.5, 127.2, 127.1, 111.1, 106.5, 35.4, 31.6, 29.1, 19.3, 9.1 ppm; HRMS: calcd for $C_{16}H_{19}NNaO^+$: 264.1364 $[M+Na]^+$; found: 264.1363. The *ee* was determinded by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate: 1.0 mL min^{-1}; $\tau_{major} = 6.1$ min, $\tau_{minor} = 6.9$ min (90% *ee*).

5b: (*Z*)-1-(4-(Hex-3-enyl)-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)-ethanone (**5b**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2/Et_2O (98:2) as an oil (45% yield). $[\alpha]_D^{20} = -233.5$ ($c = 0.11$, CH_2Cl_2); ^1H NMR: $\delta = 7.41$–7.37 (m, 2H), 7.31–7.28 (m, 1H), 7.14–7.12 (m, 2H), 6.22 (d, $J = 7.4$ Hz, 1H), 5.36 (m, 2H), 5.06 (dd, $J = 6.1$, 7.4 Hz, 1H), 3.43 (ddd, $J = 4.0$, 6.1, 8.1 Hz, 1H), 2.26 (s, 3H), 2.15–2.04 (m, 4H), 2.02 (s, 3H), 1.54–1.43 (m, 1H), 1.40–1.31 (m, 1H), 0.96 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 199.8, 147.2, 143.5, 132.0, 130.6, 129.5, 129.0, 128.7, 127.1, 111.2, 106.7, 39.1, 33.7, 29.2, 22.4, 20.5, 19.2, 14.3 ppm; HRMS: calcd for $C_{20}H_{25}NNaO^+$: 318.1834 $[M+Na]^+$; found: 318.1839. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 98:2); flow rate: 1.0 mL min^{-1}; $\tau_{major} = 6.3$ min, $\tau_{minor} = 7.7$ min (92% *ee*).

5c: Ethyl 3-acetyl-2-methyl-1-phenyl-1,4-dihydropyridine-4-carboxylate (**5c**) was obtained according to the general procedure after flash chromatography on silica gel with pentane/Et_2O (1:1) as an oil (31% yield). $[\alpha]_D^{20} = -176.8$ ($c = 0.90$, CH_2Cl_2); ^1H NMR: $\delta = 7.43$–7.39 (m, 2H), 7.35–7.31 (m, 1H), 7.19–7.17 (m, 2H), 6.20 (d, $J = 7.6$ Hz, 1H), 5.06 (dd, $J =$ 5.7, 7.6 Hz, 1H), 4.38 (d, $J = 5.7$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 2.28 (s, 3H), 2.08 (s, 3H), 1.28 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 198.2$, 173.5, 148.4, 143.0, 131.9, 129.6, 127.7, 106.8, 101.3, 61.0, 41.8, 30.3, 19.3, 14.2 ppm; HRMS: calcd for $C_{17}H_{19}NNaO_3^+$: 308.1263 $[M+Na]^+$; found: 308.1263. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 98:2); flow rate: 1.0 mL min^{-1}; $\tau_{major} = 15.2$ min, $\tau_{minor} = 14.0$ min (88% *ee*).

5d: 1-(4-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)ethanone (**5d**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2/Et_2O (98:2) as an oil (33% yield). $[\alpha]_D^{20} = -297.0$ ($c = 0.32$, CH_2Cl_2); ^1H NMR: $\delta =$ 7.41–7.37 (m, 2H), 7.32–7.27 (m, 1H), 7.14–7.11 (m, 2H), 6.22 (d, $J =$ 7.4 Hz, 1H), 5.10 (dd, $J = 6.3$, 7.4 Hz, 1H), 3.76–3.63 (m, 2H), 3.60–3.55 (m, 1H), 2.29 (s, 3H), 2.02 (s, 3H), 1.67–1.52 (m, 2H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR: $\delta = 200.1$, 147.2, 143.4, 130.6, 129.5, 127.1, 111.1, 106.7, 58.9, 42.5, 30.5, 29.2, 25.9, 19.1, 18.3, −5.3, −5.4 ppm;

HRMS: calcd for $C_{22}H_{33}NNaO_2Si^+$: 394.2178 $[M+Na]^+$; found: 394.2189. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 92:8); flow rate: 1.0 mL min^{-1}; $\tau_{major}=4.0$ min, $\tau_{minor}=6.2$ min (95% *ee*).

