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Chiral Piperazines as Efficient Catalysts for the Asymmetric Michael Addition of Aldehydes to Nitroalkenes

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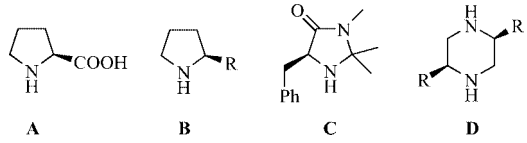
Keywords: Asymmetric catalysis / Michael addition / Aldehydes / Nitroalkenes / Piperazines

Chiral piperazines were used as efficient catalysts in the addition of unmodified aldehydes to nitroalkenes. The nature of the solvent, temperature, and catalyst load were found to influence the outcome of the reaction. The products were obtained in good yields up to 88 %, high diastereoselectivities up to 97:3, and high enantiomeric excesses up to 85 %. Plain piperazine and its monohydrochloride were used efficiently as organocatalysts in the synthesis of racemic γ-formylnitroalkanes.

Introduction

During the last six years, there has been rapid development in the field of organocatalysis, that is, in organic reactions catalyzed by small organic molecules.[1] A reaction that benefited from this novel methodology was the direct addition of unmodified aldehydes to electron-deficient olefins. Until the first report of the addition of aldehydes to nitrostyrenes by Betancort and Barbas[2] in 2001, there had been no previous examples of catalytic asymmetric conjugate additions of naked aldehydes.[3] Even the less reactive ketones had been used as nucleophiles in the Michael reaction only after preactivation by conversion into a more reactive species such as an enol or enamine equivalent. The enolates or enols of aldehydes have reactions that are more difficult to control, with polymerization and aldolization processes competing. Aldehyde equivalents, that is, molecules that provide the CH_2O moiety, for example, dianions of nitroethane or the dianion of 4-nitro-1-butene, which add exclusively in the 1,4-mode to α,β-unsaturated ketones, had been used instead.[4] Organocatalysts work in the addition of unmodified aldehydes to electron-deficient alkenes presumably by the formation of enamine intermediates. After the initial report on addition to nitrostyrenes, a few other studies appeared[5] as well as reports on the addition of aldehydes to enones,[6] to vinyl sulfones,[7] and to diethyl azodicarboxylate.[8] The organocatalysts used so far have been pyrrolidine derivatives, often diamines, which are in fact, together with proline and imidazolines (Figure 1, A–C), the catalysts used most frequently in the field of organocatalysis. The cyclic five-membered secondary amine structure is now regarded as one of the "privileged" backbones for asymmetric catalysis.[5h]



A B C D

Figure 1. Compounds **A**–**D**.

As a follow up to our interest in six-membered cyclic compounds as "backbones" for catalysts or ligands such as 1,4-dioxanes with diacetal functionality,[9] we decided to investigate the potential of the related piperazines as organocatalysts. The piperazine ring is rigid and there is an inherent 1,2-diamine functionality within the cyclic framework. Chiral piperazines were first used in catalysis by Soai et al. in 1987[10] to promote the asymmetric addition of diethylzinc to benzaldehyde, which led to high inductions (up to 90 %). Since then a few reports of their use as ligands for metal-catalyzed reactions have appeared. Although achiral piperazines have been used as additives in the asymmetric conjugate addition of nitroalkanes to enones catalyzed by proline or 5-pyrrolidin-2-yltetrazole,[11] their use as chiral organocatalysts, to the best of our knowledge, has not yet been reported. We tried 2,5-disubstituted chiral piperazines **D** (Figure 1; **1**: R = Bn, **2**: R = *i*Pr) and found that dibenzylpiperazine **1** is a very efficient catalyst for the asymmetric direct conjugate addition of aldehydes to nitroalkenes, and we present our results here. During the course of this work, a novel method to synthesize racemic 2,3-disubstituted δ-formyl nitroalkanes, in which piperazine acts as catalyst, was also developed. The results are also described here.

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Results and Discussion

The two chiral piperazines used in this study, (2*S*,5*S*)-2,5-dibenzylpiperazine (**1**) and (2*S*,5*S*)-2,5-diisopropylpiperazine (**2**), were prepared by previously reported procedures in three steps. The synthesis of each involved condensation of the respective Boc amino acid with the amino acid methyl ester hydrochloride followed by cyclization of the dipeptide produced according to Nitecki et al.[12] Reduction of the resulting diketopiperazine with $NaBH_4/TiCl_4$ according to Soai et al.[13] yielded the piperazine with C_2-symmetry.

