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C_1-Symmetric Aminosulfoximines in Copper-Catalyzed Asymmetric Vinylogous Mukaiyama Aldol Reactions

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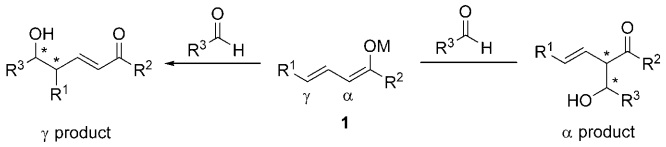
Abstract: Vinylogous Mukaiyama-type aldol reactions have been catalyzed by a combination of $Cu(OTf)_2$ and readily available C_1-symmetric aminosulfoximines. After a fine-tuning of the reaction conditions and an optimization of the modularly assembled ligand structure, high stereoselectivities and excellent yields have been achieved in catalyzed reactions involving various electrophile/nucleophile combinations. The relative and absolute configurations of two products were assigned by X-ray single crystal structure analysis and a comparison of calculated and experimental CD spectra.

Keywords: aldol reaction · asymmetric catalysis · copper · Mukaiyama reaction · sulfoximine

Introduction

The Mukaiyama aldol reaction[1] is widely recognized as one of the most versatile tools in organic synthesis for the linkage of two (or more) carbons, and its enantioselective metal-catalyzed version is attractive for both synthetic and pharmaceutical chemists.[2] Catalyzed by chiral Lewis acids, this reaction opens a convenient route to enantiomerically enriched alcohols which frequently occur in natural or biologically active compounds.[3]

By utilizing the concept of vinylogy,[4] which is understood as the transmission of electronic effects through a conjugated π-system, the "normal aldol reaction" becomes its vinylogous version, allowing the selective preparation of 1,5-difunctional subunits. More precisely, in an elegant manner the vinylogous aldol reaction provides access to δ-hydroxy-α,β-unsaturated carbonyl compounds. Thus, up to two stereogenic centers and one double bond, which can easily be further manipulated, are formed in a single step.[5] In spite of the enormous feasibility the vinylogous aldol reaction is still a highly challenging transformation because, in addition to well-defined enantio- and diastereoselectivity of ordinary aldol reactions, it appends the complexity of controlled regioselectivity where due to two nucleophilic sites α and/or γ products can be formed (Scheme 1).



Scheme 1. Regioselective attacks in the vinylogous Mukaiyama aldol reaction give γ (left pathway) and/or α products (right pathway).

A general approach to circumvent the regioselectivity issues and preferentially direct the electrophile attack to the γ-position is the use of *O*-silyl dienolates **1** (with $M = SiR_3$) in Lewis acid catalyzed vinylogous Mukaiyama-type aldol reactions (VMAR). However, exceptions are known where addition of aldehydes, acid anhydrides or nitroalkenes to *O*-silyl dienolates led to the often undesired α-products either in considerable amounts or even as sole products.[6] Furthermore, for high site selectivity electronic and steric effects of both the dienolate and catalyst complex have to be taken into account. In recent years, catalytic asymmetric VMAR has attracted considerable attention and much effort has

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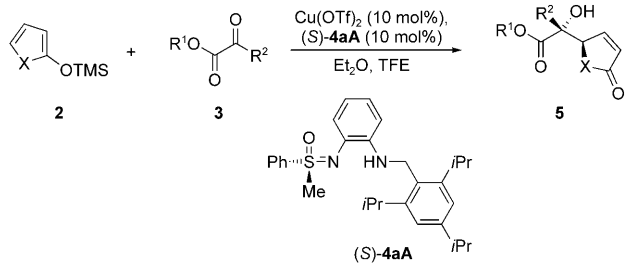
been made to overcome the remaining problems of regio-, diastereo- and enantioselectivity.[6d,7]

For a considerable time, we have been interested in demonstrating the applicability of various types of sulfoximines as ligands in transition-metal-catalyzed asymmetric reactions.[8,9] In particular, we have shown that C_1-symmetric oxazolinyl- and aminosulfoximines are very effective ligands for copper-catalyzed (V)MAR.[9a,10] In a recent communication we extended the catalytic system of aminosulfoximine (*S*)-**4aA** and $Cu(OTf)_2$ to cyclic dienol silanes **2** and ketonic electrophiles **3** (Scheme 2).[11] The resulting γ-butenolides **5** were obtained in excellent yields and top-level diastereo- and enantioselectivities. Additionally, the relative and absolute configuration of a representative product was identified beyond doubt.



