The Direct Catalytic Asymmetricα-Aminooxylation Reaction: Development of Stereoselective Routes to 1,2-Diols and 1,2-Amino Alcohols and Density Functional Calculations

ARTICLE *in* CHEMISTRY · AUGUST 2004

Impact Factor: 5.73 · DOI: 10.1002/chem.200400137 · Source: PubMed

The Direct Catalytic Asymmetric α-Aminooxylation Reaction: Development of Stereoselective Routes to 1,2-Diols and 1,2-Amino Alcohols and Density Functional Calculations

Armando Córdova,*[a] Henrik Sundén,[a] Anders Bøgevig,[a] Mikael Johansson,[a] and Fahmi Himo[b]

Abstract: Proline-catalyzed direct asymmetric α-aminooxylation of ketones and aldehydes is described. The proline-catalyzed reactions between unmodified ketones or aldehydes and nitrosobenzene proceeded with excellent diastereo- and enantioselectivities. In all cases tested, the corresponding products were isolated with >95% *ee*s. Methyl alkyl ketones were regiospecifically oxidized at the methylene carbon atom to afford enantiomerically pure α-aminooxylated ketones. In addition, cyclic ketones could be α,α′-dioxidized with remarkably high selectivity, furnishing the corresponding diaminooxylated ketones with >99% *ee*s. The reaction mechanism of the proline-catalyzed direct asymmetric α-aminooxylation was investigated, and we performed density functional theory (DFT) calculations in order to investigate the nature of the plausible transition states further. We also screened other organocatalysts for the asymmetric α-oxidation reaction and found that several proline derivatives were also able to catalyze the transformation with excellent enantioselectivities. Moreover, stereoselective routes for the synthesis of monoprotected vicinal diols and hydroxyketones were found. In addition, short routes for the direct preparation of enantiomerically pure epoxides and 1,2-amino alcohols are presented. The direct catalytic α-oxidation is also a novel route for the stereoselective preparation of β-adrenoreceptor antagonists.

Keywords: aminooxylations · asymmetric catalysis · density functional calculations · proline

Introduction

One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of functionalized optically active molecules displaying structural diversity from simple and easily available starting materials. During the last two decades, the synthesis of enantiomerically pure or enriched compounds has thus emerged as one of the most important fields in organic synthesis. Several procedures to generate optically active molecules are known and among these, asymmetric catalysis is a highly active research field.[1]

[a] Prof. Dr. A. Córdova, H. Sundén, Dr. A. Bøgevig, M. Johansson
Department of Organic Chemistry
The Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 815-4908
E-mail: acordova@organ.su.se
acordova1a@netscape.net

[b] Prof. Dr. F. Himo
Department of Theoretical Chemistry
The Royal Institute of Technology
Albanova, 106 91 Stockholm (Sweden)

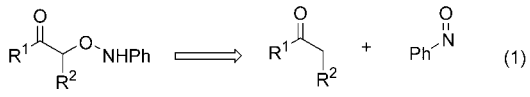
Optically active α-hydroxy carbonyl moieties are commonly found in numerous important natural products and are highly versatile functional synthons. This has led to extensive research into finding new diastereoselective and enantioselective routes for their syntheses.[2] One way of preparing these compounds is asymmetric α-hydroxylation of enolates.[3] In addition, nucleophilic additions to chiral glyoxal derivatives and chiral hydrazones have also been successfully employed.[2b,c,4] However, these methods are indirect and most of them require multiple manipulations for the desired α-hydroxy product to be obtained. Despite the extensive research in this area, it was not until recently that Yamamoto and co-workers reported a more efficient catalytic system based on AgX/binap complexes (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), which mediate indirect α-oxidation of activated tin enolates.[5] The method was further developed into a one-pot synthesis of α-hydroxy ketones with high enantioselectivity.

Asymmetric reactions catalyzed by metal-free organic catalysts have experienced a renaissance in recent years.[6] Interestingly, since the discovery of amino acid catalyzed stereoselective Robinson annulations in the early 1970s,[7] there was no intensive research on this concept for other C–C

 DOI: 10.1002/chem.200400137

bond-forming reactions for several decades, even though the reaction is frequently used in the preparation of building blocks for the total synthesis of natural products.[8] It was not until recently that researchers demonstrated that amino acid derivatives function as catalysts for direct asymmetric intermolecular reactions.[9–19]

From the elegant work of Yamamoto and co-workers and our own previous research on direct amine-catalyzed asymmetric synthesis we saw potential for an amino acid to catalyze α-aminooxylation of unmodified ketones and aldehydes [Eq. (1)].[9d,f,g,11d–11k,12a,20]



(1)

We thus embarked on the quest to develop a novel enamine-catalyzed asymmetric route for the synthesis of α-hydroxy-containing molecules. We have recently disclosed the first direct catalytic α-oxidation of ketones, yielding protected α-hydroxy ketones with excellent regioselectivity and >99% *ee*.[21] In this paper, we describe our findings, including the scope, mechanism, and applications of the highly stereoselective α-aminooxylation of unmodified ketones and aldehydes.

Results and Discussion

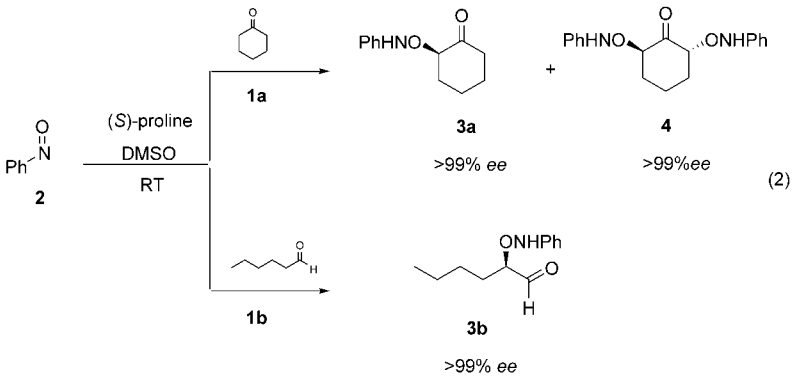
There are only a few reports of indirect reactions with silyl enol ethers as nucleophiles and nitrosoaromatic compounds as electrophiles.[22] Most of these reactions furnish the corresponding α-hydroxy amino adducts with excellent N-addition chemoselectivity. However, Momiyama and Yamamoto recently demonstrated that the chemoselectivity of the reaction with nitrosobenzene could be switched from N- to O-addition by performing the transformation in the presence of a catalytic amount of a Lewis acid.[23] They also expanded this concept to a catalytic asymmetric system mediated by AgX/binap complexes; this affords α-aminooxylated ketones with high chemo- and enantioselectivities.[5]

During our preliminary investigations of direct proline-catalyzed asymmetric Mannich and aldol reactions with unmodified ketones and aldehydes we realized the potential of utilizing this catalytic system for other stereoselective reactions.[9d,f,i,11d–11k] The basis of the catalytic cycle would be the ability of a cyclic five-membered secondary amine to form a chiral enamine and to perform a subsequent nucleophilic attack on an electrophile in a highly enantioselective fashion. Previous studies by Yamamoto and co-workers had made us interested in whether enamine catalysis could be applied in reactions with nitrosoaryl compounds.[5,23] In addition, we believed that the ability of the amino acid to act as a Brønstedt base should favor O- over N-addition.[5,23]

In an initial experiment, we treated cyclohexanone **1a** (10 mmol) with nitrosobenzene **2** (1 mmol) in the presence of a catalytic amount of (*S*)-proline (20 mol%) in DMSO (4 mL) at room temperature [Eq. (2)].

The initial light blue solution went from light green to dark green, and finally became orange within 30 minutes. The reaction was found to be complete, providing not only ketone **3a** in 70% yield and >99% *ee*, but also the corresponding C_2-symmetric α,α′-diaminooxylated ketone **4a** in 22% yield and >99% *ee*.

In parallel with this experiment, we also treated hexanal **1b** (2 mmol) with **2** (1 mmol) in the presence of a catalytic amount of (*S*)-proline (20 mol%), obtaining the corresponding α-substituted aldehyde **3b** in 61% yield with >99% *ee*. The aldehyde adduct **3b** was oligomeric in solution and less stabile than **3a** during workup and storage. We therefore decided to reduce **3b** in situ with excess $NaBH_4$ to give the corresponding more stable monoprotected terminal diol prior to workup and purification.

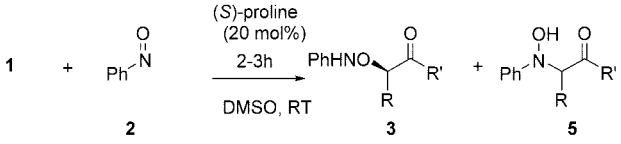


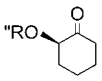
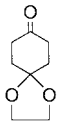
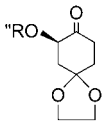
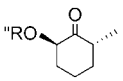
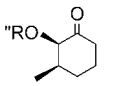
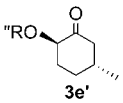
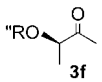
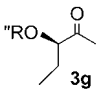
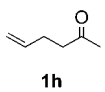
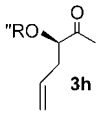
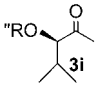
(2)

Donor component: Delighted over these results, we decided to test the reaction for different ketones and aldehydes (Tables 1 and 2). A set of different carbonyl donors was therefore treated just by stirring and mixing of the donor and nitrosobenzene in the presence of a catalytic amount of (*S*)- or (*R*)-proline in DMSO. Table 1 presents direct catalytic asymmetric α-oxidations of ketones **1a** and **1c–i**. The reactions proceeded smoothly, affording the corresponding α-aminooxylated ketones **3a** and **3c–i** in good yields and with >99% *ee*s. In addition, excellent regioselectivities were observed for α-aminooxylation of acyclic ketones, and no doubly α,α′-diaminooxylated ketones were observed. The oxidation occurred exclusively on the methylene carbons of the ketones; protected hydroxy ketone **3f**, for example, was isolated as a single regioisomer in 70% yield and with >99% *ee*. With regards to the O- or N-selectivity of the reaction, we found that the reaction was chemoselective, furnishing no N-addition products for transformations with cyclohexanones as donors.