Optimization of Reaction Conditions

In order to find the experimental conditions most suitable for the use of chiral piperazines as organocatalysts for the Michael addition of unmodified aldehydes to nitroalkenes, the addition of butyraldehyde to *trans*-β-nitrostyrene was chosen as a model reaction. It has been found by others[5] that the nature of the solvent has a large effect on the results obtained in this reaction; hence, this factor was examined first. The results are presented in Table 1.

The results in Table 1 show that there are large variations in the diastereo- as well as enantioselectivities in the addition reaction with a change in solvent; this may be seen when the results in Entry 4, *dr* 66:34, *ee* 69% in THF, are compared with those of Entry 6, *dr* 88:12, *ee* 79% in DCM/hexane, and Entry 7, *dr* 94:6, *ee* 80% in *i*PrOH. Solvent polarity does not seem to be very important as the last two results show (Entries 6 and 7). In all cases an excess of aldehyde/nitroalkene (10:1) was used. In DMF, only the desired product is formed, and no by-products such as those of aldehyde condensation can be detected. These do form in other solvents, but they can be removed easily by chromatography. Under no conditions did other nitroalkene addition products form. However, in DMF the reaction is slow, and both *dr* and *ee* are low. The solvent systems DCM/hexane (1:2) and *i*PrOH gave the best overall results.

The relative and the absolute configuration of the major Michael adduct was determined by ^{1}H NMR spectroscopic analysis and by comparison of the optical rotation with that of the known compound.[2] It was found to be *syn*, which is in agreement with the results of other workers in this field.[5] An acyclic synclinal transition state, proposed by Seebach and Golinski[14] for the Michael addition of (*E*)-enamines to (*E*)-nitroalkenes also explains the *syn* selectivity in these reactions. A gauche relationship between the donor and the acceptor π-systems is favored by electrostatic interactions between the partially positive nitrogen atom of the enamine and the partially negative nitro group in the transition state (Figure 2). The nitroalkene approaches from the less hindered face of the enamine.

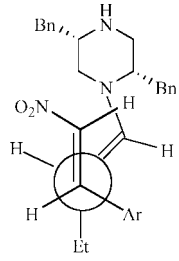
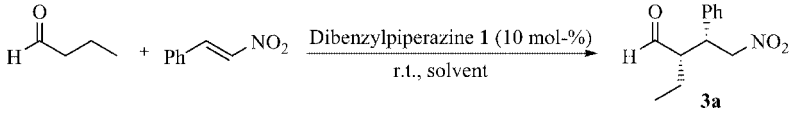


Figure 2. Proposed transition state.

Temperature was also found to have an important effect on the reaction (Table 2). In DCM/hexane, the *dr* increased from 88:12 to 97:3 and the *ee* from 79 to 84% when the temperature was lowered to 0 °C, but the reaction was retarded considerably from 5 to 48 h (Entries 5 and 6). It was also found that the percentage of catalyst had only a small influence on the outcome of the reaction; thus, an increase in the amount of catalyst used from 5 to 10 mol-% (Entries 4 and 5) speeded up the reaction but there was only a very slight increase in the *ee*, from 77 to 79%. Increasing the catalyst load to 20 mol-% increased the yield of product, but not the *dr* or *ee* (Entries 6 and 7).

Table 1. Solvent effect on the asymmetric Michael addition reaction of butyraldehyde to *trans*-β-nitrostyrene catalyzed by **1**.



Entry	Solvent	Time [h]	Conversion[a] [%]	Yield[b] [%]	*dr* (*syn*:*anti*)[c] [%]	*ee* (*syn*)[d] [%]
1	DCM/wet hexane (1:1)	17	100	54	91:9	72
2	DCM/wet hexane (1:1)	5	100	52	84:16	76
3	DCM	5	100	51	73:27	53
4	THF	5	100	80	66:34	69
5	DMF	5	64	32	62:38	59
6	DCM/hexane (1:2)	5	100	63	88:12	79
7	*i*PrOH	5	100	54	94:6	80
8	$CHCl_3$	5.5	100	90	88:12	76
9	DME	5	100	40	76:24	72

[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy of unpurified products. [d] Determined by HPLC analysis on a chiral column (Chiralpak AD-H).