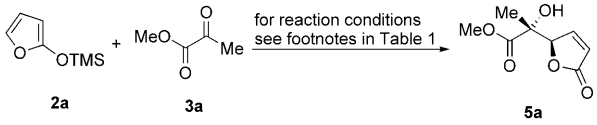
Scheme 2. Highly enantio- and diastereoselective VMAR catalyzed by an aminosulfoximine copper complex.

Here, we wish to summarize all results, present an overview on the optimization process and reveal the full scope of the reaction. Furthermore, we will show that by structural modifications of the aminosulfoximines **4** and careful selection of the optimal ligand in various reactions the yields and stereoselectivities can be increased.

Results and Discussion

2-(Trimethylsilyloxy)furan (TMSOF, **2a**) and its pyrrole- and thiophene-based analogues are conformationally constrained cyclic enolates, that can act as vinylogous nucleophiles.[12] The stereoselective synthesis of the resulting γ-butenolides **5** by means of VMAR is of great interest because hydroxyl-bearing butenolides are important building blocks[13] and common scaffolds in many natural products or biologically active compounds.[14] Unlike the use of aldehydes, which has been thoroughly investigated,[15] the application of ketonic substrates as electrophiles in VMAR has been less explored, and the few examples involve pyruvates as activated ketones.[15b,16] Apparently, various factors such as the lower reactivity of the ketones compared with the aldehydes and the more challenging differentiation between the diastereotopic faces of the former in combination with a competing retro-aldol reaction of the resulting tertiary alcohols and additional demand for high regio- and enantioselectivities have hampered process development in this field.

Development of the optimal reaction conditions: As depicted in Scheme 3, commercially available TMSOF (**2a**) and methyl pyruvate (**3a**) were chosen as starting materials for the optimization of the reaction conditions. The initial experiment was performed in dry diethyl ether at ambient temperature using a catalyst composed of 10 mol% of $Cu(OTf)_2$ and 10 mol% of sulfoximine (*S*)-**4aA** (Table 1, entry 1). Satisfyingly, γ-butenolide **5a** was obtained in good yield (83%) and high diastereoselectivity (94%) after five hours. Moreover, a very promising *ee* of 83% was achieved.



Scheme 3. Synthesis of γ-butenolide **5a** by VMAR.

Because it is known that in Mukaiyama-type reactions additives can dramatically affect enantioselectivities or catalytic turnover rates and thus enhance yields, the impact of various additives was investigated next.[17] Indeed, when hexafluoroisopropanol (HFIP) was applied the *ee* was increased to 93% while the yield was slightly reduced to 78% (entry 2). Fortunately, 2,2,2-trifluoroethanol (TFE) improved the previous results, and **5a** was isolated with 95% *ee* in 88% yield (entry 3). In all cases the diastereoselectivity remained unaffected. TMSOTf (entry 4) was inadequate in terms of yield (43%) and enantioselectivity (35%). Although it can accelerate copper(II)-catalyzed Mukaiyama-type aldol reactions,[16c] the competing role of the racemic catalyst TMSOTf most probably decreased the enantioselectivity. In none of the reactions an improved catalyst turnover was noticed. In contrast, a dramatic rate accelerating effect was observed when $BF_3{\cdot}Et_2O$ was added, and full conversion was reached in less than 45 min with γ-butenolide **5a** being isolated in 73% yield, and very good stereoselectivities of 98% *de* and 91% *ee* (entry 5). Because TFE gave the best results with respect to yield and *ee*, the subsequent experiments were carried out with this additive.

