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Highly Modular Synthesis of C_1-Symmetric Aminosulfoximines and Their Use as Ligands in Copper-Catalyzed Asymmetric Mukaiyama-Aldol Reactions

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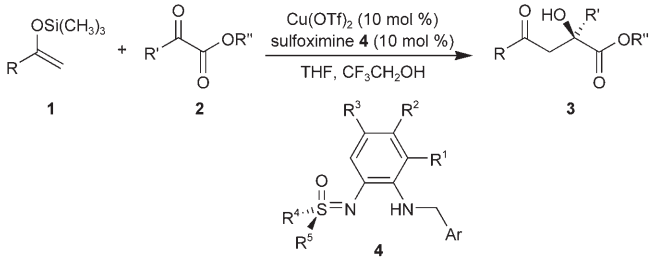
Abstract: The development of C_1-symmetric aminosulfoximines, their highly modular synthesis, and their application in enantioselective copper-catalyzed Mukaiyama-type aldol reactions between pyruvates and enolsilanes is described. In this context, the influence of the ligand architecture as well as the optimization of the reaction conditions are discussed. In detail, the dependence of the catalyst efficiency on the solvent, the metal source and the temperature are reported, and an interesting additive effect is highlighted. Furthermore, the substrate scope will be presented. With the optimized catalyst system, a number of aldol products with quaternary stereogenic centers have been obtained in high yields and with enantiomeric excesses up to 99%.

Keywords: aldol reaction · asymmetric catalysis · copper · sulfoximines

Introduction

Throughout the last two decades, the enantioselective metal-catalyzed Mukaiyama-type aldol reaction has become a useful tool in organic synthesis.[1] This elegant approach allows the convenient preparation of valuable enantiomerically enriched alcohols by using chiral Lewis acids in catalytic amounts. Consequently, a multitude of catalysts derived from metals such as tin,[2] boron,[3] titanium,[4] zirconium,[5] copper,[6] silver,[7] and scandium[8] have been reported. Most of them have been applied in additions of enolsilanes **1** to aldehydes and high enantioselectivities have been achieved. In contrast, for reactions involving activated ketones such as pyruvates **2**, the number of such powerful systems has remained rather limited.[2d,9] Thus, for the latter process, the development of new chiral Lewis acids still represents a major challenge because the resulting tertiary α-hydroxy ester derivatives **3** (Scheme 1) are desirable building blocks for biologically active molecules[10] such as pharmaceuticals.[11] Furthermore, several natural products contain tertiary alcohol groups with stereogenic centers,[12] but the access to enantiopure products of this type by aldol reactions is commonly restricted.[13] Parallel to the versatile utilizations of sulfoximines[14] as chiral auxiliaries[15] and precursors for biologically active molecules[16] such as pseudopeptides,[17] several powerful sulfoximine-based ligands have been developed for enantioselective metal catalysis.[18,19] Motivated by their effective applications in for example, asymmetric palladium and copper catalyses[20,21] by us and others, we recently focused our attention on studying the efficiency of these ligands in Cu^{II}-promoted Mukaiyama-type aldol reactions. In this context, we also prepared novel C_1-symmetric aminosulfoximines **4**, which represent a new class of electron-rich aryl-bridged sulfoximine ligands (Scheme 1).



Scheme 1. Mukaiyama-type aldol reaction catalyzed by aminosulfoximine copper complexes.

In a previous communication, we disclosed the successful employment of aminosulfoximines (**4** with $R^1 = R^2 = R^3 = H$) in the Cu^{II}-catalyzed Mukaiyama-aldol reaction between

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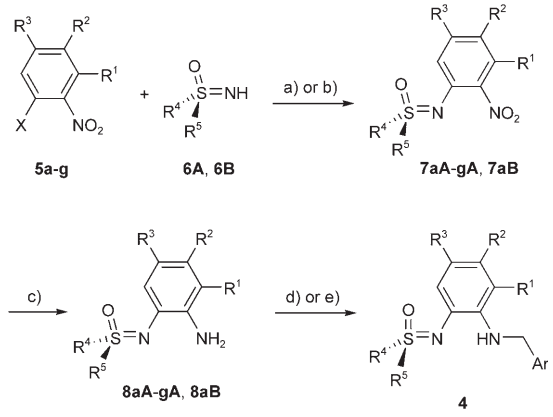
pyruvates and enolsilanes.[22,23] Several aldol products were provided in good yields and with excellent enantiomeric excesses. Here, we present a full account on the synthesis of aminosulfoximines, the optimization process and the scope of the reaction.

Results and Discussion

As outlined in Scheme 2, the novel aminosulfoximines can be readily prepared by a short and high-yielding reaction sequence: First, enantiopure sulfoximines (here **6A** or **6B**) are coupled with *o*-halonitrobenzenes **5a–g** in palladium-catalyzed Buchwald–Hartwig-type reactions or copper-mediated cross-couplings,[24] and then, the nitro groups of the resulting compounds **7** are reduced to give anilines **8**. Subsequent reductive aminations of **8** with a number of aldehydes in the presence of $NaBH_4$ or $NaBH_3CN$ afford the desired target compounds **4** in good yields ranging from 58 to 85% with respect to anilines **8**.



a: $R^1 = R^2 = R^3 = H$; (X = Br)
b: $R^1 = Me$, $R^2 = R^3 = H$; (X = Br)
c: $R^1 = R^3 = H$, $R^2 = Me$; (X = Br)
d: $R^1 = H$, $R^2 = R^3 = Me$; (X = Br)
e: $R^1 = R^3 = H$, $R^2 = OMe$; (X = I)
f: $R^1 = R^3 = H$, $R^2 = F$; (X = I)
g: $R^1 = R^3 = H$, $R^2 = CF_3$; (X = Br)

A: $R^4 = Ph$, $R^5 = Me$
B: $R^4 = Me$, $R^5 = 2$-MeO-Ph
α: Ar = Ph
β: Ar = 1-Naph
γ: Ar = 2-MeO-Ph
δ: Ar = Mes
ε: Ar = 2,4,6-(*i*Pr)$_3$-Ph
φ: Ar = 2,4,6-(MeO)$_3$-Ph

Scheme 2. Synthesis of the aminosulfoximines **4**. a) Ar-Br **5** (1.0 equiv), sulfoximine **6** (1.0–1.3 equiv), $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3 (1.4 equiv), toluene (0.05–0.20 mmol mL^{-1}), 110°C, 24 h, 73–95%; b) Ar-X **5** (2.0 equiv), sulfoximine **6** (1.0 equiv), CuI (1.0 equiv), CsOAc (2.5 equiv), DMSO (1 mmol mL^{-1}), 90°C, 12 h, 80–94%; c) Fe (3.0–4.5 equiv), AcOH (1.8 equiv), EtOH/H_2O, Δ, 3–5 h, 25–91%; d) ArCHO (1.1–1.2 equiv), AcOH (1.0–1.1 equiv), $NaBH_4$ (2.5 equiv), MeOH, 0°C → RT, overnight, 81–85%; e) ArCHO (1.2–2.5 equiv), $NaBH_3CN$ (0.9–1.0 equiv), AcOH (pH 6), MeOH, 0°C → RT, overnight, 58–86%.

Table 1. Structural identification code of aminosulfoximines **4**.

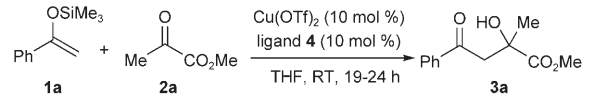
Entry	Product	R^1	R^2	R^3	R^4	R^5	Ar	Method[a]	Yield [%][a]
1	(*S*)-**4aAα**	H	H	H	Ph	Me	Ph	d	81
2	(*S*)-**4aAβ**	H	H	H	Ph	Me	1-Naph	d	85
3	(*S*)-**4aAγ**	H	H	H	Ph	Me	2-MeO-Ph	d	81
4	(*S*)-**4aAδ**	H	H	H	Ph	Me	Mes	e	85
5	(*S*)-**4aAε**	H	H	H	Ph	Me	2,4,6-(*i*Pr)$_3$-Ph	d	82
6	(*S*)-**4aAφ**	H	H	H	Ph	Me	2,4,6-(MeO)$_3$-Ph	d	85
7	(*R*)-**4aBδ**	H	H	H	Me	2-MeO-Ph	Mes	e	72
8	(*R*)-**4aBε**	H	H	H	Me	2-MeO-Ph	2,4,6-(*i*Pr)$_3$-Ph	d	64
9	(*S*)-**4bAδ**	Me	H	H	Ph	Me	Mes	e	59
10	(*S*)-**4cAδ**	H	Me	H	Ph	Me	Mes	e	86
11	(*S*)-**4dAδ**	H	Me	Me	Ph	Me	Mes	e	78
12	(*S*)-**4eAδ**	H	OMe	H	Ph	Me	Mes	e	30[b]
13	(*S*)-**4fAδ**	H	F	H	Ph	Me	Mes	e	83
14	(*S*)-**4gAδ**	H	CF_3	H	Ph	Me	Mes	e	58

[a] Referring to the reductive amination to give **4**; for details see Scheme 2 and Experimental Section. [b] Over two steps: nitro group reduction and reductive amination.

This procedure allows the combination of diverse sulfoximine precursors, different aromatic bridging units and numerous carbonyl compounds and thereby, a library of modular ligands can be easily generated. Synthetic details of the reductive amination step and the structural identification code for the aminosulfoximines **4** are depicted in Table 1.

In order to find the best ligand structure for the Mukaiyama-type aldol reaction (Scheme 1) and to establish a structure/activity/selectivity profile (SASP), the newly prepared aminosulfoximines were employed as ligands in a copper(II) catalysis by using 1-phenyl-1-(trimethylsilyloxy) ethene (**1a**) and methyl pyruvate (**2a**) as substrates. This model reaction was performed at ambient temperature in THF, and with copper(II) triflate as metal source. The results are summarized in Table 2.

Table 2. Influence of the ligand structure on the test reaction to give **3a**.[a]



Entry	Sulfoximine	Yield **3a** [%][b]	*ee* **3a** [%][c,d]
1	(*S*)-**4aAα**	64	70 (*R*)
2	(*S*)-**4aAβ**	77	83 (*R*)
3	(*S*)-**4aAγ**	72	86 (*R*)
4	(*S*)-**4aAδ**	88	93 (*R*)
5	(*S*)-**4aAε**	>99	93 (*R*)
6	(*S*)-**4aAφ**	17	72 (*R*)
7	(*R*)-**4aBδ**	87	86 (*S*)
8	(*S*)-**4bAδ**	50	91 (*R*)
9	(*S*)-**4cAδ**	75	90 (*R*)
10	(*S*)-**4dAδ**	84	91 (*R*)
11	(*S*)-**4eAδ**	77	90 (*R*)
12	(*S*)-**4fAδ**	84	93 (*R*)
13	(*S*)-**4gAδ**	60	82 (*R*)

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), aminosulfoximine **4** (0.05 mmol), THF, RT, 19–24 h. [b] After column chromatography. [c] Determined by HPLC, using a column with a chiral stationary phase (Chiralcel OD). [d] The absolute configuration of **3a** was determined by measuring the optical rotation and compared to the literature value[9] of the corresponding enantiomer.

The application of the aminosulfoximine **4aAα** was found to afford the aldol product **3a** in moderate 64% yield with a promising enantiomeric excess (*ee*) of 70% (Table 2, entry 1). Assuming that electron-donating *ortho*-substituents on the benzylamino moiety could have a positive effect on both yield and enantioselectivity due to a higher steric compression on the metal center combined with an increased metal–ligand interaction, sulfoximines with substituted benzyl groups were next applied. Indeed, by using the analogous 1-naphthyl and *o*-methoxy derivative **4aAβ** and **4aAγ**, respectively (Table 2, entries 2 and 3), higher yields and increased enantioselectivities were achieved. The introduction of a second *ortho*-substituent resulted in a further improvement of both the yield and the selectivity. Thus, mesitylene derivative **4aAδ** as well as the triisopropyl analogue **4aAε** furnished **3a** with 93% *ee* (entries 4 and 5). With the latter sulfoximine, also the best yield (>99%) was obtained. Apparently, the results of this first ligand screening confirmed our initial hypothesis. The aminosulfoximines with electron-rich *ortho*-dialkylated benzyl groups led to the highest catalytic activities and enantioselectivities. In an attempt to further utilize this effect, sulfoximine **4aA**ϕ with a 2,4,6-trimethoxybenzyl group was applied. However, in this case a significant decrease of the product yield (17%) and the *ee* (72%) was observed (entry 6). Probably, this reduced catalytic efficiency was caused by the *ortho*-methoxy groups, which interacted with the copper(II) center (intra- or intermolecularly) and thereby interfered with the course of the reaction. An analogous observation was made in a catalysis with a ligand bearing a modified sulfoximine unit. Thus, **4aBδ** having a 2-methoxy group at the sulfoximine part gave **3a** with only 86% *ee* (Table 2, entry 7).[25]

With respect to the absolute configuration of the product it was found that (*R*)-configured sulfoximine **4aBδ** favored the formation of the (*S*)-enantiomer of **3a**, whereas all other (*S*)-configured aminosulfoximines (with *S*-phenyl and *S*-methyl substituents) preferentially provided the (*R*)-enantiomer of **3a**. Thus using this approach, both enantiomers of the products are available.

