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Brønsted Acid Assisted Regio- and Enantioselective Direct O-Nitroso Aldol Reaction Catalysed by α,α-Diphenylprolinol Trimethylsilyl Ether

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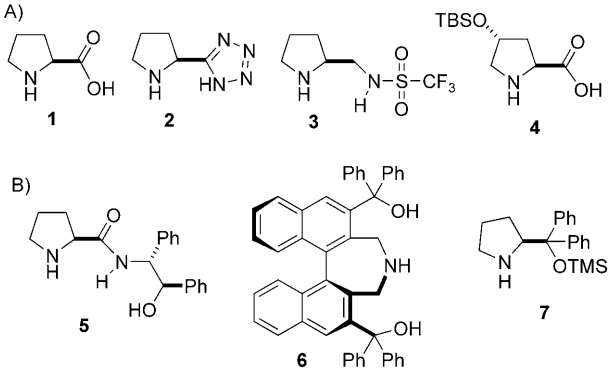
Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

Abstract: In the presence of *p*-nitrobenzoic acid, the O-nitroso aldol reaction of nitrosobenzene with enolisable aldehydes may be promoted by commercially available α,α-diphenylprolinol trimethylsilyl ether. The reaction proceeds with good yields and essentially complete enantioselectivity, with catalyst loadings in the 5–10 mol% range. The resulting α-oxyaldehyde adducts may be transformed in situ into α-oxyimines, which provide 1,2-amino alcohols upon treatment with Grignard reagents, in good overall yield (45–59%) and with typical diastereomeric ratios ≥95:5.

Keywords: amino alcohols · enamine activation · aldehydes · nitroso aldol reaction · organocatalysis

Introduction

The asymmetric O-nitroso aldol reaction is an important tool for the preparation of enantioenriched α-hydroxy carbonyl compounds.[1] In this reaction two important issues are the enantioselectivity and regioselectivity—attack through the nitrogen atom (oxyamination reaction) or oxygen atom (aminoxylation reaction).[2] First insights by Yamamoto et al. on the reaction of nitrosobenzene with silyl or metal enolates revealed that the regioselectivity of the process is dependent on the nature of the enolate and the presence or absence of a Lewis acid catalyst.[3] Later, the same author reported that in the presence of sub-stoichiometric amounts of glycolic acid the reaction of nitrosobenzene with pre-formed enamines preferentially afforded O-nitroso aldol products (aminoxylation). Conversely, in the presence of α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol (TADDOL), the α-amino derivatives were exclusively obtained (oxyamination).[4] Some examples of highly enantioselective nitroso aldol reactions have also been realised through in situ generation of the reactive enamine by using proline (**1**) and secondary amines **2–6** (Scheme 1) in sub-stoichiometric quantities.[5] A common structural feature of all these catalysts is the presence of a



Scheme 1. Organocatalysts for the nitroso aldol reaction: A) Catalysts for aminoxylation, B) Catalysts for oxyamination. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

Brønsted acid functionality as key element for controlling regioselectivity.[6] Thus, catalysts with strong acidic functionalities, such as carboxylic acids or sulfonamides (**1–4** in Scheme 1A), predominantly give α-oxygenated products, whereas those that contain less acidic functionalities, namely, hydroxy groups (**5**, **6** in Scheme 1B), afford mainly α-oxyaminated compounds.

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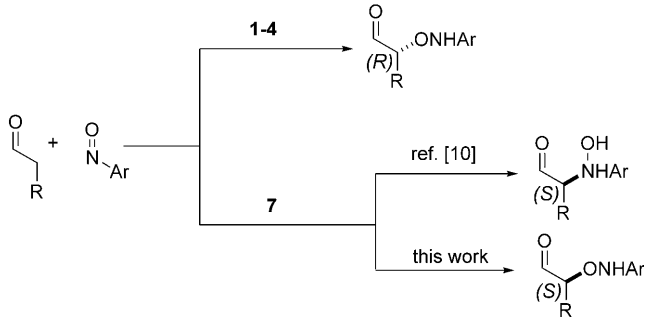
α,α-Diarylprolinol silyl ethers, such as **7**, have proven to be very effective chiral amine catalysts in a number of organocatalytic transformations.[7,8] In contrast to proline and its congeners, these catalysts work through steric control[9] and very high levels of enantioselectivity may be achieved. This concept has not been applied to the O-nitroso aldol reaction (Scheme 2) as yet. Herein, we report the first O-nitroso aldol reaction catalysed by commercially available α,α-diphenylprolinol trimethylsilyl ether (**7**), for the formation of α-aminoxylated products with extremely high regio- and enantiocontrol.