Table 1. Effect of additives on the test reaction to give γ-butenolide **5a**.

Entry	Additive[a]	Yield [%]	*de* [%][b]	*ee* [%][c]
1	none	83	94	83
2	1.2 equiv HFIP	78	94	93
3	1.2 equiv TFE	88	94	95
4	1.0 equiv TMSOTf	43	96	35
5	1.0 equiv $BF_3{\cdot}Et_2O$	73	98	91

[a] Reaction conditions: **2a** (0.22 mmol), **3a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), aminosulfoximine (*S*)-**4aA** (10 mol%), additive (0.20 or 0.24 mmol), dry Et_2O (2 mL), RT. [b] Determined by ^1H NMR analysis of the crude reaction mixture, *de* refers to *anti*/*syn* ratio. [c] Determined by CSP-HPLC for the *anti* (=major) diastereomer.

Next, the effect of the solvent was explored; Table 2 summarizes the results. When the test reaction was carried out in dichloromethane or chloroform (Table 2, entries 1 and 2) product **5a** was isolated in slightly improved yields (89 and 91%, respectively) and almost unaffected diastereoselectivities (94 and 96% *de*, respectively), the enantioselectivities were considerably lower (79 and 75% *ee*, respectively). Toluene proved superior to chlorinated solvents and its use afforded **5a** in very good yield (91%) with good stereoselectivities (85% *ee* and 96% *de*, entry 3). To our surprise, the yields and enantioselectivities varied significantly in the group of ethereal solvents. Thus, when the reaction was conducted in THF or 1,4-dioxane (compare entries 4 and 5 vs. 6) instead of diethyl ether the diastereoselectivity remained unchanged, but the yields were slightly lower (83 and 75%, respectively). Furthermore, the *ee* of γ-butenolide **5a** was drastically reduced in both solvents (52% *ee* in THF and 74% *ee* in 1,4-dioxane). Aprotic or protic polar solvents such as acetonitrile or methanol proved to be unsuitable for this reaction (entries 7 and 8). In the case of acetonitrile, **5a** was obtained in only 5% yield with low stereoselectivities (50% *de* and 10% *ee*), and use of methanol gave only traces of the product. In contrast, **5a** was isolated in 89% yield when the fluorinated alcohol TFE was used as solvent (Table 2, entry 9).[18] This result compared well with the one obtained with TFE as additive, but unfortunately, the stereoselectivities (83% *de* and 45% *ee*) were significantly lower here.

Table 2. Influence of the solvent in the VMAR between dienol silane **2a** and pyruvate **3a**.

Entry	Solvent[a]	Yield [%]	*de* [%][b]	*ee* [%][c]
1	CH_2Cl_2	89	94	79
2	$CHCl_3$	91	96	75
3	toluene	91	96	85
4	THF	83	94	52
5	1,4-dioxane	75	94	74
6	Et_2O	88	94	95
7	CH_3CN	5	50	10
8	CH_3OH	traces	n. d.	n. d.
9	TFE	89	83	45

[a] Reaction conditions: **2a** (0.22 mmol), **3a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), aminosulfoximine (*S*)-**4aA** (10 mol%), TFE (0.24 mmol), abs. or HPLC grade solvent (2 mL), RT. [b] and [c] as in Table 1.

In summary, weakly coordinating, nonpolar or aromatic solvents such as toluene or diethyl ether were the best (entries 3 and 6), and for the subsequent optimization diethyl ether was selected as solvent.