In copper-catalyzed Diels–Alder[21b] and carbonyl–ene reactions[23] we had previously observed an effect of the substitution pattern of the bridging arene on the catalyst performance. Therefore, we included aminosulfoximines **4bAδ**–**4gAδ** in the study reported here. As revealed by the data presented in Table 2 (entries 8–13), a modification of the bridging arene with electron-donating and -withdrawing substituents had only a minor impact on yield and *ee* in this case. With the exception of CF_3-substituted sulfoximine **4gAδ** which furnished **3a** with only 82% *ee*, all other ligands performed very well affording the aldol product with >90% *ee*. From this set of sulfoximines fluoro-substituted **4fAδ** proved to be the best giving **3a** with 93% *ee* in 84% yield.

For a further optimization we focused our attention on the reaction conditions and investigated the effect of the solvent and the copper(II) salt on the catalyzed reaction between **1a** and **2a** to give **3a**. Other important parameters such as the dependence of the reaction course on the temperature and the catalyst loading were also taken into consideration.

First, the variation of the solvent was investigated with a catalyst bearing **4aAδ** as ligand. Expectedly, the change from THF to the related solvent diethyl ether had only a minor effect on the enantioselectivity (Table 3, entries 1 and 2). Thus, in the latter solvent aldol product **3a** was isolated with comparably high 92% *ee*, albeit the yield was significantly lower (61%). A similar trend was observed when toluene was applied as solvent (entry 3). In this case, the product was obtained with high 91% *ee*, but the yield further decreased to 41%. Use of dioxane slightly reduced the *ee* value to 86% (entry 4). The change to the chlorinated solvents dichloromethane and chloroform led to 82 and 87% *ee*, respectively (entries 5 and 6), and the catalysis in CH_2Cl_2 gave the best yield (90%). Propionitrile, however, proved to be an unsuitable solvent, which completely inhibited the conversion (entry 7). From these experiments we deduced that weakly coordinating or aromatic solvents such as THF, diethyl ether or toluene were important for high enantioselectivities. With regard to the catalytic activity, THF proved to be the most suitable solvent.

Table 3. Influence of the solvent and the counterion on the test reaction to give **3a**.[a]

Entry	CuX_2	Solvent	Yield **3a** [%][b]	*ee* **3a** [%][c,d]
1	$Cu(OTf)_2$	THF	88	93
2	$Cu(OTf)_2$	Et_2O	61	92
3	$Cu(OTf)_2$	toluene	41	91
4	$Cu(OTf)_2$	dioxane	79	86
5	$Cu(OTf)_2$	CH_2Cl_2	90	82
6	$Cu(OTf)_2$	$CHCl_3$	57	87
7	$Cu(OTf)_2$	EtCN	–	–
8	$Cu(PF_6)_2$[e]	THF	19	0
9	$Cu(BF_4)_2$[e]	THF	48	69
10	$Cu(SbF_6)_2$[e]	THF	67	62
11	$Cu(ClO_4)_2$[e]	THF	>99	81

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), CuX_2 (0.05 mmol), aminosulfoximine **4aAδ** (0.05 mmol), solvent, RT, 19–24 h. [b] After column chromatography. [c] Determined by HPLC, using a column with a chiral stationary phase (Chiralcel OD). [d] The absolute configuration of **3a** was determined by measuring the optical rotation and compared to the literature value[9] of the corresponding enantiomer. [e] Prepared in situ from $CuCl_2$ (0.05 mmol) and AgX (0.1 mmol).

Inspired by previous findings that counterions participate in the formation of Cu^{II}–sulfoximine complexes,[26] we subsequently studied the effect of the kind of copper salt on the enantioselectivity. In general, the application of counterions different from triflate (Table 3, entry 1) resulted in a significant reduction of the product *ee*. $Cu(PF_6)_2$ showed to be an inappropriate copper(II) salt, since **3a** was obtained as a racemate in low yield (entry 8). In contrast, $Cu(BF_4)_2$ and $Cu(SbF_6)_2$ gave moderate results in terms of yield and *ee* (69 and 62% *ee*, respectively, entries 9 and 10). With respect to the yield, the copper(II) perchlorate derived catalyst (entry 11) proved superior over all other ones (>99%), but the *ee* was only 81%.

Next, we concentrated on the reduction of the catalyst loading. The reaction was found to proceed smoothly when the amount of the catalyst precursors [$Cu(OTf)_2$ and sulfoximine **4aAε**] was decreased from 10 mol% (Table 4, entry 1) to 5 mol% and to 1 mol% (entries 2 and 3, respectively). In both cases, the product was obtained in good yield and with unchanged *ee* (93%). However, a further lowering of the catalyst loading to 0.5 mol% resulted in a drastic decrease of the yield and for the first time, in a diminution of the enantioselectivity (to 89% *ee*, entry 4). Apparently, a minimal catalyst amount of 1 mol% is essential in order to achieve high yields without affecting the *ee*.

Finally, the temperature dependence of the reaction course was evaluated. As shown in Table 4 (entries 1 and 5), the *ee* increased by lowering the reaction temperature from room temperature to −10°C yielding aldol product **3a** with 96% *ee*. Performing the catalysis at −40°C led to a further increase of the *ee* (97%; entry 6), and by lowering the temperature to −55°C, the enantioselectivity was even improved to give **3a** with 98% *ee* (entry 7). However, under these conditions the reaction time had to be extended up to 10 days (entries 6 and 7) in order to isolate the product in respectable yield. At −78°C a complete inhibition of the catalysis was observed.

Based on earlier reports describing an accelerating effect of 2,2,2-trifluoroethanol on the catalytic turnover in Mukaiyama-type Michael reactions,[27] we decided to test this additive in the aldol reaction described here. Gratifyingly, the same positive effect was observed. After a significantly reduced reaction period of 15 h at −30°C, aldol product **3a** could be obtained in high yield (89%) with excellent *ee* (98%) (entry 8). Hence, also in this system a strong acceleration effect (without affecting the enantioselectivity) became evident. Unfortunately, the additive had no effect on the catalysis performed at −78°C, and still no product formation was observed.

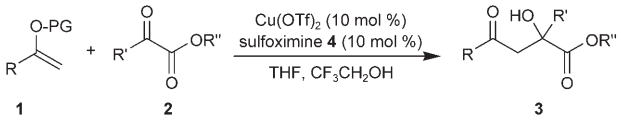
Having optimized the system consisting of sulfoximine **4aAε** as the ligand, THF as the solvent, copper(II) triflate as the copper(II) source and 2,2,2-trifluoroethanol as additive at low temperatures, we subsequently studied the substrate scope of the process and assessed various enolsilanes as well as α-keto esters. First, the ester substituent was varied and the reaction of benzyl pyruvate (**2b**) with enolsilane **1a** at −50°C was studied. The corresponding aldol product **3b** was isolated in high yield with excellent 98% *ee* (Table 5, entry 2). Use of isopropyl pyruvate (**2c**) furnished **3c** with 99% *ee* (entry 3). Hence, the catalytic system featured a

Table 4. Effect of the catalyst loading and the temperature on the test reaction to give **3a**.[a]

Entry	Cat. [mol%]	T [°C]	t [h]	Yield **3a** [%][b]	*ee* **3a** [%][c,d]
1	10	RT	19	>99	93 (*R*)
2	5	RT	24	87	93 (*R*)
3	1	RT	24	86	93 (*R*)
4	0.5	RT	24	16	89 (*R*)
5	10	−10	5	43	96 (*R*)
6	10	−40	122	78	97 (*R*)
7	10	−55	235	83	98 (*R*)
8[e]	10	−30	15	89	98 (*R*)

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), $Cu(OTf)_2$, aminosulfoximine **4aAε**, THF. [b] After column chromatography. [c] Determined by HPLC, using a column with a chiral stationary phase (Chiralcel OD). [d] The absolute configuration of **3a** was found to be *R* in all cases as determined by measuring the optical rotation and comparing it to the literature value[9] of the corresponding enantiomer. [e] Performed in the presence of CF_3CH_2OH (0.6 mmol).

Table 5. Substrate scope under optimized conditions.[a]



1a: R = Ph, PG = $SiMe_3$
1b: R = Me, PG = $SiMe_3$
1c: R = *t*BuS, PG = $SiMe_3$
1d: R = *t*BuS, PG = Si*t*BuMe_2
2a: R' = R'' = Me
2b: R' = Me, R'' = Bn
2c: R' = Me, R'' = *i*Pr
2d: R' = $(CH_2)_2$Ph, R'' = Et
2e: R' = Et, R'' = Me

3a: R = Ph, R' = R'' = Me
3b: R = Ph, R' = Me, R'' = Bn
3c: R = Ph, R' = Me, R'' = *i*Pr
3d: R = Ph, R' = $(CH_2)_2$Ph, R'' = Et
3e: R = Ph, R' = Et, R'' = Me
3f: R = R' = Me, R'' = Bn
3g: R = *t*BuS, R' = R'' = Me
3h: R = *t*BuS, R' = Me, R'' = Bn
3i: R = *t*BuS, R' = Me, R'' = *i*Pr

Entry	Sulfoximine	Enol ether	Keto ester	Product	T [°C]	t [h]	Yield [%][b]	*ee* [%][c,d]
1	(*S*)-**4aAε**	**1a**	**2a**	**3a**	−30	15	89	98 (*R*)
2	(*S*)-**4aAε**	**1a**	**2b**	**3b**	−50	47	86	98 (*R*)
3	(*S*)-**4aAε**	**1a**	**2c**	**3c**	−40	28	90	99 (*R*)
4	(*S*)-**4aAε**	**1a**	**2d**	**3d**	−20	40	86	96 (*R*)
5	(*S*)-**4aAε**	**1a**	**2e**	**3e**	RT	20	78	89 (*R*)
6	(*S*)-**4aAε**	**1b**	**2b**	**3f**	−40	46	71	91 (*R*)
7	(*S*)-**4aAε**	**1c**	**2a**	**3g**	−45	109	66	77 (*R*)
8	(*R*)-**4aBδ**	**1c**	**2a**	**3g**	−40	51	86	91 (*S*)
9	(*R*)-**4aBε**	**1c**	**2a**	**3g**	−55	48	44	67 (*S*)
10	(*R*)-**4aBδ**	**1c**	**2b**	**3h**	−50	49	79	93 (*S*)
11	(*R*)-**4aBδ**	**1c**	**2c**	**3i**	−50	72	82	98 (*S*)
12	(*R*)-**4aBδ**	**1d**	**2a**	**3g**	−5	6	76	91 (*S*)
13	(*R*)-**4aBδ**	**1d**	**2b**	**3h**	−5	6	58	91 (*S*)
14	(*R*)-**4aBδ**	**1d**	**2c**	**3i**	−5	6	76	93 (*S*)

[a] Reaction conditions: **1a–d** (0.6–0.75 mmol), **2a–e** (0.5 mmol), CF_3CH_2OH (0.6 mmol), $Cu(OTf)_2$ (0.05 mmol), aminosulfoximine **4** (0.05 mmol). [b] After column chromatography. [c] Determined by HPLC using chiral columns (Chiralcel AS, OD, OD-H or OJ). [d] The absolute configurations of **3a**, **3g** and **3h** were determined by measuring the optical rotations and compared to the literature values[9] of the corresponding enantiomers. For the other products it was assigned in analogy.

pronounced flexibility with respect to the nature of the ester moiety.

Next, the acyl part of **2** was modified, and ethyl 2-oxo-4-phenyl butyrate (**2d**) having an extended substituent on the ketone carbonyl of **2**, was treated with nucleophile **1a** at −20 °C. Also in this case, the corresponding α-hydroxy ester **3d** was obtained with a very good enantioselectivity of 96 % *ee* (Table 5, entry 4). Treatment of methyl α-keto butyrate (**2e**) with **1a** yielded product **3e** with a slightly lower *ee* (89 %) at room temperature (entry 5), and surprisingly, no conversion was observed at lower temperatures. These results reveal that the nature of the acyl substituent influences the efficiency of the catalyst, which contrasts the observations made with substrates having a structural modification in the ester moiety of **2** (see above).