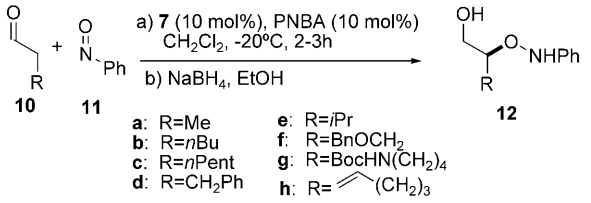


Scheme 2. Catalytic nitroso aldol reaction promoted by secondary amine catalysts **1**–**4** and **7**.

Results and Discussion

Background, catalyst screening and conditions: Previously, we reported that the reaction of aldehydes with nitrosobenzene may be promoted by catalyst **7** to produce α-oxyaminated products as single regioisomers.[10] We envisaged that in the presence of an external Brønsted acid a switch in regiocontrol might occur in the above reaction, as a result of a protonation of the nitrogen atom of nitrosobenzene.[11] The question was to establish whether O-nitroso aldol adducts would be produced as sole reaction products to render the procedure operationally simple and practical. In this way, generation of both α-amino and α-hydroxy carbonyl compounds from a common chiral source should be made feasible, which would be useful from a practical viewpoint. The resulting O-nitroso aldol adducts could be easily transformed in situ into 1,2-diols and related compounds, which are of considerable interest because these structural moieties are widely found in biologically active natural products and synthetic pharmaceuticals.[12]

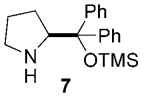
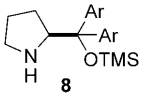
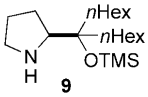
From the outset we realised that the search for reaction conditions under which the oxyamination would be slow or totally suppressed would be central for the success of this approach. In our initial studies, it was observed that the reaction of nitrosobenzene with freshly distilled enolisable aldehydes proceeds efficiently in CH_2Cl_2 at temperatures ≥ 0 °C (typically in the range 0 °C–RT), or in THF at −20 °C for long-chain aldehydes. In all cases 20 mol % of catalyst **7** was required for the reaction to proceed and the resulting N-nitroso aldol products were obtained in 60–75 % yield, with 91–99 % enantiomeric excess (*ee*).[13] We were pleased to find that in CH_2Cl_2 at −20 °C a catalyst loading between 2 and 10 mol % sufficed for the O-nitroso aldol reaction to proceed with the assistance of a Brønsted acid, without appreciable formation of N-nitroso aldol products (Scheme 3).



Scheme 3. O-Nitroso aldol reaction between aldehydes **10** and nitrosobenzene (**11**), catalysed by **7**. PNBA = *p*-nitrobenzoic acid, Boc = *tert*-butyloxycarbonyl, Bn = benzyl.

For example, compound **12a**, obtained from the reaction of propanal with nitrosobenzene (**11**) in the presence of catalyst **7** (2 mol %) and benzoic acid (5 mol %), followed by in situ reduction with $NaBH_4$, was formed with essentially complete regio- and enantioselectivity (Table 1, entry 1).

Table 1. Brønsted acid screening for the O-nitroso aldol reaction of propanal (**10a**) with nitrosobenzene (**11**) promoted by catalysts **7–9**.[a]

Entry	Catalyst	Additive	Yield of **12a**[b] [%]	*ee*[c] [%]
1		$PhCO_2H$	50	>99
2		4-$MeOC_6H_4CO_2H$	22	>99
3	**7**	4-$NO_2C_6H_4CO_2H$	81	>99
4		CH_3CO_2H	35	>99
5		$ClCH_2CO_2H$	52	>99
6	 **8** Ar=3,5-$(CF_3)_2C_6H_3$	4-$NO_2C_6H_4CO_2H$	<5	nd[d]
7	 **9**	4-$NO_2C_6H_4CO_2H$	70	>99

[a] Reactions performed on a 1 mmol scale in CH_2Cl_2 (2 mL) with catalyst (2 mol %), Brønsted acid (5 mol %) and **10a** (3 equiv) at −20 °C for 16 h. [b] Isolated yield after flash column chromatography. [c] Determined by HPLC analysis after flash chromatography; see the Supporting Information for details. [d] Not determind.

