Tetrahedron: *Asymmetry* 20 (2009) 2467–2473

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric nitroaldol reaction catalyzed by copper–diamine complexes: selective construction of two contiguous stereogenic centers

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ARTICLE INFO

Article history:
Received 16 July 2009
Accepted 2 October 2009
Available online 2 November 2009

ABSTRACT

Chiral copper(II) complexes of secondary bisamines derived from 1,2-diaminocyclohexane were successfully used in the diastereoselective nitroaldol reaction. The reactions were carried out in the presence of 10 mol % of the Cu(II) complex and 7.7 mol % of *i*-Pr_2NEt in 2-propanol at −30 °C. Good to excellent yields, enantioselectivities of up to 99%, and moderate to excellent diastereoselectivities were obtained for both aromatic or aliphatic aldehydes and various prochiral nitrocompounds forming the corresponding β-nitroalcohols with two contiguous stereocenters.

1. Introduction

The nucleophilic addition of nitroalkanes to carbonyl compounds (Henry reaction) is an attractive synthetic tool in organic synthesis. Facile reduction of β-nitroalcohols makes β-aminoalcohols available, while the Nef reaction offers access to the corresponding α-hydroxy acids.[1] Both of them are highly valuable building blocks in asymmetric synthesis. Hence, the stereoselective nitroaldol reaction has already been applied in the synthesis of various useful compounds.[1,2]

Many catalytic systems for the asymmetric Henry reaction of aldehydes and nitromethane have been developed so far.[3] However, only few of them were also successful in the reaction of prochiral nitroalkanes.[3f,4a,b,d,e,5a,b,d] An additional substituent at the nitronate anion increases the activation energy and raises the problem of reaction reversibility.[6a] In fact, examples of the diastereoselective variant of the nitroaldol reaction are still rare.[4,5] Thus, the construction of two or more new stereogenic centers in a single-catalyzed nitroaldol reaction is still a synthetic challenge.

We have recently found that the simple diamine–copper(II) complexes are efficient catalysts in the direct asymmetric nitroaldol reaction.[3j] Herein, we report our results demonstrating their effectiveness in the creation of two contiguous stereogenic centers.

2. Results and discussion

2.1. Optimization of the catalytic system

In the first round of tests we investigated the reaction of benzaldehyde with nitroethane catalyzed by the in situ formed complex of copper acetate and *N*,*N*′-di(4-chlorobenzyl)-(1*R*,2*R*)-diaminocyclohexane. Previously, under these conditions, benzaldehyde with nitromethane gave nitroalcohol of 91% ee and 95% yield.[3j] Unfortunately, replacing nitromethane by nitroethane and using the previously developed procedure gave an unsatisfactory result (19% total yield, ca. 1:1 dr, up to 30% ee). Since nitroethane and nitropropane are less reactive in comparison with nitromethane,[4a] the acetate anion might be an unsuitable base for proton abstraction. Thus, an additional base was needed for deprotonation of the nitrocompound. However, the nitroaldol reaction is sensitive to both the strength and amount of the base.[4e,7] In spite of the presence of a chiral Lewis acid catalyst, because of the non-catalytic reaction facilitated by a stronger base, a racemic product may be predominantly formed. Moreover, we have already noted that when the isolated (crystalline) complex **1** was used, the reaction of benzaldehyde with nitromethane performed poorly. When an additional base (Hünig's base, DIPEA) was applied to the reaction at 0 °C (2 mol %), it resulted in 77% yield and 92% ee.[3j] Now, careful optimization of the amount of DIPEA (7.7 mol %) and temperature (−30 °C)[8] led to the desired product in 95% ee. Application of the complex derived from (1*S*,2*S*)-diaminocyclohexane (12 mol %) and $Cu(OAc)_2·H_2O$ (10 mol %), generated in situ along with DIPEA gave 89% of the product with the opposite configuration and with 93% ee (Scheme 1).

With the optimized procedure in hands, the complex **1** or the catalysts formed in situ from the ligands **2a–f** and copper acetate were applied in the Henry reaction of benzaldehyde and nitroethane (Scheme 2, Table 1).

At first glance nearly all the ligands studied led to the products in very good yield and relatively high enantioselectivities for the *syn* isomer. However, the diastereoselectivity observed was far from desired and usually the *anti* isomer was a major one. Thus, the ratio of *anti*/*syn* was between 2.12/1 and 1/1. An increase of the reaction temperature from −30 °C to 0 °C resulted in the

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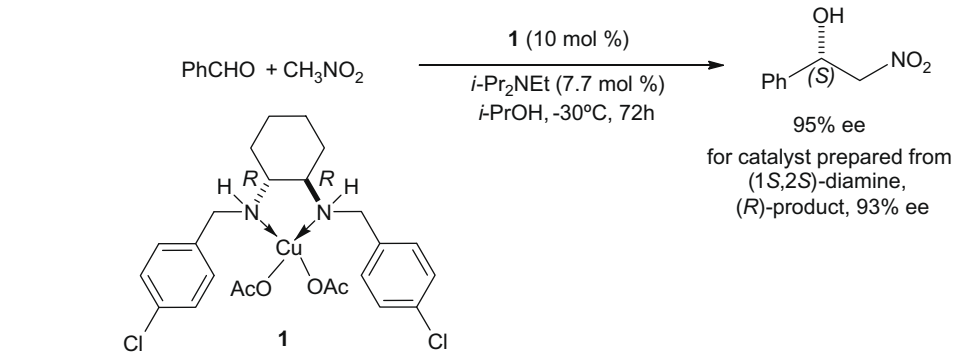
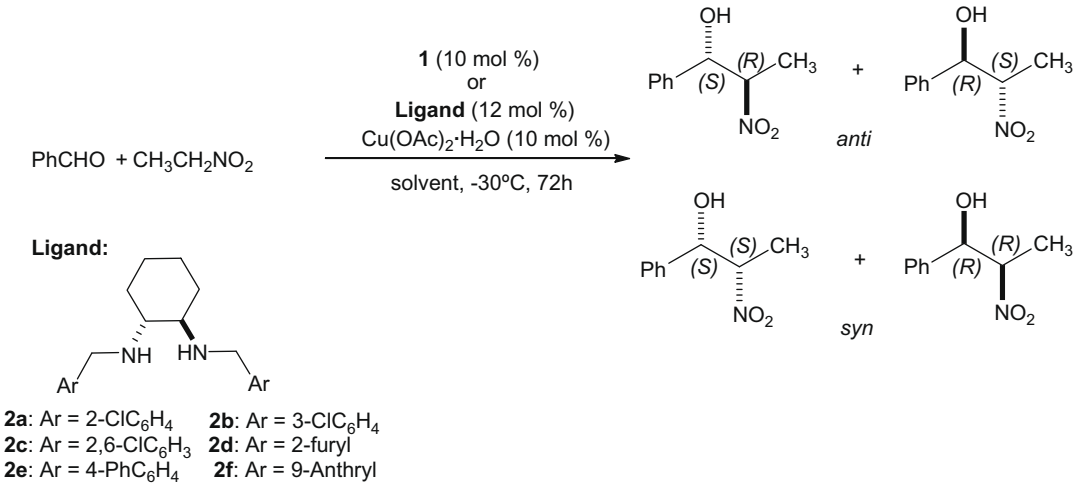
doi:10.1016/j.tetasy.2009.10.001



