β- and δ-Amino acids (2,3- and 3,4-*trans*-CHA) as catalysts in Knoevenagel condensation and asymmetric aldol reactions

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Abstract

The efficacy of the β- and δ-amino acids (5*S*,6*S*)-6-amino-5-hydroxycyclohexa-1,3-diene-carboxylic acid (2,3-*trans*-CHA) and (3*R*,4*R*)-4-amino-3-hydroxycyclohexa-1,5-dienecarboxylic acid (3,4-*trans*-CHA) as catalysts in Knoevenagel condensation and aldol addition reactions is studied. Synthesis of the zinc(II) complexes of 2,3- and 3,4-*trans*-CHA provided precipitated material of sufficient purity for use. The catalytic Knoevenagel reactions were carried out with the β-amino acid 2,3-*trans*-CHA and the δ-amino acid 3,4-*trans*-CHA, resulting in a product yield of up to 61%. The asymmetric aldol addition reactions were carried out with catalytic amounts of the zinc(II) complexes of 2,3- and 3,4-*trans*-CHA. In this case, it was observed that the *ee* of the product (up to 90%) depends on the conversion and/or the reaction time.

Keywords: Organocatalysis; chemoenzymatic synthesis; synthetic biology; diversity-oriented synthesis; chorismate; shikimate

Introduction

Organocatalysis has attracted the attention of many synthetic chemistry groups worldwide. Indeed, the beginnings of organocatalysis can be traced back to early in the nineteenth century.[1,2] In 1909, Dakin reported the organocatalytic behavior of some naturally occurring amino acids, peptides and proteins in aldol reactions.[3] Additionally, it was noted that primary amines catalyze the decarboxylation of α-ketocarboxylic acids to produce the corresponding aldehydes.[4,5] In 1953, Prout reported the catalytic effect of ʟ- and ᴅ-amino acids as well as the catalytic behavior of β-

amino acids in Knoevenagel condensations; good yields were achieved using β-alanine as a catalyst.[6]

In the 1970s, L-proline was introduced as a catalyst in the asymmetric Robinson annulation reaction.[7,8] It is now established as a chiral organocatalyst and as a source of chirality in the syntheses of many products.[9,10] Several aspects were taken into consideration in the development of L-proline as a catalyst, including its small size, rigidity, inexpensiveness and ready availability.[9] This secondary amine has been used as a catalyst in intermolecular aldol reactions.[11-15] It has been proposed that proline catalyzes the aldol reaction according to a mechanism involving an enamine intermediate.[16] This provides hydrogen bonding between the carboxylic acid group of proline and the carbonyl group of the substrate.[7,8,17-19] A stereoselective Mannich reaction has also been achieved using L-proline catalysis.[19-21]

The use of primary amino acids as chiral catalysts has been thoroughly studied and improved within the past decade.[22-25] In 2005, Amedjkouh reported the L-valine-catalyzed intermolecular aldol addition of acetone with aromatic aldehydes; sufficient yields and enantiomeric excesses were achieved.[26] Other natural primary amino acids were also used.[27-29] Cordova and co-workers have reported that primary amino acids serve as powerful organocatalysts in intermolecular aldol reactions of cyclic ketones.[30-32]

We were intrigued by the idea of using nonproteinogenic, yet natural, primary β- and δ-amino acids as catalysts. (5S,6S)-6-Amino-5-hydroxycyclohexa-1,3-dienecarboxylic acid (2,3-*trans*-CHA, **2**) and (3R,4R)-4-amino-3-hydroxycyclohexa-1,5-dienecarboxylic acid (3,4-*trans*-CHA, **4**) (Scheme 1) are nonproteinogenic primary amino acid metabolites of the shikimate pathway[33] and are accessible through metabolic engineering of recombinant *E. coli* strains.[34] The shikimate pathway is an instructive example of diversity-oriented biosynthesis of a wide spectrum of natural products (Scheme 1).[35,36] Shikimate- and chorismate-derived metabolites and their enzymatic transformations have been applied in synthesis, notably by Frost *et al.*[37] and by Müller *et al.*[38-42] These multifunctionalized and conformationally restricted natural products could serve as valuable chiral auxiliaries, chiral ligands, and organocatalysts in asymmetric transformations. Here, we focus on the production of the microbial nonproteinogenic amino acids 2,3-*trans*-CHA and 3,4-*trans*-CHA (**4**), and derivatives thereof, and their use as potent (organo)catalysts.