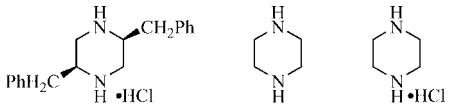
Table 2. Effect of catalyst structure, catalyst loading, and temperature on the Michael addition reaction of butyraldehyde to *trans*-β-nitrostyrene.

Entry	Catalyst	Catalyst load [mol-%]	Conditions (Solvent,[a] temp., time)	Conversion[b] [%]	Yield[c] [%]	*dr* [d] (*syn:anti*) [%]	*ee*[e] [%]
1	**1**	5	DCM, room temp., 5 h	44	14	83:17	59
2	**1**	10	DCM, room temp., 5 h	100	51	73:27	53
3	**1**	10	DCM, 0 °C, 17 h	67	56	76:24	75
4	**1**	5	DCM/hexane, room temp., 17 h	100	72	94:6	77
5	**1**	10	DCM/hexane, room temp., 5 h	100	63	88:12	79
6	**1**	10	DCM/hexane, 0 °C, 48 h	100	63	97:3	84
7	**1**	20	DCM/hexane, 0 °C, 48 h	100	80	87:13	79
8[f]	**2**	10	DCM/hexane, 0 °C, 48 h	100	76	87:13	41
9	**4**	10	DCM/hexane, room temp., 5 h	76	43	81:19	78
10	**4**	10	DCM/hexane, room temp., 7 h	90	55	92:8	78
11	**4**	10	DCM/hexane, room temp., 10 h	100	98	90:10	77
12	**4**	10	DCM/hexane, 0 °C, 48 h	100	ND[g]	87:13	53
13	**4**	10	*i*PrOH, room temp., 10 h	100	71	92:8	82

[a] DCM/hexane refers to a 1:2 solution of the two solvents. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product after chromatography. [d] Determined by ^{1}H NMR spectroscopy of unpurified products. [e] Determined by HPLC analysis on a chiral column (Chiralpak AD-H). [f] Propionaldehyde was used instead of butyraldehyde. [g] ND = Not determined.

It has been shown that protonated chiral diamines can be very versatile organocatalysts,[15] and indeed some of the previous reports on this reaction describe the use of protonated organocatalysts.[5b,5d,5f,5g,5i–5l] A protonated catalyst may activate the substrate by hydrogen bonding, which would create a more ordered transition state that could lead to higher asymmetric inductions, or even speed up the reaction as it reduces the electron density of the electrophile. In doing so, the organocatalyst mimics Nature's catalysts (i.e. enzymes) which accelerate a wide range of reactions by hydrogen bonding, for example type II aldolases, serine proteases, etc.

The addition of butyraldehyde to *trans*-β-nitrostyrene was also attempted with the monohydrochloride of dibenzylpiperazine **1** (**4**, Figure 3), and the results are also included in Table 2.[16]



4 **5** **6**

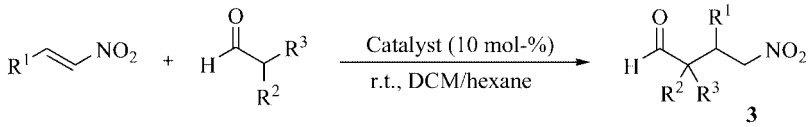
Figure 3. Catalysts **4**–**6**.

The reaction was slower with butyraldehyde, although more selective (no aldehyde condensation was observed). The combined *dr* and *ee* were better with the unprotonated catalyst, however, and so this was used in the application of the method to other aldehydes and nitroolefins, and DCM/hexane (1:2) at 0 °C were selected as reaction conditions. Diisopropylpiperazine **2** was not as effective as the other catalysts, and the enantiomeric excess obtained in the reaction of propionaldehyde with *trans*-β-nitrostyrene was only 41% (Entry 8).