Scheme 1.



Scheme 2.

Table 1
Diastereoselective nitroaldol reaction of benzaldehyde and nitroethane catalyzed by complexes of chiral diamines and copper(II) acetate[a]

Entry	Ligand/complex[b]	Solvent	Yield[c] (%)	dr[d] (*anti*/*syn*)	ee[e] (%) (*anti*/*syn*)
1	**1**	EtOH	96	58:42	68 (1*S*,2*R*)/82 (1*S*,2*S*)
2[f]	**1**	EtOH	80	41:59	11/60
3	**1**	*i*-PrOH	83	61:39	79/88
4	**2a**	*i*-PrOH	100	58:42	43/81
5	**2b**	*i*-PrOH	86	50:50	66/85
6	**2c**	*i*-PrOH	63	62:38	70/79
7	**2d**	*i*-PrOH	73	60:40	74/82
8	**2e**	*i*-PrOH	80	55:45	72/82
9	**2f**	EtOH	87	58:42	81/87
10	**2f**	*i*-PrOH	72	68:32	86/87
11[g]	**2f**	*i*-PrOH	73	64:36	89/89
12[h]	**2f**	*i*-PrOH	87	65:35	92/91

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of respective diamine **2a–f**, 10 mol % of $Cu(OAc)_2 \cdot nH_2O$ or complex **1**, 10 equiv of $CH_3CH_2NO_2$ and 7.7 mol % of *i*-Pr_2NEt in 2-propanol at −30 °C for 70 h.
[b] Ligand structure according to Scheme 2.
[c] Yield of isolated products as a mixture of possible diastereomers.
[d] Diastereomeric ratios were determined using ^1H NMR after column chromatography.
[e] Enantiomeric excess determined by HPLC using Chiralpak AD-H columns. For each case, *anti*-(1*S*,2*R*) and *syn*-(1*S*,2*S*) were formed predominantly.
[f] Reaction was carried out at 0 °C.
[g] Reaction was carried out at −78 °C for 2 h and then warmed to −30 °C. Further steps according to the general procedure (see Section 4).
[h] Reactions were performed on a 1.0 mmol scale, 6 mol % of the **2f**, 5 mol % of $Cu(OAc)_2 \cdot nH_2O$, 10 equiv of $CH_3CH_2NO_2$ and 3.8 mol % of *i*-Pr_2NEt in 2-propanol at −30 °C for 70 h.

reversal of dr to the value of 0.69/1 (entry 2). Better selectivity was obtained for the reactions carried out in 2-propanol.

Further optimization of the catalytic system concerned the influence of the size and electronic nature of the aryl moiety in the diamine ligands. Thus, in comparison with **1** (4-chlorobenzyl-substituted), the application of 2-chlorobenzyl-substituted ligand **2a** (Scheme 2) gave the products with lower dr and decreased enantioselectivity for the *anti* isomer. However, additional substi-

tuent at the 6 positions in **2c** resulted in stereoselectivity similar to that for complex **1** (entry 6). For the diamine **2b** enantioselectivity remained unchanged but no diastereoselection was observed. In order to find the key structural elements in the diamine ligands responsible for the transfer of chirality **2d** and **2e**, different sizes of the aryl substituent were examined. Surprisingly, both ligands gave similar results (entries 7 and 8).

The results of previous studies on the metal-catalyzed, diastereoselective Henry reaction[4a,d,6] suggested an increase of the steric hindrance in close proximity to the Lewis acid center. Therefore, ligand **2f** with bulky aromatic substituents was chosen. Indeed, the enantioselectivity increased for both the *anti* (86% ee) and *syn* (87% ee) isomers, although with only a small improvement of their ratio (entry 10). Lowering the temperature at the initial period of the reaction for 2 h to −78 °C did not result in a change of diastereoselectivity. It was also found that halving the amount of ligand **2f**, copper salt, and DIPEA (entry 12), gave products with comparable ee for the *syn* isomer.

The Lewis acidity of the copper ion in the catalytic complex seemed to be important for the activation of the aldehyde.[9] However, when we used a less coordinating counter ion ($Cu(OTf)_2$ instead of $Cu(OAc)_2$), a substantial decrease of reactivity was observed and only a trace amount of the desired nitroalcohol was detected.[10]

2.2. Scope of the catalytic system. The reaction of various aldehydes and prochiral nitrocompounds

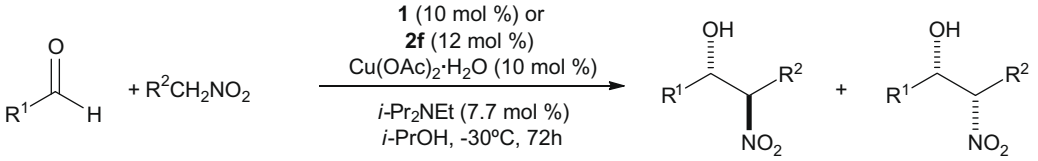
Thus, the observed differences in the catalytic performance of the ligands showed that the aryl moieties affect mainly the asymmetric induction ability. Among them, **2f**–copper(II) acetate–*i*-Pr_2NEt and **1**–*i*-Pr_2NEt in 2-propanol gave the best overall results. For this reason, the scope of application of both **1** and **2f**–$Cu(OAc)_2$ catalysts was examined in the reaction of various aldehydes and nitroalkanes (Scheme 3, Table 2).