When this reaction was conducted in the absence of acid, no α-oxyaminated nor α-aminoxylated adducts were detected by ^{1}H NMR spectroscopy. Other Brønsted acids[14] were examined and it was found that PNBA (Table 1, entry 3) was superior in terms of both chemical yield and enantioselectivity, whereas the less acidic *p*-methoxybenzoic acid (Table 1, entry 2) provided the product in lower yield. Similarly, the more acidic chloroacetic acid provided better yield than acetic acid (Table 1, entries 4 and 5).

For comparison, other catalysts that work through steric control (Table 1, entries 6 and 7) were tested. Catalyst **8**,[7a,b] which has proven to be very effective in diverse enamine-based reactions,[8,15] did not lead to the expected adducts, whereas the α,α-dihexylprolinol silyl ether **9**[16] behaved similarly to the commercially available catalyst **7**.

Screening of other solvents for this reaction (Table 2) revealed that $CHCl_3$ and 1,2-dichloroethane were also effective. Diethyl ether and THF, or more polar solvents such as methanol and DMF, were not appropriate. In acetonitrile and toluene the yield was modest but could be improved by increasing the catalyst loading to 10 mol% (Table 2, entries 1 versus 2 and 9 versus 10).

Table 2. Solvent screening for the aminoxylation reaction of propanal (**10a**) with nitrosobenzene (**11**) promoted by catalyst **7**.[a]

Entry	Solvent	Yield of **12a**[b] [%]	*ee*[c] [%]
1	toluene	22	>99
2	toluene	67[d]	>99
3	Et_2O	10	nd[e]
4	THF	<10	nd[e]
5	$CHCl_3$	71	>99
6	CH_2Cl_2	80	>99
7	$ClCH_2CH_2Cl$	71	>99
8	MeOH	<10	nd[e]
9	CH_3CN	41	>99
10	CH_3CN	53[d]	>99
11	DMF	<10	nd[e]

[a] Reactions conducted with **10a** (3 equiv), **7** (2 mol%) and PNBA (5 mol%) at −20°C for 16 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis; see the Supporting Information for further details. [d] Reactions conducted with catalyst **7** (10 mol%) and PNBA (10 mol%). [e] Not determined.

Results obtained from the reaction of **11** with other aldehydes are shown in Table 3. The reactions were carried out by addition of the aldehyde **10a–h** (3 equiv) to a solution of the catalyst (10 mol%), PNBA (10 mol%) and **11** in dichloromethane at −20°C. The reaction was easily monitored by complete disappearance of the initial green colour. The resulting adducts were reduced in situ by treatment with sodium borohydride in ethanol to afford the aminoxylated compounds **12** as one regioisomer.[17] Both, short- and long-chain aldehydes, as well as functionalised aldehydes, are tolerated. Even the less reactive isovaleraldehyde was converted to **12e**, although afforded the expected adduct in somewhat lower yield (Table 3, entries 7 and 8). The reactions of freshly distilled hydrocinnamaldehyde with **11** conducted under these conditions, but in the absence of PNBA, afforded neither N- nor O-nitroso aldol products.[13] In general, we have employed 10 mol% of catalyst for the O-nitroso aldol reaction, although it can be reduced to 5 mol% without detriment to the yield or *ee* value (Table 3, entries 3 and 6). With the exception of propanal, the use of 2 mol% of catalyst was not effective.

Table 3. Catalytic asymmetric O-nitroso aldol reactions of aldehydes **10** with nitrosobenzene (**11**) promoted by catalyst **7**.[a]

Entry	R	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Me	**12a**	16	80[d]	>99
2	*n*Pr	**12b**	2	78	>99
3	*n*Pr	**12b**	16	71[e]	>99
4	*n*Bu	**12c**	2	81	>99
5	CH_2Ph	**12d**	5	68	>99
6	CH_2Ph	**12d**	16	68[e]	>99
7	*i*Pr	**12e**	2	55	>99
8	*i*Pr	**12e**	3	59[f]	>99
9	$BnOCH_2$	**12f**	16	45	95
10	$BocHN(CH_2)_4$	**12g**	3	88	>99
11		**12h**	4	66	>99