Next, the effects of various metal triflates and variations of other important parameters such as catalyst loading, temperature and microwave irradiation on the reaction between dienol silane **2a** and electrophile **3a** were investigated. Considering that the appropriate choice of the metal plays a crucial role in catalysis, a test reaction was carried out with $Fe(OTf)_2$ (Table 3, entry 1). Although yield and *de* were satisfying (86 and 89%), the *ee* of only 12% was unacceptable. Use of $Zn(OTf)_2$ and $Bi(OTf)_3$ gave **5a** in good yields (Table 3, entries 3 and 7), but the enantioselectivities were low (47 and 33% *ee*, respectively). Additionally, the reactions were less diastereoselective. $Sn(OTf)_2$, $Mg(OTf)_2$ and $Sc(OTf)_3$ were found to be unsuitable affording only racemic **5a**, albeit in moderate to good yields of 54–78% and diastereoselectivities of 73–90% (Table 3, entries 2, 4 and 6).

Table 3. Screening of metal source, catalyst loading and temperature effects in the formation of γ-butenolide **5a**.[a]

Entry	$M(OTf)_2$	Catalyst loading [mol%]	*T*	Yield [%]	*de* [%][b]	*ee* [%][c]
1	$Fe(OTf)_2$	10	RT	86	89	12
2	$Sn(OTf)_2$	10	RT	78	90	0
3	$Zn(OTf)_2$	10	RT	81	86	47
4	$Mg(OTf)_2$	10	RT	54	73	0
5	$Cu(OTf)_2$	10	RT	88	94	95
6	$Sc(OTf)_3$	10	RT	78	81	0
7	$Bi(OTf)_3$	10	RT	43	72	33
8	$Cu(OTf)_2$	5	RT	88	94	83
9	$Cu(OTf)_2$	1	RT	20	46	32
10	$Cu(OTf)_2$	10	−68°C	88	95	94
11	$Cu(OTf)_2$	10	80°C[d]	97	91	51

[a] Reaction conditions: **2a** (0.22 mmol), **3a** (0.2 mmol), $M(OTf)_2$ (*x* mol%), aminosulfoximine (*S*)-**4aA** (*x* mol%), TFE (0.24 mmol), dry Et_2O (2 mL), temperature. [b] and [c] as in Table 1. [d] The reaction was carried out in THF under microwave irradiation.

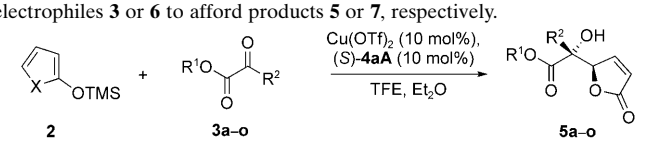
Because $Cu(OTf)_2$ gave the best results (Table 3, entry 5), a reduction of the catalyst loading was studied next. The reaction still proceeded smoothly when the amount of $Cu(OTf)_2$ and (*S*)-**4aA** was reduced from 10 to 5 mol% giving γ-butenolide **5a** in unchanged yield and *de* but decreased *ee* (entry 8 vs. 5). Further lowering of the catalyst loading to 1 mol% had a detrimental effect and even after 24 h the conversion was still incomplete. At that stage, the yield of **5a** was only 20% and the products had been formed with significantly reduced stereoselectivities (46% *de* and 32% *ee*, entry 9).

Varying the temperature did not lead to improved results (Table 3, entry 10). Thus, VMAR product **5a** was obtained in essentially the same yield and with identical stereoselectivity as at ambient temperature when the reaction was performed at −68°C, but the reaction time had to be prolonged to 16 h for achieving full conversion. On the other hand, when the reaction was carried out at 80°C (in THF under microwave irradiation) **5a** was formed in excellent yield (97%) after only 15 min (Table 3, entry 11). Whereas the *de* of **5a** was high (91%), its *ee* was only moderate (51%). Although these results were not superior to the previous ones, it is noteworthy that, to the best of our knowledge, this is the first example of a microwave-accelerated stereoselective Mukaiyama-type aldol reaction.[19]

Scope of the VMAR with $Cu(OTf)_2$/(*S*)-4aA: With the reaction system being optimized to a $Cu(OTf)_2$ and sulfoximine