Thus, different aldehydes were converted into the diastereomeric mixture of nitroaldol adducts with moderate to excellent yields and enantioselectivities of up to 95% and 99% for the aromatic (entry 4) and aliphatic (entry 13) compounds, respectively. Generally, the *anti* products were favored in the reaction of aromatic aldehydes, whereas the *syn* adducts were predominant for the aliphatic reactants.

The lowest induction was observed for the most reactive 4-nitrobenzaldehyde (entries 6 and 7). Nevertheless, the reaction with nitropropane catalyzed by **2f**–$Cu(OAc)_2$ led to the *anti* adduct with 90% ee (entry 8).

In contrast, very good results were obtained for cyclohexylcarbaldehyde and a 13:87 (*anti*/*syn*) diastereomeric ratio was observed for the reaction with nitroethane (entry 15). The reaction with nitropropane gave even better results leading practically to only one diastereomer.[11] Thus, the *syn* adduct was formed with 99% ee.

According to the generally accepted stereochemical models involving coordination of both substrates, the *anti*-selection in the metal-catalyzed diastereoselective nitroaldol reaction might be surprising.[4d,6] Nevertheless, there is a literature precedent for the aminopyridine ligands and copper acetate system giving mainly an *anti*-selective nitroaldol reaction.[5d] Assignments of the relative configuration (*syn*/*anti*) was made based on the analysis of ^1H NMR and ^{13}C NMR spectra of diastereomers. It was reported



Scheme 3.

Table 2
Scope and limitations in the diastereoselective nitroaldol reaction of aldehydes and nitroalkanes catalyzed by **1** or **2f**–$Cu(OAc)_2$[a]

Entry	**1**/**2f**[b]	R^1	R^2	Yield[c] (%)	dr[d] *anti*/*syn*	ee[e] *anti*/*syn* (%)
1	**1**	Ph	CH_3	83	61:39	79 (1*S*,2*R*)/88 (1*S*,2*S*)
2	**2f**	Ph	CH_3	72	68:32	86 (1*S*,2*R*)/87 (1*S*,2*S*)
3	**1**	4-Cl–C_6H_4	CH_3	80	64:36	83 (1*S*,2*R*)/87 (1*S*,2*S*)
4	**2f**	4-Cl–C_6H_4	CH_3	93	74:26	95 (1*S*,2*R*)/89 (1*S*,2*S*)
5	**2f**	4-Cl–C_6H_4	CH_3CH_2	77	66:34	92 (1*S*,2*R*)/93 (1*S*,2*S*)
6	**1**	4-NO_2–C_6H_4	CH_3	97	70:30	66/66
7	**2f**	4-NO_2–C_6H_4	CH_3	94	78:22	85/76
8	**2f**	4-NO_2–C_6H_4	CH_3CH_2	96	60:40	90 (1*S*,2*R*)/62 (1*S*,2*S*)
9	**2f**	1-Naphthyl	CH_3	88	75:25	75 (1*S*,2*R*)/84 (1*S*,2*S*)
10	**1**	*c*-C_6H_{12}	CH_3	67	19:81	85/95
11	**2f**	*c*-C_6H_{12}	CH_3	69	13:87	96/96
12	**1**	*c*-C_6H_{12}	CH_3CH_2	74	14:86	nd./93 (1*S*,2*S*)
13	**2f**	*c*-C_6H_{12}	CH_3CH_2	76	2:98	nd./99 (1*S*,2*S*)
14[f]	**1**	Ph	Ph	67	<1:99	62[g]
15[f]	**2f**	*c*-C_6H_{12}	Ph	92	12/88	99/95
16[f]	**1**	Ph	$PhCH_2$	82	41/59	8 (1*S*,2*R*)/57 (1*S*,2*S*)
17[f]	**2f**	Ph	$PhCH_2$	86	40/60	18 (1*S*,2*R*)/64 (1*S*,2*S*)
18[f]	**2f**	$PhCH_2CH_2$	$OHCH_2$	72	28:72	84 (2*R*,3*S*)/87 (2*R*,3*R*)
19[f]	**2f**	*n*-C_5H_{11}	$OHCH_2$	88	35:65	92/92

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of ligand **2f**, 10 mol % of $Cu(OAc)_2 \cdot nH_2O$ or complex **1** (10 mol %), 10 equiv of the respective nitroalkane and 7.7 mol % of *i*-Pr_2NEt in 2-propanol at −30 °C for 70 h.
[b] Ligand structure according to Scheme 2.
[c] Yield of isolated products as a mixture of possible diastereomers.
[d] Diastereomeric ratios were determined using ^1H NMR after column chromatography.
[e] Enantiomeric excess was determined by HPLC using Chiracel OD-H or Chiralpak AD-H columns, for the details, see Section 4. Absolute configurations were assigned by the comparison with literature data (Ref. 4b,d,e,5a,d,15). The predominant enantiomers given in parentheses.
[f] Reactions were performed using 1.0 equiv of nitrocompound.
[g] Stereochemistry of the product is assigned as *syn* (1*S*,2*S*) by the comparison with the known analogue (Table 2, entry 15, Ref. 4b). For the details, see text below.