Results and Discussion

The aim of this study was to prove the efficiency of the β- and δ-amino acids 2,3-*trans*-CHA (**2**) and 3,4-*trans*-CHA (**4**) as catalysts in Knoevenagel condensation and asymmetric aldol addition reactions. The reference compound in this work was the proteinogenic amino acid L-proline (**6**), which was used as an organocatalyst in its pure form and as the zinc(II) complex in Knoevenagel and aldol reactions, respectively.

L-Proline (**6**) is a secondary α-amino acid, while **2** and **4** are primary β- and δ-amino acids, respectively. L-Proline and both the amino alcohols **2** and **4** are chiral, and all three possess conformational restrictions with somewhat rigid structures.
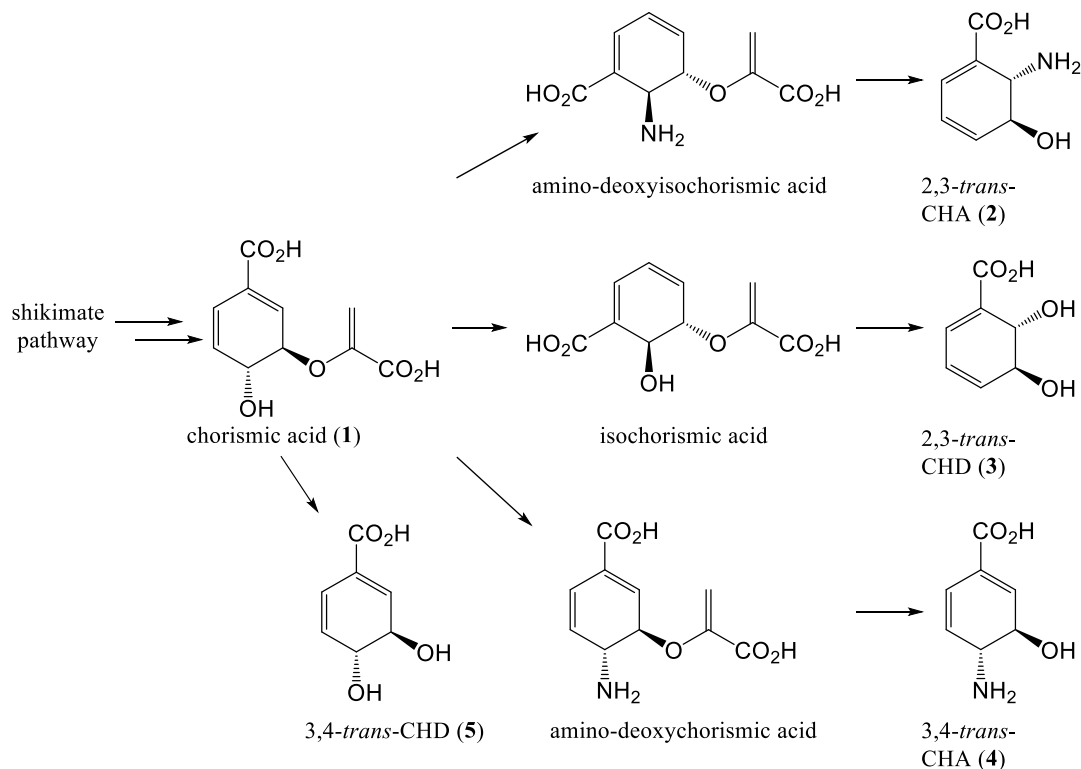

Scheme 1. Amino acids and 1,2-diol metabolites derived from chorismic acid (**1**) as a branching point.[33]

Compounds **2** and **4** are metabolites of the shikimate biosynthetic pathway (Scheme 1). Microbial access to **2** was realized by heterologous expression of *phzDE* in *E. coli* cells, which allowed the production of up to 12 g·L^{-1} of **2**.[33,43] By using a 300-L fed-batch culture approach, **2** was produced on a kg scale.[44] Isolation of **2** was performed by concentration of the cell-free fermentation broth and crystallization from water at 4 °C.