5e: 1-(4-(Furan-2-yl)-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)-ethanone (**5e**) was obtained by varying the general procedure and performing the reaction in toluene at 4°C. After flash chromatography on silica gel with CH_2Cl_2/Et_2O (99:1), the product **3e** was isolated as an oil (35% yield). $[\alpha]_D^{20}=-81.0$ ($c=0.55$, CH_2Cl_2); ^{1}H NMR: $\delta=7.42$–7.38 (m, 2H), 7.34–7.32 (m, 2H), 7.17–7.15 (m, 2H), 6.30 (dd, $J=1.8$, 3.0 Hz, 1H), 6.22 (d, $J=7.4$ Hz, 1H), 6.04 (dt, $J=0.7$, 3.0 Hz, 1H), 5.16 (dd, $J=6.0$, 7.4 Hz, 1H), 4.74 (d, $J=6.0$ Hz, 1H), 2.25 (s, 3H), 2.10 ppm (s, 3H); ^{13}C NMR: $\delta=199.3$, 159.4, 148.2, 143.3, 141.5, 130.9, 129.6, 127.5, 124.8, 110.3, 107.4, 104.7, 104.1, 34.4, 29.5, 19.3 ppm; HRMS: calcd for $C_{18}H_{17}NNaO_2^+$: 302.1157 $[M+Na]^+$; found: 302.1166. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; $\tau_{major}=12.0$ min, $\tau_{minor}=13.7$ min (64% *ee*).

5f: 1-(4-Isopropyl-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)ethanone (**5f**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2/Et_2O (99:1) as an oil (33% yield). $[\alpha]_D^{20}=-240.0$ ($c=0.06$, CH_2Cl_2); ^{1}H NMR: $\delta=7.40$–7.36 (m, 2H), 7.30–7.26 (m, 1H), 7.12–7.10 (m, 2H), 6.29 (d, $J=7.5$ Hz, 1H), 4.93 (dd, $J=6.1$, 7.5 Hz, 1H), 3.40 (dd, $J=4.4$, 6.1 Hz, 1H), 2.27 (s, 3H), 2.00 (s, 3H), 1.56–1.48 (m, 1H), 0.90 ppm (d, $J=6.7$ Hz, 6H); ^{13}C NMR: $\delta=201.0$, 146.5, 143.6, 131.3, 129.4, 129.1, 127.0, 111.1, 103.5, 40.7, 35.6, 29.0, 19.2, 18.6, 16.8 ppm; HRMS: calcd for $C_{17}H_{21}NNaO^+$: 278.1521 $[M+Na]^+$; found 278.1523. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 97:3); flow rate: 1.0 mL min^{-1}; $\tau_{major}=8.8$ min, $\tau_{minor}=9.6$ min (92% *ee*).

5g: Methyl 4-ethyl-2-methyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (**5g**) was obtained according to the general procedure after flash chromatography on Iatrobeads 6RS-8060 with pentane/Et_2O (95:5) as an oil (41% yield). $[\alpha]_D^{20}=-240.0$ ($c=0.12$, CH_2Cl_2); ^{1}H NMR: $\delta=7.40$–7.36 (m, 2H), 7.32–7.26 (m, 1H), 7.13–7.11 (m, 2H), 6.17 (d, $J=7.5$ Hz, 1H), 4.90 (dd, $J=6.0$, 7.5 Hz, 1H), 3.7 (s, 3H), 3.48–3.44 (m, 1H), 2.08 (s, 3H), 1.50–1.33 (m, 2H), 0.90 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR: $\delta=169.7$, 148.9, 143.7, 130.6, 129.4, 127.3, 127.0, 106.5, 100.9, 50.7, 34.3, 30.7, 18.5, 8.9 ppm; HRMS: calcd for $C_{16}H_{19}NNaO_2^+$: 280.1313 $[M+Na]^+$; found: 280.1324. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 99:1); flow rate: 1.0 mL min^{-1}; $\tau_{major}=7.1$ min, $\tau_{minor}=10.1$ min (91% *ee*).

5h: Methyl 2,4-dimethyl-1-phenyl-1,4-dihydropyridine-3-carboxylate (**5h**) was obtained according to the general procedure after flash chromatography on Iatrobeads 6RS-8060 with pentane/Et_2O (95:5) as an oil (39% yield). $[\alpha]_D^{20}=-352.0$ ($c=1.25$, CH_2Cl_2); ^{1}H NMR: $\delta=7.37$ (t, $J=7.6$ Hz, 2H), 7.28 (d, $J=7.3$ Hz, 1H), 7.12 (d, $J=8.4$ Hz, 2H), 6.07 (d, $J=7.5$ Hz, 1H), 4.92 (dd, $J=7.4$ Hz, 1H), 3.69 (s, 3H), 3.51–3.38 (m, 1H), 2.05 (s, 3H), 1.07 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR: $\delta=165.4$, 155.7, 139.4, 134.4, 131.0, 128.7, 126.2, 124.1, 65.0, 29.4, 20.7, 14.4 ppm; HRMS: calcd for $C_{15}H_{17}NNaO_2^+$: 266.1157 $[M+H]^+$; found: 266.1158. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 99:1); flow rate: 1.0 mL min^{-1}; $\tau_{major}=6.7$ min, $\tau_{minor}=9.0$ min (82% *ee*).