that in the case of aromatic β-nitroaldols, as analogues of 2-nitro-1-phenylpropane for which the absolute stereochemistry of all possible diastereomers is established,[5b] the value of ^3J coupling constants of carbinol's and C*H*NO_2 protons for the *threo* isomer is larger than the respective one for the *erythro* isomer.[6b] Moreover, the signal of C*H*OH of the *anti* isomer is observed in the lower field with smaller or no coupling constants, compared to that for the *syn* nitroalcohol (e.g., broad singlet at 6.26 ppm and $J = 0$ Hz and doublet at 5.77 ppm, $J = 9.3$ Hz for the *anti*-1-(naphthalene-1-yl)-2-nitropropan-1-ol and *syn*-1-(naphthalene-1-yl)-2-nitropropan-1-ol, respectively). On the contrary, the C*H*NO_2 signal for the *anti* isomer is observed at the higher field in comparison with the *syn* form (4.90 ppm and 5.06–5.14 ppm for *anti*-1-(naphthalene-1-yl)-2-nitropropan-1-ol and *syn*-1-(naphthalene-1-yl)-2-nitropropan-1-ol, respectively). Thus the order of signals in the ^{1}H NMR spectra was analogous to those observed for 2-nitro-1-phenylpropane. Additionally, the assignment of the absolute stereochemistry can be supported by comparison of the order of elution for all isomers of 2-nitro-1-phenylpropane, where the reported array is: *anti* (1*S*,2*R*), (1*R*,1*S*) and *syn* (1*S*,2*S*) and (1*R*,2*R*) on the OD-H HPLC column. This assignment is also in agreement with the stereochemical outcomes of the nitroaldol reaction of aldehydes and nitromethane catalyzed by Cu(II) complexes of secondary chiral (1*R*,2*R*)-diaminocyclohexane complexes. Hence, in these reactions, the products of (*S*)-configuration were favored.[3j] The same sense of stereochemical induction was also reported by Bandini et al.[12] Based on the above-mentioned considerations, we conclude that for the results presented (Tables 1 and 2), the *anti* (1*S*,2*R*) isomer is preferred, while for the *syn* form, the (1*S*,2*S*) configuration is predominant.

Although the excess of the major diastereomer was often unsatisfactory, we were able to separate the isomers formed using flash chromatography on silica gel. Thus, when the reaction of 1-naphthaldehyde and nitroethane was carried out on a 2.5 mmol scale, chromatographic separation led to the crystalline, major *anti* diastereomer (78% ee, 93:7 dr) obtained in 56% yield. Additional recrystallization gave the product of 99% de and 99.8% ee.

In order to learn more about stereoselection in the processes catalyzed by **1** and **2f**–$Cu(OAc)_2$, we also studied the reactions of nitrocompounds, that are rather rarely tested in this reaction (Table 2, entries 14–19). It was interesting to examine how the size of substituent at the nucleophilic carbon of the nitronate influences the reaction outcome. Thus, we expected that the reaction of large phenylnitromethane with benzaldehyde will occur stereoselectively. Unfortunately, this reaction with the more sterically demanding **2f**–$Cu(OAc)_2$ catalyst failed to give any nitroalcohol. However, the application of complex **1** provided the desired product exclusively as a single diastereomer with 67% yield and 62% ee (Table 2, entry 14). However, the reaction of cyclohexylcarbaldehyde with phenylnitromethane catalyzed by **2f**–$Cu(OAc)_2$ proceeded smoothly in high yield, with the diastereoselectivity slightly diminished (Table 2, entry 15). Interestingly, the change of nitronate source from phenylnitromethane to 2-phenylnitroethane resulted in a further deterioration of stereoselectivity.

Effective coordination of the substrates by chiral complexes in the catalytic cycle is crucial for stereoselectivity. This coordination should be facilitated for a bidentate reactant. Thus, we expected that the reaction of aldehydes with 2-hydroxynitroethane (entries 18 and 19) would give products with high diastereoselectivity. The reaction of *n*-hexanal was used as a test for the effectiveness of catalyst for the synthesis of *threo*-dihydroxysphingosine.[4a] In our case, in spite of good yield and high ees of the products, diastereoselectivity was only moderate.

Table 3
Diastereoselective reaction of 2-phenylpropanal and nitromethane[a]

Entry	CH_3NO_2 (equiv)	Yield[b] (%)	dr[c] *anti*/*syn*	ee[d] *anti*/*syn*(%)
1	10	82	46:54	99/83
2	2	76	45:55	99/84
3	1	57	29:71	99/91
4	0.5	41	17:83	99/90

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of **2f**, 10 mol % of $Cu(OAc)_2 \cdot nH_2O$, an adequate amount of CH_3NO_2, *i*-Pr_2NEt (7.7 mol %) in 2-propanol at −30 °C for 70 h.
[b] Yield of isolated products as a mixture of possible diastereomers.
[c] Diastereomeric ratios were determined using ^{1}H NMR after column chromatography.
[d] Enantiomeric excess determined by HPLC using Chiralpak AD-H columns.

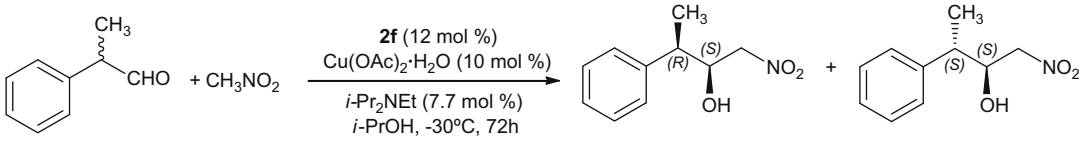
2.3. Construction of multiple stereocenters using the chiral aldehyde

Another strategy leading to the construction of multiple stereocenters in a one-pot nitroaldol reaction is the application of a chiral aldehyde.[13] Our efforts were focused on the application of chiral, but racemic 2-phenylpropanal and nitromethane, and thus generation of the non-racemic product with the two contiguous stereogenic centers (Scheme 4, Table 3).

The application of a standard procedure gave a mixture of the two possible diastereomers with 46:54 dr preferring the *syn* isomer[14] with good yield and enantioselectivities of up to 99% (entry 1). A sequential decrease of the amount of the nitromethane led to a significant decrease of the yield, but the stereoselectivity of this transformation was improved (entry 3). The observed increase of diastereoselectivity could be rationalized as a result of different reactivity of enantiomers of 2-phenylpropanal adding to nitromethane. Thus, it may be assumed that the energies of transition states for the formation of diastereomers are different that is prerequisite for the kinetic resolution. Thus, the reaction using only 0.5 equiv of nitromethane was performed (entry 4). The desired products were obtained in 41% yield (based on the amount of aldehyde), with a 17:83 ratio of *anti*/*syn* diastereomers and 90% ee for the *syn* isomer.