A concentration of 1.7 g·L^{-1} of 3,4-*trans*-CHA (**4**) was obtained by combining the *pabAB* gene and *phzD* gene in a recombinant *E. coli* strain.[33,45] Amino acid **4** was isolated from the fermentation broth by cation-exchange chromatography.

Preparation of the zinc complexes **8**–**10** was carried out according to the procedure of Darbre and Machuqueiro (Scheme 2).[46]
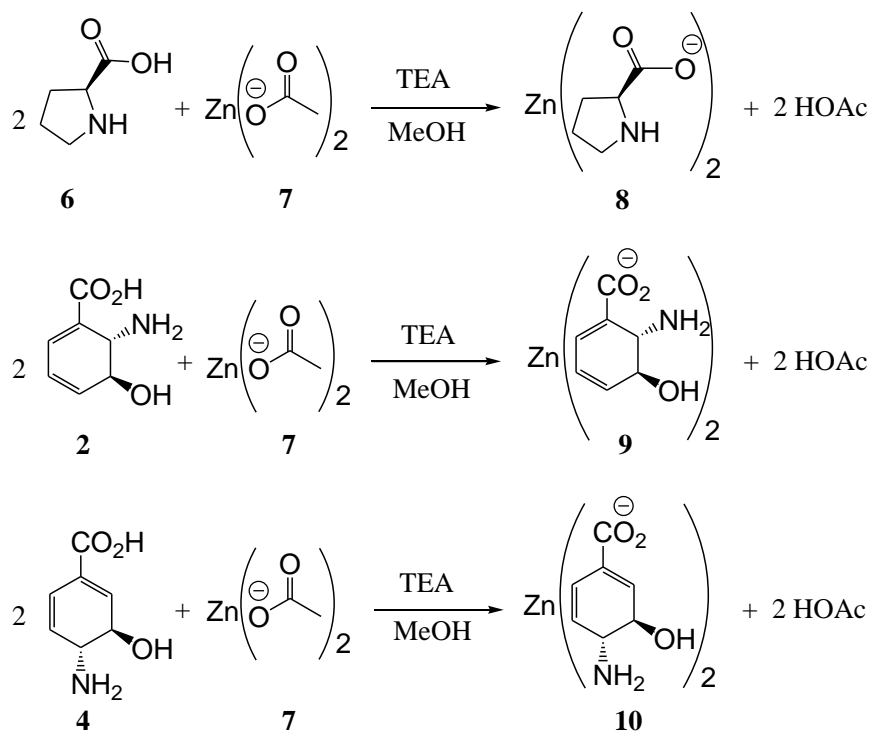
Scheme 2. Synthesis of the zinc complexes **8**–**10** of L-proline (**6**), 2,3-*trans*-CHA (**2**), and 3,4-*trans*-CHA (**4**).

The zinc complexes **8**–**10**, which precipitated from the reaction mixtures and were sufficiently pure for use without the need for further purification steps, were obtained in 52–84% yield. These complexes were tested in the asymmetric aldol addition reaction of acetone and *p*-nitrobenzaldehyde (see below).

The Knoevenagel condensation of dimethyl malonate (**11**) and 3-methylbutyraldehyde (**12**) was tested using L-proline (**6**), as well as the two amino acids **2** and **4**. In the case of L-proline (**6**), the reaction was carried out using 13 mol% of the catalyst, and the product **13** was obtained in 97% chemical yield (Scheme 3).
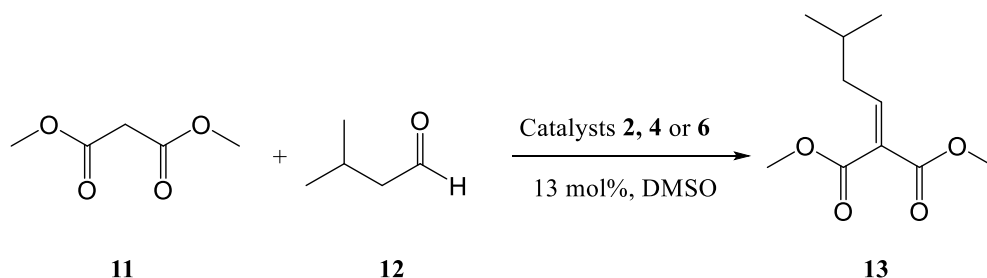

Scheme 3. Knoevenagel condensation using L-proline (**6**), 2,3-*trans*-CHA (**2**), and 3,4-*trans*-CHA (**4**) as catalysts (13 mol%).