α-Oxidation of acyclic ketones, however, afforded small amounts (<25%) of the corresponding 2-amino ketones **5** with the same regioselectivity as the O-addition adducts and

Table 1. Proline-catalyzed direct asymmetric α-aminooxylation of unmodified ketones.[a]

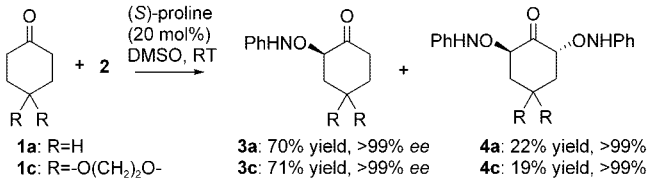


Entry	Donor	Product	Yield [%][b]	3:5	*ee* [%] of **3**[c]	*ee* [%] of **5**[c]
1	 **1a**	 **3a**	70 (99)[d]	>100:1 (100:1)[d]	>99 (>99)[d]	
2	 **1c**	 **3c**	71 (94)[d]	>100:1 (100:1)[d]	>99 (>99)[d]	
3	 **1d**	 **3d**	66 (82)[d]	>100:1 (100:1)[d]	>99 (>99)[d]	
4	 **1e**	 **3e**  **3e'**	68 (88)[d]	>100:1 (100:1)[d] >100:1 (100:1)[d]	>99 (>99)[d] >99 (>99)[d]	
5	 **1f**	 **3f**	93	81:19	>99	11
6	 **1g**	 **3g**	66	98:2	99	7
7	 **1h**	 **3h**	87	78:22	>99	<5
8	 **1i**	 **3i**	64	90:10	>99	<5

[a] Method A: A mixture of **1** (10 mmol, 10 equiv), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 2–3 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Isolated combined yield of **3** and **5** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses. [d] Method B: A mixture of **2** (1 mmol) was added by syringe pump to a vial containing **1** (2 mmol, 2 equiv) and (*S*)-proline and the reaction mixture was stirred at room temperature for 2–8 h. The crude product obtained after aqueous workup was purified by column chromatography.

with a minor chiral induction. Furthermore, the sterically hindered racemic 2-methylcyclohexanone (**1d**) was also efficiently α-aminooxylated, providing the corresponding keto adduct **3d** as a 3:1 (*trans*/*cis*) diastereomeric mixture in >99% *ee* (Table 1, entry 3). In this case, excellent O-selectivity was observed, since no N-addition product was formed. The proline-catalyzed α-oxidation reaction between (3*R*)-methylcyclohexanone (**1e**) and **2** furnished the two regiomers **3e** and **3e′** as a 1:1 mixture of regioisomers in 68% combined yield and each with >99% *ee*. NMR analyses of **3e** revealed a *cis* relationship between the substituents. Hence, **3e** had a (2*R*,3*R*) absolute configuration of the 2-oxyaminophenyl group and methyl group, respectively. We also performed the reaction with racemic 3-methylcyclohexanone as the donor (vide infra), to obtain regiomers **3e** and **3e′** with >99% *ee*. Interestingly, (3*R*,2*R*)-3-methyl-2-(*N*-phenylaminoxy) (**3e**) was formed exclusively as determined by HPLC and NMR analyses. (*S*)-Proline thus reacted more rapidly with (3*R*)- and (2*R*)-methylcyclohexanone than with (3*S*)- and (2*S*)-methylcyclohexanone, respectively. In addition to α- ketones **3**, the reactions between cyclohexanones with two α-methylene carbons and **2** provided the corresponding C_2-symmetric α,α′-diketones **4**, each as a single diastereomer with >99% *ee* (Scheme 1).

For example, the protected dihydroxy ketone **4c** was isolated in 19% yield and with >99% *ee*. These types of enantiomerically pure ketones are generally prepared in six steps in overall yields of 15–20% and are useful synthetic building blocks in natural product chemistry.[24] The second O-addition exhibited remarkable high selectivity, since no *meso*-diadduct was detected either by NMR or by HPLC analyses during the progress of the reaction. This is the first time that this type of double stereoselective nucleophilic attack onto an electrophile has been reported in a proline-catalyzed reaction; this indicates that nitrosobenzene is more reactive and/or provides less steric hindrance than other electrophiles such as diazocarboxylates or α-iminoglyoxylates.[12c,11d] We also investigated the possibility of increasing the yield of **3** by slow addition of electrophile **2** to the reaction mixture by syringe pump. We believed that this

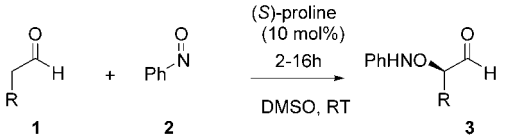


Scheme 1. Direct catalytic asymmetric synthesis of mono- and diprotected hydroxy ketones.

procedure should reduce the formation of the dioxidized adducts **4** and dimerization of **2**. Indeed, this method significantly increased the yield of the α-aminooxylated ketones **3** and allowed for the employment of only two equivalents of the donor. For example, ketone **3a** was isolated in 99% yield with >99% *ee*. In addition, we were able to increase the yield of **4** by subsequent addition of the electrophile **2** by syringe pump to the **3** obtained from the first addition. The yields of **4a** and **4c**, for example, were improved to 30 and 25%, respectively, by this process.

Table 2 shows the results of α-oxidations of different unmodified aldehydes in DMSO. The reactions proceeded smoothly, affording the corresponding adducts **3b** and **3j–s**

Table 2. Proline-catalyzed direct asymmetric α-aminooxylation of unmodified aldehydes.[a]

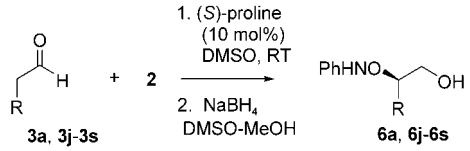


Entry	R	Product	Yield[%][b]	*ee* [%] of **3**[c]
1	*n*Bu	**3b**	78	>99
2	Et	**3j**	75	>99
3	Me	**3k**	79	>99
4	*n*-pentane	**3l**	74	>99
5	CH_2OBn	**3m**	76	>99
6	*i*Pr	**3n**	74	>99
7	$CH_2CH{=}CH_2$	**3o**	79	>99
8	CH_2Ph	**3p**	77	>99
9	*n*-hexane	**3q**	76	>99
10	*cis*-$CH_2CH{=}CH(CH_2)_5CH_3$	**3r**	78	>99
11	*cis*-$(CH_2)_4CH{=}CHCH_2)CH_3$	**3s**	77	>99

[a] Experimental procedure: a mixture of **1** (2 mmol, 2 equiv), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 2–3 h and the aldehyde products **3** were reduced in situ to the corresponding alcohols. The crude products obtained after aqueous workup were purified by column chromatography. [b] Isolated yield of the corresponding alcohol after silica gel column chromatography. [c] The enantiomeric excesses were determined by chiral-phase HPLC analyses of the corresponding alcohol adducts.

with >99% *ee*s. The α-aminooxylated aldehyde adducts are important synthons, and the mild reaction conditions allowed for a variety of aldehydes with functional groups to be used. For example, aldehyde adduct **3r** is a key intermediate in the syntheses of leukotrienes and isoprostanes.[25] The aldehydes were reduced in situ, yielding the corresponding more stable monoprotected terminal diols **6b** and **6j–s** without loss of stereoselectivity (Scheme 2).

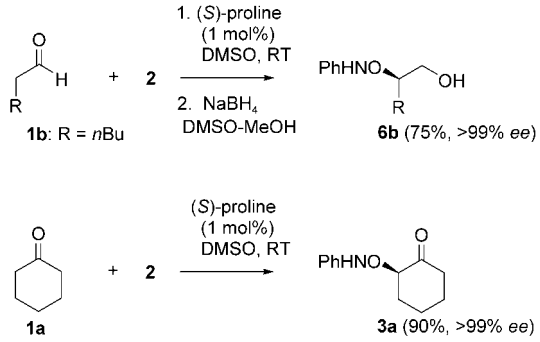
The unsaturated diols **6o**, **6r**, and **6s**, for instance, were isolated in 79, 78, and 77% yields, respectively, each with



Scheme 2. One-pot catalytic asymmetric synthesis of monoprotected terminal diols.

>99% *ee*. The α-oxidation of unsaturated aldehydes can thus be regarded as a chemo- and regioselective route for the asymmetric dihydroxylation of olefins.[26] Moreover, direct catalytic asymmetric α-aminooxylation was also an efficient route for the synthesis of orthogonally protected triols (Table 2, entry 5). The reactions with unmodified aldehydes were highly chemoselective, and only O-addition was observed. Moreover, the increased reactivity of the aldehyde donors in relation to the acyclic ketones allowed us to employ only 1.5 equivalents of the aldehyde donor without the need for slow addition of the electrophile to the reaction mixture.

The direct catalytic asymmetric α-oxidation reactions with ketones and aldehydes were readily performed on multigram scales in the presence of air. The catalyst loading could be decreased to as little as 1 mol% without affecting the yield or enantioselectivity of the α-aminooxylation of unmodified aldehydes and cyclohexanones (Scheme 3).



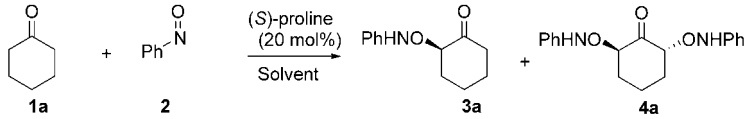
Scheme 3. Direct catalytic asymmetric α-aminooxylation reactions with 1 mol% (*S*)-proline.

In addition, the progress of the reaction could be simply monitored by the human eye, since the reaction mixture switches color from light blue to green and finally to orange, which indicates that the reaction has been completed.

Solvent: We also performed a solvent screen of the direct catalytic asymmetric α-aminooxylation of ketone **1a** and aldehyde **1b**. Proline-catalyzed direct asymmetric α-aminooxylations between **1a** and **2** were successful in all solvents tested, affording **3a** with excellent enantioselectivity (Table 3).

The highest reactivity was observed in DMSO, followed by $CHCl_3$, CH_3CN, DMF, and *N*-methylpyrrolidone (NMP). Interestingly, the formation of **4a** was solvent-dependent. For example, the reaction in $CHCl_3$ only afforded **3a**, which was isolated in 91% yield with >99% *ee*. However, **4a** was formed in DMSO, DMF, NMP, and CH_3CN. In addition, the direct catalytic α-aminooxylation of acyclic ketones only provided insignificant amounts of adducts **3** in $CHCl_3$. Notably, slow addition of the electrophile **2** to the reaction mixture by syringe pump significantly increased the yield of **3**, which was isolated in 99% yield and >99% *ee* in DMF, CH_3CN, and DMSO. Furthermore, the reaction could tolerate up to 10% water without its yield and *ee* being affected (Table 3, entry 11).