3. Conclusions

In conclusion, the usefulness of diamine–copper(II) complexes in the creation of two stereogenic centers in the stereoselective Henry reaction was presented. The readily available catalyst (10 mol %) provides the expected products in high yields, good to excellent enantioselectivities, and moderate to high diastereoselectivities. The reaction takes place in mild conditions without any precautions of air and moisture with the formation of predominant *anti* products



Scheme 4.

for aromatic aldehydes and *syn* for the aliphatic ones. Optimization of the reaction conditions allows for separation of the diastereomerically pure nitroaldols. The transformation of chiral but racemic 2-phenylpropanal led to the diastereomers of 99% and 90% ee and 17:83 dr. All the results obtained illustrate a simple synthetic approach to β-nitroalcohols with two contiguous stereogenic centers, selectively introduced in one catalytic reaction.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance DRX (^{1}H, 300 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE HRMS apparatus using ESI technique. The enantiomeric compositions of nitroaldols were determined by HPLC analysis using a chiral stationary phase (Chiracel OD–H or Daicel Chiralpak AD–H). All of the analyzed mixtures of isomers were compared with the samples of the appropriate racemates. The absolute stereochemistry of both diastereomers was assigned by a comparison of the retention times in HPLC to the literature data.[4b,d,e,5a,b,d,15] Diastereomeric ratios of *anti*/*syn* products were determined using ^{1}H NMR. For the stereochemical notation of β-nitroalcohols, that is, (1*S*,2*R*), 1 refers to the C–OH carbon and 2 refers to the C–NO_2 carbon, except 1,3-diols. The yield of the products refers to the total yield of both diastereomers. Separations of the products by flash chromatography were performed on Silica Gel 60 (0.040–0.063 mm) purchased from Fluka. Thin layer chromatography analyses were performed using Silica Gel 60 percolated plates (Fluka). For the general applications ethanol (96% aq) and 2-propanol were used without additional drying for all enantioselective reactions, which were carried out in test tubes with a PET or glass stoppers. Commercial reagents were used as purchased. Liquid aldehydes were freshly distilled before use. No special precautions were taken for the exclusion of air or moisture.

4.2. Synthesis

Complex **1**[3j] was prepared according to the literature precedent with 75% yield. Ligands **2a–c**,[3j] **2e**,[16] and **2f**[17] were prepared by a two-step procedure[18], and the spectral data of the products were identical with the reported ones.

4.2.1. Ligand 2d

Ligand **2d** was prepared according to the literature procedure:[18] potassium bicarbonate (anhydrous, 25 mmol, 2.0 equiv) was added to vigorously stirred suspension of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (3.31 g, 12.5 mmol, 1.0 equiv) in water (50 mL) at rt. Then ethanol (96%, 20 mL) was added followed by a solution of given aldehyde (2.4 g, 25 mmol, 2.0 equiv) and CH_3SO_3H (0.1 mL) in dichloromethane (50 mL). The biphasic mixture was stirred at rt overnight, refluxed for 2 h, and concentrated in vacuo to evaporate organic solvents. After cooling, ethyl acetate was added (50 mL), phases were separated, and the water layer was washed with AcOEt (3 × 50 mL). Combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo giving a crude diimine (3.25 g of a waxy solid). Part of it was directly used in the next step. An analytical sample was obtained by crystallization (CH_2Cl_2/*n*-hexane): Mp 106–108 °C, $[\alpha]_D = -244.9$ (*c* 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 2H, *H*C=N), 7.39 (s, 2H, ArH), 6.52 (d, *J* = 3.3 Hz, 2H, ArH), 6.34 (dd, *J* = 3.3 Hz, *J* = 1.8 Hz, 2H, ArH), 3.13 (m, 2H, 2 × C*H*N), 1.17–1.18 (m, 6H, 3 × CH_2), 1.39–1.43 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.3 (C=N), 149.4 ($C_{IV°Ar}$), 144.4 (C_{Ar}), 114.2 (C_{Ar}), 111.4 (C_{Ar}), 74.0 (CHN), 33.0 (CH_2), 24.4 (CH_2). ^{1}H NMR and ^{13}C NMR spectroscopic data are in accordance with those reported in the literature.[19]

The crude diimine (1.0 g, 3.7 mmol, 1.0 equiv) was dissolved in MeOH (10 mL). The resulting mixture was cooled on an ice-bath, and $NaBH_4$ (420 mg, 11.4 mmol, 3.0 equiv) was added in one portion. Stirring at this temperature was maintained until gas evolution stopped and then the mixture was allowed to reach rt and then refluxed for 2 h. Solvents were removed in vacuo and the residue was treated with water (50 mL) and dichloromethane (50 mL). Phases were separated and the upper layer was washed with CH_2Cl_2 (3 × 50 mL), the combined organic fractions were dried (K_2CO_3), and the solvent was evaporated in vacuo. The product was purified using column chromatography on silica gel (50 g, gradient $CHCl_3$ to $CHCl_3$/MeOH, 10:1, v/v) giving the desired product (940 mg, 3.4 mmol, 93% yield based on diimine) as a light yellow oil, R_f = 0.14 ($CHCl_3$), $[\alpha]_D = -57.1$ (*c* 0.2, MeOH). IR (film, ν_{max}): 3302, 3115, 2929, 2855, 1505, 1452, 1149, 1010, 805, 733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.31 (m, 2H, ArH), 6.27 (dd, *J* = 3.3 Hz, *J* = 1.8 Hz, 2H, ArH), 6.12 (d, *J* = 3.3 Hz, 2H, ArH), 3.82 (d, *J* = 14.4 Hz, 2H, CH_AH$_B$), 3.67 (d, *J* = 14.4 Hz, 2H, CH$_A$$H_B$), 2.17 (m, 2H, C*H*N), 2.00 (dd, *J* = 10.5 Hz, *J* = 3.0 Hz, 2H, CH_2), 1.91 (br s, 2H, NH), 1.65–1.69 (m, 2H, CH_2), 1.14–1.22 (m, 2H, CH_2), 0.97–1.04 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6 ($C_{IV°Ar}$), 141.5 (C_{Ar}), 110.1 (C_{Ar}), 106.4 (C_{Ar}), 60.6 (CHN), 45.4 (CH_2N), 31.4 (CH_2), 25.0 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{16}H_{22}N_2O_2+H]^+$ 275.1760; found 275.1765.