The transformation using 2,3-*trans*-CHA (**2**) and 3,4-*trans*-CHA (**4**) was achieved by employing similar reaction conditions. In this case, the product **13** was obtained in 61% and 46% yield, respectively, clearly showing that the β- and δ-amino acids can be used as catalysts in the Knoevenagel condensation.

Intermolecular aldol condensation of acetone (**15**) and *p*-nitrobenzaldehyde (**14**) was achieved in the presence of a catalytic amount (5 mol%) of Zn(L-proline)$_2$ complex (**8**) (Table 1, entry 1). After 4 hours, there was 83% conversion, and (*S*)-**16** was obtained in 11% *ee* (as determined by chiral-phase HPLC).

Table 1. Intermolecular aldol addition reaction of *p*-nitrobenzaldehyde (**14**) and acetone (**15**)
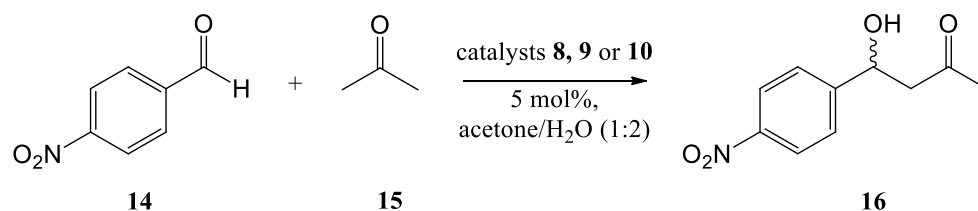

Entry	Catalyst	Reaction time (h)	Yield (%)	*ee* (%)
1	**8**	4	83	11 (*S*-**16**)
2	**9**	43	22	88 (*R*-**16**)
3	**9**	70	88	26 (*R*-**16**)
4	**10**	42	24	90 (*R*-**16**)
5	**10**	70	43	84 (*R*-**16**)

The reaction of **14** and **15** was carried out under similar conditions with complexes **9** and **10**. We observed that the *ee* of the product **16** depends on two factors: the conversion and the reaction time. In the presence of Zn(2,3-*trans*-CHA)$_2$ complex (**9**), the transformation showed a low yield of 22% with a high *ee* of 88% after 43 hours; after 70 hours, the conversion increased to 88% and the *ee* decreased to 26% (Table 1, entries 2, 3). The conversion continued to increase and the *ee* to decrease with increasing reaction time. We observed similar results in the case of Zn(3,4-*trans*-CHA)$_2$ complex (**10**). A conversion of 24% with 90% *ee* was observed after 42 hours; after 70 hours, the conversion increased to 43% and the *ee* decreased to 84% (Table 1, entries 4, 5). For both catalysts **9** and **10**, the (*R*)-enantiomer of the aldol product **16** was obtained predominantly, which nicely complements the *S*-selectivity of the L-proline-derived complex **8**. A similar dependency of the enantiomeric excess on reaction time (or catalyst loading) has recently been described by Gröger, Berkessel and co-workers.[47]

No product formation was detected when the aldol reaction was carried out using 2,3-*trans*-CHA (**2**) or 3,4-*trans*-CHA (**4**) in the pure forms. Also, the condensation product (elimination of water with formation of the α,β-unsaturated ketone) was not observed.