5i: 1-(2-Methyl-1,4-diphenyl-1,4-dihydropyridin-3-yl)ethanone (**5i**) was obtained by varying the general procedure and performing the reaction in ethanol at 4°C. After flash chromatography on Iatrobeads 6RS-8060 with CH_2Cl_2/Et_2O (97:3), the product **5i** was isolated as an oil (60% yield). $[\alpha]_D^{20}=-95.2$ ($c=0.1$, CH_2Cl_2); ^{1}H NMR: $\delta=7.44$–7.40 (m, 2H), 7.37–7.31 (m, 4H), 7.24–7.18 (m, 3H), 7.16–7.01 (m, 1H), 6.08 (d, $J=7.5$ Hz, 1H), 5.10 (dd, $J=5.6$, 7.5 Hz, 1H), 4.66 (d, $J=5.6$ Hz, 1H), 2.14 (s, 3H), 2.09 ppm (s, 3H); ^{13}C NMR: $\delta=199.9$, 147.6, 143.3, 129.6, 128.9, 128.8, 127.5, 127.1, 126.5, 109.9, 108.1, 41.2, 29.8, 19.5 ppm; HRMS: calcd for $C_{20}H_{19}NNaO^+$: 312.1364 $[M+Na]^+$; found: 312.1362. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; $\tau_{major}=10.9$ min, $\tau_{minor}=11.8$ min (38% *ee*).

5j: 1-(4-Ethyl-1-isopropyl-2-methyl-1,4-dihydropyridin-3-yl)ethanone (**5j**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2 as an oil (39% yield). $[\alpha]_D^{20}=-220.1$ ($c=0.12$, CH_2Cl_2); ^{1}H NMR: $\delta=6.11$ (d, $J=7.5$ Hz, 1H), 5.06 (dd, $J=6.5$, 7.5 Hz, 1H), 4.11 (sept., $J=6.7$ Hz, 1H), 3.23 (dt, $J=4.8$, 6.5 Hz, 1H), 2.34 (s, 3H), 2.21 (s, 3H), 1.32–1.24 (m, 2H), 1.21 (d, $J=6.7$ Hz, 3H), 1.20 (d, $J=6.7$ Hz, 3H), 0.80 ppm (s, 3H); ^{13}C NMR: $\delta=200.1$, 147.9, 123.8, 109.5, 107.7, 47.1, 35.4, 31.4, 29.7, 29.1, 22.4, 21.1, 16.2 ppm; HRMS: calcd for $C_{13}H_{21}NNaO^+$: 230.1521 $[M+Na]^+$; found: 230.1527. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralcel OD column (hexane/*i*PrOH 99:1); flow rate: 1.0 mL min^{-1}; $\tau_{major}=8.5$ min, $\tau_{minor}=9.7$ min (90% *ee*).

5k: 1-(1-(4-Bromophenyl)-4-ethyl-2-methyl-1,4-dihydropyridin-3-yl)ethanone (**5k**) was obtained according to the general procedure after flash chromatography on silica gel with CH_2Cl_2/Et_2O (98:2) as an oil (48% yield). $[\alpha]_D^{20}=-285.0$ ($c=0.10$, CH_2Cl_2); ^{1}H NMR: $\delta=7.50$ (d, $J=8.7$ Hz, 1H), 7.44 (d, $J=8.7$ Hz, 1H), 7.00 (d, $J=8.7$ Hz, 1H), 6.17 (d, $J=7.5$ Hz, 1H), 5.01 (dd, $J=6.0$, 7.5 Hz, 1H),3.41–3.37 (m, 1H), 2.26 (s, 3H), 2.00 (s, 3H), 1.44–1.30 (m, 2H), 0.90 (s, 3H); ^{13}C NMR: $\delta=200.4$, 146.1, 142.6, 132.6, 128.7, 120.5, 118.7, 111.9, 106.9, 35.4, 31.6, 29.1, 19.2, 9.1; HRMS: calcd for $C_{16}H_{18}BrNNaO^+$; 342.0469 $[M+Na]^+$; found: 342.0470. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate: 1.0 mL min^{-1}; $\tau_{major}=7.1$ min, $\tau_{minor}=8.9$ min (92% *ee*).

11: Ethyl 2-hydroxy-2-phenylacetate (**11**) was obtained according to the general procedure as an oil. $[\alpha]_D^{20}=-105.6$ ($c=2.0$, CH_2Cl_2); (literature, $[\alpha]_D^{20}=-123°$ ($c=1.0$, $CHCl_3$)[17]); ^{1}H NMR: $\delta=7.44$–7.32 (m, 5H), 5.16 (d, $J=5.8$ Hz, 1H), 4.31–4.13 (m, 2H), 3.45 (d, $J=5.8$ Hz, 1H), 1.23 (d, $J=7.8$ Hz, 3H); ^{13}C NMR data was in agreement with literature values;[17] HRMS: calcd for $C_{10}H_{12}NaO_3^+$: 203.0684 $[M+H]^+$; found: 203.0685. The *ee* was determined by HPLC analysis of the corresponding 1,4-dihydropyridine by using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; $\tau_{major}=9.7$ min, $\tau_{minor}=9.0$ min (91% *ee*).

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