Table 3. Solvent screen of the proline-catalyzed α-aminooxylation of unmodified ketones.[a]



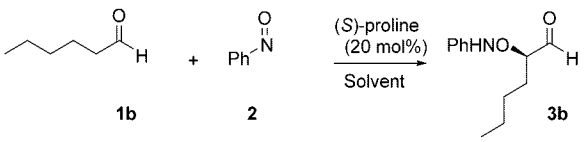
1a 2 3a 4a

Entry	Solvent	t [h]	T [°C]	Yield [%][b]	**3**:**4**	*ee* [%] of **3**[c]	*ee* [%] of **4**[c]
1	DMSO	3	RT	92	3:1	>99	>99
2	DMSO	5	RT	99[d]	>20:1[d]	>99[d]	n.d.[d]
3	DMF	8	RT	68	10:1	>99	>99
4	DMF	16	4	99[d]	>20:1[d]	>99[d]	n.d.[d]
5	CH_3CN	6	RT	66	19:1	>99	n.d.
6	$CHCl_3$	5	RT	91	>20:1	>99	n.d.
7	NMP	8	RT	65	10:1	>99	>99
8	THF	16	RT	45	>20:1	99	n.d.
9	dioxane	16	RT	41	>20:1	99	n.d.
10	Et_2O	17	RT	25	>20:1	99	n.d.
11	DMSO/H_2O 9:1	3	RT	91	3:1	>99	>99

[a] Reaction conditions: see Method A in the Experimental. [b] Isolated combined yield of **3a** and **4a** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses. [d] Reactions performed according to Method B in the Experimental Section.

The solvent screen of the reaction with hexanal revealed that the best solvents for obtaining **3b** with high enantioselectivity were DMSO, DMF, CH_3CN, and $CHCl_3$ (Table 4). In particular, the reactions in DMSO and DMF proceeded

Table 4. Solvent screen of the proline-catalyzed α-aminooxylation of unmodified aldehydes.[a]

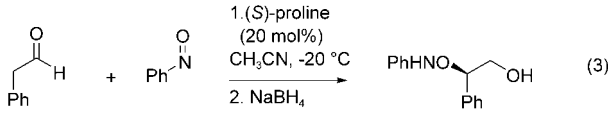


1b 2 3b

Entry	Solvent	t [h]	T [°C]	Yield [%][b]	*ee* [%] of **3b**[c]
1	DMSO	17	RT	92	>99
2	DMSO	0.7	RT	64	>99
3	DMF	16	RT	70	>99
4	CH_3CN	17	RT	24	99
5	CH_3CN	2h	4	42	97
6	CH_3CN	16	4	50	93
7	CH_3CN	24	−20	86	95
8	$CHCl_3$	0.7	4	64	93
9	$CHCl_3$	17	RT	40	97
10	$CHCl_3$	16	4	48	96
11	dioxane	17	RT	traces	n.d.

[a] Reaction conditions: See Experimental Section. [b] Isolated combined yield of the corresponding alcohol **6b** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses of the corresponding alcohol **6b**.

with almost absolute stereocontrol. The enantioselectivity of the α-aminooxylation of **1b** was slightly lower in other solvents, in which **3b** was furnished with 93–99% *ee*s. The enantioselectivity of the direct α-aminooxylation of aldehydes was thus affected slightly by the solvent used as compared to the α-aminooxylation of unmodified ketones. Interestingly, the best solvent for α-aminooxylation of 2-substituted acetaldehydes was CH_3CN. The proline-catalyzed asymmetric α-aminooxylation of 2-phenylacetaldehyde (**1t**) with **2** at −20°C, for example, furnished the corresponding alcohol **6t** after in situ reduction with $NaBH_4$ in 79% yield with an *ee* of 99% [Eq. (3)].



(3)

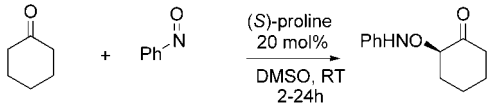
1t 2 **6t**: 79% yield, 99% *ee*

Catalyst: We also screened different organic amines as potential catalysts for the direct asymmetric α-aminooxylation reaction (Table 5). Of the limited number of catalysts screened, proline and hydroxyproline derivatives provided enantiomerically pure **3a**. In addition, all the successful catalysts afforded product **3a** with the same absolute configuration, as determined by optical rotation and chiral HPLC analyses. Ether- and amine-functionalized pyrrolidine derivatives provided **3a** in trace amounts, establishing the importance of the carboxyl group and its acidic proton. Interestingly, pipecolinic acid was not a catalyst for the reaction, confirming the significance of the cyclic five-membered secondary amine structural motif for achievement of high enantioselectivity. Similar observations have also been made in amine-catalyzed direct asymmetric aldol and Mannich reactions.[9a,b,11f]

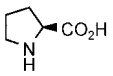
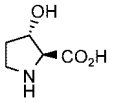
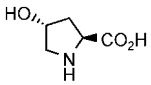
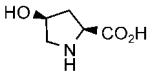
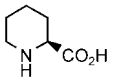
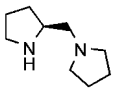
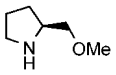
Stereoselective synthesis of chiral synthons: The α-aminooxylated aldehydes and ketones are valuable synthetic intermediates. For instance, we developed an efficient synthesis of vicinal diols (Scheme 4).

Hence, monoprotected diols **6** were derived through one-pot sequential catalytic asymmetric α-aminooxylation–reduction reactions of the unmodified aldehydes and ketones. Subsequent removal of the aniline by hydrogenolysis (PtO_2 Adams' catalyst, H_2) or with a catalytic amount of $CuSO_4 \cdot 5H_2O$ furnished the corresponding enantiomerically pure diols **7**. For example, enantiomerically pure diol (−)-**7n** was isolated from the (*R*)-proline-catalyzed reaction between isovaleraldehyde and **2** in 73% yield, over two steps (Scheme 4a). Determination of the optical rotation and comparison to the literature revealed that the direct catalytic asymmetric α-aminooxylations of aldehydes catalyzed by (*S*)-proline and by (*R*)-proline afforded (2*R*)-1,2-diols and (2*S*)-1,2-diols, respectively.[27] The catalytic asymmetric α-aminooxylation–reduction sequence was also investigated with unmodified **1a** as the donor. Hence, (*S*)-proline-derived α-amino hydroxy ketone **3a** was readily reduced in situ with $NaBH_4$ to the corresponding monoprotected diol **6a**, which was isolated in 88% yield, over the two steps, with a *dr* of 2:1 (*trans*/*cis*) and >99% *ee* (Scheme 4b). Removal of the aniline with Adams' catalyst and H_2 or catalytic $CuSO_4$ fur-

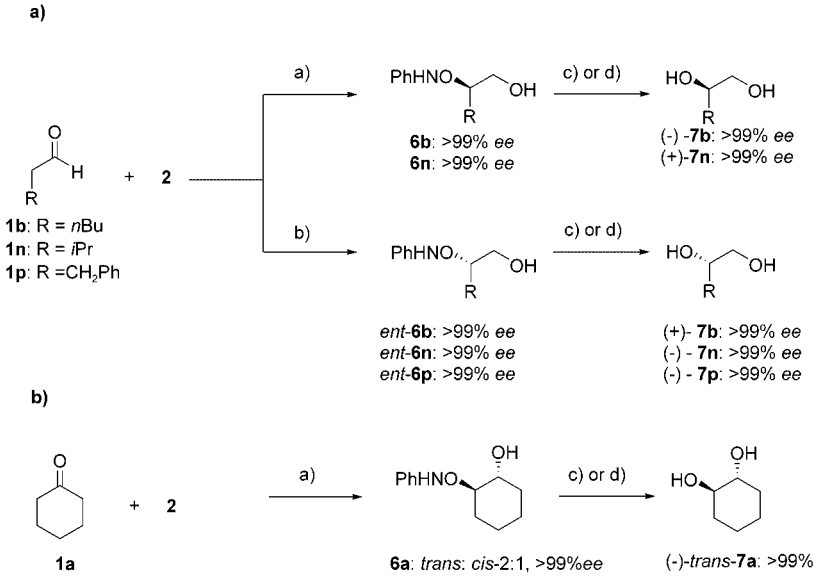
Table 5. Catalyst screen.[a]



1a 2 3a

Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1		70	>99
2		64	>99
3		66	>99
3		67	>99
4		trace	n.d.
6		trace	n.d.
7		trace	n.d.

[a] Reaction conditions: see Method A in the Experimental. [b] Isolated yield of **3a** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses.



Scheme 4. Direct catalytic asymmetric synthesis of vicinal diols. a) i) (*S*)-proline, DMSO, RT; ii) $NaBH_4$, MeOH/DMSO, RT; b) (*R*)-proline, DMSO, RT; ii) $NaBH_4$, MeOH/DMSO, RT, c) Adams' catalyst (PtO_2), H_2, MeOH, RT; d) $CuSO_4 \cdot 5H_2O$, MeOH, 0 °C.

nished the known (1*S*,2*S*)-*trans*-1,2-cyclohexanediol (**7a**) and *cis*-1,2-cyclohexanediol in 96% combined yield, with >99% *ee* for the optically active diol.[28] As selective reduction of α-hydroxy ketones to both *syn*- and *anti*-1,2-diols are known, this procedure is one practical route for the preparation of all the possible stereoisomers of chiral 1,2-diols. In addition, the direct catalytic asymmetric α-aminooxylation of aldehydes and ketones can be regarded as an alternative to Sharpless asymmetric dihydroxylation.[26]

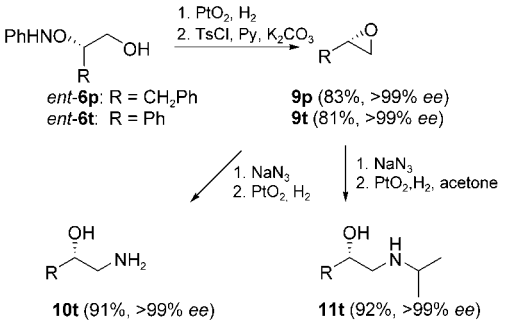
The catalytic α-aminooxylation of unmodified ketones **1** could also be readily combined in one-pot fashion with $CuSO_4$-mediated aniline removal of the ketone adducts **3** generated in situ, which afforded α-hydroxy and α,α′-dihydroxy ketones without loss of stereoselectivity. For example, **3a** was converted into the corresponding optically pure α-hydroxy ketone adduct (2*R*)-**8a** in 92% yield [Eq. (4)].[5,29]

1a 8a: 92% yield, >99%*ee*

Determination of the optical rotations of **7a** and **8a** and comparison with the literature revealed that α-aminooxylation of unmodified ketones catalyzed by (*S*)-proline afforded (2*R*)-α-ketones and (*R*)-α-hydroxy ketones, respectively.[28,29] In accordance, (*S*)-proline also catalyzed the formation of C_2-symmetric (2*R*,6*R*)-α,α′-diketones and (2*R*,6*R*)-α,α′-dihydroxy ketones.