Our results confirm that amino acids, irrespective of the position of the amino group (α-, β- and δ-amino acids were tested in parallel), are valuable chiral (organo)catalysts. While the two amino acids 2,3-*trans*-CHA (**2**) and 3,4-*trans*-CHA (**4**) proved to be just as good as the L-proline catalyst with respect to enantioselectivity, they intrinsically possess several advantages. As we and others have shown for **2** and **4**, and for the respective diols 2,3-*trans*-CHD (**3**) and 3,4-*trans*-CHD (**5**),[39,41,48,49] the carboxylate moiety and the vicinal diol or amino alcohol moieties can be protected selectively. The 1,3-diene system of these compounds can be modified highly specifically through oxidative or reductive processes (e.g., epoxidation, dihydroxylation, selective hydrogenation), as well as via pericyclic reactions such as Diels–Alder and hetero-Diels–Alder additions (Scheme 5).
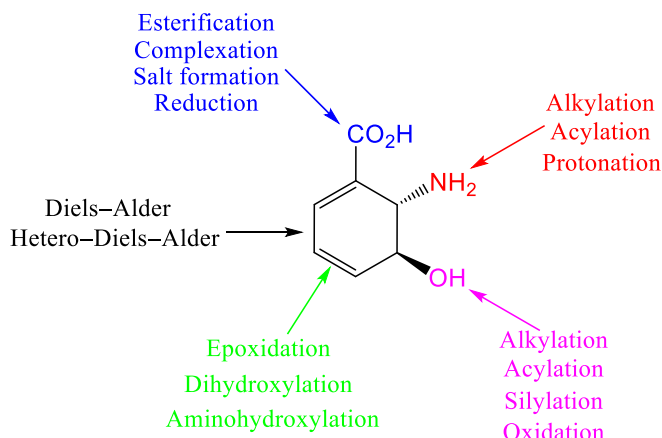
Scheme 5. The diversity of the possible modifications of 2,3-*trans*-CHA (**2**).

In the case of proline (**6**), modification of the amino and carboxylate groups, as well as hydroxylation at C3 and C4, is restricted. Recently, Al-Momani and Lataifeh have studied the efficiency of some proline modifications and the resulting catalytic behavior in aldol reactions.[50] Hence, the catalysts **2** and **4** and derivatives thereof should be able to be tailored specifically and optimized with respect to selectivity and reactivity through the adjustment of steric or electronic effects. Moreover, these amino acids are natural products, easily accessible on a large scale starting from renewable resources. Thus, the diversity-oriented aspects of chorismate in biosynthesis have been successfully transferred to the diversity-oriented application of its derivatives in synthesis and catalysis.

Experimental Section

General. All reagents used were of analytical grade. ^{1}H NMR spectra were recorded on an AMX 300 or DRX 400 instrument (Bruker Physik AG, Germany) with CD_3OH (δ 4.87 ppm), $CHCl_3$ (δ 7.27 ppm) or HDO (δ 4.81 ppm) as internal standard; ^{13}C NMR spectra were calibrated with [13]CD_3OD (δ 49.1 ppm), [13]$CDCl_3$ (δ 77.2 ppm) or sodium 3-(trimethylsilyl)-1-propanoate as

internal standard. Enantiomeric excesses were determined by chiral-phase HPLC [Chiralpak AS, Daicel; eluent: 2-propanol/hexane (30:70); flow rate: 1.0 mL/min; detection: UV 254 nm].

Isolation and purification of cyclohexadiene acids 2 and 4

(5S,6S)-6-Amino-5-hydroxycyclohexa-1,3-dienecarboxylic acid (2,3-*trans*-CHA, 2). The cell-free fermentation broth (LB or SOC medium)[33] was concentrated at 60 °C by rotary evaporation (>10 g/L of **2**), and further dried *in vacuo*. The brownish residue was washed with cold methanol and crystallized from water at 4 °C. A yield of 80% (purity >95%) of the product **2** (mp 185–188 °C) was obtained. ^{1}H NMR (CD$_3$OD, 300 K, ppm): δ 4.28 (d, J = 5.7 Hz, 1H), 4.46 (dd, J = 5.7, 4.6 Hz, 1H), 6.22 (dd, J = 9.5, 4.6 Hz, 1H), 6.34 (dd, J = 9.5, 5.7 Hz, 1H), 7.01 (d, J = 5.7 Hz, 1H). ^{13}C NMR (CD$_3$OD, 300 K, ppm): δ 51.9, 66.0, 125.7, 128.1, 130.5, 132.8, 173.0.