4.3. General procedure for nitroaldol reaction (Tables 1–3)

The test tube with a stirring bar was charged with ligand (0.06 mmol, 12 mol %), copper(II) acetate hydrate (10.0 mg, 0.05 mmol, 10 mol %), and 2-propanol (1.0 mL). The resulting suspension was gently heated for 30 s and stirred for 1 h to ensure completion of the complex formation. Then a solution of aldehyde (0.5 mmol, 1 equiv) in 2-propanol (0.3 mL) was added at 23 °C, the whole mixture was cooled to −30 °C for 15 min, treated with nitromethane, nitroethane, or nitropropane, respectively (5.0 mmol, 10 equiv) via a syringe. After 5 min a solution of *i*-Pr$_2$NEt (5.0 mg, 7.7 mol %) in 2-propanol (0.2 mL) was added via a syringe. The mixture was stirred for 5 h at −30 °C and left in a refrigerator at −25 °C for 65 h. Purification by flash chromatography on silica gel (30 g, *n*-hexane/AcOEt, 7:1, v/v) afforded the desired β-nitroalcohols as a mixture of diastereomers. The ratio of isomers was determined using ^{1}H NMR. The ratio of enantiomers was determined using HPLC on chiral stationary phases.

For the reactions reported in Table 2, entries 14–19, the general procedure was applied, with the exception that only 1.0 equiv of nitrocompound as a solution in 2-propanol (0.3 mL) was used avoiding its separation from the desired product. Similarly, the results from Table 3 refer to the general procedure with the exception that 2, 1, or 0.5 equiv of nitromethane was added as a solution in 2-propanol (0.3 mL).

4.3.1. HPLC conditions for determining the enantiomeric excesses and spectroscopic data for diastereomerically pure or unknown compounds

4.3.1.1. 2-Nitro-1-phenylpropan-2-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 1.0 mL/min, λ = 225 nm, *anti*$_{major}$ (1*S*,2*R*) t_r = 13.0 min, *anti*$_{minor}$ (1*R*,2*S*) t_r = 14.7 min, *syn*$_{major}$ (1*S*,2*S*) t_r = 18.0 min, *syn*$_{minor}$ (1*R*,2*R*) t_r = 20.2 min. Absolute stereochemistry of both diastereomers was assigned by comparison of the retention times in HPLC with the literature data.[5b,d] (lit.:[5d] *anti* (1*S*,2*R*) t_r = 13.7 min, *anti* (1*R*,2*S*) t_r = 15.0 min, *syn* (1*S*,2*S*) t_r = 18.6 min, *syn* (1*R*,2*R*) t_r = 21.1 min). Diastereomeric ratio (*anti*/*syn*) was determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1,

C-2 as well as methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.2. 1-(4-Chlorophenyl)-2-nitropropan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 1.0 mL/min, λ = 225 nm, $anti_{major}$ (1*S*,2*R*) t_r = 15.2 min, $anti_{minor}$ (1*R*,2*S*) t_r = 16.6 min, syn_{minor} (1*R*,2*R*) t_r = 21.9 min, syn_{major} (1*S*,2*S*) t_r = 24.4 min (lit.:[5d] *anti* (1*S*,2*R*) t_r = 15.0 min, *anti* (1*R*,2*S*) t_r = 16.4 min, *syn* (1*R*,2*R*) t_r = 21.9 min, *syn* (1*S*,2*S*) t_r = 24.0 min). The chemical shifts of protons adjacent to carbons C-1, C-2 as well as the methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.3. 1-(4-Chlorophenyl)-2-nitrobutan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 1.0 mL/min, λ = 225 nm, $anti_{major}$ (1*S*,2*R*) t_r = 12.0 min, $anti_{minor}$ (1*R*,2*S*) t_r = 13.0 min, syn_{minor} (1*R*,2*R*) t_r = 17.1 min, syn_{major} (1*S*,2*S*) t_r = 21.1 min (lit.:[5d] *anti* (1*S*,2*R*) t_r = 12.4 min, *anti* (1*R*,2*S*) t_r = 13.3 min, *syn* (1*R*,2*R*) t_r = 17.8 min, *syn* (1*S*,2*S*) t_r = 21.6 min). The chemical shifts of protons adjacent to carbons C-1, C-2 as well as the methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.4. 2-Nitro-1-(4-nitrophenyl)propan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 225 nm, *anti* t_r = 19.5 min, syn_{minor} t_r = 29.5 min, syn_{major} t_r = 36.5 min; Chiralcel OD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 225 nm, $anti_{minor}$ t_r = 19.7 min, $anti_{major}$ t_r = 26.2 min, *syn* t_r = 24.5 min. Diastereomeric ratios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as the methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.5. 2-Nitro-(4-nitrophenyl)butan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 225 nm, *anti* t_r = 12.4 min, syn_{minor} (1*R*,2*R*) t_r = 19.3 min, syn_{major} (1*S*,2*S*) t_r = 30.4 min; Chiralcel OD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 225 nm, $anti_{minor}$ (1*R*,2*S*) t_r = 13.5 min, $anti_{major}$ (1*S*,2*R*) t_r = 14.9 min, *syn* t_r = 18.9 min (lit.:[5d] Chiralpak AD-H *anti* t_r = 12.8 min, *syn* (1*R*,2*R*) t_r = 19.1 min, *syn* (1*S*,2*S*) t_r = 29.2 min; Chiralcel OD-H, *anti* (1*R*,2*S*) t_r = 12.2 min, *anti* (1*S*,2*R*) t_r = 13.1 min, *syn* t_r = 16.0 min). Diastereomeric ratios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as the methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.6. 1-(Naphthalen-1-yl)-2-nitropropan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, 0.5 mL/min, λ = 210 nm, $anti_{major}$ t_r = 16.8 min, $anti_{minor}$ t_r = 20.8 min, syn_{major} t_r = 28.1 min, syn_{minor} t_r = 32.7 min. The mixture of diastereomers was separated using flash chromatography (silica gel, 30 g, *n*-hexane/AcOEt, 8:1, v/v) giving diastereomerically pure nitroaldols:

Anti-(1S,2R)-1-(Naphthalene-1-yl)-2-nitropropan-1-ol: Colorless solid, mp 83.5–85 °C (75% ee), $[\alpha]_D$ = −30.4 (*c* 0.6, $CHCl_3$, 75% ee); IR (KBr, ν_{max}): 3547, 3068, 1543, 1319, 809, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 1H, ArH), 7.90 (d, *J* = 7.8 Hz, 1H, ArH), 7.83 (d, *J* = 8.4 Hz, 1H, ArH), 7.77 (d, *J* = 7.2 Hz, 1H, ArH), 7.48–7.59 (m, 3H, ArH), 6.26 (br s, 1H, C*H*OH), 4.90 (dq, *J* = 6.7 Hz, *J* = 2.4 Hz, 1H, C*H*NO_2), 2.70 (s, 1H, O*H*), 1.42 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.8 ($C_{IV°Ar}$), 133.6 ($C_{IV°Ar}$), 129.38 ($C_{IV°Ar}$), 129.30 (C_{Ar}), 129.1 (C_{Ar}), 127.0 (C_{Ar}), 125.9 (C_{Ar}), 125.4 (C_{Ar}), 124.0 (C_{Ar}), 121.7 (C_{Ar}), 85.6 (COH), 70.9 (CNO_2), 11.0 (CH_3). HRMS (ESI, $[M+Na]^+$) calcd for $[C_{13}H_{13}NO_3+Na]^+$ 254.0788; found 254.0793. This compound is described in the literature,[5a] however the spectroscopic data were not reported.

Reaction performed according to the general procedure on 2.5 mmol scale of aldehyde, followed by purification using column chromatography (silica gel, 100 g, *n*-hexane/AcOEt, 8:1, v/v), led to the first fraction (*anti*/*syn* 93:7 dr, 78% ee, 306 mg, 56% yield). Single crystallization from cyclohexane/dichloromethane gave the desired product with 99.8% ee and 99% dr (163 mg, 53% recovery), colorless crystals, mp 99–100 °C, $[\alpha]_D$ = −37.8 (*c* 0.5, $CHCl_3$, 99% ee).

Syn-(1S,2S)-(1-Naphthalene-1-yl)-2-nitropropan-1-ol: Light yellow oil, $[\alpha]_D$ = +30.4 (*c* 0.3, $CHCl_3$, 84% ee); IR (film, ν_{max}): 3535, 3053, 2992, 1551, 1389, 1360, 1053, 804, 781 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.1 Hz, 1H, ArH), 7.87 (t, *J* = 9.0 Hz, 2H, ArH), 7.45–7.59 (m, 4H, ArH), 5.77 (d, *J* = 9.3 Hz, 1H, C*H*OH), 5.06–5.16 (m, 1H, C*H*NO_2), 2.74 (br s, 1H, OH), 1.24 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.0 ($C_{IV°Ar}$), 133.97 ($C_{IV°Ar}$), 130.8 ($C_{IV°Ar}$), 129.8 (C_{Ar}), 129.2 (C_{Ar}), 126.8 (C_{Ar}), 126.1 (C_{Ar}), 125.6 (C_{Ar}), 125.4 (C_{Ar}), 123.2 (C_{Ar}), 88.5 (COH), 73.7 (CNO_2), 16.8 (CH_3). HRMS (ESI, $[M+Na]^+$) calcd for $[C_{13}H_{13}NO_3+Na]^+$ 254.0788; found 254.0791.

4.3.1.7. 1-Cyclohexyl-2-nitropropan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 97:3, 1.0 mL/min, λ = 210 nm, $anti_{minor}$ t_r = 16.0 min, $anti_{major}$ t_r = 18.7 min, syn_{major} t_r = 17.1 min, syn_{minor} t_r = 25.7 min. Diastereomeric ratios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as the methyl groups were in agreement with those reported in the literature.[4b,d]

4.3.1.8. 1-Cyclohexyl-2-nitrobutan-1-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 97:3, 0.5 mL/min, λ = 210 nm, syn_{major} t_r = 29.2 min, syn_{minor} t_r = 46.6 min.

Syn-(1S,2S)-1-Cyclohexyl-2-nitrobutan-2-ol: Colorless oil, $[\alpha]_D$ = −9.2 (*c* 0.7, MeOH, 99% ee). IR (film, ν_{max}): 3452, 2929, 2974, 1554, 1451, 1378, 1112, 811 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.55 (ddd, *J* = 10.5 Hz, *J* = 6.3 Hz, *J* = 4.5 Hz, 1H, C*H*NO_2), 3.56–3.63 (m, 1H, C*H*OH), 2.11 (d, *J* = 8.4 Hz, 1H, OH), 1.99–2.07 (m, 1H, C*H*CHCH$_3$), 1.64–1.88 (m, 6H, CHC*H*CH$_3$ and H_{Cy}), 1.32–1.38 (1H, m, H_{Cy}), 1.14–1.28 (5H, m, H_{Cy}), 0.97 (t, *J* = 7.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 91.9 (CNO_2), 75.9 (COH), 40.2 (CH), 29.8 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 10.2 (CH_3). ^{1}H NMR and ^{13}C NMR spectroscopic data were identical to those reported in the literature.[4e]

4.3.1.9. (1*S*,2*S*)-2-Nitro-1,2-diphenylethanol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 97:3, 0.5 mL/min, λ = 210 nm minor isomer t_r = 110.2 min, major t_r = 115.6 min; waxy light yellow solid, $[\alpha]_D$ = −35.7 (*c* 0.7, MeOH, 62% ee). IR (film, ν_{max}): 3440, 3035, 2925, 1554, 1364, 1055, 725, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.29 (m, 5H, ArH), 7.17–7.20 (m, 3H, ArH), 7.10–7.14 (m, 2H, ArH), 5.35–5.61 (m, 2H, C*H*NO_2 and C*H*OH), 2.68 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5 ($C_{IV°Ar}$), 131.3 ($C_{IV°Ar}$), 130.0 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 127.1 (C_{Ar}), 96.8 ($CHNO_2$), 75.9 (CHOH). HRMS (ESI, $[M+Na]^+$) calcd for $[C_{14}H_{13}NO_3+Na]^+$ 266.0788; found 266.0793.