[a] Reactions performed on a 1 mmol scale in CH_2Cl_2 (2 mL) at −20°C with **7** (10 mol%), PNBA (10 mol%) and **10** (3 equiv). [b] Isolated yield after flash column chromatography. [c] Determined by HPLC analysis after flash chromatography; see the Supporting Information for details. [d] Reaction performed with catalyst **3** (2 mol%) and PNBA (5 mol%). [e] Reaction conducted with catalyst **7** (5 mol%). [f] Reaction performed with catalyst **7** (20 mol%) and PNBA (20 mol%).

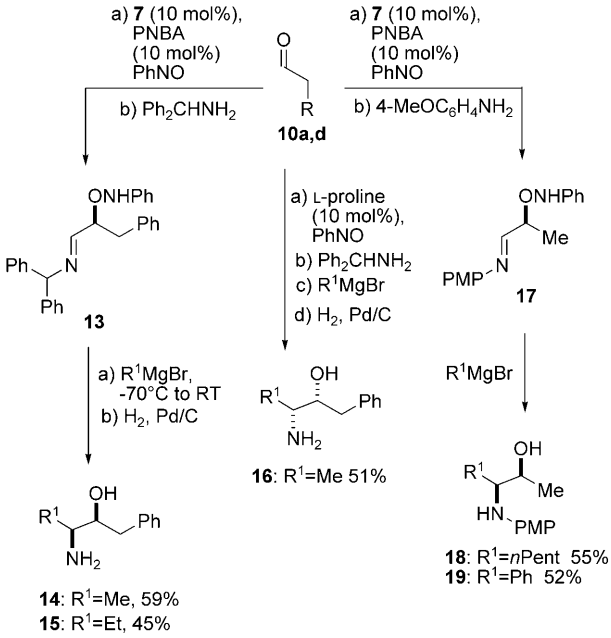
For comparison, other catalysts that work through steric control (Table 1, entries 6 and 7) were tested. Catalyst **8**,[7a,b] which has proven to be very effective in diverse enamine-based reactions,[8,15] did not lead to the expected adducts, whereas the α,α-dihexylprolinol silyl ether **9**[16] behaved similarly to the commercially available catalyst **7**.

Screening of other solvents for this reaction (Table 2) revealed that $CHCl_3$ and 1,2-dichloroethane were also effective. Diethyl ether and THF, or more polar solvents such as methanol and DMF, were not appropriate. In acetonitrile and toluene the yield was modest but could be improved by increasing the catalyst loading to 10 mol% (Table 2, entries 1 versus 2 and 9 versus 10).

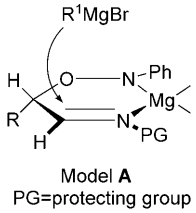
The absolute configuration of the adduct **12b** from the reaction of **10b** with **11** was determined by comparison of the value of the optical rotation of the free diol with that previously described and was found to be *S*.[5f] This approach provides (*S*)-aminoxylated aldehydes from the *S*-prolinol silyl ether **7**, thus complements the results obtained with *S*-proline and its congeners, which afford the *R* enantiomer.[18]

Synthetic applications: The α-oxyaldehyde adducts are generally unstable and must be isolated as the corresponding alcohols. Nonetheless, they may undergo reactions typical of aldehydes,[12] such as Grignard additions to produce 1,2-disubstituted diols with remarkably high diastereoselectivity.[12a] We now show that 1,2-aminoalcohols, common structural motifs in naturally occurring and synthetic molecules,[19] may also be produced with equal efficiency by Grignard addition to the corresponding imines.