(3R,4R)-4-Amino-3-hydroxycyclohexa-1,5-dienecarboxylic acid (3,4-*trans*-CHA, 4)
Cell-free fermentation broth (200 mL LB or SOC medium)[33] was basified by addition of aqueous sodium hydroxide (2 M, 10 mL). The turbid liquid was centrifuged, and the supernatant was passed through a column with ion-exchange resin (Dowex 50WX8, H$^+$ form). The column was washed with water (300 mL) and **4** eluted with 0.5 M NH$_3$. The product-containing solution was lyophilized; 350 mg of a white powder containing 14% of compound **4** (by comparison with internal standard in the ^{1}H NMR spectrum) was obtained as the main NMR-active compound. ^{1}H NMR (D$_2$O, 300 K, ppm): δ 4.13 (dt, J = 11.2, 2.7 Hz, 1H), 4.67 (dd, J = 11.2, 3.5 Hz, 1H), 5.96 (dd, J = 10.0, 3.2 Hz, 1H), 6.57 (d, J = 10.0 Hz, 1H), 6.83 (m, 1H). ^{13}C NMR (D$_2$O, 300 K, ppm): δ 52.8, 67.8, 122.7, 125.0, 128.5, 138.2, 168.0.

Preparation of the zinc complexes 8–10

Zn(L-proline)$_2$ complex (8). L-Proline (**6**; 499 mg, 4.34 mmol) was dissolved in MeOH (30 mL), then TEA (0.6 mL, 4.34 mmol) was added. The mixture was stirred at rt for 10 min, then zinc acetate (**7**; 476 mg, 2.17 mmol) was added. A colorless precipitate appeared immediately. After the mixture was stirred for 1 h, the solid material was collected by filtration and dried under vacuum to give Zn(L-proline)$_2$ complex (**8**); yield: 532 mg (84%). ^{1}H NMR (D$_2$O, 300 K, ppm): δ 1.87 (bs, 3H), 2.29 (bm, 1H), 3.04 (bs, 1H), 3.19 (bm, 1H), 3.92 (bs, 1H).

Zn(2,3-*trans*-CHA)$_2$ complex (9). 2,3-*trans*-CHA (**2**; 350 mg, 2.26 mmol) was dissolved in MeOH/H$_2$O (1:1, 30 mL), then TEA (312 µL, 2.27 mmol) was added. The mixture was stirred at rt for 10 min, then zinc acetate (**7**; 248 mg, 1.13 mmol) was added. After the mixture was stirred for 1 h, the solid material was removed by filtration. After 3 h, a white solid precipitated from the filtrate. The precipitate was separated and dried under vacuum to give Zn(2,3-*trans*-CHA)$_2$ complex (**9**); yield: 244 mg (58%). ^{1}H NMR (D$_2$O, 300 K, ppm): δ 3.98 (bs, 1H), 4.33 (bs, 1H), 6.22 (bm, 1H), 6.34 (bm, 1H), 6.92 (bm, 1H).

Zn(3,4-*trans*-CHA)$_2$ complex (10). 3,4-*trans*-CHA (**4**; 167 mg, 1.08 mmol) was dissolved in MeOH (7 mL). The same amount of water was added to obtain a clear solution. This was followed by addition of TEA (150 µL, 1.08 mmol). The mixture was stirred at rt for 10 min, then zinc acetate (**7**; 119 mg, 0.54 mmol) was added. After the mixture was stirred for 1 h, the solid material was removed by filtration. From the filtrate, a white solid precipitated after addition of TEA (240 µL).

The precipitate was separated and dried under vacuum to give Zn(3,4-*trans*-CHA)$_2$ complex (**10**); yield: 104 mg (52%). ^{1}H NMR (D$_2$O, 300 K, ppm): δ 4.01 (bm, 1H), 4.56–4.60 (bm, 1H), 5.89–5.92 (bm, 1H), 6.51–6.54 (bm, 2H).