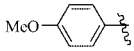
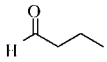
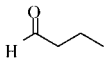
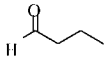
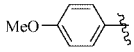
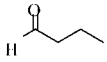
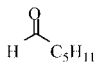
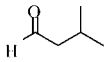
Simple Diastereoselective Addition of Aldehydes to Nitroalkenes: Preparation of Racemic Standards

By using the knowledge gained in the first experiments, an attempt was made to develop a method to synthesize achiral γ-nitroaldehydes also using organocatalysis. The racemic products so prepared would then have an immediate application as standards for the determination of enantiomeric excesses by HPLC or NMR of the products prepared with the asymmetric method. A simple, inexpensive candidate for a catalyst that required no synthetic manipulation was unsubstituted piperazine **5**, which was used as its monohydrochloride, **6**. The results are presented in Table 3. The products were obtained in good yields (up to 86%) and high diastereoselectivities (up to 98:2, *syn*). However, branching at the β-position, for example in isovaleraldehyde, retarded the reaction considerably (Entry 11) and after 5 d there was only 24% conversion. When free piperazine **5** was used as the catalyst, there was complete conversion within this period of time in good yield (64%) although the diastereoselectivity was lower (Entry 12). With α-branching, the reaction was very slow, and there was only 24% conversion after 11 d with isobutyraldehyde (Entry 13). Hagiwara et al.[3b] used diethylamine as the catalyst for the addition of naked aldehydes to ketones. The method was applied to the addition of propionaldehyde to β-nitrostyrene (Entry 2) and *p*-methoxy-β-nitrostyrene (Entry 4). In the first case, the diastereoselectivity was lower than that obtained when piperazine monohydrochloride was used as the catalyst. With isobutyraldehyde, there were only traces of product after 20 h. The method developed by Hagiwara et al.[3b] for vinylketones needs high temperatures and pressure. The method presented here for the synthesis of achiral γ-nitroaldehydes with catalytic amounts of piperazine or its monohydrochloride involves a reaction at room temperature, atmospheric pressure, and the diastereoselectivities ob-

Table 3. Simple diastereoselective addition of aldehydes to nitroalkenes catalyzed by piperazine **5** or piperazine hydrochloride **6**.



3

Entry	Aldehyde	R^1	Catalyst	Time	Yield [%][a]	*dr* (*syn:anti*)[b]	Product
1			**6**	18 h	53	88:12	*rac*-**3b**
2			**6**	17 h	66	83:17[c]	*rac*-**3b**
3			**6**	24 h	74	83:17	*rac*-**3c**
4			**6**	24 h	53	75:25[c]	*rac*-**3d**
5			**6**	16 h	77	94:6	*rac*-**3a**
6			**6**	18 h	48	91:9	*rac*-**3e**
7			**5**	21 h	86	88:12	*rac*-**3f**
8			**6**	22 h	72	98:2	*rac*-**3f**
9			**6**	66 h	61	96:4	*rac*-**3g**
10			**6**	66 h	62	90:10	*rac*-**3h**
11			**5**	5 d	64	84:16	*rac*-**3i**
12			**6**	5 d	20 + SM[d]	96:4	*rac*-**3i**
13			**5**	11 d	24 + SM[e]	–	*rac*-**3j**

[a] Yield of isolated product after chromatography. [b] Calculated from the ^{1}H NMR spectrum of the crude product. [c] Prepared via direct addition in the presence of catalytic diethylamine.[3b] [d] SM = starting material; only 24% conversion. [e] Only 35% conversion.

tained are high. To the best of our knowledge this is the first report on the synthesis of these racemic materials from unmodified aldehydes.

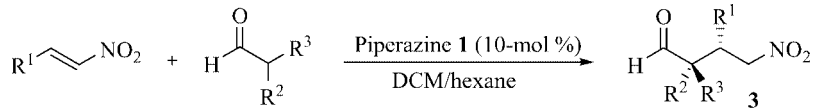
Application of the New Organocatalytic Method to the Asymmetric Synthesis of 2,3-Disubstituted γ-Formylnitroalkanes

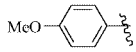
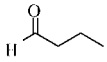
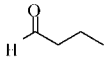
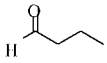
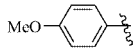
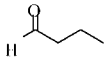
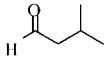
With the use of the optimized reaction conditions obtained in this work, we synthesized several chiral 2,3-disubstituted γ-formylnitroalkanes, which may be converted into many other useful building blocks, such as 1,4-amino alcohols, amino acids, or pyrrolidines, structural units found in many products containing biological activity.[5c] The results are presented in Table 4. Some structural effects were observed. Generally the reactions proceeded in a very high diastereoselective and enantioselective manner (*dr* varied from 80:20 to 97:3 and *ee* varied from 66 to 85%). An increase in the length of the aldehyde carbon chain, that is, an increase in R^2 from methyl to ethyl to butyl, caused an increase in *ee* up to the C_4 chain as a result of strain on the enamine allylic system, then a decrease was observed as the reaction is slowed down further and further with longer chain lengths. Heteroaromatic substituents, electron donating aryl groups, as well as electron deficient aryl groups could be used. A branched aldehyde, isovaleraldehyde, gave good enantioselectivity, although it was slow to react: 66% yield was obtained after 6 d. Interestingly, the synthesis of the racemic equivalent could not be carried out efficiently with the protonated catalyst, which indicates that a different mechanism is most probably at work.