Finally, the effect of the nucleophile was examined and the reaction between the acetone-derived enolsilane **1b** and benzyl pyruvate (**2b**) was studied (Table 5, entry 6). Although the steric hindrance of enolsilane **1b** is very different to that of **1a**, product **3f** was also obtained with a remarkable enantioselectivity (91 % *ee* at −40 °C). Disappointingly, treatment of thioketene acetal **1c** with methyl pyruvate (**2a**) gave succinate derivate **3g** with only a moderate *ee* (77 %, entry 7). A modification of the ligand architecture, however, and use of aminosulfoximine **4aBδ** having a 2-methoxyphenyl moiety on the sulfoximine part[25] caused a significant increase of the asymmetric induction and the corresponding product **3g** was obtained with an *ee* of 91 % (entry 8). On the other hand, a negative impact on the course of the reaction was observed, when the more bulky triisopropyl analogue **4aBε** was applied. In this case both the activity and the selectivity (67 % *ee*) of the catalytic species were affected (entry 9). Guided by this discovery, aminosulfoximine **4aBδ** was also selected as ligand in other reactions involving thioketene acetals. To our delight this approach proved successful and catalyses with **1c** in combination with α-keto esters **2b** and **2c** having sterically more demanding ester substituents (entries 10 and 11) afforded the corresponding succinate derivatives (**3h** and **3i**, respectively) with even higher *ee* values (than the 91 % *ee* for the conversion of **2a**). Thus, by reacting **1c** with benzyl pyruvate (**2b**) product **3h** with 93 % *ee* was obtained, and the catalysis between isopropyl pyruvate (**2c**) and **1c** provided **3i** with 98 % *ee*. TBDMS-analogue **1d** proved to be a suitable enolsilane for the synthesis of **3g**, **3h** and **3i** as well and similarly good results as with **1c** were obtained (entries 12–14). Unfortunately, the increased steric bulk of **1d** showed no further positive effect on the enantioselectivities.

In the light of the results presented in this part it can be stated, that the catalytic system is sensitive to the nature of the enolsilane, and that the high modularity of the aminosulfoximines has so far allowed to rapidly find an effective ligand for every substrate pair.

Conclusion

We have described the development of a new ligand class consisting of C_1-symmetric aryl-bridged aminosulfoximines which proved to be powerful ligands in copper(II)-catalyzed enantioselective Mukaiyama-type aldol reactions. Their application allows the preparation of a variety of synthetically interesting α-hydroxy esters with quaternary stereogenic centers. The high yields (up to 90 %) and the outstanding enantioselectivities (up to 99 % *ee*) compare well with the results obtained with Evans' well-established [Cu^{II}-*t*Bubox]$^{2+}$ and [Sn^{II}-pybox]$^{2+}$ complexes.[2d,9] Currently, investigations to identify relevant intermediates by spectroscopic means and computational studies are in progress. Here, it appears reasonable to find copper-ligand-substrate complexes, which are similar to the one, which has recently been identified in mixtures of bissulfoximines, copper(II) triflate and chelating substrates related to pyruvates.[26] Through those explorations, we hope to be able to establish a mechanistic model and to explain the origin of the high enantioselectivities.

Experimental Section

General methods: All experiments were carried out under Ar using standard Schlenk techniques. If necessary, solvents were dried and deoxygenated by standard procedures. Flash chromatography was carried out with Merck silica gel 60 (63–100 mesh). Analytical TLC was performed with Merck silica gel 60 F_{254} plates, and the products were visualized by UV detection or by utilization of phosphomolybdic acid. The optical rotations were measured at room temperature, $\lambda = 589$ nm using a Perkin–Elmer Model 241. Melting points are uncorrected and were obtained on a Büchi B-450 apparatus in open capillaries. The NMR spectra were recorded on a Varian Inova 400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) or a Varian Gemini (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz) instrument, the spectra were recorded in $CDCl_3$ by using TMS as internal standard, and the positions of the signals are reported in ppm. ^{1}H NMR data are reported as: (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration, proton assignment). The IR spectra were measured on a Perkin–Elmer FT/IR 1760 instrument, the samples were prepared as KBr pellets or as films. The MS spectra were recorded on a Varian MAT 212 system. Elemental analyses were measured with a Heraeus Model CHN Rapid. Analytical HPLC measurements were carried out on a Gynkotek (Dionex) machine (autosampler GINA 50, UV/VIS detector UVD 170S, gradient pump M480G, degasser DG 503) using a Chiralcel AS, OD, OD-H or OJ column (0.46 cm × 25 cm) from Daicel. Alternatively, an Agilent system (1100 series) was employed consisting of a degasser G1379A, a quaternary pump G1311A, an autosampler G1313A, an oven G1316A, and an UV-detector G1315B.

o-Bromonitrobenzene (**5a**), methyl pyruvate (**2a**), *o*-anisaldehyde and 2,4,6-trimethylbenzaldehde were purchased from Aldrich. 1-Bromo-3-methyl-2-nitrobenzene (**5b**), 1-bromo-4-methyl-2-nitrobenzene (**5c**) and CsOAc were obtained from Acrôs. 4,5-Dimethyl-2-nitroaniline, 1-iodo-4-methoxy-2-nitrobenzene (**5e**), 4-fluoro-1-iodo-2-nitrobenzene (**5f**), 1-bromo-2-nitro-4-trifluoromethylbenzene (**5g**) were purchased from Lancaster. The silyl enol ethers **1a** and **1b**, benzaldehyde and 1-naphthaldehyde were purchased from Fluka. Silyl enol ethers **1c** and **1d**,[28] α-keto esters **2b**, **2c** and **2e**,[29] sulfoximines **6A**[30] and **6B**[19g] and triisopropylbenzaldehyde[31] were prepared according to literature procedures.

1-Bromo-4,5-dimethyl-2-nitrobenzene (5d): A solution of 4,5-dimethyl-2-nitroaniline (3.0 g, 18.0 mmol) in a mixture of distilled water (114 mL)

and an aqueous solution of HBr (48%, 32 mL) was stirred for 30 min to 70°C. After cooling to −5°C a solution of $NaNO_2$ (7.8 g, 113.0 mmol) in distilled water (38 mL) was added. The temperature was maintained at −5°C for 15 min and then a freshly prepared and cooled solution of CuBr (32.7 g, 243.0 mmol) in an aqueous solution of HBr (48%, 62 mL) was added to the resulting mixture. After heating for 15 min to 70°C, the mixture was extracted three times with chloroform (200 mL). The combined organic extracts were washed with an aqueous solution of NaOH (10%, 200 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography (silica gel, pentane/EtOAc 9:1) to afford (**5d**) as a yellow solid (3.6 g, 15.7 mmol, 87%). M.p. 60°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.28$ (s, 3H, CH_3), 2.30 (m, 3H, CH_3), 7.45 (s, 1H, Ar-H), 7.64 ppm (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.4$, 19.7, 111.2, 126.5, 135.5, 137.6, 143.8, 147 ppm; IR (KBr): $\tilde{\nu} = 2926$, 2863, 1521, 1347, 1021, 889 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 229.0 (99) $[M]^+$; elemental analysis calcd (%) for $C_8H_8BrNO_2$ (230.06): C 41.77, H 3.50, N 6.09; found: C 41.64, H 3.75, N 5.87.

General procedure 1 (Pd-catalyzed Buchwald–Hartwig-type reaction): A flame-dried Schlenk-flask was charged with the bromonitrobenzene (**5a–c**, 1.0 equiv), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**] or (*R*)-*S*-(methoxyphenyl)-*S*-methylsulfoximine [(*R*)-**6B**, 1.00–1.25 equiv], $Pd(OAc)_2$ (5 mol-%), *rac*-BINAP (7.5 mol-%) and Cs_2CO_3 (1.4 equiv). Subsequently, dry toluene ($c = 0.05$–0.20 mmol mL^{-1}) was added, and the mixture was heated to 110°C for 24 h. The suspension was then filtered over Celite with ethyl acetate as eluent. Subsequently, the solvent was evaporated and the product was purified by flash chromatography (silica gel).

General procedure 2 (Cu-mediated cross-coupling reaction): Under an argon atmosphere a dry Schlenk tube was charged with (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 1.0 equiv], the aryl halide (2.0 equiv), CuI (1 equiv) and CsOAc (2.5 equiv). The mixture was dissolved in degassed DMSO (1.0 mmol mL^{-1}). After heating to 90°C for 12 h, the mixture was cooled to room temperature and neutralized with aqueous HCl (20 mL). The aqueous layer was extracted with dichloromethane three times (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica gel) afforded the *N*-arylated sulfoximines.

(*S*)-*N*-(2-Nitrophenyl)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7aA]: The product was prepared according to the general procedure 1 by using *o*-bromonitrobenzene (**5a**, 2.42 g, 12.0 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 1.86 g, 12.0 mmol], $Pd(OAc)_2$ (135 mg, 0.60 mmol), *rac*-BINAP (561 mg, 0.90 mmol), Cs_2CO_3 (5.47 g, 16.8 mmol) and toluene (60 mL). The product was purified by flash chromatography (silica gel, pentane/EtOAc 4:1) to yield (*S*)-**7aA** as a yellow oil (2.96 g, 10.7 mmol, 89%). $[\alpha]_D^{20} = -33.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 3.27 (s, 3H, CH_3), 6.91–6.96 (m, 1H, Ar-H), 7.21–7.30 (m, 2H, Ar-H), 7.54–7.67 (m, 4H, Ar-H), 8.05–8.09 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.8$, 121.3, 124.4, 124.5, 128.6, 129.7, 132.5, 133.8, 138.6, 139.1 ppm; IR (film): $\tilde{\nu} = 3066$, 3025, 2930, 1601, 1522, 1479, 1359, 1289, 1209, 1099, 1021, 774, 747, 689, 508 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 276 (100) $[M]^+$, 167 (26), 141 (40), 125 (31), 77 (56), 51 (13); elemental analysis calcd (%) for $C_{13}H_{12}N_2O_3S$ (276.31): C 56.51, H 4.38, N 10.14; found: C 56.50, H 4.65, N 10.12.

(*R*)-*N*-(2-Nitrophenyl)-*S*-2-(methoxyphenyl)-*S*-methylsulfoximine [(*R*)-7aB]: The product was prepared according to the general procedure 1 by using *o*-bromonitrobenzene (**5a**, 808 mg, 4.00 mmol), (*R*)-*S*-(methoxyphenyl)-*S*-methylsulfoximine [(*R*)-**6B**, 741 mg, 4.00 mmol], $Pd(OAc)_2$ (45 mg, 0.20 mmol), *rac*-BINAP (187 mg, 0.30 mmol), Cs_2CO_3 (1.83 g, 5.62 mmol) and toluene (40 mL). The product was purified by flash chromatography (silica gel, pentane/EtOAc 4:1 → 2:1) to yield (*R*)-**7aB** as a yellow solid (893 mg, 2.92 mmol, 73%). $[\alpha]_D^{20} = +133.9$ ($c = 0.99$ in $CHCl_3$); m.p. 95°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.42$ (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.84–6.89 (m, 1H, Ar-H), 6.94–6.98 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.04–7.09 (m, 1H, Ar-H), 7.14–7.23 (m, 2H, Ar-H), 7.50–7.57 (m, 2H, Ar-H), 8.02–8.06 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.1$, 55.8, 112.1, 120.3, 120.8, 123.9, 124.1, 125.0, 131.6, 131.7, 135.4, 138.9, 156.7 ppm; IR (KBr): $\tilde{\nu} = 3043$, 3018, 1596, 1517, 1477, 1440, 1359, 1319, 1288, 1249, 1197, 1165, 1013, 766, 747, 659 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 306 (100) $[M]^+$, 171 (23), 156 (34), 141 (21), 125 (23), 97 (15), 77 (23); elemental analysis calcd (%) for $C_{14}H_{14}N_2O_4S$ (306.34): C 54.89, H 4.61, N 9.14; found: C 54.77, H 4.21, N 9.03.

(*S*)-*N*-[3-Methyl-2-nitrophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7bA]: The product was prepared according to the general procedure 1 by using 1-bromo-3-methyl-2-nitrobenzene (**5b**, 1.00 g, 4.6 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 0.90 g, 5.8 mmol], $Pd(OAc)_2$ (52 mg, 0.23 mmol), *rac*-BINAP (215 mg, 0.35 mmol), Cs_2CO_3 (2.10 g, 6.4 mmol) and toluene (80 mL). The target compound was afforded as a yellow solid (1.28 g, 4.4 mmol, 95%) after flash chromatography (silica gel, pentane/EtOAc 4:1). $[\alpha]_D^{20} = -51.7$ ($c = 1.15$ in $CHCl_3$); m.p. 75–81°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.23$ (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.71–6.75 (m, 1H, Ar-H), 6.97–7.05 (m, 2H, Ar-H), 7.51–7.64 (m, 3H, Ar-H), 7.96–7.99 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 16.9, 45.7, 120.3, 123.1, 128.3, 129.5, 129.6, 133.5, 137.0, 138.2, 147.2 ppm; IR (KBr): $\tilde{\nu} = 3022$, 1527, 1306, 1109, 750 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 290.1 (100) $[M]^+$, 181.1 (13), 141 (42), 125 (22), 77.1 (60); elemental analysis calcd (%) for $C_{14}H_{14}N_2O_3S$ (290.34): C 57.92, H 4.86, N 9.65; found: C 57.99, H 4.67, N 10.01.