As illustrated in Scheme 4, the nitroso aldol reaction from hydrocinnamaldehyde (**10d**) with catalyst **7** provided the corresponding aldehyde adduct **12d**, which could be transformed in situ to the imine **13**. At this stage, Grignard addition[20] afforded the expected adducts with concomitant partial cleavage of the phenylaminoxy group.[12a] Subsequent hydrogenation provided the expected (*S,S*)-amino alcohols **14** and **15** in good yields over four steps and, most remarkably, with essentially perfect diastereocontrol.[21] As predicted, the same sequence of reactions and the use of L-proline for the nitroso aldol addition[5b] led to the production of (*R,R*)-amino alcohol **16**. N-Aryl imines[22] can also be formed and treated with Grignard reagents. For instance, following the same sequence, the aldehyde adduct from the reaction of propanal with **11** afforded imine **17** after treatment with *p*-anisidine. Subsequent reaction with Grignard reagents provided adducts **18** and **19** in good overall yields and with diastereomeric ratios of 95:5.[23] In this case, complete deprotection of the phenylaminoxy group occurred during the Grignard addition, thus the final hydrogenation was no longer necessary and, as a result, the protocol was rendered compatible with aryl Grignard reagents. The simplified model **A** explains the observed stereochemical out-



Scheme 4. 1,2-Amino alcohols from a nitroso aldol reaction, imine formation and Grignard addition sequence.



come of the Grignard addition, although a five-membered-chelate model should not be excluded.[20]

Mechanistic insights: To firmly establish the origin of regio- and enantioselectivity in the present catalytic system, we computed the different transition states for the formation of the C–N and C–O bonds in the reaction between propionaldehyde and nitrosobenzene, promoted by catalyst **7** in the presence of hydrogen-bond donors, by density functional theory (DFT). On the basis of evidence for enamine formation,[24] we assumed that the reaction proceeds through an enamine mechanism[6,9] (rather than via an enol intermediate)[25] and that the activation of the oxygen and nitrogen atoms of **11** takes place by hydrogen bonding, with participation of two molecules of acid.[26] In each case, the activation energies were computed by the difference between the transition-state energy and the energy of the corresponding pre-transition-state complexes. After an extensive conformational search, we found that the lowest-energy transition states (**TS-N** and **TS-O**) involve the attack of **11** from the opposite face to the bulky $-C(Ph)_2OSiMe_3$ directing group (in accordance with previous observations on related enamine-based reactions).[9] Also the enamine double bond is in the *E* configuration and *anti* to the silyl group. The energy data clearly point to a hydrogen-bond reduction of the Gibbs free energy of activation ($\Delta G^{\neq}$) in the presence of PNBA, from 21.4 (absence of catalyst) to 1.3 kcal mol^{-1}. More interestingly, the N-selectivity computed in the absence of catalyst, or in the presence of the weak hydrogen-bond-donor water, is reversed to a clear O-selective addition for the acid species (benzoic acid and PNBA), see Figure 1.

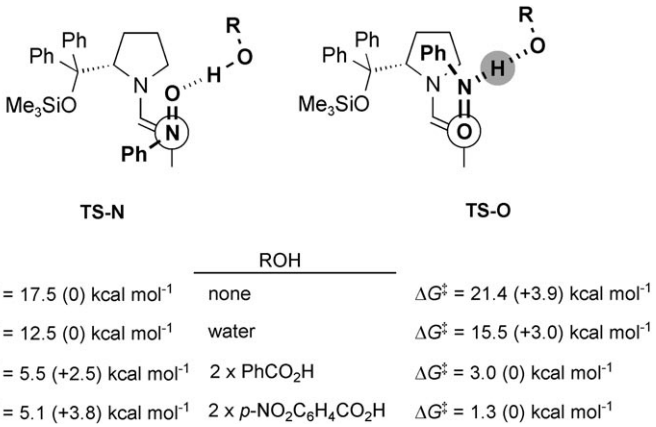


Figure 1. N- and O-selective transition states calculated at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory in the gas phase.

Conclusion

We have demonstrated that commercially available α,α-diphenylprolinol trimethylsilyl ether (**7**) in the presence of a Brønsted acid is a very effective and general catalyst for the reaction of aldehydes with nitrosobenzene to afford O-nitroso aldol adducts with both high enantio- and regioselectivity. Because *S* enantiomers are produced, this procedure complements the (*S*)-proline (**1**)-catalysed reaction, in which *R* enantiomers are formed, and provides a new entry to enantiomerically pure (*S*,*S*)- and (*R*,*R*)-1,2-aminoalcohols.