Conclusions

We have shown that chiral piperazines are efficient catalysts for the addition of naked aldehydes to nitroalkenes. The catalysts may be synthesized easily, in good yields, in

Table 4. Catalytic asymmetric Michael addition of aldehydes to nitroalkenes catalyzed by dibenzylpiperazine **1**.



Entry	Aldehyde	R^1	T [°C]	Time	Yield [%][a]	*dr* (*syn*:*anti*)[b]	*ee* (*syn*) [%][c]	Product
1			0	17 h	78	97:3	81	**3b**
2			0	41 h	52	94:6	69[d]	**3c**
3			0	40 h	68	94:6	74[d]	**3d**
4			0	48 h	63	97:3	84	**3a**
5			0	42 h	78	95:5	77[d]	**3e**
6			0	44 h	57	97:3	84	**3f**
7			rt	68 h	67	80:20	85	**3g**
8			0	5 d	ND[e]	96:4	75	**3h**
9			0	6 d	66	89:11	68	**3i**
10			rt	11 d	36[f] + SM	–	75	**3j**

[a] Yield of isolated product after chromatography. [b] Calculated from the ^{1}H NMR spectrum of the crude product. [c] Determined by HPLC analysis (Chiralpak AD-H column). [d] Determined by ^{1}H NMR *ee* assay after reaction with L-Val-OMe.[17] [e] ND = Not determined. [f] SM = starting material; only 60% conversion.

three steps, and to the best of our knowledge this is the first report of organocatalysis by these cyclic diamines with six-membered rings. The reactions proceeded in both a highly diastereoselective [*dr* (*syn*) up to 97:3] and enantioselective manner [*ee* (*syn*) up to 85%]. The *syn* product formed preferentially, which agrees with the observations of other researchers in this area. This also supports the idea that the mechanism of the reaction involves the formation of an intermediate enamine, since a similar stereochemical outcome has been obtained by Seebach and Golinski in reactions of preformed enamines with nitroalkenes. Plain piperazine was also found to be an efficient organocatalyst for the synthesis of racemic products. Good yields (up to 86%) and high diastereoselectivities (up to 98:2) were obtained. The γ-formylnitroalkanes obtained in these reactions may be converted into other useful products, namely 1,4-amino alcohols, amino acids, and pyrrolidines, which are structural units of many biologically active compounds.

Experimental Section

General Remarks: All reactions were carried out under an atmosphere of argon. Solvents were purified by standard procedures and distilled before use. Reagents and starting materials obtained from commercial suppliers were used without further purification unless otherwise stated. Propionaldehyde and butyraldehyde were distilled regularly prior to use. Column chromatography was carried out on Mackerey-Nagel GmbH & Co silica gel (230–400 mesh) or Merck silica gel 60 (230–400 mesh). For thin layer chromatography silica gel plates Merck 60 F_{254} were used. Melting points were measured with an Electrothermal Melting Point apparatus. Optical rotations (0.5 dm cell, 1 mL capacity) were measured with an AA–1000 Polarimeter from Optical Activity Ltd. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer. Chemical shifts are reported relative to TMS. The DEPT sequence was used for multiplicity assignments of ^{13}C NMR spectra signals. Two-dimensional spectra (COSY 45, HMQC) were recorded whenever necessary for structure elucidation. IR spectra were obtained with a Mattson Instruments Satellite FTIR spectrometer. Mass spectra were recorded

with a Micromass GCT spectrometer, operating in the electron impact mode, and were supplied by the Mass Spectrometry Services of the Chemistry Department/REQUIMTE, FCT, UNL. HPLC analyses were performed with a Merck Hitachi instrument equipped with a Chiralpak AD-H column from Daicel, and a Merck-Hitachi-4250 UV/Vis detector.