(*S*)-*N*-[4-Methyl-2-nitrophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7cA]: The product was prepared according to the general procedure 1 by using 1-bromo-4-methyl-2-nitrobenzene (**5c**, 500 mg, 2.31 mmol) and (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 450 mg, 2.89 mmol], $Pd(OAc)_2$ (26 mg, 0.12 mmol), *rac*-BINAP (108 mg, 0.17 mmol), Cs_2CO_3 (1.05 g, 3.2 mmol) and toluene (40 mL). The target compound was afforded as a yellow oil (630 mg, 2.2 mmol, 95%) after flash chromatography (silica gel, pentane/EtOAc 4:1). $[\alpha]_D^{20} = -85.1$ ($c = 1.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.19$ (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 7.11 (d, $J =$ 8.2 Hz, 1H, Ar-H), 7.38 (d, $J = 1.9$ Hz, 1H, Ar-H), 7.98–8.00 (m, 2H, Ar-H), 7.45–7.58 (m, 3H, Ar-H), 7.98 ppm (dd, $J = 8.2$, 1.9 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.5$, 45.7, 124.5, 124.7, 128.6, 129.6, 131.5, 133.40, 133.7, 136.3, 138.7, 144.8 ppm; IR (KBr): $\tilde{\nu} = 3064$, 1496, 1278, 1213, 756 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 290.1 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_3S$ (290.34): C 57.92, H 4.86, N 9.65; found: C 57.61, H 4.90, N 9.69.

(*S*)-*N*-[4,5-Dimethyl-2-nitrophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7dA]: The product was prepared according to the general procedure 2 by using 1-bromo-4,5-dimethyl-2-nitrobenzene (**5d**, 1.0 g, 4.35 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 337 mg, 2.18 mmol]. The target compound was afforded as a yellow solid (527 mg, 1.73 mmol, 80%) after flash chromatography (silica gel, pentane/EtOAc 4:1). $[\alpha]_D^{20} =$ −62.0 ($c = 1.2$ in $CHCl_3$); m.p. 104°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.16 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.11 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 7.53–7.66 (m, 3H, Ar-H), 8.08–8.10 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 19.9, 45.4, 125.3, 125.6, 128.4, 129.4, 130.3, 133.4, 136.7, 138.7, 142.4, 142.5 ppm; IR (KBr): $\tilde{\nu} =$ 3031, 2936, 1521, 1300, 1221, 1105, 989, 726 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 304.2 (100) $[M]^+$; elemental analysis calcd (%) for $C_{15}H_{16}N_2O_3S$ (304.36): C 59.19, H 5.30, N 9.20; found: C 59.14, H 5.32, N 9.25.

(*S*)-*N*-[4-Methoxy-2-nitrophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7eA]: The product was prepared according to the general procedure 2 by using 1-iodo-4-methoxy-2-nitrobenzene (**5e**, 502 mg, 1.80 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 140 mg, 0.90 mmol]. The target compound was afforded as an orange oil (220 mg, 0.72 mmol, 80%) after flash chromatography (silica gel, pentane/EtOAc 7:3). $[\alpha]_D^{20} = -124.5$ ($c =$ 0.59 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.19$ (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.79 (dd, $J = 9.1$, 3.1 Hz, 1H, Ar-H), 7.13 (d, $J = 3.1$ Hz, 1H, Ar-H), 7.17 (d, $J = 9.1$ Hz, 1H, Ar-H), 7.46–7.59 (m, 3H, Ar-H), 7.97–8.00 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 45.4, 55.9, 109.0, 119.8, 126.1, 128.7, 129.7, 132.0, 133.8, 138.7, 145.2, 154.2 ppm; IR (KBr): $\tilde{\nu} = 2928$, 1524, 1494, 1278, 1225, 1098 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 306.0 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_4S$ (306.34): C 54.89, H 4.61, N 9.14; found: C 54.87, H 4.24, N 9.28.

(*S*)-*N*-[4-Fluoro-2-nitrophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7fA]: The product was prepared according to the general procedure 2 by using 4-fluoro-1-iodo-2-nitrobenzene (**5f**, 51 mg, 0.19 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 15 mg, 0.10 mmol]. The target compound was afforded as a yellow solid (27 mg, 0.09 mmol, 94%) after flash chroma-

tography (silica gel, dichloromethane/methanol 99:1). $[\alpha]_D^{20} = -98.5$ ($c = 0.99$ in $CHCl_3$); m.p. 81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.19$ (s, 3H, CH_3), 6.95–6.98 (m, 1H, Ar-H), 7.18–7.22 (m, 1H, Ar-H), 7.30–7.33 (m, 1H, Ar-H), 7.47–7.61 (m, 3H, Ar-H), 7.85–7.98 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.8$, 111.8 (d, $J_{CF} = 24$ Hz, CH), 119.9 (d, $J_{CF} = 24$ Hz, CH), 125.7 (d, $J_{CF} = 8$ Hz, CH), 128.6, 129.8, 133.9, 135.5, 138.4, 142.0, 156.4 ppm (d, $J_{CF} = 241$ Hz, CF); IR (KBr): $\tilde{\nu} = 1532$, 1485, 1214 cm^{-1}; MS (70 eV, EI): m/z (%): 294.0 (100) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{11}FN_2O_3S$ (294.30): C 53.05, H 3.77, N 9.52; found: C 52.67, H 4.13, N 9.20.

(*S*)-*N*-[2-Nitro-4-trifluoromethylphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-7gA]: The product was prepared according to the general procedure 2 by using 1-bromo-2-nitro-4-trifluoromethylbenzene (**5g**, 1.0 g, 3.70 mmol), (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**6A**, 286 mg, 1.85 mmol]. The target compound was afforded as a yellow oil (540 mg, 1.57 mmol, 85%) after flash chromatography (silica gel, pentane/EtOAc 4:1). $[\alpha]_D^{20} = -14.1$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.24$ (s, 3H, CH_3), 7.26 (d, $J = 8.7$ Hz, 1H, Ar-H), 7.36 (dd, $J = 8.7$, 2.2 Hz, 1H, Ar-H), 7.49–7.63 (m, 3H, Ar-H), 7.81 (d, $J = 2.2$ Hz, 1H, Ar-H), 7.96–8.01 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.5$, 121.5, 123 (q, $J_{CF} = 35$ Hz, C), 123.4 (q, $J_{CF} = 272$ Hz, CF_3), 124.1, 128.5, 129.1, 130.0, 134.3, 138.0, 142.7, 144.5 ppm; IR (KBr): $\tilde{\nu} = 1623$, 1534, 1324, 1215, 1125 cm^{-1}; MS (70 eV, EI): m/z (%): 344.0 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{11}F_3N_2O_3S$ (344.31): C 48.84, H 3.22, N 8.14; found: C 48.91, H 3.29, N 8.12.

(*S*)-*N*-(2-Aminophenyl)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8aA]: Compound (*S*)-**7aA** (2.96 g, 10.7 mmol) was dissolved in a mixture of EtOH (70 mL) and H_2O (35 mL) and then treated with glacial acetic acid (11.0 mL, 19.2 mmol) and Fe (2.68 g, 48.2 mmol). After refluxing for 3 h, the mixture was cooled to room temperature and then partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were washed with sat. aqueous Na_2CO_3 (50 mL) and dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography on silica gel (EtOAc/pentane 4:1 with 1% of Et_3N) to afford (*S*)-**8aA** as a beige solid (2.2 g, 8.83 mmol, 83%). $[\alpha]_D^{20} = -6.8$ ($c = 1.0$ in $CHCl_3$); m.p. 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.25$ (s, 3H, CH_3), 3.74 (brs, 2H, NH_2), 6.45–6.51 (m, 1H, Ar-H), 6.68–6.77 (m, 2H, Ar-H), 6.88–6.91 (m, 1H, Ar-H), 7.49–7.61 (m, 3H, Ar-H), 7.96–8.00 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.9$, 114.9, 118.5, 122.0, 122.7, 128.5, 129.5, 131.6, 133.3, 139.3, 140.7 ppm; IR (KBr): $\tilde{\nu} = 3418$, 3335, 3020, 1610, 1585, 1499, 1446, 1291, 1251, 1190, 1146, 1096, 1018, 966, 751, 688, 538 cm^{-1}; MS (70 eV, EI): m/z (%): 246 (100) $[M]^+$, 141 (48), 125 (20), 106 (37), 79 (12); elemental analysis calcd (%) for $C_{13}H_{14}N_2OS$ (246.33): C 63.39, H 5.73, N 11.37; found: C 63.41, H 5.73, N 11.49.

(*R*)-*N*-(2-Aminophenyl)-*S*-2-(methoxyphenyl)-*S*-methylsulfoximine [(*R*)-8aB]: Compound (*R*)-**7aB** (893 mg, 2.9 mmol) was dissolved in a mixture of EtOH (50 mL) and H_2O (25 mL) and then treated with glacial acetic acid (3.0 mL, 5.2 mmol) and Fe (734 mg, 13.1 mmol). After refluxing for 3 h and cooling to room temperature, the pH was adjusted to 14 by careful addition of solid NaOH. Subsequently, the resulting suspension was refluxed for 5 min, then filtered immediately, and the remaining residue was washed with EtOH (40 mL) and CH_2Cl_2 (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, EtOAc/pentane 4:1 with 1% of Et_3N) to afford (*R*)-**8aB** as a brownish solid (700 mg, 2.53 mmol, 87%). $[\alpha]_D^{20} = -149.5$ ($c = 1.0$ in $CHCl_3$); m.p. 72–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.38$ (s, 3H, CH_3), 3.70 (brs, 2H, NH_2), 3.95 (s, 3H, OCH_3), 6.46–6.53 (m, 1H, Ar-H), 6.62–6.66 (m, 1H, Ar-H), 6.70–6.77 (m, 1H, Ar-H), 6.92–7.10 (m, 3H, Ar-H), 7.49–7.56 (m, 1H, Ar-H), 8.01–8.05 ppm (m, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.1$, 56.0, 112.3, 114.8, 118.3, 120.8, 122.9, 123.1, 126.8, 131.5, 131.7, 135.1, 141.3, 156.7 ppm; IR (KBr): $\tilde{\nu} = 3435$, 3347, 1593, 1491, 1282, 1249, 1187, 1014, 749 cm^{-1}; MS (70 eV, EI): m/z (%): 276 (100) $[M]^+$, 171 (69), 153 (66), 125 (17), 106 (16), 97 (8), 79 (9); elemental analysis calcd (%) for $C_{14}H_{16}N_2O_2S$ (276.35): C 60.85, H 5.84, N 10.14; found: C 60.90, H 6.05, N 9.88.

(*S*)-*N*-[2-Amino-3-methylphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8bA]: Compound (*S*)-**7bA** (700 mg, 2.41 mmol) was dissolved in a mixture of EtOH (20 mL) and H_2O (30 mL) and then treated with glacial acetic acid (2.40 mL, 4.19 mmol) and Fe (403 mg, 7.23 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, dichloromethane/methanol 99:1 with 1% of Et_3N) to afford (*S*)-**8bA** as a beige solid (157 mg, 0.60 mmol, 25%). $[\alpha]_D^{20} = -40.2$ ($c = 0.522$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.20$ (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 4.19 (brs, NH_2), 6.46 (t, $J = 7.7$ Hz, 1H, Ar-H), 6.65 (d, $J = 7.7$ Hz, 1H, Ar-H), 6.79 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.47–7.62 (m, 3H, Ar-H), 7.96–8.00 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$, 45.9, 118.6, 119.4, 123.2, 124.0, 128.5, 129.6, 131.9, 133.2, 137.6, 139.3 ppm; IR (KBr): $\tilde{\nu} =$ 3456, 3364, 3060, 1444, 1174, 667 cm^{-1}; MS (70 eV, EI): m/z (%): 260.1 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{16}N_2OS$ (260.35): C 64.58, H 6.19, N 10.76; found: C 64.67, H 6.10, N 10.59.