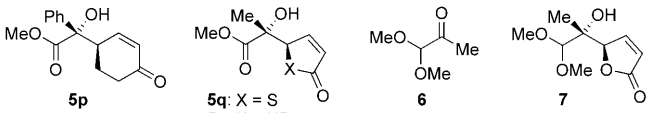
(*S*)-**4aA** ratio of 1:1 (10 mol% each) and TFE as additive (1.2 equiv) in dry Et_2O at ambient temperature, the substrate scope was subsequently studied. In this screening, various ketonic electrophiles **3** or **6** and cyclic dienol silanes **2** (1.1 equiv) were applied. The findings are collected in Table 4.

Table 4. Substrate scope in the VMAR between dienol silanes **2** and electrophiles **3** or **6** to afford products **5** or **7**, respectively.



2 **3a–o** **5a–o**

2a: X = O **3a**: $R^1 = R^2$ = Me **3f**: R^1 = Et, R^2 = Me **3k**: R^1 = Et, R^2 = *p*NO_2-Ph
2b: X = $(CH_2)_2$ **3b**: R^1 = Me, R^2 = Et **3g**: R^1 = Et, R^2 = *i*Pr **3l**: R^1 = Et, R^2 = CH_2Bn
2c: X = S **3c**: R^1 = Me, R^2 = CF_3 **3h**: R^1 = Et, R^2 = *t*Bu **3m**: R^1 = Et, R^2 = C(O)OEt
2d: X = NBoc **3d**: R^1 = Me, R^2 = Ph **3i**: R^1 = Et, R^2 = CF_3 **3n**: R^1 = *i*Pr, R^2 = Me
2e: X = NMe **3e**: R^1 = Me, R^2 = Bn **3j**: R^1 = Et, R^2 = Ph **3o**: R^1 = Bn, R^2 = Me



5p **5q**: X = S **6** **7**
5r: X = NBoc
5s: X = NMe

Entry	Dienol silane	Electrophile	Product[a]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	**2a**	**3a**	**5a**	88	94 (94)	95/n.d.
2	**2a**	**3b**	**5b**	79	98 (99)	97/n.d.
3	**2a**	**3c**	**5c**	75	92 (99)	4/3
4	**2a**	**3d**	**5d**	99	94 (99)	97/70
5	**2a**	**3e**	**5e**	20	92 (92)	93/n.d.
6	**2a**	**3f**	**5f**	92	96 (96)	96/n.d.
7	**2a**	**3g**	**5g**	99	99 (99)	99/n.d.
8[e]	**2a**	**3h**	**5h**	66	99 (99)	99/n.d.
9	**2a**	**3i**	**5i**	88	83 (99)	4/4
10	**2a**	**3j**	**5j**	95	96 (99)	98/n.d.
11	**2a**	**3k**	**5k**	96	85 (99)	91/95
12	**2a**	**3l**	**5l**	91	99 (99)	98/n.d.
13	**2a**	**3m**	**5m**	91	–	28
14	**2a**	**3n**	**5n**	84	94 (99)	98/n.d.
15	**2a**	**3o**	**5o**	84	96 (96)	95/n.d.
16	**2b**	**3d**	**5p**	38	16 (99)[f]	92/50
17[g]	**2c**	**3a**	**5q**	52	7 (7)	82/80
18[e]	**2d**	**3a**	**5r**	46	91 (91)	98/76
19[e]	**2e**	**3a**	**5s**	87	90 (90)	76/79
20	**2a**	**6**	**7**	87	99 (99)	94/n.d.

[a] Reaction conditions: **2** (0.22 mmol), **3** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), (*S*)-**4aA** (10 mol%), TFE (0.24 mmol), Et_2O (2 mL), RT, 2–6 h. [b] Yield of all stereoisomers after column chromatography. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture; in parentheses, *de* (referring to the *anti*/*syn* ratio) of the product after column chromatography. [d] Determined by CSP-HPLC; given for *anti* and *syn* isomers. [e] Reaction conditions as in [a] but at −20 °C, overnight. [f] Diastereomers were separated by preparative HPLC. [g] Reaction conditions as in [a] but at −15 °C, overnight.