Catalyst Synthesis: Catalysts **1**, (2*S*,5*S*)-2,5-dibenzylpiperazine, and **2**, (2*S*,5*S*)-2,5-diisopropylpiperazine, were prepared according to literature procedures.[10,12] Catalyst **5**, piperazine, is available commercially. The dihydrochlorides of **1** and **5** were prepared as follows: a methanolic solution of the respective free amines was saturated with gaseous HCl. The crystals which formed overnight were filtered, washed with cold solvent and dried. Monochlorides **4** and **6** were formed in situ by mixing equivalent amounts of dihydrochloride salt and free amine in the reaction solvent.[18] The solutions were stirred 10–15 min at room temperature prior to the addition of the other reaction components according to the general procedure, whenever these catalysts were used.

General Procedure for the Asymmetric Michael Addition of Aldehydes to Nitroalkenes: To piperazine (0.023 mmol), dissolved in solvent (0.24 mL), was added the appropriate nitroalkene (0.225 mmol) and the desired aldehyde (2.25 mmol). The reaction vessel was wrapped in aluminium foil, and the resulting solution was stirred under an argon atmosphere for the appropriate time and at the temperature indicated in the tables. The reaction was then quenched with aq. NaCl solution and the product was extracted four times with DCM. The organic fractions were filtered through anhydrous sodium sulfate and the volatiles were removed on a rotary evaporator. The products were purified by preparative chromatography on silica gel as indicated below. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR and ^{13}C NMR spectra, chiral HPLC analysis and optical rotation values. The stereochemistry of aldehydes **3f** and **3g** have been tentatively assigned by comparison to analogous compounds on the basis of the generally accepted stereochemical course of the reaction.

Preparation of Racemic γ-Formylnitroalkanes: The method described above for the synthesis of chiral adducts was followed with the use of piperazine or piperazine monohydrochloride as the catalyst as indicated in Table 3.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-phenylbutanal (3a): Prepared from butanal and *trans*-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel ($CHCl_3$). Spectroscopic data are in agreement with the published data.[2] Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 97:3. The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 3% 2-propanol in hexane, flow 0.9 mL/min, λ = 254 nm): t_R = 13.2 (*syn*, minor), 13.8 (*anti*, minor), 14.0 (*anti*, major), 14.8 (*syn*, major) min; *ee* (*syn*) 84%, *ee* (*anti*) could not be determined because of partial overlap of peaks.

(2*S*,3*R*)-2-Methyl-4-nitro-3-phenylbutanal (3b): Prepared from propanal and *trans*-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:2). Spectroscopic data are in agreement with the published data.[2] Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 97:3. The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 0.6% 2-propanol in hexane, flow 1.2 mL/min, λ = 254 nm): t_R = 42.5 (*syn*, minor), 51.1 (*anti*, minor), 52.4 (*syn*, major), 59.0 (*anti*, major) min; *ee* (*syn*) 81%, *ee* (*anti*) 78%.

(2*S*,3*R*)-2-Methyl-4-nitro-3-(thien-2-yl)butanal (3c): Prepared from propanal and *trans*-2-(2-nitrovinyl)thiophene according to the general procedure. Purified by preparative chromatography on silica gel ($CHCl_3$). Spectroscopic data are in agreement with the published data.[5e] Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 94:6. The enantiomeric excesses were determined by ^{1}H NMR *ee* assay of the imines formed after in situ reaction with L-Val-OMe in CD_3CN:[17] *ee* (*syn*) 69%, *ee* (*anti*) 61%.