(*S*)-*N*-[2-Amino-4-methylphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8cA]: Compound (*S*)-**7cA** (5OO mg, 1.72 mmol) was dissolved in a mixture of EtOH (14 mL) and H_2O (21 mL) and then treated with glacial acetic acid (1.70 mL, 2.97 mmol) and Fe (288 mg, 5.16 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, EtOAc/petrolum ether 3:7 with 1% of Et_3N) to afford (*S*)-**8cA** as a brown oil (144 mg, 0.55 mmol, 25%). $[\alpha]_D^{20} = +6.33$ ($c = 0.50$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.12$ (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 4.10 (brs, NH_2), 6.29 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 6.77 (d, $J =$ 8.0 Hz, 1H, Ar-H), 7.54–7.56 (m, 3H, Ar-H), 7.93–7.97 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.8$, 45.5, 115.7, 118.9, 121.7, 128.2, 128.9, 129.3, 131.9, 132.9, 139.1, 140.1 ppm; IR (KBr): $\tilde{\nu} = 3564$, 3229, 3013, 1612, 1507, 748 cm^{-1}; MS (70 eV, EI): m/z (%): 260.1 (88%) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{16}N_2OS$ (260.35): C 64.58, H 6.19, N 10.76; found: C 64.46, H 5.91, N 11.04.

(*S*)-*N*-[2-Amino-4,5-dimethylphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8dA]: Compound (*S*)-**7dA** (721 mg, 2.37 mmol) was dissolved in a mixture of EtOH (20 mL) and H_2O (30 mL) and then treated with glacial acetic acid (2.4 mL, 4.19 mmol) and Fe (396 mg, 7.10 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, dichloromethane/methanol 99:1 with 1% of Et_3N) to afford (*S*)-**8dA** as a brown oil (459 mg, 1.68 mmol, 71%). $[\alpha]_D^{20} = +35.0$ ($c = 1.10$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.98$ (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.87 (brs, NH_2), 6.50 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 7.49–7.61 (m, 3H, Ar-H), 7.98–8.01 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 19.2, 45.5, 116.6, 123.4, 126.0, 128.3, 128.9, 129.3, 130.4, 132.9, 138.2, 139.4 ppm; IR (KBr): $\tilde{\nu} = 3073$, 3000, 2963, 2863, 1621, 1515, 1452, 1226, 757 cm^{-1}; MS (70 eV, EI): m/z (%): 274.1 (100) $[M]^+$; HRMS (EI): m/z: calcd for $C_{15}H_{18}N_2OS$: 274.1140; found 274.1140 $[M]^+$.

(*S*)-*N*-[2-Amino-4-methoxyphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8eA]: Compound (*S*)-**7eA** (438 mg, 1.43 mmol) was dissolved in a mixture of EtOH (12 mL) and H_2O (18 mL) and then treated with glacial acetic acid (1.4 mL, 2.44 mmol) and Fe (239 mg, 4.29 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, dichloromethane/methanol 99:1 with 1% of Et_3N) to afford (*S*)-**8eA**. Without fur-

ther characterization this product was directly used in the reductive amination. (The yield is then given for the two-step sequence.)

(*S*)-*N*-[2-Amino-4-fluorophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8 fA]: Compound (*S*)-**7 fA** (100 mg, 0.34 mmol) was dissolved in EtOH (0.93 mL) and H_2O (1.40 mL) and then treated with glacial acetic acid (0.34 mL, 0.59 mmol) and Fe (57 mg, 1.02 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, dichloromethane with 1% of Et_3N) to afford (*S*)-**8 fA** as a brown oil (48 mg, 0.18 mmol, 53%). $[\alpha]_D^{20} = -3.4$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.22$ (s, 3H, CH_3), 4.33 (br s, NH_2), 6.10–6.19 (m, 1H, Ar-H), 6.36–6.43 (m, 1H, Ar-H), 7.75–7.84 (m, 1H, Ar-H), 7.46–7.60 (m, 3H, Ar-H), 7.90–7.95 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.6$, 101.8 (d, $J_{CF} = 26$ Hz, CH), 104.2 (d, $J_{CF} = 22$ Hz, CH), 122.4 (d, $J_{CF} = 10$ Hz, CH), 127.5, 128.4, 129.6, 134.4, 138.8, 141.8 (d, $J_{CF} = 11$ Hz, C), 159.0 ppm (d, $J_{CF} = 238$ Hz, CF); IR (KBr): $\tilde{\nu} = 3364$, 3063, 3014, 1503, 1247, 753 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 264.1 (100) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{13}FN_2OS$ (264.32): C 59.07, H 4.96, N 10.60; found: C 59.16, H 5.04, N 10.76.

(*S*)-*N*-[2-Amino-4-trifluoromethylphenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-8 gA]: Compound (*S*)-**7 gA** (540 mg, 1.57 mmol) was dissolved in EtOH (13 mL) and H_2O (19.5 mL) and then treated with glacial acetic acid (1.6 mL, 2.79 mmol) and Fe (262 mg, 4.70 mmol). After refluxing for 5 h and cooling to room temperature, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted three times with CH_2Cl_2 (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography (silica gel, dichloromethane/methanol 99:1 with 1% of Et_3N) to afford (*S*)-**8 gA** as a brown solid (449 mg, 1.43 mmol, 91%). $[\alpha]_D^{20} = -20.0$ ($c = 1.20$ in $CHCl_3$); m.p. 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.29$ (s, 3H, CH_3), 4.21 (br s, NH_2), 6.70 (d, $J = 8.4$ Hz, 1H), 6.89 (s, 1H, Ar-H), 6.90 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.51–7.66 (m, 3H, Ar-H), 7.93–7.96 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 46.3$, 110.9, 115.2, 120.8, 124.2 (q, $J_{CF} = 30$ Hz, C), 124.6 (q, $J_{CF} = 272$ Hz, CF_3), 128.4, 129.8, 133.6, 134.8, 138.6, 140.8 ppm; IR (KBr): $\tilde{\nu} = 3463$, 3357, 3105, 3000, 2926, 1621, 1515, 1442, 1336, 1242, 1105, 747 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 314.1 (100) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{13}F_3N_2OS$ (314.33): C 53.50, H 4.17, N 8.91; found: C 53.32, H 4.18, N 8.66.

General procedure 3 (reductive amination with $NaBH_4$): A solution of aminosulfoximines **8 aA** or **8 aB** in MeOH ($c = 0.1$ mmol mL^{-1}) was treated with the corresponding aldehyde (1.1–1.2 equiv) and glacial acetic acid (1.0–1.1 equiv) After stirring at room temperature for 3 h, the mixture was cooled to 0 °C and $NaBH_4$ (2.5 equiv) was added in small portions over a period of 10–20 min. The resulting mixture was stirred over night at room temperature and then partitioned between 10% aqueous K_2CO_3 (10–20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10–20 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The product was then purified by flash chromatography (silica gel).

General procedure 4 (reductive amination with $NaBH_3CN$): A solution of aminosulfoximines **8 aA**–**gA** or **8 aB** in MeOH ($c = 0.5$ mmol mL^{-1}) and the corresponding aldehyde (1.2–2.5 equiv) was treated with $NaBH_3CN$ (0.9–1.0 equiv) at 0 °C. Then the pH was adjusted to 6 by dropwise addition of glacial acetic acid. After stirring at room temperature over night, the mixture was diluted with CH_2Cl_2 (20 mL) and hydrolyzed with 10% aqueous K_2CO_3 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Then the product was purified by flash chromatography (silica gel).

(*S*)-*N*-(2-Benzylaminophenyl)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4 aAα]: The product was prepared according to the general procedure 3 by using benzaldehyde (122 μL, 1.20 mmol), aminosulfoximine (*S*)-**8 aA** (246 mg, 1.00 mmol), glacial acetic acid (570 μL, 1.0 mmol) and $NaBH_4$ (94.6 mg, 2.50 mmol). The target compound was afforded as a colorless solid (271 mg, 0.81 mmol, 81%) after flash chromatography (silica gel, pentane/EtOAc 3:1 → 2:1 with 1% Et_3N). $[\alpha]_D^{20} = -82.6$ ($c = 1.0$ in $CHCl_3$); m.p. 129–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.23$ (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 5.20 (br s, 1H, NH), 6.40–6.45 (m, 1H, Ar-H), 6.54 (dd, $J = 8.0$, 1.4 Hz, 1H, Ar-H), 6.75–6.79 (m, 1H, Ar-H), 6.90 (dd, $J = 8.0$, 1.4 Hz, 1H, Ar-H), 7.26–7.29 (m, 1H, Ar-H), 7.33–7.37 (m, 2H, Ar-H), 7.40–7.42 (m, 2H, Ar-H), 7.49–7.53 (m, 2H, Ar-H), 7.56–7.61 (m, 1H, Ar-H), 7.93–7.96 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.9$, 48.1, 110.0, 116.6, 121.0, 122.6, 126.8, 127.1, 128.2, 128.3, 129.3, 130.9, 133.1, 139.1, 140.0, 142.1 ppm; IR (KBr): $\tilde{\nu} = 3416$, 3015, 1582, 1512, 1443, 1253, 1206, 1128, 1096, 1021, 742, 686 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 336 (39) $[M]^+$, 195 (64), 119 (100), 105 (16), 91 (26), 78 (8); elemental analysis calcd (%) for $C_{20}H_{20}ON_2S$ (336.45): C 71.40, H 5.99, N 8.33; found: C 71.30, H 5.74, N 8.30.

(*S*)-*N*-{2-[(Naphthalene-1-ylmethyl)-amino]-phenyl}-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4 aAβ]: The product was prepared according to the general procedure 3 by using 1-naphthaldehyde (82 μL, 0.60 mmol), aminosulfoximine (*S*)-**8 aA** (123 mg, 0.50 mmol), glacial acetic acid (31 μL, 0.54 mmol) and $NaBH_4$ (47.3 mg, 1.25 mmol). The target compound was afforded as a yellow solid (164 mg, 0.42 mmol, 85%) after flash chromatography (silica gel, pentane/EtOAc 4:1 with 1% Et_3N). $[\alpha]_D^{20} = -140.5$ ($c = 1.0$ in $CHCl_3$); m.p. 170–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.13$ (s, 3H, CH_3), 4.80/4.86 (AB system, $J = 14.1$ Hz, 2H, CH_2), 6.43–6.49 (m, 1H, Ar-H), 6.65–6.68 (dd, $J = 7.9$, 1.5 Hz, 1H, Ar-H), 6.80–6.85 (m, 1H, Ar-H), 6.93–6.96 (dd, $J = 7.9$, 1.4 Hz, 1H, Ar-H), 7.40–7.58 (m, 7H, Ar-H), 7.80–7.85 (m, 3H, Ar-H), 7.90–7.93 (m, 1H, Ar-H), 8.14–8.18 ppm (m, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.8$, 46.4, 110.1, 116.9, 121.2, 122.9, 123.6, 125.6, 125.7, 125.8, 126.1, 127.8, 128.4, 128.8, 129.5, 131.2, 131.6, 133.2, 133.9, 135.0, 139.2, 142.7 ppm; IR (KBr): $\tilde{\nu} = 3411$, 3056, 2918, 1586, 1513, 1438, 1253, 1207, 1132, 1094, 1020, 789, 739, cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 386 (21) $[M]^+$, 245 (40), 141 (34), 128 (6), 119 (100), 105 (5), 78 (3); elemental analysis calcd (%) for $C_{24}H_{22}ON_2S$ (386.51): C 74.58, H 5.74, N 7.25; found: C 74.48, H 5.99, N 7.56.

(*S*)-*N*-[2-(2-Methoxybenzylamino)phenyl]-*S*-methyl-*S*-phenyl-sulfoximine [(*S*)-4 aAγ]: The product was prepared according to the general procedure 3 by using *o*-anisaldehyde (99.0 mg, 0.73 mmol), aminosulfoximine (*S*)-**8 aA** (150 mg, 0.61 mmol), glacial acetic acid (37.0 μL, 0.65 mmol) and $NaBH_4$ (57.5 mg, 1.52 mmol). The target compound was afforded as a colorless solid (181 mg, 0.49 mmol, 81%) after flash chromatography (silica gel, pentane/EtOAc 2:1 with 1% Et_3N). $[\alpha]_D^{20} = -95.5$ ($c = 1.0$ in $CHCl_3$); m.p. 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.24$ (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2), 5.30 (br s, 1H, NH), 6.39–6.44 (m, 1H, Ar-H), 6.57 (dd, $J = 8.1$, 1.4 Hz, 1H, Ar-H), 6.75–6.81 (m, 1H, Ar-H), 6.90–6.95 (m, 3H, Ar-H), 7.22–7.28 (m, 1H, Ar-H), 7.33–7.35 (m, 1H, Ar-H), 7.47–7.62 (m, 3H, Ar-H), 7.94–7.98 ppm (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.0$, 45.9, 55.3, 110.1, 110.3, 116.5, 120.5, 121.2, 122.9, 127.9, 128.1, 128.4, 128.5, 129.5, 131.2, 133.2, 139.4, 142.5, 157.3 ppm; IR (KBr): $\tilde{\nu} = 3428$, 2919, 1585, 1513, 1490, 1437, 1271, 1245, 1204, 1132, 1110, 1020, 740 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 366 (26) $[M]^+$, 225 (75), 122 (24), 119 (100), 105 (6), 91 (26), 77 (6); elemental analysis calcd (%) for $C_{21}H_{22}O_2N_2S$ (366.48): C 68.82, H 6.05, N 7.64; found: C 68.53, H 5.82, N 7.42.