As can be deduced from the summarized data, most substrates reacted well and the VMAR products were obtained in excellent yields and stereoselectivities. In many cases the major diastereomer could be isolated by chromatographic techniques. Products from α-substitution were never detected. The steric demand of the ester group had only a minor influence on the stereoselectivities (94–96% *de* and 95–98% *ee*), but the yields for products **5n** and **5o**, bearing isopropyl and benzyl substituents, respectively, were slightly lower than for methyl ester **5a** and ethyl ester **5f** (compare Table 4, entries 1, 6, 14 and 15).

On the contrary, the ketonic substitution pattern played a decisive role. For example, a trifluoromethyl group in the ketoester proved not suitable (entries 3 and 9). Although products **5c** and **5i** were obtained in good yields (75 and 88%, respectively) and high diastereoselectivities (92 and 83%, respectively), the major isomers of **5c** and **5i** were almost racemic (4% *ee* for both). Unfortunately, the enantioselectivity could not be raised by decreasing the reaction temperature to 0 or even to −30 °C. Since the spatial demand of a trifluoromethyl group corresponds approximately to those of an isopropyl or a *tert*-butyl group we wondered whether the *ee* was low due to steric reasons. However, as entries 7 and 8 indicate this was not the case. Thus, γ-butenolide **5g**, stemming from 3-methyl-2-oxobutyrate (**3g**) and TMSOF (**2a**) was not only isolated in nearly quantitative yield but also with 99% *de* and 99% *ee* (entry 7). Roughly the same result was obtained for ethyl 3,3-dimethyl-2-oxobutyrate (**3h**) which gave VMAR product **5h** with a *tert*-butyl substituent in 99% *de* and 99% *ee* (entry 8). While the yield of **5h** was rather low (16%), and a considerable amount of undesired furan-2(5*H*)-one was detected in the initial reaction at room temperature, it could significantly be raised to 66% by performing the catalysis at −20 °C. Also other experiments with ketoester **3c** indicated that not steric but electronic effects caused the low *ee* of product **5c**. Thus, in the absence of the copper–sulfoximine complex the electron-withdrawing CF_3 substituent of 3,3,3-trifluoropyruvate (**3c**) sufficiently activated the keto functionality to react with TMSOF (**2a**) and to generate racemic **5c**.

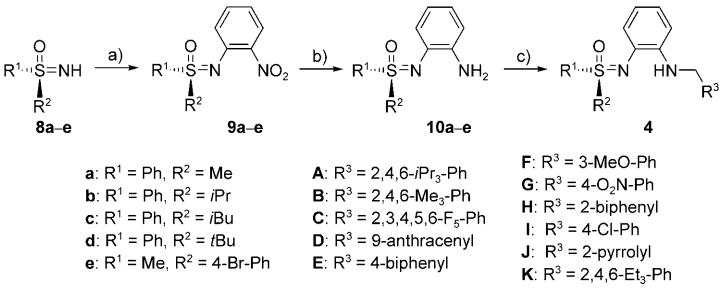
In reactions with phenylpyruvic acid methyl ester (**3e**) and TMSOF (**2a**) the resulting γ-butenolide **5e** was obtained with high stereoselectivities (92% *de* and 93% *ee*), but in only 20% yield (Table 4, entry 5). Like in the synthesis of **5h** a significant amount of furan-2(5*H*)-one was observed in this catalysis which led to the hypothesis that products with *tert*-butyl or benzyl substituents at the newly generated stereogenic center had a high tendency to undergo retro-aldol reactions (entries 5 and 8). Apparently, in the reactions of TMSOF (**2a**) with other electrophiles (Table 4, entries 10–12) retro-aldolization was less favorable, and the resulting VMAR products could be isolated in high yields (up to 96%) and with excellent diastereo- and enantioselectivities (up to 99% *de* and 98% *ee*).