We also investigated the possibility of utilizing the direct catalytic asymmetric α-aminooxylation as a direct route for the catalytic asymmetric syntheses of epoxides and 1,2-amino alcohols (Scheme 5). Chiral 1,2-amino alcohols are important structural elements in chiral ligands for asymmetric catalysis as well as biologically active compounds (e.g., β-adrenergic receptor blockers and immune stimulants).[30,31]

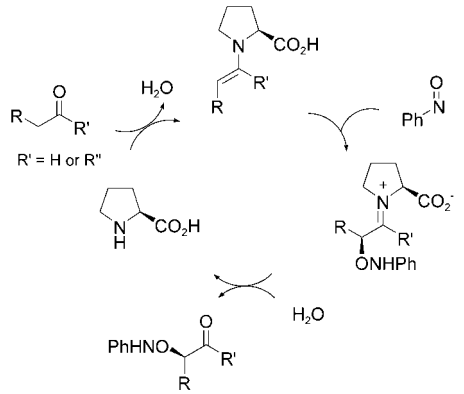
For example, the enantiomerically pure alcohols *ent*-**6p** and *ent*-**6t** obtained from (*R*)-proline catalysis were efficiently converted into the corresponding epoxides **9p** and **9t** in 83% and 81% yields, respectively, each with an *ee* of >99%. The direct catalytic asymmetric α-oxidation can thus be regarded as an efficient route for the stereoselective synthesis of epoxides. The regioselective ring-opening of **9t** with NaN_3 according to literature procedures, followed by hydrogenation of the corresponding azide with Adams' catalyst, afforded **10t** or **11t** in 91% and 92% yields, respectively.[32] The 1-isopropylamino-2-alcohol structural motif of compound **11t** is the core moiety of β-adrenoreceptor antagonists,[33] and so the direct catalytic asymmetric α-aminooxy-



Scheme 5. Asymmetric synthesis of epoxides and 1,2-amino alcohols.

lation can also be viewed as a novel synthetic route for the preparation of antihypertensive drugs (β-blockers). Importantly, employment of (*R*)-proline catalysis afforded the active *S* enantiomers of the drugs.

Mechanism: The mechanism of the proline-catalyzed direct asymmetric α-aminooxylation reactions is depicted in Scheme 6. Accordingly, the aldehyde donor reacts with proline, resulting in an enamine. Next, the nitrosobenzene **2** reacts with the enamine to give (after hydrolysis) the enantiomerically pure α-adduct and the catalytic cycle can be repeated.



Scheme 6. The mechanism of the proline-catalyzed direct catalytic α-aminooxylation of unmodified aldehydes and ketones.

We did not observe any nonlinear effect in the proline-catalyzed reaction (Figure 1),[34] so it is likely that a single proline molecule is involved in the transition state and mechanism, acting as a molecular robot/enzyme (Figure 2).

From the absolute configuration, which is opposite to that of the adducts **3** derived from Yamamoto's reaction,[5] we propose transition state models **I** and **III** to account for the

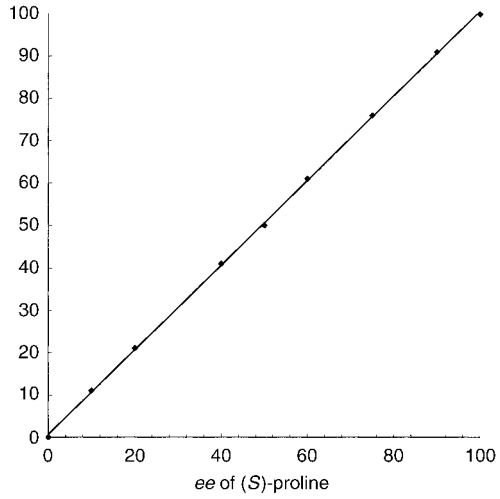


Figure 1. Linear effect in the (*S*)-proline-catalyzed α-aminooxylation of cyclohexanone with nitrosobenzene in DMSO ($y=0.99x+0.70$, $R^2=0.998$).

regio- and enantioselectivities of the α-aminooxylation reactions of unmodified aldehydes and ketones, respectively (Figure 2). Hence, (*S*)-proline forms an enamine with the aldehyde or ketone, and this is attacked from its *si* face, providing (2*R*)-α-aminooxylated aldehydes and ketones, respectively. The six-membered metal-free Zimmermann–Traxler transition state is stabilized by hydrogen bonding between the nitrogen of the nitrosobenzene and the carboxylic acid group of proline. We have performed density functional theory (DFT) calculations to investigate the nature of these transition states further. In the calculations, the phenol ring of the nitrosobenzene was modeled with a suitable methyl group. The optimized transition state geometries corresponding to structures **I–IV** in Figure 2 are displayed in Figure 3.

The main result from the calculations is that **TS-I** and **TS-III** were found to have energies 6.6 and 7.2 kcal mol^{-1} lower than **TS-II** and **TS-IV**, respectively. This explains the exceptionally high stereoselectivity observed for the reaction. The O–C bond to be formed is shorter (ca. 0.2 Å) in **TS-I** and **TS-III** than in the corresponding **TS-II** and **TS-IV**. The N–H bond length is also quite short in all transition state structures: 1.08–1.16 Å. We have also performed calculations to test the reaction mechanism proposed by MacMillan and co-

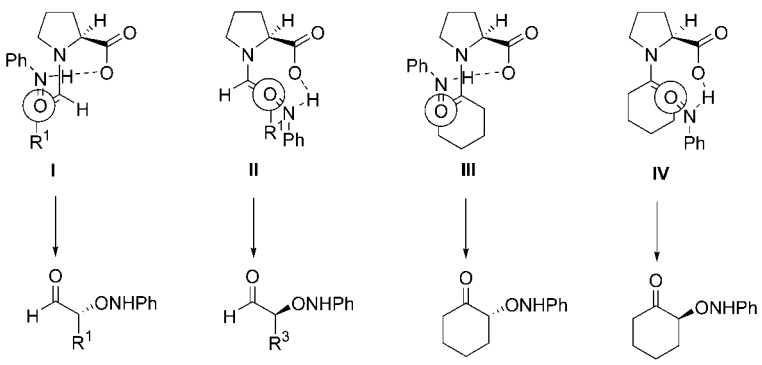


Figure 2. Plausible transition states for the (*S*)-proline-catalyzed reactions.

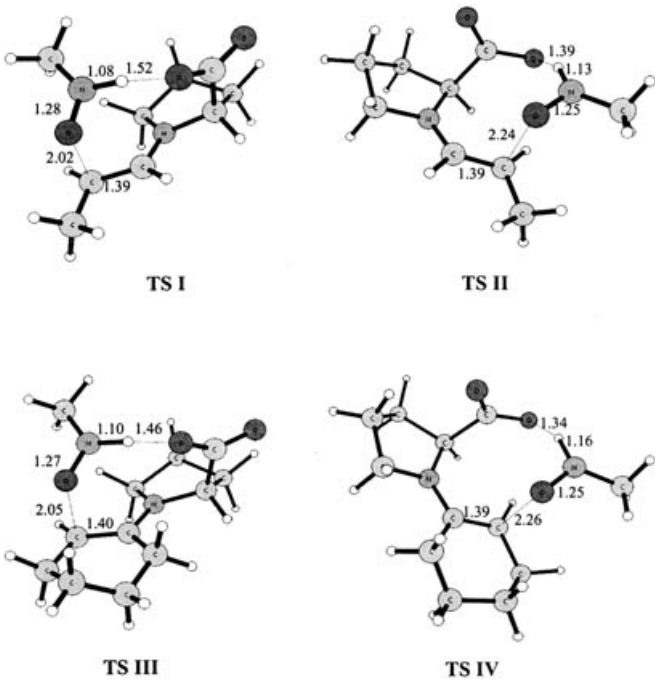


Figure 3. DFT-optimized transition state geometries, corresponding to structures **I**–**IV** in Figure 2.

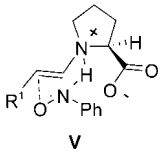


Figure 4. Plausible transition state **V**.

workers.[20b] Every attempt to optimize the key transition state of that mechanism (**TS-V** in Figure 4) resulted in a structure very similar to that of **TS-I**.

Conclusion

Novel direct catalytic enantioselective α-aminooxylations of ketones and aldehydes have been described. The stereoselective reactions between unmodified ketones or aldehydes with nitrosobenzene are new starting points for the chemo-, regio-, and enantioselective syntheses of either enantiomer of enantiomerically pure 1,2-diols, 1,2-amino alcohols, epoxides, and α-hydroxy ketones. In most cases, the reaction proceeds with absolute stereocontrol. The novel direct α-aminooxylation furnishes β-adrenoreceptor antagonists with $>99\,\%$ *ee*s. In addition, reactions with α-unsubstituted cyclic ketones as donors in DMSO were remarkably selective, affording the corresponding C_2-symmetric α,α′-diketones with $>99\,\%$ *ee*s. The direct catalytic asymmetric reactions are readily scaled up, operationally simple, and do not require an inert atmosphere. In addition, the reactions could be conducted in up to 10% water without loss of enantioselectivity. The reaction was also catalyzed by other proline derivatives with excellent stereoselectivity. The reaction does not display nonlinear effects and so only one proline molecule was involved in the transition state. From the stereochemistry of the α-aminooxylated adducts and functional density theory calculations, the mechanism and transition state models of the catalytic asymmetric α-oxidations are discussed. Taken as a whole, the reported transformation should be an inexpensive and useful route for the synthesis of optically active alcohol and amino alcohol molecules.