Knoevenagel condensations

With L-proline (**6**). 3-Methylbutyraldehyde (**12**; 172 μL, 1.55 mmol) was dissolved in DMSO (10 mL). L-Proline (**6**; 23 mg, 0.2 mmol) was added and, after 5 min, dimethyl malonate (**11**; 459 μL, 4.00 mmol) was added. The mixture was stirred at rt overnight, then diluted with ethyl acetate (20 mL), and washed twice with water (2 × 20 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated to give dimethyl 2-(3-methylbutylidene)malonate (**13**); yield: 297 mg (97%). ^{1}H NMR (400 MHz, 298 K, ppm, in CDCl$_3$): δ 7.07 (t, *J*=7.9 Hz, 1H, =CH), 3.84 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 2.21 (dd, *J*=6.9 Hz, *J*=7.8 Hz, 2H, CH$_2$), 1.83 (m, 1H, *CH*(CH$_3$)$_2$), 0.96 (s, 3H, CH$_3$), 0.95 (s, 3H, CH$_3$).

With 2,3-*trans*-CHA (**2**). Aldehyde **12** (172 μL, 1.55 mmol) was dissolved in DMSO (10 mL). 2,3-*trans*-CHA (**2**; 31 mg, 0.2 mmol) was added and, after 5 min, dimethyl malonate (**11**; 459 μL, 4.00 mmol) was added. The mixture was stirred at rt overnight, then diluted with ethyl acetate (20 mL) and washed twice with water (2 x 20 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated to give product **13**; yield: 188 mg (61%).

With 3,4-*trans*-CHA (**4**). In a similar transformation of aldehyde **12** and malonate **11** with 3,4-*trans*-CHA (**4**) as catalyst, the product **13** was obtained in 46% yield after a 70 h reaction time.

Aldol Additions

With Zn(L-proline)$_2$ complex (**8**). *p*-Nitrobenzaldehyde (**14**; 151 mg, 1.0 mmol) was dissolved in acetone (**15**, 5 mL). A solution of Zn(L-proline)$_2$ complex (**8**; 15 mg, 0.05 mmol) in water (10 mL) was added and the mixture was stirred under inert conditions (N$_2$). After 4 h, the mixture was concentrated and the residue was dissolved in chloroform (20 mL). The insoluble material was removed by filtration. The filtrate was concentrated by rotatory evaporation to give 4-hydroxy-4-(4-nitrophenyl)butan-2-one (*S*-**16**); yield: 173 mg (83%); 11% *ee* of the *S*-isomer. The *ee* was determined by chiral-phase HPLC; (*R*)-**16**, t_R = 13.7 min; (*S*)-**16**, t_R = 17.8 min. ^{1}H NMR (CDCl$_3$, 300 K, ppm): δ 2.23 (s, 3H), 2.86 (m, 2H), 3.61 (bs, 1H, OH), 5.28 (dd, *J*=7.7, 4.6 Hz, 1H), 7.55 (d, *J*=9.1 Hz, 2H), 8.22 (d, *J*=9.1 Hz, 2H). ^{13}C NMR (CDCl$_3$, 300 K, ppm): δ 30.9 (CH$_3$), 51.7 (CH$_2$), 69.1 (CH), 124.0 (2 x CH), 126.6 (2 x CH), 150.1 (2 x C$_q$), 208.8 (C=O).

With Zn(2,3-*trans*-CHA)$_2$ complex (**9**). A similar transformation was undertaken with Zn(2,3-*trans*-CHA)$_2$ complex (**9**; 18.8 mg, 0.05 mmol) as catalyst. After 70 h, the filtrate was concentrated by rotatory evaporation to give (*R*)-**16**; yield: 184 mg (88%); 26% *ee*. The *ee* of the product showed a dependence on the reaction time and conversion. After a reaction time of 43 h (22% conversion), the product was highly enantioenriched [88% *ee*, (*R*)-**16**].

With Zn(3,4-*trans*-CHA)$_2$ complex (**10**). A similar transformation was undertaken with Zn(3,4-*trans*-CHA)$_2$ complex (**10**; 18.8 mg, 0.05 mmol) as catalyst. After 70 h, the filtrate was concentrated by rotatory evaporation to give (*R*)-**16**; yield: 90 mg (43%); 84% *ee*. The *ee* of the product showed a dependence on the reaction time and conversion. After a reaction time of 42 h (24% conversion), the product was highly enantioenriched [90% *ee*, (*R*)-**16**].

Acknowledgements

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