Experimental Section

General methods: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware, with efficient magnetic stirring. CH_2Cl_2 was distilled from CaH_2. Toluene, THF and Et_2O were dried in the presence of sodium metal. Reagent grade methanol, ethyl acetate and DMF were used. Purification of reaction products was carried out by flash column chromatography on silica gel 60 (0.040–0.063 mm, 230–400 mesh). Analytical TLC was performed on 0.25 mm silica gel 60-F plates. Visualisation was accomplished with UV light and by dipping the developed plate into a solution of cerium ammonium molybdate (ammonium molybdate (21 g), cerium sulfate (1 g), concentrated sulfuric acid (31 mL), water (470 mL)), followed by heating. Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance-500 (or 300) spectrometer and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane (TMS). Analytical HPLC was performed on Waters-600E, Waters-2996 and Hewlett–Packard series 1050 chromatographs equipped with diode array UV detectors and Daicel Chiralpak AD-H and OD-H columns. Optical rotations were recorded on a Jasco P-2000 polarimeter. MS spectra were recorded on an ESI ion-trap mass spectrometer (Agilent 1100 series LC/MSD, SL model). Prolinol trimethylsilyl ether catalysts **7** and **8** were purchased from Aldrich and used without further purification. Catalyst **9** was prepared by a previously described procedure.[15]

General procedure for the aminoxylation reaction: Nitrosobenzene (1 mmol, 1 equiv) and the freshly distilled aldehyde[27] (3 mmol, 3 equiv) were successively added to a solution of the catalyst (0.1 mmol, 10 mol%) and PNBA (0.1 mmol, 10 mol%) in CH_2Cl_2 (2 mL) at −20°C. The resulting green solution was stirred at −20°C until the colour turned yellow. EtOH (2 mL) and $NaBH_4$ (8 mmol) were added successively at −20°C. After stirring for 30 min, the reaction was quenched with a saturated aqueous solution of NaCl (3 mL) and allowed to reach room temperature. After extraction with CH_2Cl_2 (3×4 mL), the combined organic phases were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford the expected adducts. The regioselectivity of the process was determined by ^1H NMR spectroscopy analysis of the crude products and was found to be >99:1 in all cases.

*(S)-2-(Phenylaminooxy)propan-1-ol (**12a**)*: Prepared according to the general procedure from propanal (0.22 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20) to give **12a** as a yellow oil (80%, 133 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 90:10, flow rate = 1 mL min^{-1}; retention times: 14.5 min (major), 20.1 min (minor)). $[\alpha]_D^{25} = -1.1$ ($c = 1$, $CHCl_3$).

*(S)-2-(Phenylaminooxy)pentan-1-ol (**12b**)*: Prepared according to the general procedure from pentanal (0.32 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 85:15) to give **12b** as a yellow oil (78%, 152 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 95:5, flow rate = 0.8 mL min^{-1}; retention times: 20.5 min (major), 24.5 min (minor)). $[\alpha]_D^{25} = -24.8$ ($c = 0.9$, $CHCl_3$).

*(S)-2-(Phenylaminooxy)hexan-1-ol (**12c**)*: Prepared according to the general procedure from hexanal (0.36 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 85:15) to give **12c** as a yellow oil (81%, 169 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95:5, flow rate = 0.8 mL min^{-1}; retention times: 19.3 min (major) and 24.6 min (minor)). $[\alpha]_D^{25} = -21.1$ ($c = 1$, $CHCl_3$).

*(S)-3-Phenyl-2-(phenylaminooxy)propan-1-ol (**12d**)*: Prepared according to the general procedure from hydrocinnamaldehyde (0.39 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 85:15) to give **12d** as an orange oil (68%, 164 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 95:5, flow rate = 0.8 mL min^{-1}; retention times: 40.1 min (major) and 54.8 min (minor)). $[\alpha]_D^{25} = -43.1$ ($c = 1$, $CHCl_3$).

*(S)-3-Methyl-2-(phenylaminooxy)butan-1-ol (**12e**)*: Prepared according to the general procedure from isovaleraldehyde (0.32 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 85:15) to give **12e** as a yellow oil (56%, 109 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95:5, flow rate = 0.8 mL min^{-1}; retention times: 13.9 min (major) and 16.1 min (minor)). $[\alpha]_D^{25} = -32.6$ ($c = 1$, $CHCl_3$).