Experimental Section

General methods: Chemicals and solvents were either purchased puriss p. A. from commercial suppliers or were purified by standard techniques. For thin layer chromatography (TLC), Merck 60 F254 silica gel plates were used and compounds were viewed by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) and subsequent heating. Flash chromatography was performed on Merck 60 silica gel (particle size 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400 instrument. Chemical shifts are given in δ relative to tetramethylsilane (TMS); the coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ or CD_3OD as solvents at room temperature, TMS served as internal standard ($\delta=0$ ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard ($\delta=77.0$ ppm) for ^{13}C NMR. HPLC was carried out on a Hitachi organizer consisting of a D-2500 Chromato-Integrator, an L-4000 UV-Detector, and a L-6200A Intelligent Pump, and a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin–Elmer 241 Polarimeter ($\lambda=589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for the direct α-aminooxylation of ketones (Method A): The ketone (10 equiv) was added to a vial containing nitrosobenzene (1 mmol) and a catalytic amount of (*S*)-proline (20 mol%) in DMSO (4 mL). The reaction was quenched after 2–3 h of vigorous stirring by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure after purification of the crude product mixture by silica gel column chromatography (EtOAc/pentane 1:8) to afford the corresponding α-ketone **3**. The *ee*s of the ketones were determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda=$ 244 nm, $v=0.5$ mL min^{-1}, Hex/IPA).

Typical experimental procedure for the direct α-oxidation of ketones (Method B): A solution of nitrosobenzene in DMSO (1 M, 1 mL) was added by syringe pump (0.2 mL h^{-1}) to a vial containing the ketone (2 equiv) and a catalytic amount of (*S*)-proline (20 mol%) in DMSO (4 mL). The reaction was quenched after 5–7 h of vigorous stirring by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure after purification of the crude product mixture by silica gel column chromatography (EtOAc/pentane 1:8) to afford the corresponding α-aminooxylated ketone **3**. The *ee*s of the ketones were determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda=244$ nm, $v=0.5$ mL min^{-1}).

(2*R*)-2-(*N*-Phenylaminooxy)cyclohexanone (3a): $[\alpha]_D=+111.3$ ($c=0.15$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.71$–1.79 (m, 4H; $CH_2CH_2CH_2$), 2.00–2.02 (m, 2H; CH_2CH_2CH), 2.34–2.48 (m, 2H; CH_2CH_2CO), 4.35 (q, $J=$ 6.0 Hz, 1H; $CHONHAr$), 6.94 (t, $J=8.1$ Hz, 3H; Ar*H*), 7.25 (t, $J=$ 8.4 Hz, 2H; Ar*H*), 7.82 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: $\delta=\delta=23.7$, 27.2, 32.5, 40.8, 86.2, 114.3, 122.0, 128.8, 148.0, 209.9 ppm; MALDI-TOF MS: m/z calcd for $C_{12}H_{15}NO_2$: 228.100; found: 228.101 $[M+Na]^+$; elemental analysis calcd (%) for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.86; found: C 70.22, H 7.41, N 6.90; HPLC (hexanes/*i*PrOH 90:10): major isomer: $t_R=30.31$ min; minor isomer: $t_R=25.79$ min.

(7*R*)-7-(*N*-Phenylaminooxy)-1,4-dioxaspiro[4,5]decan-8-one (3c): $[\alpha]_D=$ $+65.6$ ($c=2.45$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.97$–2.05 (m, 2H; CH_2), 2.20 (t, $J=0.04$ Hz, 1H; CH_2), 2.38–2.52 (m, 2H; CH_2), 2.61–2.74 (m, 1H; CH_2), 4.14–4.00 (m, 4H; OCH_2CH_2O), 4.65 (dd, $J=0.04$ Hz,

0.02 Hz, 1H; C*H*ONHAr), 6.93 (t, J=8.1 Hz, 3H; Ar*H*), 7.25 (t, J=8.4 Hz, 2H; Ar*H*), 7.83 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=34.4, 36.0, 39.7, 64.8, 64.9, 82.7, 107.6, 114.5, 122.1, 128.9, 148.0, 208.7 ppm; MALDI-TOF MS: m/z calcd for $C_{14}H_{17}NO_4$: 228.1055; found: 286.106 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 90:10): major isomer: t_R=78.72 min; minor isomer: t_R=68.57 min.

(2*R*)-2-Methyl-(6*R*)-(*N*-phenylaminooxy)cyclohexanone (3d): $[\alpha]_D$=+99.6 (c=0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.10 (d, J=6.3 Hz, 3H; CH_3), 1.51 (m, 2H; $CH_2CH_2CH_2$), 1.71 (m, 2H; CH_2CH), 2.01 (m, 2H; CH_2CH), 2.87 (m, 1H; C*H*CH$_3$), 4.35 (m, 1H; CHON*H*Ar), 6.94 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.28 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=15.3, 20.0, 32,7, 35.7, 43.0, 85.0, 114.9, 122.7, 129.2, 148.3, 213.1 ppm; MALDI-TOF MS: m/z calcd for 242.116: $C_{13}H_{17}NO_2$; found: 242.116 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=46.11 min; minor isomer: t_R=38.72 min.

(3*R*,2*R*)-3-Methyl-2-(*N*-phenylaminooxy)cyclohexanone (3e): $[\alpha]_D$=+62.6 (c=0.8 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.01 (d, J=6.8 Hz, 3H; CH_3), 1.91 (m, 4H; RCH_2CH_2R), 2.35 (m, 1H; CH_2CH_2CO), 2.51 (m, 1H; CH_2CH_2CO), 2.63 (m, 1H; C*H*CH$_3$), 4.42 (dd, J=4.9, 0.8 Hz, 1H; C*H*ONHAr), 6.94 (m, 3H), 7.25 (m, 2H), 7.51 ppm (brs, 1H; ONHAr); ^{13}C NMR: δ=14.0, 23.3, 30.2, 31.1, 37.2, 40.1, 89.5, 114. 7, 122.4, 129.1, 148.3, 210.7 ppm; MALDI-TOF MS: m/z calcd for $C_{13}H_{17}NO_2$: 219.1259; found: 219.1260 $[M]^+$; HPLC (hexanes/*i*PrOH 98:2 for 5 min, then gradient up to 90:10): major isomer: t_R=39.12 min; minor isomer: t_R=21.2 min.

(3*R*,6*R*)-3-Methyl-(6*R*)-(*N*-phenylaminooxy)cyclohexanone (3e′): $[\alpha]_D$=+67.2 (c=0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.05 (d, J=8.4 Hz, 3H; CH_3), 1.47 (m, 1H; CH_2), 1.77 (m, 1H; CH_2), 1.81 (m, 1H; CH_2), 2.14 (dd, J=15.8, 0.8 Hz; CH_2), 2.46 (m, 3H; CHCH_2CO, C*H*CH$_3$), 4.61 (dd, J=8.2, 0.04 Hz, 1H; C*H*ONHAr), 6.95 (m, 3H), 7.25 (m, 2H), 8.01 ppm (brs, 1H; ONHAr); ^{13}C NMR: δ=22.2, 31.3, 32.6, 35.3, 49.1, 86.1, 114.6, 122.3, 129.1, 148.2, 209.4 ppm; MALDI-TOF MS: m/z calcd for $C_{13}H_{17}NO_2$: 219.1259; found:219.1260 $[M]^+$; HPLC (hexanes/*i*PrOH 98:2 for 5 min, then gradient up to 90:10): major isomer: t_R=37.05 min; minor isomer: t_R=20.2 min.

(3*R*)-3-(*N*-Phenylaminooxy)butane-2-one (3f): $[\alpha]_D$=+62 (c=2.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.14 (d, J=6.4 Hz, 3H; CH_3), 2.21 (s, 3H; CH_3), 4.44 (q, 1H; C*H*ONHAr), 6.94 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.34 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=15.8, 25.9, 84.75, 114.8, 122.7, 129.2, 148.1, 209.4 ppm; MALDI-TOF MS: m/z calcd for $C_{10}H_{13}NO_2$: 202.084; found: 202.087 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 99:1): major isomer: t_R=97.11 min; minor isomer: t_R=72.62 min.

(2*R*)-2-(*N*-Phenylaminooxy)pentane-3-one (3g): $[\alpha]_D$=+57.7 (c=2.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.11–1.72 (t, J=7.1 Hz, 3H; CH_3CH$_2$), 1.43 (d, J=6.0 Hz, 3H; CHCH_3), 2.55 (m, 2H; CH_2CH$_3$), 4.48 (q, J=7.1 Hz, 1H; C*H*ONHAr), 6.94 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.32 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=7.3, 15.9, 31.5, 84.1, 114.5, 122.8, 131.1, 147.9, 211.7 ppm; MALDI TOF-MS: m/z calcd for $C_{11}H_{15}NO_2$: 216.100; found: 216.098 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=34.01 min; minor isomer: t_R=40.1 min.

(3*R*)-3-(*N*-Phenylaminooxy)hex-5-en-2-one (3h): $[\alpha]_D$=+88.6 (c=3.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=2.11 (s, 3H; CH_3), 2.39 (m, 2H; CHCH_2CH), 4.41 (q, J=7.1 Hz, 1H; C*H*ONHAr), 5.22 (m, 2H; CH=CH_2), 5.91 (m, 1H; C*H*=CH$_2$), 6.94 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.32 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=26.8, 35.1, 88.2, 114.9, 118.8, 122.8, 128.5, 129.2, 135.9, 148.0, 208.4 ppm; MALDI-TOF MS: m/z calcd for $C_{12}H_{15}NO_2$: 228.100; found: 228.105 $[M+H]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=44.57 min; minor isomer: t_R=38.0 min.

(3*R*)-4-Methyl-(3-*N*-phenyl-aminooxy)pentan-2-one (3i): $[\alpha]_D$=+94.1 (c=3.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.03 (d, J=7.1 Hz, 3H; CH_3), 1.15 (d, J=6.9 Hz, 3H; CH_3), 2.14 (m, 1H; CH(CH_3)$_2$), 2.18 (s, 3H; CH_3CO), 4.17 (d, J=7.1 Hz, 1H; CHON*H*Ar), 6.94 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.28 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: δ=17.8, 19.7, 27.0, 30.1, 93.5, 114.9, 122.7, 129.2, 148.3, 209.4 ppm; MALDI-TOF MS: m/z calcd for $C_{12}H_{17}NO_2$: 230.116; found: 230.118 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=45.72 min; minor isomer: t_R=26.37 min.

(2*S*,6*S*)-2,6-Bis(*N*-phenylaminooxy)cyclohexanone (4a): $[\alpha]_D$=+115.4 (c=0.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.94–2.06 (m, 2H; $CH_2CH_2CH_2$), 2.08–2.14 (m, 4H; CH_2CH_2CH), 4.68 (q, J=6.0 Hz, 2H; C*H*ONHAr), 6.94 (m, 6H; Ar*H*), 7.24 ppm (m, 4H; Ar*H*); ^{13}C NMR: δ=18.9, 32.6, 85.5, 115.2, 122.9, 129.2, 147.9, 208.9 ppm; MALDI-TOF MS: m/z calcd for $C_{18}H_{20}N_2O_3$: 335.137; found: 335.133 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 90:10): major isomer: t_R=52.87 min; minor isomer: t_R=49.33 min.