4.3.1.10. 1-Cyclohexyl-2-nitro-2-phenylethanol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 97:3, 1.0 mL/min, λ = 210 nm, $anti_{major}$ t_r = 23.7 min, $anti_{minor}$ t_r = 36.9 min, syn_{major} t_r = 27.7 min, syn_{minor} t_r = 32.0 min. Diastereomeric ratios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as methyl groups were in agreement with those reported in the literature.[4b]

4.3.1.11. 2-Nitro-1,3-diphenylpropan-1-ol. Chiralcel OD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 210 nm, $anti_{minor}$ (1*R*,2*S*) t_r = 11.0 min, $anti_{major}$ (1*S*,2*R*) t_r = 19.8 min, syn_{minor} (1*R*,2*R*) t_r = 13.1 min, syn_{major} (1*S*,2*S*) t_r = 14.8 min (lit.:[5d] *anti* (1*R*,2*S*) t_r = 10.1 min, *anti* (1*S*,2*R*) t_r = 14.9 min, *syn* (1*R*,2*R*) t_r = 11.1 min, *syn* (1*S*,2*S*) t_r = 12.7 min). Our analysis of the corresponding racemates suggested that the reported peak[5d] of 14.9 min was previously ascribed to the (1*S*,2*R*) enantiomer. Perhaps, it could result from some impurity instead. Diastereomeric ra-

tios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as methyl groups were in agreement with those reported in the literature.[5d]

4.3.1.12. 2-Nitro-5-phenylpentan-1,3-diol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 210 nm, *anti*$_{major}$ (2*R*, 3*S*) t_r = 15.5 min, *anti*$_{minor}$ (2*S*, 3*R*) t_r = 16.7 min, *syn*$_{major}$ (2*R*, 3*R*) t_r = 21.1 min, *syn*$_{minor}$ (2*S*, 3*S*) t_r = 23.1 min (lit.:[15] Chiralpak AD, *n*-hexane/*i*-PrOH, 9:1, 0.7 mL/min, *anti* (2*R*, 3*S*) t_r = 17 min, *anti* (2*S*, 3*R*) t_r = 18 min, *syn* (2*R*, 3*R*) t_r = 22.6 min, *syn* (2*S*, 3*S*) t_r = 24 min). Diastereomeric ratios (*anti*/*syn*) were determined by ^{1}H NMR. The chemical shifts of protons adjacent to carbons C-1, C-2 as well as methyl groups were in agreement with those reported in the literature.[15]

4.3.1.13. 2-Nitrooctane-1,3-diol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, 1.0 mL/min, λ = 210 nm, *anti*$_{major}$ t_r = 10.4 min, *anti*$_{minor}$ t_r = 11.0 min, *syn*$_{minor}$ t_r = 13.8 min, *syn*$_{major}$ t_r = 14.6 min The recorded ^{1}H NMR spectra is in agreement with data reported in the literature.[20] The ratio of diastereomers was assigned using ^{1}H NMR by the analogy to the 2-nitrooctane-3-ol[6b] and 2-nitro-5-phenylpentan-1,3-diol.[15]

4.3.1.14. 1-Nitro-3-phenylbutan-2-ol. Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 1.0 mL/min, λ = 210 nm; A_{minor} t_r = 13.4 min, A_{major} t_r = 14.6 min, B_{major} t_r = 16.7 min, B_{minor} t_r = 21.7 min. IR (film, ν_{max}): 3544, 3439, 3029, 2872, 1558, 1384, 767, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ = 7.29–7.35 (m, 4H, ArH, *anti* + *syn*), 7.23–7.27 (m, 3H, ArH, *anti* + *syn*), 7.18 (br d, *J* = 6.9 Hz, 3H, ArH, *anti* + *syn*), 4.43–4.84 (m, 1H, *syn* C*H*NO$_2$), 4.34–4.41 (m, 1H, *anti* C*H*NO$_2$), 4.17–4.31 (m, 4H, C*H*$_2$NO$_2$, *anti* + *syn*), 2.90 (qw, *J* = 6.9 Hz, 1H, *syn* C*H*CH$_3$), 2.81 (qw, *J* = 7.5 Hz, 1H, *anti* C*H*CH$_3$), 2.70 (br s, 1H, *anti* OH), 2.35 (br s, 1H, *syn* OH), 1.40 (d, *J* = 6.9 Hz, 3H, *anti* CH$_3$), 1.36 (d, *J* = 7.5 Hz, 3H, *syn* CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ = 142.0 (2 × C$_{IV°Ar}$), 129.1 (*anti* C$_{Ar}$), 129.0 (*syn* C$_{Ar}$), 128.1 (2 × C$_{Ar}$), 127.5 (*anti* C$_{Ar}$), 127.4 (*syn* C$_{Ar}$), 79.5 (*anti* CHNO$_2$), 79.3 (*syn* CHNO$_2$), 73.3 (*anti* CHOH), 72.8 (*syn* CHOH), 43.8 (*anti* C*H*(CH$_3$)CHOH), 43.5 (*syn* C*H*(CH$_3$)CHOH), 29.8, 17.5 (*anti* CH$_3$), 17.3 (*syn* CH$_3$). The recorded ^{1}H NMR spectra is in agreement with data reported in the literature.[14] HRMS (ESI, [M+Na]$^+$) calcd for [$C_{10}H_{13}NO_3$+Na]$^+$ 218.0788; found 218.0801.

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