(*S*)-*N*-[2-(2,4,6-Trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4 aAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (369 μL, 2.50 mmol), aminosulfoximine (*S*)-**8 aA** (246 mg, 1.00 mmol) and $NaBH_3CN$ (62.9 mg, 1.00 mmol). The target compound was afforded as a yellow solid (320 mg, 0.85 mmol, 85%) after flash chromatography (silica gel, pentane/EtOAc 6:1 → 4:1 → 2:1 with 1% Et_3N). $[\alpha]_D^{20} = -177.3$ ($c = 0.4$ in $CHCl_3$); m.p. 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 2.41 (s, 6H, CH_3), 3.14 (s, 3H, CH_3), 4.19/4.27 (AB system, $J = 11.4$ Hz, 2H, CH_2), 6.42–6.47 (m, 1H, Ar-H), 6.73 (dd, $J = 8.0$, 1.5 Hz, 1H, Ar-H), 6.86–6.93 (m, 4H, Ar-H), 7.42–7.48 (m, 2H, Ar-H), 7.52–7.57 (m, 1H, Ar-H), 7.83–7.87 (m, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.5$, 21.0, 42.7, 46.1, 109.9, 116.6, 121.2, 122.9, 128.5, 129.0, 129.5, 131.3, 132.8, 133.1, 137.0, 137.7, 139.4, 142.9 ppm; IR (KBr): $\tilde{\nu} = 3398$, 2920, 1587, 1509, 1428, 1256, 1190, 1124, 1022, 734, 688, cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 378 (74) $[M]^+$, 246 (14), 237 (44), 221 (20), 181 (9),

133 (58), 119 (100), 105 (10), 91 (6), 77 (5); elemental analysis calcd (%) for $C_{23}H_{26}N_2OS$ (378.53): C 72.98, H 6.92, N 7.40; found: C 73.15, H 6.86, N 7.53.

(*S*)-*N*-[2-(2,4,6-Triisopropylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4aAε]: The product was prepared according to the general procedure 3 by using 2,4,6-triisopropylbenzaldehyde (837 mg, 3.60 mmol), aminosulfoximine (*S*)-**8aA** (739 mg, 3.00 mmol), glacial acetic acid (172 μL, 3.00 mmol) and $NaBH_4$ (284 mg, 7.50 mmol). The target compound was afforded as a colorless solid (1.14 g, 2.46 mmol, 82%) after flash chromatography (silica gel, pentane/EtOAc 10:1). $[\alpha]_D^{20} = -164.2$ ($c = 0.5$ in $CHCl_3$); m.p. 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (d, $J = 6.9$ Hz, 18H, CH_3), 2.89–2.98 (m, 1H, CH), 3.12 (s, 3H, CH_3), 3.28–3.38 (m, 2H, CH), 4.22/4.31 (AB system, $J = 11.5$ Hz, 2H, CH_2), 4.58 (brs, 1H, NH), 6.44 (t, $J = 7.7$ Hz, 1H, Ar-H), 6.74 (d, $J = 7.6$ Hz, 1H, Ar-H), 6.87–6.90 (m, 2H, Ar-H), 7.10 (s, 2H, Ar-H), 7.42–7.47 (m, 2H, Ar-H), 7.52–7.57 (m, 1H, Ar-H), 7.84 ppm (d, $J = 7.4$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.0$, 24.7, 24.8, 29.4, 34.3, 40.8, 46.3, 109.6, 116.5, 120.8, 121.2, 122.6, 128.5, 129.5, 130.3, 131.3, 133.1, 139.3, 142.5, 148.2 ppm; IR (KBr): $\tilde{\nu} = 3408$, 2960, 2867, 1590, 1502, 1426, 1261, 1241, 1195, 1125, 1094, 1024, 740, 688 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 462 (39) $[M]^+$, 307 (34), 246 (100), 216 (27), 201 (21), 173 (6), 119 (8), 105 (7); elemental analysis calcd (%) for $C_{29}H_{38}N_2OS$ (462.69): C 75.28, H 8.28, N 6.05; found: C 75.43, H 8.19, N 5.86.

(*S*)-*N*-[2-(2,4,6-Trimethoxybenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4aAϕ]: The product was prepared according to the general procedure 1 by using 2,4,6-trimethoxybenzaldehyde (108 mg, 0.55 mmol), aminosulfoximine (*S*)-**8aA** (123 mg, 0.50 mmol), glacial acetic acid (31 μL, 0.54 mmol) and $NaBH_4$ (47.3 mg, 1.25 mmol). The target compound was afforded as a colorless solid (182 mg, 0.42 mmol, 85%) after flash chromatography (silica gel, pentane/EtOAc 3:2 → 1:1 with 1% Et_3N). $[\alpha]_D^{20} = -40.0$ ($c = 0.38$, $CHCl_3$); m.p. 199 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 3.09$ (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.77 (s, 6H, OCH_3), 4.21/4.27 (AB system, 2H, CH_2), 5.10 (brs, 1H, NH), 6.09 (s, 2H, Ar-H), 6.19–6.25 (m, 1H, Ar-H), 6.65–6.74 (m, 3H, Ar-H), 7.37–7.43 (m, 2H, Ar-H), 7.47–7.52 (m, 1H, Ar-H), 7.74–7.78 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 36.1$, 45.9, 55.4, 55.8, 90.7, 108.7, 110.5, 115.8, 120.7, 122.6, 128.4, 129.4, 131.6, 133.1, 139.5, 142.9, 159.3, 160.5 ppm; IR (KBr): $\tilde{\nu} = 3406$, 2932, 1591, 1507, 1464, 1417, 1255, 1224, 1194, 1134, 812, 742 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 426 (26) $[M]^+$, 285 (93), 181 (100), 168 (8), 136 (10), 121 (13); elemental analysis calcd (%) for $C_{23}H_{26}N_2O_4S$ (426.53): C 64.77, H 6.14, N 6.57; found: C 64.44, H 5.78, N 6.32.

(*R*)-*N*-[2-(2,4,6-Trimethylbenzylamino)phenyl]-*S*-(2-methoxy-phenyl)-*S*-methylsulfoximine [(*R*)-4aBδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (184 μL, 1.25 mmol), aminosulfoximine (*R*)-**8aB** (138 mg, 0.5 mmol) and $NaBH_3CN$ (31.4 mg, 0.50 mmol). The target compound was afforded as a colorless solid (148 mg, 0.36 mmol, 72%) after flash chromatography (silica gel, pentane/EtOAc 3:1 with 1% Et_3N). $[\alpha]_D^{20} = -64.7$ ($c = 1.0$ in $CHCl_3$); m.p. 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, CH_3), 2.33 (s, 6H, CH_3), 3.24 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 4.54 (brs, 1H, NH), 6.49–6.54 (m, 1H, Ar-H), 6.67–6.70 (m, 1H, Ar-H), 6.83–6.87 (m, 1H, Ar-H), 6.89–6.95 (m, 3H, Ar-H), 7.00–7.07 (m, 2H, Ar-H), 7.46–7.51 (m, 1H, Ar-H), 7.95–7.99 ppm (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.5$, 20.9, 42.5, 42.8, 55.1, 109.4, 112.0, 116.1, 120.4, 122.9, 123.1, 128.7, 130.2, 131.0, 132.8, 134.6, 136.6, 137.6, 143.5, 156.4 ppm; IR (KBr): $\tilde{\nu} = 3386$, 2933, 1587, 1508, 1478, 1432, 1259, 1190, 1018, 765, 737 cm^{-1}; MS (70 eV, EI,): *m*/*z* (%): 408 (42) $[M]^+$, 237 (32), 221 (14), 171 (6), 133 (49), 119 (100), 105 (5); elemental analysis calcd (%) for $C_{24}H_{28}N_2O_2S$ (408.56): C 70.55, H 6.91, N 6.86; found: C 70.87, H 6.60, N 6.74.

(*R*)-*N*-[2-(2,4,6-Triisopropylbenzylamino)phenyl]-*S*-(2-methoxyphenyl)-*S*-methylsulfoximine [(*R*)-4aBε]: The product was prepared according to the general procedure 3 by using 2,4,6-triisopropylbenzaldehyde (139 mg, 0.60 mmol), aminosulfoximine (*R*)-**8aB** (138 mg, 0.50 mmol), glacial acetic acid (30 μL, 0.54 mmol), and $NaBH_4$ (47.3 mg, 1.25 mmol). The target compound was afforded as a colorless oil (157 mg, 0.32 mmol, 64%) after flash chromatography (silica gel, pentane/EtOAc 10:1 with 1% Et_3N), which slowly crystallized under reduced pressure. $[\alpha]_D^{20} = -45.4$ ($c = 2.85$ in $CHCl_3$); m.p. 56 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (d, $J = 6.9$ Hz, 6H, CH_3), 1.27 (d, $J = 6.9$ Hz, 12H, CH_3), 2.92 (sep., $J = 6.9$ Hz, 1H, CH), 3.13 (s, 3H, CH_3), 3.18 (s, 3H, OCH_3), 3.28 (sep., $J = 6.8$ Hz, 2H, CH), 4.23 (s, 2H, CH_2), 4.7 (brs, 1H, NH), 6.53–6.59 (m, 1H, Ar-H), 6.74 (dd, $J = 8.0$ Hz, 1.1 Hz, 1H, Ar-H), 6.83 (d, $J = 8.2$ Hz, 1H, Ar-H), 6.94–6.99 (m, 1H, Ar-H), 7.00–7.05 (m, 1H, Ar-H), 7.07 (s, 2H, Ar-H), 7.11 (dd, $J = 7.6$, 1.3 Hz, 1H, Ar-H), 7.45–7.50 (m, 1H, Ar-H), 7.99 ppm (dd, $J = 7.7$ Hz, 1.6 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.1$, 24.5, 24.7, 29.2, 34.3, 40.5, 42.1, 54.8, 109.3, 111.9, 116.2, 120.4, 121.0, 123.1, 123.2, 127.1, 130.1, 130.6, 130.8, 134.7, 143.4, 148.1, 148.2, 156.4 ppm; IR (KBr): $\tilde{\nu} = 3383$, 2961, 2868, 1590, 1501, 1431, 1265, 1191, 1070, 1047, 1021, 801, 742 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 492 (58) $[M]^+$, 307 (72), 276 (100), 217 (10), 171 (9), 153 (8); elemental analysis calcd (%) for $C_{30}H_{40}N_2O_2S$ (492.72): C 73.13, H 8.18, N 5.69; found: C 73.32, H 8.25, N 5.37.

(*S*)-*N*-[3-Methyl-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4bAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (90 mg, 0.61 mmol), aminosulfoximine (*S*)-**8bA** (132 mg, 0.51 mmol), $NaBH_3CN$ (32 mg, 0.51 mmol) and methanol (7 mL). The target compound was afforded as a yellow oil (117 mg, 0.30 mmol, 59%) after flash chromatography (silica gel, dichloromethane/methanol 99:1). $[\alpha]_D^{20} = -56.5$ ($c = 1.32$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.28$ (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.46 (s, 6H, CH_3), 3.08 (s, 3H, CH_3), 4.12/4.22 (AB system, $J = 11.5$ Hz, 2H, CH_2), 6.26 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.53–6.58 (m, 1H, Ar-H), 6.67–6.75 (m, 1H, Ar-H), 6.89 (s, 2H, Ar-H), 7.38–7.56 (m, 3H, Ar-H), 7.65–7.69 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.6$, 20.0, 21.2, 45.7, 46.7, 118.4, 121.1, 124.8, 128.4, 129.0, 129.4, 129.5, 133.1, 134.5, 136.3, 136.6, 137.4, 139.2, 142.2 ppm; IR (KBr): $\tilde{\nu} = 3326$, 3011, 1445, 1264, 746 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 392.2 (22) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{28}N_2OS$ (392.56): C 73.43, H 7.19, N 7.14; found C 73.54, H 7.30, N 7.03.