(7*S*,9*S*)-7,9-Bis(*N*-phenylaminooxy)-1,4-dioxa-spiro[4,5]decan-8-one (4c): $[\alpha]_D$=+42.1 (c=1.85 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=2.40 (s, 4H; CHCH_2CH), 4.10 (s, 4H; O(CH_2)$_2$O), 4.78 (t, J=0.02 Hz, 2H; C*H*ONHAr), 6.95 (m, 6H; Ar*H*), 7.25 ppm (m, 4H; Ar*H*); ^{13}C NMR: δ=36.1, 61.2, 78.0, 103.4, 111.2, 118.9, 125.2, 144.0, 203.0 ppm; MALDI-TOF MS: m/z calcd for $C_{20}H_{22}N_2O_5$: 393.1426; found: 393.1424 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 90:10): major isomer: t_R=161.98 min; minor isomer: t_R=138.33 min.

Typical experimental procedure for the direct α-aminooxylation of aldehydes and synthesis of 2-aminooxylated alcohols: The aldehyde (2 equiv) was added at room temperature to a vial containing nitrosobenzene (1 mmol) and a catalytic amount of (*S*)-proline (10 mol%) in DMSO (5 mL). After 2–3 h reaction time, the temperature was lowered to 0°C, followed by dilution with anhydrous MeOH (2.0 mL) and careful addition of excess $NaBH_4$ (0.25 g). The reaction was quenched after 10 minutes by pouring of the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired α-alcohols. The *ee*s of the alcohols **6** were determined by chiral-phase HPLC analyses (Daicel AD column, λ=244 nm, v=0.5 mL min^{-1}).

(2*R*)-2-(*N*-Phenylaminooxy)hexan-1-ol (6b): $[\alpha]_D$=+22.1 (c=0.8 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=0.92 (t, J=7.2 Hz, 3H; CH_3), 1.22–1.75 (m, 6H; $CH_2CH_2CH_2$), 3.78 (m, 2H; CH_2OH), 3.94 (dq, J=6.1, 2.4 Hz, 1H; C*H*ONHAr), 6.94 (m, 3H; ArH), 7.25 (m, 2H; ArH), 7.32 ppm (brs, 1H; ON*H*Ar); ^{13}C NMR: 14.1, 22.9, 27.9, 29.7, 65.5, 83.9, 114.8, 122.4, 128.9, 148.2 ppm; MALDI-TOF MS: m/z calcd for $C_{12}H_{20}NO_2$ 210.1494; found: 210.1491 $[M]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=32.4 min; minor isomer: t_R=27.4 min.

(2*S*)-2-(*N*-Phenylaminooxy)hexan-1-ol (*ent*-6b): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D$=−22.0 (c=0.7 in $CHCl_3$); HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=27.4 min; minor isomer: t_R=32.4 min.

(2*R*)-(*N*-Phenylaminooxy)butan-1-ol (6j): $[\alpha]_D$=+20.5 (c=0.7 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=0.96 (t, J=6.9 Hz, 3H; CH_3), 1.35–1.75 (m, 2H; CH_3CH_2CH), 3.78 (m, 2H; CHCH_2OH), 3.94 (dq, 1H, J=6.6, 2.6 Hz, C*H*ONHAr), 6.95 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.32 ppm (brs, 1H); ^{13}C NMR: δ=14.3, 30.7, 65.5, 83.9, 114.8, 122.4, 128.9, 148.2 ppm; MALDI-TOF MS: m/z calcd for $C_{10}H_{15}NO_2$ 181.1103; found: 181.1106 $[M]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=35.4 min; minor isomer: t_R=26.4 min.

(2*R*)-2-(*N*-Phenylaminooxy)propan-1-ol (6k): $[\alpha]_D$=+1.21 (c=0.8 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.25 (t, J=6.0 Hz, 3H; CH_3), 3.77 (m, 2H; CH_2OH), 4.12 (m, 1H; C*H*ONHAr), 6.95 (m, 3H; Ar*H*), 7.25 ppm (m, 2H; Ar*H*); ^{13}C NMR: δ=15.5, 66.5, 80.0, 114.6, 122.3, 128.9, 148.3 ppm; MALDI-TOF MS: m/z calcd for $C_{11}H_{18}NO_2$: 168.1024; found: 168.1023 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: t_R=17.1 min; minor isomer: t_R=14.4 min.

(2*R*)-2-(*N*-Phenylaminooxy)heptan-1-ol (6l): $[\alpha]_D$=+19.7 (c=4.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=0.91 (t, J=7.2 Hz, 3H; CH_3), 1.22–1.54 (m, 7H; $CH_2CH_2CH_2$), 1.68 (m, 1H; $CH_2CH_2CH_2$), 3.76 (dd, J=12.0, 6.4 Hz, 1H; CH_2OH), 3.86 (dd, J=12.1, 2.6 Hz, 1H; CH_2OH), 3.94 (m, 1H; C*H*ONHAr), 6.94 (m, 3H; ArH), 7.25 ppm (m, 2H; ArH); ^{13}C NMR: δ=14.2, 22.8, 25.6, 30.1, 32.2, 65.5, 84.2, 115.1, 122.6, 129.2, 148.7 ppm; MALDI-TOF MS: m/z calcd for $C_{13}H_{21}NO_2$: 223.1572; found: 223.1576 $[M]^+$; HPLC (hexanes/*i*PrOH 98:2): major isomer: t_R=31.4 min; minor isomer: t_R=26.4 min.

(2*R*)-3-Benzyloxy-2-(*N*-phenylaminooxy)propan-1-ol (6m): $[\alpha]_D$=+3.4 (c=0.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=3.77 (m, 2H; CH_2OH), 3.90 (m, 2H; BnOCH_2), 4.12 (m, 1H; C*H*ONHAr), 4.56 (s, 2H; OCH_2Ph), 6.96 (m, 3H; Ar*H*), 7.25 (m, 2H; Ar*H*), 7.33 ppm (m, 5H); ^{13}C NMR: δ=62.8, 69.4, 73.6, 82.5, 114.6, 122.3, 127.5, 127.6, 128.4, 128.9, 137.9, 148.3 ppm; MALDI-TOF MS: m/z calcd for $C_{12}H_{19}NO_2$: 296.1263;

found: 296.1260 $[M+Na]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 41.1$ min; minor isomer: $t_R = 36.3$ min.

(2*R*)-3-Methyl-2-(*N*-phenylaminooxy)butan-1-ol (6n): $[\alpha]_D = +39.1$ ($c = 0.9$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.99$ (d, $J = 6.6$ Hz, 3H; C*H*$_3$), 1.04 (d, $J = 6.6$ Hz, 3H; C*H*$_3$), 2.03 (m, 1H; C*H*(CH$_3$)$_2$), 2.88 (br s, 1H; O*H*), 3.72 (m, 1H; C*H*ONHAr), 3.85 (m, 2H; C*H*$_2$OH), 6.95 (m, 3H; Ar*H*), 7.06 (s, 1H; ON*H*Ar), 7.25 ppm (m, 2H; Ar*H*); ^{13}C NMR: $\delta = 18.7$, 18.8, 28.8, 63.8, 88.7, 114.9, 122.4, 128.9, 148.1 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{11}H_{18}NO_2$ 196.1337; found: 196.1339 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 15.1$ min; minor isomer: $t_R = 11.3$ min.

(2*S*)-3-Methyl-2-(*N*-phenylaminooxy)butan-1-ol (*ent*-6n): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = -39.0$ ($c = 0.7$ in $CHCl_3$); HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 11.3$ min; minor isomer: $t_R = 15.1$ min.

(2*R*)-2-(*N*-Phenylaminooxy)pent-4-en-1-ol (6o): $[\alpha]_D = +8.1$ ($c = 0.8$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 1.80$ (m, 1H; O*H*), 2.51–2.67 (m, 2H; C*H*$_2$CH=CH$_2$), 3.76 (dd, $J = 11.7$, 6.0 Hz, 1H; C*H*$_2$OH), 3.85 (dd, $J = 11.7$, 2.7 Hz, 1H; C*H*$_2$OH), 3.96 (dq, $J = 6.6$, 2.7 Hz, 1H; C*H*ONHAr); 4.98 (d, $J = 10.2$ Hz, 1H), 5.05 (d, $J = 17.4$ Hz, 1H), 5.82 (m, 1H), 6.97 (m, 3H), 7.06 (s, 1H), 7.25 ppm (m, 2H); ^{13}C NMR: $\delta = 29.2$, 29.9, 65.1, 83.3, 114.8, 115.0, 122.4, 128.9, 137.8, 148.2 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{12}H_{18}NO_2$: 208.1337; found: 208.1339 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 26.3$ min; minor isomer: $t_R = 19.8$ min.

(2*R*)-3-Phenyl-2-(*N*-Phenylaminooxy)propan-1-ol (6p): $[\alpha]_D = +42.1$ ($c = 0.9$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 2.84$ (dd, $J = 13.8$, 6.6 Hz, 1H), 3.04 (dd, $J = 13.8$, 6.6 Hz, 1H), 3.71 (dd, $J = 12.3$, 6.3 Hz, 1H), 3.85 (dd, $J = 12.3$, 3.0 Hz, 1H), 4.09 (m, 1H), 6.82 (d, $J = 8.4$ Hz, 2H), 6.92 (t, $J = 7.5$ Hz, 1H), 7.14–7.31 ppm (m, 7H); ^{13}C NMR: $\delta = 36.6$, 64.3, 85.1, 114.5, 122.2, 126.3, 128.3, 128.8, 129.3, 137.6, 148.1 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{15}H_{18}NO_2$: 244.1337; found: 208.1340 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 31.7$ min; minor isomer: $t_R = 21.4$ min.

(2*S*)-3-Phenyl-2-(*N*-phenylaminooxy)propan-1-ol (*ent*-6p): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = -42.2$ ($c = 0.9$ in $CHCl_3$); HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 21.4$ min; minor isomer: $t_R = 31.7$ min.