(2*S*,3*R*)-2-Methyl-4-nitro-3-(4-methoxyphenyl)butanal (3d): Prepared from propanal and 1-methoxy-4-(2-nitrovinyl)benzene according to the general procedure. Purified by preparative chromatography on silica gel ($CHCl_3$). Spectroscopic data are in agreement with the published data.[5h] Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 94:6. The enantiomeric excesses were determined by ^{1}H NMR *ee* assay of the imines formed after in situ reaction with L-Val-OMe in CD_3CN:[17] *ee* (*syn*) 74%, *ee* (*anti*) 62%.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-(thien-2-yl)butanal (3e): Prepared from butanal and *trans*-2-(2-nitrovinyl)thiophene according to the general procedure. Purified by preparative chromatography on silica gel (hexane/$CHCl_3$, 1:1). Spectroscopic data are in agreement with the published data.[5f] Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 95:5. The enantiomeric excesses were determined by ^{1}H NMR *ee* assay of the imines formed after in situ reaction with L-Val-OMe in CD_3CN:[17] *ee* (*syn*) 77%, *ee* (*anti*) 83%.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-(4-methoxyphenyl)butanal (3f): Prepared from butanal and 1-methoxy-4-(2-nitrovinyl)benzene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:2). Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 93:7. The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 1.0% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R = 44.6 (*syn*, minor), 52.1 (*anti*, minor), 55.8 (*syn*, major), 60.2 (*anti*, major) min; *ee* (*syn*) 84%, *ee* (*anti*) 82%. Major diastereoisomer (*syn*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 8.0 Hz, 3 H, CH_3), 1.47–1.55 (m, 2 H, C*H*$_2$CH$_3$), 2.59–2.66 (m, 1 H, C*H*CHO), 3.70–3.79 (*syn* + *anti*) (m, 1 H, C*H*Ph), 3.79 (s, 3 H, OCH_3), 4.58 (dd, *J* = 9.6, 12.4 Hz, 1 H, C*H*HNO$_2$), 4.68 (dd, *J* = 4.8, 12.4 Hz, 1 H, CH*H*NO$_2$), 6.86 (d, *J* = 8.4 Hz, 2 H, Ar–H), 7.09 (*syn* + *anti*) (d, *J* = 8.4 Hz, 2 H, Ar–H), 9.71 (d, *J* = 2.4 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 (CH_3), 20.3 (CH_2), 42.1 (CH), 55.2 (CH_3), 78.7 (CH_2NO_2), 114.5 (Ar–CH), 129.0 (Ar–CH), 129.3 (Ar–C_q), 159.3 (Ar–C_q), 203.3 (CO) ppm. Minor diastereoisomer (*anti*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.60–1.82 (m, 2 H, C*H*$_2$CH$_3$), 2.50–2.56 (m, 1 H, C*H*CHO), 3.70–3.79 (*syn* + *anti*) (m, 1 H, C*H*Ph), 3.77 (s, 3 H, OCH_3), 4.66–4.80 (2 × dd, partially overlapped, 2 H, CH_2NO_2), 6.83–6.87 (d, partially overlapped, 2 H, Ar-H) 7.09 (*syn* + *anti*) (d, *J* = 8.4 Hz, 2 H, Ar-H), 9.47 (d, *J* = 3.2 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4 (CH_3), 20.7 (CH_2), 43.5 (CH), 55.0 (CH_3), 78.2 (CH_2NO_2), 114.5 (Ar–CH), 128.5 (Ar–CH), 159.3 (Ar–C_q), 203.3 (CHO) ppm. MS (EI, diastereoisomer mixture): *m*/*z* (%) = 252 (1) [M + 1]$^+$, 251 (8) [M]$^+$, 204 (10), 175 (22), 161 (12), 147 (6), 135 (8), 134 (100), 121 (26), 119 (11), 115 (5), 108 (6), 91 (14).

(2*S*,3*R*)-2-Ethyl-4-nitro-3-(2-trifluoromethylphenyl)butanal (3g): Prepared from butanal and *trans*-β-nitro-2-(trifluoromethyl)styrene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:1). Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 80:20. The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 3.0% 2-propanol in hexane, flow 0.4 mL/min, λ = 254 nm): t_R = 20.9 (*syn*, minor), 22.6 (*syn*, major), 26.7 (*anti*, major), 27.7 (*anti*, minor) min;