*(R)-3-(Benzyloxy)-2-(phenylaminooxy)propan-1-ol (**12f**)*: Prepared according to the general procedure from 3-(benzyloxy)propanal (0.48 mL, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20) to give **12f** as an orange oil (45%, 122 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[5a] The enantiomeric excess (95%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95:5, flow rate = 1 mL min^{-1}; retention times: 55.8 min (major) and 64.0 min (minor)). $[\alpha]_D^{25} = +7.2$ ($c = 1$, $CHCl_3$).

*(S)-tert-Butyl-6-hydroxy-5-(phenylaminooxy)hexylcarbamate (**12g**)*: Prepared according to the general procedure from 6-(*tert*-butoxycarbonylamino)-1-hexanal (645 mg, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 60:40) to give **12g** as an orange oil (88%, 306 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[28] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 92:8, flow rate = 1 mL min^{-1}; retention times: 26.5 min (minor) and 30.3 min (major)). $[\alpha]_D^{25} = -8.4$ ($c = 1$, $CHCl_3$).

*(S)-2-(Phenylaminooxy)hex-5-en-1-ol (**12h**)*: Prepared according to the general procedure from hexen-5-al (294 mg, 3 mmol). The crude material was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20) to give **12h** as a yellow oil (66%, 134 mg). Spectroscopic data are in agreement with published data for the *R* enantiomer.[28] The enantiomeric excess (>99%) was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 94:6, flow rate = 1 mL min^{-1}; retention times: 15.8 min (major) and 19.5 min (minor)). $[\alpha]_D^{25} = -1.4$ ($c = 1$, $CHCl_3$).

General procedure for the preparation of 1,2-amino alcohols: Method A: Nitrosobenzene (1 mmol, 1 equiv) and aldehyde (3 mmol, 3 equiv) were added successively to a solution of the catalyst (0.1 mmol, 10 mol%) and PNBA (0.1 mmol, 10 mol%) in CH_2Cl_2 (2 mL) at −20°C. The resulting green solution was stirred at −20°C until the colour turned yellow. Anhydrous $MgSO_4$ (0.250 g) and benzhydryl amine (3 mmol, 3 equiv) were added to this solution. The reaction was allowed to reach 0°C and the mixture was stirred at this temperature for 2 h before the solution was filtered and the solvent evaporated. The residue was dissolved in THF (2 mL) and the solution was cooled to −60°C. The corresponding Grignard reagent (3 M in diethyl ether, 15 mmol, 15 equiv) was added dropwise at this temperature; the mixture was allowed to reach room temperature and was stirred overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), extracted with ethyl acetate (2×15 mL), washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel and then hydrogenated in EtOH (2 mL mmol^{-1}) over Pd/C (20% w/w) for 48 h at atmospheric pressure. The mixture was filtered through Celite, evaporated and purified by an acid–base workup. This yielded the expected 1,2-aminoalcohols as almost single diastereomers.

General method B: Nitrosobenzene (1 mmol, 1 equiv) and aldehyde (3 mmol, 3 equiv) were added successively to L-proline (0.1 mmol, 10 mol%) in $CHCl_3$ (1 mL) at 0°C and the resulting green solution was stirred at 0°C until the colour turned yellow. The solution was then concentrated and CH_2Cl_2 (2 mL), anhydrous $MgSO_4$ (0.250 g) and benzhydryl amine (3 mmol, 3 equiv) were added. The reaction was stirred at 0°C for 2 h before the solution was filtered and evaporated. The residue was dissolved in THF (2 mL) and cooled to −60°C. The corresponding Grignard reagent (3 M in diethyl ether, 15 mmol, 15 equiv) was added dropwise at this temperature, the mixture was allowed to reach room temperature and was stirred overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), extracted with ethyl acetate (2×15 mL), washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel and then hydrogenated in EtOH (2 mL mmol^{-1}) over Pd/C (20% w/w) for 48 h at atmospheric pressure. The mixture was filtered through Celite, evaporated and purified by an acid–base workup. This yielded the expected 1,2-aminoalcohols as almost single diastereomers.