(*S*)-*N*-[4-Methyl-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4cAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (66 mg, 0.45 mmol), aminosulfoximine (*S*)-**8cA** (97 mg, 0.37 mmol), $NaBH_3CN$ (23 mg, 0.37 mmol) and methanol (5 mL). The target compound was afforded as a brown solid (125 mg, 0.32 mmol, 86%) after flash chromatography (silica gel, dichloromethane/methanol 99:1). $[\alpha]_D^{20} = -128.8$ ($c = 1.09$ in $CHCl_3$); m.p. 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.24$ (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.40 (s, 6H, CH_3), 3.11 (s, 3H, CH_3), 4.17/4.26 (AB system, $J = 11.3$ Hz, 2H, CH_2), 4.40 (brs, NH), 6.26 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 6.82 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.93 (s, 2H, Ar-H), 7.40–7.55 (m, 3H, Ar-H), 7.83–7.85 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.5$, 20.9, 21.4, 42.6, 45.9, 100.7, 116.8, 120.9, 128.2, 128.4, 128.8, 129.2, 132.1, 132.6, 132.8, 136.7, 137.4, 139.2, 142.4 ppm; IR (KBr): $\tilde{\nu} = 3393$, 2915, 1578, 1244, 1090 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 392.2 (39) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{28}N_2OS$ (392.56): C 73.43, H 7.19, N 7.14; found C 73.20, H 7.46, N 6.92.

(*S*)-*N*-[4,5-Dimethyl-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4dAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (110 mg, 0.74 mmol), aminosulfoximine (*S*)-**8dA** (204 mg, 0.74 mmol), $NaBH_3CN$ (42 mg, 0.67 mmol) and methanol (11.9 mL). The target compound was afforded as an orange solid (236 mg, 0.58 mmol, 78%) after flash chromatography (silica gel, pentane/EtOAc 8.5:1.5). $[\alpha]_D^{20} = -78$ ($c = 1.14$ in $CHCl_3$); m.p. 157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.41 (s, 6H, CH_3), 3.11 (s, 3H, CH_3), 4.16/4.25 (AB system, $J = 11.1$ Hz, 2H, CH_2), 6.54 (s, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 6.92 (s, 2H, Ar-H), 7.40–7.57 (m, 3H, Ar-H), 7.84–7.88 (m, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.5$, 19.6, 21.0, 43.1, 45.9, 112.0, 123.1, 124.1, 128.5, 128.8, 129.0, 129.4, 130.4, 133.0, 133.1, 136.8, 137.6, 139.7, 140.9 ppm; IR (KBr): $\tilde{\nu} = 3421$, 3000, 2915, 2852, 1610, 1515, 1442, 1242, 1126, 1015, 852 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 406.2 (76) $[M]^+$; elemental analysis calcd (%) for $C_{25}H_{30}N_2OS$ (406.58): C 73.85, H 7.44, N 6.89; found C 73.63, H 7.17, N 6.65.

(*S*)-*N*-[4-Methoxy-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4eAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (114 mg, 0.77 mmol), aminosulfoximine (*S*)-**8eA** (214 mg, 0.77 mmol), $NaBH_3CN$ (44 mg, 0.70 mmol) and methanol (12.4 mL). The target compound was afforded as a yellow oil [172 mg, 0.42 mmol, 30% yield over two steps (nitro group reduction and reductive amination)] after flash chromatography (silica gel, pentane/EtOAc 8.5:1.5). $[\alpha]_D^{20} = -101$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 2.40 (s, 6H, CH_3), 3.11 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.16/4.23 (AB system, $J = 11.5$ Hz, 2H, CH_2), 4.47 (brs, NH), 5.98 (dd, $J = 8.5$, 2.8 Hz, 1H, Ar-H), 6.30 (d, $J = 2.8$ Hz, 1H, Ar-H), 6.84 (d, $J = 8.5$ Hz, 1H, Ar-H), 6.92 (s, 2H, Ar-H), 7.41–7.56, (m, 3H, Ar-H), 7.81–7.85 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.5$, 20.9, 42.4, 45.7, 55.1, 97.3, 99.2, 121.5, 124.5, 128.3, 128.8, 129.2, 132.3, 132.9, 136.8, 137.4, 139.2, 143.7, 155.9 ppm; IR (KBr): $\tilde{\nu} = 3410$, 3063, 3010, 2926, 2873, 1621, 1584, 1510, 1447, 1421, 1258, 1211, 1052, 752 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 408.2 (100) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{28}N_2O_2S$ (408.56): C 70.55, H 6.91, N 6.86; found C 70.31, H 6.61, N 6.70.

(*S*)-*N*-[4-Fluoro-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4fAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (22 mg, 0.15 mmol), aminosulfoximine (*S*)-**8fA** (33 mg, 0.12 mmol), $NaBH_3CN$ (7.5 mg, 0.12 mmol) and methanol (2 mL). The target compound was afforded as a yellow solid (40 mg, 0.10 mmol, 83%) after flash chromatography (silica gel, dichloromethane/methanol 99:1). $[\alpha]_D^{20} = -174.4$ ($c = 1.01$ in $CHCl_3$); m.p. 165°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 2.40 (s, 6H, CH_3), 3.13 (s, 3H, CH_3), 4.14/4.21 (AB system, $J = 11.4$ Hz, 2H, CH_2), 4.56 (brs, NH), 6.08–6.13 (m, 1H, Ar-H), 6.39–6.44 (m, 1H, Ar-H), 6.79–6.83 (m, 1H, Ar-H), 6.93 (s, 2H, Ar-H), 7.44–7.58 (m, 3H, Ar-H), 7.80–7.83 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.5$, 20.9, 42.3, 45.9, 97.0 (d, $J_{CF} = 27$ Hz, CH), 101.4 (d, $J_{CF} = 22$ Hz, CH), 121.1 (d, $J_{CF} = 10$ Hz, CH), 126.6, 128.2, 128.7, 129.3, 131.9, 133.0, 136.9, 137.4, 138.9, 143.8 (d, $J_{CF} = 11$ Hz, C), 159.5 ppm (d, $J_{CF} = 237$ Hz, CF); IR (KBr): $\tilde{\nu} = 3019$, 2926, 1257, 759 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 396.2 (54) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{25}FN_2OS$ (396.52): C 69.67, H 6.35, N 7.06; found C 69.91, H 6.61, N 6.73.

(*S*)-*N*-[4-Trifluoromethyl-2-(2,4,6-trimethylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4gAδ]: The product was prepared according to the general procedure 4 by using 2,4,6-trimethylbenzaldehyde (73 mg, 0.49 mmol), aminosulfoximine (*S*)-**8gA** (154 mg, 0.49 mmol), $NaBH_3CN$ (28 mg, 0.44 mmol) and methanol (7.9 mL). The target compound was afforded as a yellow solid (127 mg, 0.29 mmol, 58%) after flash chromatography (silica gel, pentane/EtOAc 8.5:1.5). $[\alpha]_D^{20} = -170$ ($c = 1.05$ in $CHCl_3$); m.p. 45–50°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H, CH_3), 2.41 (s, 6H, CH_3), 3.16 (s, 3H, CH_3), 4.19/4.27 (AB system, $J = 11.5$ Hz, 2H, CH_2), 4.63 (brs, NH), 6.66 (d, $J = 8.0$ Hz, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 6.89 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.94 (s, 1H, Ar-H), 7.44–7.59 (m, 3H, Ar-H), 7.79–7.83 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.7$, 21.1, 42.6, 46.6, 105.6, 113.4, 119.8, 124.3 (q, $J_{CF} = 32$ Hz, C), 125.0 (q, $J_{CF} = 271$ Hz, CF_3), 128.3, 129.1, 129.7, 132.1, 133.5, 134.5, 137.2, 137.6, 138.6, 142.6 ppm; IR (KBr): $\tilde{\nu} = 3389$, 3105, 3031, 2926, 2873, 1605, 1521, 1442, 1263, 1105, 1015, 742 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 446.2 (60) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{25}F_3N_2OS$ (446.53): C 64.55, H 5.64, N 6.27; found C 64.38, H 5.64, N 6.23.

General procedure 5 (Mukaiyama-aldol reaction): A flame-dried Schlenk-flask under argon atmosphere was charged with $Cu(OTf)_2$ (18 mg, 0.05 mmol) and the corresponding aminosulfoximine **4** (0.05 mmol). Then, dry THF (2 mL) was added and the resulting deep green solution was stirred for 30 min at room temperature. Subsequently, the selected temperature was adjusted and the corresponding α-keto ester **2a–e** (0.50 mmol), the corresponding enolsilane **1a–d** (0.60–0.75 mmol) and 2,2,2-trifluoroethanol (0.60 mmol, 44 μL) were added. After stirring for the indicated period of time, the mixture was warmed to room temperature and filtered through a plug of silica gel with Et_2O (50 mL). The solvent was evaporated and the product was purified by flash chromatography (silica gel).

(−)-(*R*)-Methyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate [(*R*)-3a]: The product was prepared according to the general procedure 5 by using methyl pyruvate (**2a**, 46 μL, 0.50 mmol), enolsilane **1a** (123 μL, 0.60 mmol) and aminosulfoximine (*S*)-**4aAε** (23.1 mg, 0.05 mmol). After stirring for 15 h at −30°C, the product was obtained as a colorless oil (99 mg, 0.45 mmol, 89%, 98% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1 → 4:1). $[\alpha]_D^{20} = -86.7$ ($c = 1.0$ in $CHCl_3$); lit: $[\alpha]_D^{20} = +84.4$ ($c = 3.5$ in $CHCl_3$) for (*S*), 99% *ee*;[9] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$ (s, 3H, CH_3), 3.36 (d, $J = 17.6$ Hz, 1H, CH_2), 3.67 (d, $J = 17.9$ Hz, 1H, CH_2), 3.78 (s, 3H, CH_3), 3.99 (brs, 1H, OH), 7.45–7.49 (m, 2H, Ar-H), 7.57–7.61 (m, 1H, Ar-H), 7.93–7.96 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.4$, 47.9, 52.7, 72.6, 128.0, 128.5, 133.5, 136.1, 176.2, 198.6 ppm; IR (film): $\tilde{\nu} = 3512$, 2985, 2953, 1742, 1683, 1597, 1450, 1365, 1218, 1115, 1008, 986, 759, 692 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 223 (49) $[M+H]^+$, 163 (100), 105 (22); elemental analysis calcd (%) for $C_{12}H_{14}O_4$ (222.24): C 64.85, H 6.35; found: C 65.20, H 6.62; HPLC: $t_r(R) = 25.3$ min, $t_r(S) = 31.5$ min (Chiralcel OD, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 95:5, $\lambda = 254$ nm, 25°C).

(−)-(*R*)-Benzyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate [(*R*)-3b]: The product was prepared according to the general procedure 5 by using benzyl pyruvate (**2b**, 123 mg, 0.69 mmol), silyl enol ether **1a** (170 μL, 0.83 mmol), aminosulfoximine (*S*)-**4aAε** (32 mg, 0.07 mmol) and 2,2,2-trifluoroethanol (61 μL, 0.83 mmol). After stirring for 47 h at −50°C, the product was obtained as a colorless oil (176 mg, 0.59 mmol, 86%, 98% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1 → 4:1). $[\alpha]_D^{20} = -41.8$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$ (s, 3H, CH_3), 3.35 (d, $J = 17.6$ Hz, 1H, CH_2), 3.67 (d, $J = 17.5$ Hz, 1H, CH_2), 4.03 (brs, 1H, OH), 5.18/5.22 (AB system, $J = 12.3$ Hz, 2H, CH_2), 7.28–7.30 (m, 5H, Ar-H), 7.44–7.48 (m, 2H, Ar-H), 7.56–7.60 (m, 1H, Ar-H), 7.90–7.93 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.4$, 47.8, 67.3, 72.7, 127.9, 128.0, 128.1, 128.3, 128.5, 133.5, 135.3, 136.1, 175.5, 198.5 ppm; IR (film): $\tilde{\nu} = 3533$, 2981, 1740, 1682, 1597, 1452, 1365, 1217, 1111, 754, 693, cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 299 (25) $[M+H]^+$, 163 (20), 121 (41), 91 (100); elemental analysis calcd (%) for $C_{18}H_{18}O_4$ (298.34): C 72.47, H 6.08; found: C 72.27, H 5.98; HPLC: $t_r(R) = 29.7$ min, $t_r(S) = 34.4$ min (Chiralcel OD, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 95:5, $\lambda = 254$ nm, 25°C). The absolute configuration was assigned in analogy to **3a**.