ee (*syn*) 85%, *ee* (*anti*) 86%. Major diastereoisomer (*syn*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.2 Hz, 3 H, CH_3), 1.33–1.43 (m, 1 H, C*H*HCH$_3$), 1.55–1.68 (*syn* + *anti*) (m, CH*H*CH$_3$), 2.86–2.96 (m, 1 H, C*H*CHO), 4.14–4.20 (m, 1 H, CH–Ar), 4.64 (dd, J = 4.8, 12.4 Hz, 1 H, C*H*H–NO$_2$), 4.81 (dd, J = 7.2, 12.4 Hz, 1 H, CH*H*–NO$_2$), 7.35 (*syn* + *anti*) (d, J = 8 Hz, 1 H, Ar–H), 7.44 (t, J = 8 Hz, 1 H, Ar–H), 7.58 (t, J = 8 Hz, 1 H, Ar–H), 7.73 (d, J = 8 Hz, 1 H, Ar–H), 9.77 (d, J = 2.8 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (CH_3), 21.3 (CH_2), 38.3 (CH), 55.5 (CH–Ar), 77.9 (CH_2NO_2), 122.7 (Ar–C_q, *syn* or *anti*), 125.5 (Ar–C_q, *syn* or *anti*), 126.87 (Ar–CH, *syn* or *anti*), 126.93 (Ar–CH, *syn* or *anti*), 128.2 (Ar–CH, *syn* or *anti*), 128.6 (Ar–C_q, *syn* or *anti*), 132.6 (Ar–CH, *syn* or *anti*), 136.3 (Ar–C_q, *syn* or *anti*), 203.0 (CHO) ppm. Minor diastereoisomer (*anti*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.2 Hz, 3 H, CH_3), 1.55–1.68 (*syn* + *anti*) (m, CH*H*CH$_3$), 1.71–1.83 (m, CH*H*CH$_3$), 2.75–2.80 (m, 1 H, C*H*CHO), 4.25–4.30 (m, 1 H, CH–Ar), 4.71–4.75 (m, 2 H, CH_2–NO_2), 7.35 (*syn* + *anti*) (d, J = 8 Hz, 1 H, Ar–H), 7.40–7.46 (t, superimposed, 1 H, Ar–H), 7.55–7.60 (t, superimposed, 1 H, Ar–H), 7.71–7.74 (d, superimposed, 1 H, Ar–H), 9.47 (d, J = 2.8 Hz, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5 (CH_3), 20.0 (CH_2), 38.6 (CH), 55.5 (CH–Ar), 77.1 (CH_2NO_2), 122.7 (Ar–C_q, *syn* or *anti*), 125.5 (Ar–C_q, *syn* or *anti*), 126.87 (Ar–CH, *syn* or *anti*), 126.93 (Ar–CH, *syn* or *anti*), 128.2 (Ar–CH, *syn* or *anti*), 128.6 (Ar–C_q, *syn* or *anti*), 132.6 (Ar–CH, *syn* or *anti*), 136.3 (Ar–C_q, *syn* or *anti*), 201.7 (CHO) ppm. MS (EI, diastereoisomer mixture): *m*/*z* (%) = 213 (24) [M – 76]$^+$, 200 (22), 199 (12), 191 (45), 186 (10), 185 (53), 173 (79), 172 (89), 171 (73), 169 (23), 165 (32), 164 (12), 160 (9), 159 (100), 155 (9), 153 (51), 151 (75), 147 (14), 145 (13), 143 (9), 141 (7), 133 (26), 131 (19), 129 (10), 128 (9), 127 (12), 122 (5), 115 (15), 109(9), 103 (5), 69 (9), 57 (10).

(2*S*)-[(*R*)-2-Nitro-1-phenylethyl]hexanal (3h): Prepared from hexanal and *trans*-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:1). Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 96:4. Spectroscopic data are in agreement with the published data.[2] The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 3.4% 2-propanol in hexane, flow 0.4 mL/min, λ = 254 nm): t_R = 22.1 (*syn*, minor), 23.8 (*anti*, major), 24.8 (*syn*, major), 26.4 (*anti*, minor) min; *ee* (*syn*) 75%, *ee* (*anti*) 54%.

(2*S*,3*R*)-2-(Methylethyl)-4-nitro-3-phenylbutanal (3i): Prepared from isovaleraldehyde and *trans*-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:1). Obtained as a mixture of diastereoisomers, *syn*/*anti* ratio 89:11. Spectroscopic data are in agreement with published data.[2] The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 5.0% 2-propanol in hexane, flow 0.8 mL/min, λ = 254 nm): t_R = 9.6 (*anti*, minor), 10.2 (*anti*, major), 11.0 (*syn*, minor), 12.7 (*syn*, major) min; *ee* (*syn*) 68%, *ee* (*anti*) 82%.

(*S*)-2,2-Dimethyl-4-nitro-3-phenylbutanal (3j): Prepared from isobutyraldehyde and *trans*-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (Et_2O/hexane, 1:1). Spectroscopic data are in agreement with the published data.[5d] The enantiomeric excesses were determined by HPLC (Chiralpak AD-H, 3.0% 2-propanol in hexane, flow 0.6 mL/min, λ = 254 nm): t_R = 17.7 (minor), 18.5 (major) min; *ee* (*syn*) 75%.

Supporting Information (see footnote on the first page of this article): ^{13}C NMR spectra of **3f** and **3g**, ^{1}H NMR spectra of **3c**–**e**, HPLC chromatograms of **3a**, **3b**, **3f**–**j**.

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