General method C: Nitrosobenzene (1 mmol, 1 equiv) and aldehyde (3 mmol, 3 equiv) were added successively to a solution of the catalyst (0.1 mmol, 10 mol%) and PNBA (0.1 mmol, 10 mol%) in CH_2Cl_2 (2 mL) at −20°C and the resulting green solution was stirred at −20°C until the colour turned yellow. Anhydrous $MgSO_4$ (0.250 g) and *p*-anisidine (3 mmol, 3 equiv) were added to this solution. The reaction was allowed to reach 0°C and the mixture was stirred at this temperature for 2 h before the solution was filtered and evaporated. The residue was dissolved in THF (2 mL) and cooled to −60°C. The corresponding Grignard reagent (3 M in diethyl ether, 15 mmol, 15 equiv) was added dropwise at this temperature and the solution was allowed to reach room temperature and stirred overnight. The reaction was quenched with a saturated

aqueous solution of NH_4Cl (10 mL), extracted with ethyl acetate (2× 15 mL), washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel.

*(2S, 3S)-3-Amino-1-phenylbutan-2-ol (**14**)*: Prepared according to the general method A from hydrocinnamaldehyde (0.39 mL, 3 mmol) and methyl magnesium bromide. Compound **14** was obtained as an orange oil (60%, 90 mg). Spectroscopic data are in agreement with published data.[28] $[\alpha]_D^{25} = -17.8$ ($c = 0.5$, CH_2Cl_2).

*(2S, 3S)-3-Amino-1-phenylpentan-2-ol (**15**)*: Prepared according to the general method A from hydrocinnamaldehyde (0.39 mL, 3 mmol) and ethyl magnesium bromide. Compound **15** was isolated as an orange oil (45%, 74 mg). $[\alpha]_D^{25} = -20.6$ ($c = 0.5$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.5$ Hz, 3H), 1.72–1.40 (m, 2H), 1.72–1.56 (m, 1H), 2.71–2.60 (m, 1H), 2.91–2.75 (m, 2H), 3.74–3.62 (m, 1H), 4.99 (s, 2H), 7.37–7.16 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 10.0$, 24.5, 40.2, 57.2, 73.3, 126.4, 128.4, 129.5, 138.2 ppm.

*(2R, 3R)-3-Amino-1-phenylbutan-2-ol (**16**)*: Prepared according to the general method B from hydrocinnamaldehyde (0.39 mL, 3 mmol) and methyl magnesium bromide. Compound **16** was isolated as an orange oil (51%, 77 mg). Spectroscopic data are in agreement with published data.[28] $[\alpha]_D^{25} = +20.0$ ($c = 0.5$, CH_2Cl_2).

*(2S, 3S)-3-(4-Methoxyphenylamino)octan-2-ol (**18**)*: Prepared according to the general method C from propionaldehyde (0.22 mL, 3 mmol) and pentyl magnesium bromide. Compound **18** was obtained as an orange oil (55%, *syn*/*anti* 95:5, 155 mg). $[\alpha]_D^{25}$ (95:5 *syn*/*anti* non-separable mixture) = +6.8 ($c = 1$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, major *syn* diastereomer): $\delta = 0.93$–0.80 (m, 5H), 1.49–1.74 (m, 10H), 3.15–4.04 (m, 1H), 3.76–3.65 (m, 2H), 3.78 (s, 3H), 6.67 (d, $J = 9.0$ Hz, 2H), 6.80 ppm (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, major *syn* diastereomer): $\delta = 14.0$, 19.9, 22.5, 25.6, 32.0, 32.3, 55.8, 61.8, 69.7, 115.0, 115.3, 128.7, 142.8, 152.6 ppm.

*(1S,2S)-1-(4-Methoxyphenylamino)-1-phenylpropan-2-ol (**19**)*: Prepared according to the general method C from propionaldehyde (0.22 mL, 3 mmol) and phenyl magnesium bromide. Compound **19** was obtained as an orange oil (52%, *syn*/*anti* 94:6, 134 mg). $[\alpha]_D^{25}$(94:6 *syn*/*anti* non-separable mixture) = +8.2 ($c = 1$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, major *syn* diastereomer): $\delta = 1.25$ (d, $J = 6.3$ Hz, 3H), 3.73 (s, 3H), 3.99 (m, 1H), 4.14 (d, $J = 6.3$ Hz, 1H), 6.59 (d, $J = 8.9$ Hz, 2H), 6.74 (d, $J = 8.9$ Hz, 2H), 7.40–7.26 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, major *syn* diastereomer): $\delta = 20.0$, 55.7, 66.1, 71.7, 114.8, 115.6, 127.1, 127.5, 128.7, 141.3, 141.5, 152.5 ppm.

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