***cis*-(2*R*)-2-(*N*-Phenylaminooxy)dec-7-en-1-ol (6s)**: $[\alpha]_D = +11.9$ ($c = 1.03$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.96$ (t, $J = 0.019$ Hz, 3H), 1.23–1.57 (m, 5H), 1.63–1.73 (m, 1H), 2.01–2.08 (m, 4H), 3.75–3.81 (m, 1H), 3.84–3.89 (m, 1H), 3.97–4.03 (m, 1H), 5.27–5.41, (m, 2H), 7.02 (m, 3H), 7.29 ppm (m, 2H); ^{13}C NMR: $\delta = 14.6$, 20.7, 25.6, 27.1, 30.1, 30.0, 65.7, 84.2, 115.1, 122.9, 128.9, 129.3, 132.1 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{16}H_{25}NO_2$: 263.1885; found: 263.1887 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 21.7$ min; minor isomer: $t_R = 14.4$ min.

(2*R*)-2-Phenyl-2-(*N*-phenylaminooxy)ethanol (6t): $[\alpha]_D = -142.1$ ($c = 0.9$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 2.66$ (dd, $J = 4.4$, 7.7 Hz; O*H*), 3.86–3.85 (m, 1H; C*H*$_2$OH), 3.91–4.03 (m, 1H; C*H*$_2$OH), 5.01 (dd, $J = 4.4$, 7.7 Hz, 1H; C*H*ONHAr), 6.95 (m, 4H; Ar*H*, ON*H*Ar), 7.25 ppm (m, 2H; Ar*H*); ^{13}C NMR: $\delta = 66.7$, 86.8, 115.3, 122.8, 127.3, 128.9, 129.3, 138.0, 148.3 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{14}H_{15}NO_2$: 229.2744; found: 229.2747 $[M]^+$; HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 33.7$ min; minor isomer: $t_R = 22.4$ min.

(2*S*)-2-Phenyl-2-(*N*-phenylaminooxy)ethanol (*ent*-6t): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = +141.9$ ($c = 0.8$ in $CHCl_3$); HPLC (hexanes/*i*PrOH 95:5): major isomer: $t_R = 22.4$ min; minor isomer: $t_R = 33.7$ min.

(2*R*)-2-(*N*-Phenylaminooxy)-(1*R*)cyclohexanol (6a): *dr* = 2:1 (*anti*:*syn*); $[\alpha]_D = +93.7$ ($c = 0.4$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 1.21$–1.44 (m, 4H), 1.59 (m, 2H), 1.66 (m, 4H), 1.88 (m, 2H), 1.93 (m, 1H), 2.14 (m, 1H), 3.65 (m, 1H; *syn* isomer), 3.92 (m, 1H; *anti* isomer), 4.11 (m, 1H; *anti* isomer); 6.94 (m, 4.5H), 7.25 (m, 3H), 7.28 ppm (br s, 1.5H); ^{13}C NMR: $\delta = 21.3$, 22.8, 24.1, 24.4, 26.4, 29.5, 30.8, 69.2, 74.5, 82.9, 86.5, 114.8, 115.3, 122.4, 122.8, 129.2, 148.6, 148.7 ppm; MALDI-TOF MS: *m*/*z* calcd for $C_{12}H_{17}NO_2$: 230.116; found: 230.117 $[M+H]^+$; HPLC (hexanes/*i*PrOH 90:10): major isomer: $t_R = 88.09$ min; minor isomer: $t_R = 69.32$ min.

Typical experimental procedure for N–O bond cleavage by catalytic hydrogenation with Adams' catalyst: Methanol (3 mL) and Adams' catalyst (10 mol %) were added to a 20 mL hydrogenation vial equipped with a magnetic stirrer bar and charged with the α adduct (0.5 mmol). Next, the reaction mixture was flushed with H_2 (90 MPa) for 1 h and the resulting clear solution was filtered through Celite. The filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (EtOAc/pentane 1:2) to afford the corresponding deprotected adduct.

Typical experimental procedure for $CuSO_4$-mediated N–O bond cleavage: A catalytic amount of $CuSO_4 \cdot H_2O$ (30 mol %) was added at 0 °C to a vial containing the α-adduct (1 mmol) in MeOH (3 mL). The reaction mixture was stirred at this temperature until completion as determined by TLC analyses and then quenched by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure after purification of the crude product mixture by silica gel column chromatography (EtOAc/pentane 1:2) to afford the corresponding α-deprotected adduct.

(2*R*)-Hexane-1,2-diol (7b): This product was obtained from (*S*)-proline catalysis. $[\alpha]_D = +22.2$ ($c = 1.1$ in EtOH); ^1H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H; C*H*$_3$), 1.51–1.84 (m, 6H; CH$_2$C*H*$_2$CH$_2$), 3.17 (br s, 2H; O*H*), 3.80 (m, 1H; C*H*$_2$OH), 4.06 ppm (m, 2H; C*H*$_2$OH, C*H*OH); ^{13}C NMR: $\delta = 14.6$, 23.3, 33.4, 67.4, 72.9 ppm.

(2*S*)-Hexane-1,2-diol (*ent*-7b): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = -22.0$ ($c = 0.9$ in EtOH).[35]

(2*R*)-3-Methylbutane-1,2-diol (7n): This product was obtained from (*S*)-proline catalysis. $[\alpha]_D = -11.1$ ($c = 0.6$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.91$ (d, $J = 6.5$ Hz, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.71 (m, 1H), 3.42 (m, 1H), 3.51 (dd, $J = 10.5$, 8.0 Hz, 1H), 3.71 ppm (dd, $J = 10.5$, 3.0 Hz, 1H); ^{13}C NMR: $\delta = 18.2$, 18.7, 30.9, 64.9 ppm.[27]

(2*S*)-3-Methylbutane-1,2-diol (*ent*-7n): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = +11.0$ ($c = 0.6$ in $CHCl_3$).

(2*S*)-3-Phenylpropane-1,2-diol (*ent*-7p): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = -18.6$ ($c = 1.3$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 1.85$ (br s, 2H; O*H*), 2.78 (m, 2H; PhC*H*$_2$CH), 3.54 (m, 1H; C*H*$_2$OH), 3.70 (m, 1H; C*H*$_2$OH), 3.95 (m, 1H; C*H*OH), 7.24 (m, 3H; Ar*H*), 7.33 ppm (m, 2H; Ar*H*); ^{13}C NMR: $\delta = 40.0$, 66.3, 73.3, 126.9, 128.9, 129.6, 137.9 ppm.

(1*S*)-1-Phenylethane-1,2-diol (*ent*-7q): This product was obtained from (*R*)-proline catalysis. $[\alpha]_D = -38.1$ ($c = 1.2$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 2.56$ (s, 2H; O*H*), 3.67 (dd, $J = 8.4$, 11.6 Hz, 1H; C*H*$_2$OH), 3.77 (dd, $J = 10.8$ Hz, 1H; C*H*$_2$OH), 4.83 (dd, $J = 3.6$, 8.0 Hz, 1H; ArC*H*OH), 7.29–7.34 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta = 68.1$, 74.4, 126.0, 128.0, 128.6, 140.5 ppm; HPLC (hexanes/*i*PrOH 95:5, $\lambda = 254$ nm): major isomer: $t_R = 33.0$ min; minor isomer: $t_R = 30.2$ min.

***trans*-(1*S*,2*S*)-Cyclohexane-1,2-diol (7a)**: This product was obtained from (*S*)-proline catalysis. $[\alpha]_D = -39.1$ ($c = 0.2$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 1.26$ (m, 4H; C*H*$_2$), 1.75 (m, 2H; C*H*$_2$), 1.98 (m, 2H; C*H*$_2$), 3.34 ppm (m, 2H; C*H*OH); ^{13}C NMR: $\delta = 24.5$, 33.1, 76.1 ppm.[28]

***cis*-Cyclohexane-1,2-diol (7a)**: ^1H NMR ($CDCl_3$): $\delta = 1.26$ (m, 2H; C*H*$_2$), 1.76 (m, 4H; C*H*$_2$), 1.91 (m, 2H; C*H*$_2$), 3.34 ppm (m, 1H; C*H*OH); ^{13}C NMR: $\delta = 21.6$, 30.1, 70.8 ppm.

(2*R*)-2-Hydroxyketone 8a: This product was obtained from (*S*)-proline catalysis. $[\alpha]_D = +24.1$ ($c = 0.72$ in $CHCl_3$).[29]

Direct asymmetric synthesis of epoxides: Freshly distilled pyridine (4 mL) and toluenesulfonyl chloride (7.36 g, 40 mmol) were added to a solution of **7** (20 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 12 h at 0 °C and was then acidified with HCl (2 N). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to furnish the monotosylate. The crude monotosylate was dissolved in methanol (50 mL) and was treated with potassium carbonate (2.1 g, 15 mmol) at 4 °C. The reaction was quenched after 1 h by addition of water and extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$, and the solvent was subsequently removed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (pentane/EtOAc mixtures) to afford the corresponding epoxides **9**.

(*S*)-(2,3-Epoxypropyl)benzene (9q): $[\alpha]_D = 17.6$ ($c = 1.9$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 2.55$ (dd, $J = 4.8$, 2.8 Hz, 1H), 2.79 (m, 1H), 2.81 (dd, 1H), 2.92 (dd, 1H), 3.19 (m, 1H), 7.27 (m, 3H), 7.31 ppm (m, 2H); ^{13}C NMR: 39.0, 47.1, 52.7, 126.9, 128.7, 129.2, 138.2 ppm.

(*S*)-Phenylethylene oxide (9t): $[\alpha]_D = 23.9$ ($c = 0.8$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 3.18$ (dd, $J = 4.8$, 2.8 Hz, 1H), 3.55 (dd, $J = 5.4$, 4.4 Hz, 1H),

4.25 ppm (dd, $J=4.0$, 2.4 Hz 1H); ^{13}C NMR: $\delta=51.8$, 53.0, 126.1, 128.8, 129.1, 138.2 ppm.

Asymmetric synthesis of (*S*)-2-amino-1-phenylethanol (10t): The enantiomerically pure epoxide **9t** originating from (*R*)-proline-catalyzed α-oxidation of aldehyde **1t** (1 mmol) was regioselectively ring-opened according to reference [32]. The crude azido alcohol product was dissolved in MeOH (10 mL), and PtO_2 (24 mg, 0.10 mmol) was added. The flask was then flushed with hydrogen at 1 bar, and the reaction mixture was stirred for 2 h at room temperature. The mixture was filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc 1:2) to afford compound **10t** as a white solid (127 mg, 91%). All spectroscopic data were identical to those of the commercially available compound. ^{1}H NMR ($CDCl_3$): $\delta=2.14$ (br s, 2H; N*H*$_2$), 2.82 (dd, $J=12.6$, 8.0 Hz, 2H; C*H*$_2$NH$_2$), 3.01 (dd, $J=12.8$, 4.0 Hz, 1H; C*H*$_2$NH$_2$), 4.64 (dd, $J=5.6$, 4.0 Hz, 1H; C*H*OH), 7.33 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta=49.74.5$, 126.2, 127.9, 128.7, 139.2 ppm.