(−)-(*R*)-*Iso*propyl 2-hydroxy-2-methyl-4-oxo-4-phenyl butanoate [(*R*)-3c]: The product was prepared according to the general procedure 5 by using isopropyl pyruvate (**2c**, 65 mg, 0.50 mmol), enolsilane **1a** (123 μL, 0.60 mmol) and aminosulfoximine (*S*)-**4aAε** (23.1 mg, 0.05 mmol). After stirring for 28 h at −40°C, the product was obtained as a colorless oil (112 mg, 0.45 mmol, 90%, 99% *ee*) after flash chromatography (silica gel, pentane/EtOAc 12:1 → 10:1). $[\alpha]_D^{20} = -58.6$ ($c = 2.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (d, $J = 6.3$ Hz, 3H, CH_3), 1.27 (d, $J = 6.3$ Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.34 (d, $J = 17.6$ Hz, 1H, CH_2), 3.64 (d, $J = 17.6$ Hz, 1H, CH_2), 3.96 (brs, 1H, OH), 5.07–5.12 (m, $J = 6.3$ Hz, 1H, CH), 7.45–7.49 (m, 2H, Ar-H), 7.57–7.61 (m, 1H, Ar-H), 7.93–7.95 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 21.6, 26.4, 47.8, 69.2, 72.5, 127.9, 128.5, 133.4, 136.3, 175.2, 198.4 ppm; IR (film): $\tilde{\nu} = 3533$, 3019, 2983, 1732, 1684, 1598, 1451, 1375, 1217, 1104, 757, 690 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 251 (48) $[M+H]^+$, 209 (100), 191 (22), 163 (74); elemental analysis calcd (%) for $C_{14}H_{18}O_4$ (250.29): C 67.18, H 7.25; found C 67.47, H 7.05; HPLC: $t_r(S) = 18.7$ min, $t_r(R) = 22.2$ min (Chiralcel OJ, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 90:10, $\lambda = 254$ nm, 25°C). The absolute configuration was assigned in analogy to **3a**.

(−)-(*R*)-Ethyl 2-hydroxy-4-oxo-4-phenyl-[2-phenylethyl] butanoate [(*R*)-3d]: The product was prepared according to the general procedure 5 by using ethyl 2-oxo-4-phenyl butyrate (**2d**, 95 μL, 0.50 mmol), enolsilane **1a** (123 μL, 0.60 mmol) and aminosulfoximine (*S*)-**4aAε** (23.1 mg, 0.05 mmol). After stirring for 40 h at −20°C, the product was obtained as a colorless oil (140 mg, 0.43 mmol, 86%, 96% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1). $[\alpha]_D^{20} = -28.5$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.07–2.11 (m, 2H, CH_2), 2.53–2.61 (m, 1H, CH_2), 2.86–2.93 (m, 1H, CH_2), 3.44 (d, $J = 17.3$ Hz, 1H, CH_2), 3.58 (d, $J = 17.3$ Hz, 1H, CH_2), 3.98 (brs, 1H, OH), 4.24 (q, $J = 7.1$ Hz, 2H, CH_2), 7.18–7.21 (m, 3H, Ar-H), 7.27–7.31

(m, 2H, Ar-H), 7.45–7.49 (m, 2H, Ar-H), 7.57–7.61 (m, 1H, Ar-H), 7.91–7.94 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 29.5, 41.3, 47.2, 61.8, 74.9, 125.8, 128.0, 128.2, 128.3, 128.5, 133.4, 136.3, 141.2, 175.0, 198.1 ppm; IR (film): $\tilde{\nu}$ = 3516, 2980, 2929, 1735, 1684, 1598, 1451, 1363, 1215, 1090, 1019, 755, 695 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 327 (74) $[M+H]^+$, 309 (20), 253 (100), 189 (41), 121 (54); elemental analysis calcd (%) for $C_{20}H_{22}O_4$ (326.39): C 73.60, H 6.79; found: C 73.92, H 7.08; HPLC: $t_r(R)$ = 33.1 min, $t_r(S)$ = 43.8 min (Chiralcel OD column, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 95:5, λ = 254 nm, 25 °C). The absolute configuration was assigned in analogy to **3a**.

(−)-(*R*)-Methyl 2-ethyl-2-hydroxy-4-oxo-4-phenyl butanoate [(*R*)-3e]: The product was prepared according to the general procedure 5 by using methyl 2-oxobutyrate (**2e**, 58 mg, 0.50 mmol), enolsilane **1a** (123 μL, 0.60 mmol) and aminosulfoximine (*S*)-**4aAε** (23 mg, 0.05 mmol). After stirring for 20 h at room temperature, the product was obtained as a yellow oil (92 mg, 0.39 mmol, 78%, 89% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1 → 5:1). $[\alpha]_D^{20}$ = −46.0 (*c* = 1.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3H, CH_3), 1.82 (q, *J* = 7.4 Hz, 2H, CH_2), 3.41 (d, *J* = 17.6 Hz, 1H, CH_2), 3.57 (d, *J* = 17.6 Hz, 1H, CH_2), 3.72 (br s, 1H, OH), 3.78 (s, 3H, OCH_3), 7.45–7.49 (m, 2H, Ar-H), 7.57–7.61 (m, 1H, Ar-H), 7.93–7.96 ppm (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 32.5, 46.9, 52.6, 75.5, 128.0, 128.5, 133.4, 136.3, 175.7, 198.4 ppm; IR (film): $\tilde{\nu}$ = 3522, 2971, 1740, 1684, 1597, 1449, 1360, 1248, 1218, 1020, 757, 692 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 237 (61) $[M+H]^+$, 219 (18), 177 (100), 121 (20); elemental analysis calcd (%) for $C_{13}H_{16}O_4$ (236.27): C 66.09, H 6.83; found: C 65.84, H 6.76; HPLC: $t_r(R)$ = 19.8 min, $t_r(S)$ = 27.0 min (Chiralcel OD column, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 95:5, λ = 254 nm, 25 °C). The absolute configuration was assigned in analogy to **3a**.

(−)-(*R*)-Benzyl-(2-hydroxy-2-methyl-4-methyl-4-oxo)-butanoate [(*R*)-3f]: The product was prepared according to the general procedure 5 by using benzyl pyruvate (**2b**, 89 mg, 0.50 mmol), enolsilane **1b** (147 μL, 0.75 mmol) and aminosulfoximine (*S*)-**4aAε** (23.1 mg, 0.05 mmol). After stirring for 46 h at −40 °C, the product was obtained as a colorless oil (84 mg, 0.35 mmol, 71%, 91% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1 → 3:1). $[\alpha]_D^{20}$ = −29.6 (*c* = 0.5 in $CHCl_3$); lit: $[\alpha]_D^{20}$ = +42.9 (*c* = 3.7 in $CHCl_3$) for (*S*), 93% *ee*;[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.80 (d, *J* = 17.5 Hz, 1H, CH_2), 3.12 (d, *J* = 17.5 Hz, 1H, CH_2), 3.87 (br s, 1H, OH), 5.18 (s, 2H, CH_2), 7.30–7.39 ppm (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 30.5, 52.2, 67.3, 72.5, 128.0, 128.2, 128.4, 135.2, 175.3, 207.4 ppm; IR (film): $\tilde{\nu}$ = 3510, 2982, 1739, 1498, 1456, 1367, 1282, 1179, 1121, 968, 752, 700 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 237 (4) $[M+H]^+$, 181 (5), 119 (5), 101 (23), 91 (100); elemental analysis calcd (%) for $C_{13}H_{16}O_4$ (236.26): C 66.09, H 6.83; found: C 65.97, H 6.58; HPLC: $t_r(R)$ = 26.6 min, $t_r(S)$ = 34.3 min (Chiralcel AS, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 90:10, λ = 210 nm, 25 °C).

(+)-(*S*)-*tert*-Butyl 3-hydroxy-3-methoxycarbonyl butanthioate [(*S*)-3g]: The product was prepared according to the general procedure 5 by using methyl pyruvate (**2a**, 46 μL, 0.50 mmol), enolsilane **1c** (153 μL, 0.60 mmol) and aminosulfoximine (*R*)-**4aBδ** (20.4 mg, 0.05 mmol). After stirring for 51 h at −40 °C, the product was obtained as a colorless oil (101 mg, 0.43 mmol, 86%, 91% *ee*) after flash chromatography (silica gel, pentane/EtOAc 10:1). $[\alpha]_D^{20}$ = +24.3 (*c* = 0.54 in $CHCl_3$); lit: $[\alpha]_D^{20}$ = +25.1 (*c* = 5.2 in $CHCl_3$) for (*S*), 99% *ee*;[9] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3H, CH_3), 1.45 (s, 9H, CH_3), 2.84 (d, *J* = 15.9 Hz, 1H, CH_2), 3.07 (d, *J* = 16.0 Hz, 1H, CH_2), 3.73 (br s, 1H, OH), 3.80 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 29.7, 48.6, 52.8, 52.9, 72.9, 175.6, 198.0 ppm; IR (film): $\tilde{\nu}$ = 3514, 2961, 2926, 1743, 1682, 1456, 1395, 1367, 1271, 1216, 1163, 1117, 1008, 958, 932, 787 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 235 (5) $[M+H]^+$, 179 (8), 175 (8), 145 (82), 117 (100), 85 (6); elemental analysis calcd (%) for $C_{10}H_{18}O_4S$ (234.31): C 51.26, H 7.74; found: C 51.23, H 7.68; HPLC: $t_r(R)$ = 17.7 min, $t_r(S)$ = 19.3 min (Chiralcel OD-H, flow rate 1.0 mL min^{-1}, heptane/*i*PrOH 99:1, λ = 230 nm, 25 °C).

(+)-(*S*)-*tert*-Butyl 3-benzoylcarboxy-3-hydroxy butanthioate [(*S*)-3h]: The product was prepared according to the general procedure by using benzyl pyruvate (**2b**, 89 mg, 0.50 mmol), enolsilane **1c** (153 μL, 0.60 mmol) and aminosulfoximine (*R*)-**4aBδ** (20 mg, 0.05 mmol). After stirring for 49 h at −50 °C, the product was obtained as a colorless oil (123 mg, 0.39 mmol, 79%, 93% *ee*) after flash chromatography (silica gel, pentane/EtOAc 15:1). $[\alpha]_D^{20}$ = −19.3 (*c* = 0.93 in $CHCl_3$); lit: $[\alpha]_D^{20}$ = −18.1 (*c* = 6.3 in $CHCl_3$) for (*S*), 99% *ee*;[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3H, CH_3), 1.43 (s, 9H, CH_3), 2.85 (d, *J* = 16.2 Hz, 1H, CH_2), 3.10 (d, *J* = 15.9 Hz, 1H, CH_2), 3.74 (br s, 1H, OH), 5.19/5.23 (AB system, *J* = 12.1 Hz, 2H, CH_2), 7.32–7.37 ppm (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 29.7, 48.6, 52.9, 67.5, 72.8, 128.1, 128.2, 128.4, 135.2, 175.1, 197.9 ppm; IR (film): $\tilde{\nu}$ = 3523, 3034, 2963, 1740, 1681, 1456, 1394, 1366, 1272, 1202, 1113, 1006, 965, 783, 747, 699 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 311 (42) $[M+H]^+$, 193 (22), 181 (30), 119 (11), 91 (100); elemental analysis calcd (%) for $C_{16}H_{22}O_4S$ (310.41): C 61.91, H 7.14; found: C 61.58, H 7.25; HPLC: $t_r(R)$ = 9.7 min, $t_r(S)$ = 10.8 min (Chiralcel OD-H, flow rate 1.0 mL min^{-1}, heptane/*i*PrOH 99:1, λ = 230 nm, 25 °C).

(+)-(*S*)-*tert*-Butyl 3-hydroxy-3-isopropoxycarbonyl butanthioate [(*S*)-3i]: The product was prepared according to the general procedure 5 by using isopropyl pyruvate (**2c**, 65 mg, 0.50 mmol), enolsilane **1c** (153 μL, 0.60 mmol) and aminosulfoximine (*R*)-**4aBδ** (20 mg, 0.05 mmol). After stirring for 72 h at −50 °C, the product was obtained as a colorless oil (107 mg, 0.41 mmol, 82%, 98% *ee*) after flash chromatography (silica gel, pentane/EtOAc 20:1). $[\alpha]_D^{20}$ = +0.5 (*c* = 0.53 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.2 Hz, 6H, CH_3), 1.38 (s, 3H, CH_3), 1.45 (s, 9H, CH_3), 2.83 (d, *J* = 16.1 Hz, 1H, CH_2), 3.08 (d, *J* = 16.3 Hz, 1H, CH_2), 3.73 (br s, 1H, OH), 5.10 ppm (sep. *J* = 6.3 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 21.7, 26.2, 29.7, 48.6, 52.9, 69.6, 72.7, 174.9, 198.0 ppm; IR (film): $\tilde{\nu}$ = 3515, 2977, 2929, 1735, 1684, 1457, 1370, 1274, 1214, 1166, 1106, 1005, 945, 918, 790, 634 cm^{-1}; MS (70 eV, CI, CH_4): *m*/*z* (%): 263 (100) $[M+H]^+$, 173 (67), 145 (23), 131 (34), 119 (10), 103 (30); elemental analysis calcd (%) for $C_{12}H_{22}O_4S$ (262.37): C 54.93, H 8.45; found: C 55.08, H 8.26; HPLC: $t_r(R)$ = 11.1 min, $t_r(S)$ = 11.9 min (Chiralcel OD-H, flow rate 0.5 mL min^{-1}, heptane/*i*PrOH 99:1, λ = 230 nm, 25 °C). The absolute configuration was assigned in analogy to **3g** and **3h**.

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