Asymmetric synthesis of (*S*)-2-(2-propylamino)-1-phenylethanol (11t): The enantiomerically pure epoxide **9t** originating from (*R*)-proline-catalyzed α-oxidation of aldehyde **1t** (1 mmol) was regioselectively ring-opened according to reference [32]. The crude azido alcohol product was dissolved in MeOH (10 mL), and PtO_2 (12 mg, 0.05 mmol), molecular sieves (3 Å, 0.45 g), and acetone (110 μL, 1.1 mmol) were added. The flask was then flushed with hydrogen at 1 bar, and the reaction mixture was stirred for 5 h at room temperature. The mixture was filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc 1:2) to afford compound **11t** as a white solid (237 mg, 92%). All spectroscopic data were identical to those of the previously described compound. ^{1}H NMR ($CDCl_3$): $\delta=0.96$ (d, $J=8.9$ Hz, 6H; C*H*$_3$), 2.49–2.65 (m, 2H), 3.40–3.53 (m, 1H), 4.58–4.65 (m, 1H; C*H*OH), 7.33 ppm (m, 5H; Ar*H*).[36]

Computational details: All geometries and energies presented in this study were computed by use of the B3LYP[37] density functional theory method as implemented in the Gaussian 98 program package.[38] Geometry optimizations were performed with the double zeta plus polarization basis set 6–31G(d,p). From these geometries, single-point calculations with the larger 6–311+G(2d,2p) basis set were performed in order to obtain more accurate energies. Hessians for evaluation of zero-point vibrational effects were calculated at the B3LYP/6–31G(d,p) level of theory.

Acknowledgment

Support by Prof. J.-E. Bäckvall and Stockholm University is gratefully acknowledged. We thank Prof. H. Adolfsson for valuable discussions and the Swedish National Research council, the Lars Hierta Foundation, and the Wenner–Gren Foundation for financial support.

[1] a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**; b) R. Noyori, *Asymmetric Catalysis in Asymmetric in Organic Synthesis*, Wiley, New York, **1994**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed, Wiley-VCH, New York, **2000**.

[2] a) F. A. Davis, B. C. Chen, *Methods of Organic Chemistry (Houben–Weyl) Vol. E21* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, p. 4497; b) D. Enders, U. Reinhold, *Liebigs Ann.* **1996**, 11; c) D. Enders, U. Reinhold, *Synlett* **1994**, 792.

[3] a) F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919. and references therein; b) B. B. Lohray, D. Enders, *Helv. Chim. Acta* **1989**, *72*, 980.

[4] a) L. Colombo, M. D. Giacomo, *Tetrahedron Lett.* **1999**, *40*, 1977; b) E. L. Eliel, *Asymmetric Synth.* **1983**, *2A*, 125, and references therein.

[5] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038.

[6] a) P. I. Dalko, L. Moisan *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) J. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 515; *Angew. Chem. Int. Ed.* **2001**, *40*, 529; d) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; e) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975.

[7] a) Z. G. Hajos, D. R. Parrish, Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent. DE 2102623, July 29, 1971; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; c) U. Eder, G. Sauer, R. Wiechert, Optically Active 1,5-Indanone and 1,6-Naphthalenedionene. German Patent DE 2014757, October 7, 1971; d) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed.* **1971**, *10*, 496; e) C. Agami, *Bull. Soc. Chim. Fr.* **1988**, 499.

[8] For example, the total synthesis of taxol: S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 2843.

[9] Aldol reactions, see: a) B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; c) K. Saktihvel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; d) A. Córdova, W. Notz, C. F. Barbas, III, *J. Org. Chem.* **2002**, *67*, 301; e) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573; f) A. Córdova, W. Notz, C. F. Barbas, III, *Chem. Commun.* **2002**, 3034; g) A. Bøgevig, K. Juhl, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; h) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; i) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas, III, *Tetrahedron Lett.* **2002**, *43*, 9591; j) C. Pidathala, L. Hoang, N. Vignola, B. List *Angew. Chem.* **2003**, *115*, 2891; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; k) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y. D. Wu, *J. Am. Chem. Soc.* **2003**; *125*, 5262.

[10] Mannich reactions see: a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; b) B. List, P. Porjaliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827; c) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas, III, *Tetrahedron Lett.* **2001**, *42*, 199; d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, III, *J. Am. Chem. Soc.* **2002**, *124*, 1844; e) A. Córdova, *Synlett* **2003**, 1651; f) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1957; g) A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz, C. F. Barbas, III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; h) A. Córdova, C. F. Barbas, III, *Tetrahedron Lett.* **2002**, *43*, 7749; i) A. Córdova, C. F. Barbas, III, *Tetrahedron Lett.* **2003**, *44*, 1923; j) S.-I. Watanabe, A. Córdova, F. Tanaka, C. F. Barbas, III, *Org. Lett.* **2002**, *4*, 4519; k) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; l) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.

[11] α-Aminations see: a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254.

[12] Michael reactions see: a) B. List, P. Pojarliev, H. B. Martin, *Org. Lett.* **2001**, *3*, 2423; b) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520; c) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223; c) M. Yamaguchi, Y. Igarashi, T. Shiraishi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233; d) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; e) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas, III, *Tetrahedron Lett.* **2001**, *42*, 4441; f) J. M. Betancort, C. F. Barbas, III, C. F. *Org. Lett.* **2001**, *3*, 3737; g) D. J. Hortsmann, D. J. Guerin, S. J. Miller, *Angew. Chem.* **2000**, *112*, 3781; *Angew. Chem. Int. Ed.* **2000**, *39*, 3635; h) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; i) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134; j) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; k) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; l) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, *2559*; m) D. Enders, A. Seki, *Synlett* **2002**, 26.

[13] Diels–Alder reactions see: a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458; b) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. Hetero-Diels–Alder reactions see: c) K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498; d) Y. Huang, K. Unni, A. N. Thadani, V. Rawal, *Nature* **2003**, *424*, 146.

[14] Intramolecular alkylation see: N. Vignola, B. List *J. Am. Chem. Soc.* **2004**, *126*, 450.
[15] Alkylation of electron-rich benzene systems see: a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894.
[16] 1,3-Dipolar cycloadditions see: a) W. C. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; b) S. Karlsson, H. Högberg, *Tetrahedron: Asymmetry* **2002**, *13*, 923.
[17] Strecker reaction: P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[18] α-Chlorinations see: a) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790; b) M. P. Brochu, Sp. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108.
[19] Other see: a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831; b) B. R. Sculimbrene, A. J. Morgan, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 11653; c) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058.
[20] During the preparation of this manuscript, three excellent independent reports of proline-catalyzed α-oxidations of aldehydes were reported; see: a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293.
[21] a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109. The reaction was also developed independently by Hayashi et al. See: b) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43* 1112.
[22] a) T. Sasaki, K. Mori, M. Ohno, *Synthesis* **1985**, 279; b) T. Sasaki, K. Mori, M. Ohno, *Synthesis* **1985**, 280; c) W. Oppolzer, G. Tamura, *Tetrahedron Lett.* **1990**, *31*, 991; d) W. Oppolzer, G. Tamura, M. Sundarababu, M. Signer, *J. Am. Chem. Soc.* **1992**, *114*, 5900; e) N. Momiyama, H. Yamamoto, *Org. Lett.* **2002**, *4*, 3579.
[23] N. Momiyama, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3112; *Angew. Chem. Int. Ed.* **2002**, *41*, 2986.
[24] a) S. Kirsch, T. Bach, *Angew. Chem.* **2003**, *115*, 4833; *Angew. Chem. Int. Ed.* **2003**, *42*, 4685; b) S. Hatakeyama, H. Numata, K. Osani, S. Takana, *J. Org. Chem.* **1989**, *54*, 3515.
[25] a) G. Solladie, C. Hamdouchi, C. Ziani-Cherif, *Tetrahedron: Asymmetry* **1991**, *2*, 457; b) D. F. Taber, M. Xu, J. L. Hartnett, *J. Am. Chem. Soc.* **2002**, *124*, 13121.
[26] a) M. A. Andersson, R. Epple, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 490; *Angew. Chem. Int. Ed.* **2002**, *41*, 472 and references therein; b) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449; *Angew. Chem. Int. Ed.* **1996**, *35*, 451.
[27] a) B. T. Cho, Y. S. Chun, *J. Org. Chem.* **1998**, *63*, 5280; b) B. T. Cho, Y. S. Chun, *Tetrahedron: Asymmetry* **1999**, *10*, 1843.
[28] The optical rotation of **7a** was $[\alpha]_D = -39.1$ ($c = 0.2$ in $CHCl_3$) ($[\alpha]_D = -39.0$ ($c = 1.2$ in $CHCl_3$) for (1*S*, 2*S*)-cyclohexane-1,2-diol purchased from Aldrich).
[29] L. G. Lee, G. M. Whitesides, *J. Org. Chem.* **1986**, *51*, 25.
[30] a) H.-U. Blasser, *Chem. Rev.* **1992**, *92*, 935; b) H. C. Kolb, M. S. Van Nieeuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[31] J. R. Powell, I. W. Waimer, D. E. Drayer, In *Drug Stereochemistry Analytical Methods and Pharmacology*, Dekker, New York, **1998**.
[32] M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557.
[33] See for example: a) F. Ostermayer, M. Zimmermann, US 4460580, 1984; b) Z. M. Wang, X. L. Zhang, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 2267; c) M. R. Bristow, R. E. Hersberger, J. D. Port, W. Minobe, R. Rasmussen, *Mol. Pharmacol.* **1989**, *35*, 295.
[34] a) C. Agami, C. Puchot, *Tetrahedron Lett.* **1986**, *27*, 1501; b) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.
[35] J. Hasegawa, M. Ogura, S. Tsuda, S. Maemoto, H. Kutsuki, T. Ohashi, *Agric. Biol. Chem.* **1990**, *54*, 1819.
[36] P. Saravanan, B. Alakesh, S. Baktharaman, M. Chandrasekhar, V. K. Sing *Tetrahedron* **2002**, 4693.
[37] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev.* **1988**, B37, 785; b) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 1372; c) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648.
[38] Gaussian98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.

Received: February 10, 2004
Published online: June 8, 2004