Subsequently, ketodiester **3m** and pyruvic aldehyde dimethyl acetal (**6**) were tested as electrophiles (Table 4, entries 13 and 20). Although the reaction of **3m** with dienol silane **2a** gave γ-butenolide **5m** in high yield (91%), the *ee* was low (28%). Presumably, the asymmetric catalysis between activated ketodiester **3m** and **2a** could not compete with an uncatalyzed background reaction leading to racemic product. To our delight, ketone **6** with the adjacent masked

aldehyde functionality reacted well with **2a**, and product **7** was isolated in very good yield (87%) and excellent stereoselectivities (99% *de* and 94% *ee*).

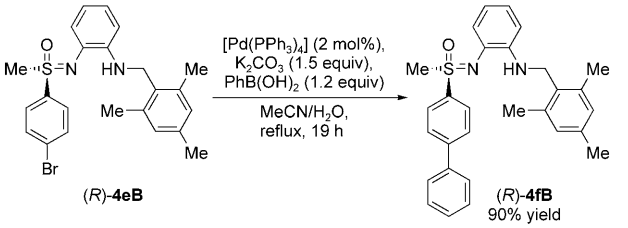
Finally, our attention was directed to the variation of nucleophiles **2**. Replacing TMSOF (**2a**) with cyclic silyl dienol ether **2b** gave rise to α,β-unsaturated ketone **5p** in moderate yield (38%). While the diastereoselectivity was low (16% *de*),[20] the *ee* of the major diastereomer (92%) was high (Table 4, entry 16). Also replacing oxygen by sulfur and utilizing 2-(trimethylsilyloxy)thiophene (TMSOT, **2c**) as nucleophile had a major influence on the catalysis (entry 17). While only traces of **5q** were isolated at room temperature, the yield was significantly increased to 52% at −15°C. Albeit the reaction proceeded with low diastereoselectivity (7% *de*), the *ee* of both diastereomers was good (82 and 80%, respectively). 1-(*tert*-Butoxycarbonyl)-2-(trimethylsilyloxy)pyrrole (**2d**) could also be employed (entry 18). Again, a reduced reaction temperature was needed to form VMAR product **5r** in an acceptable yield (46%). Then, however, α,β-unsaturated lactam **5r** was obtained with high diastereo- (91%) and excellent enantioselectivity (98%). Due to the rather low yield of **5r** we hypothesized that the sterically demanding Boc group hampered the catalysis and, consequently, 1-methyl-2-(trimethylsilyloxy)pyrrole (**2e**, entry 19) was tested. Indeed, the yield of the corresponding product **5s** almost doubled to 87% (compared to 46% for **5r**). However, while the change from Boc to methyl at the nitrogen had no influence on the diastereoselectivity (90%), the *ee* of **5s** was lower (76%) than for Boc-containing **5r**.

Structural variation of aminosulfoximines and their influence on the catalysis: Although most products shown in Table 4 were formed with high stereoselectivities and isolated in good to excellent yields, some substrates were converted less efficiently and the resulting VMAR products could only be obtained with yields, diastereo- or enantioselectivities below average. It was presumed that those results could be improved by applying modified ligands with optimized structures. In our previous work a straightforward synthesis of the highly modular ligands **4** had been established.[10a,b] This allowed to study the influence of the substitution pattern of the 1,2-benzene linker and the *N*-benzyl group on the stereoselectivity of the aldol reaction. Less attention was paid to the variation of the alkyl or aryl moiety at the stereogenic center. Consequently, it was decided to extend the ligand portfolio by preparing new C_1-symmetric aminosulfoximines **4** with altered electronic or steric properties. For their synthesis, the originally reported approach towards aminosulfoximines **4** was modified, now using a Cu^I-catalyzed *N*-arylation of enantiopure sulfoximines **8a–e**[21] with 2-iodonitrobenzene and K_2CO_3 (instead of the more expensive Cs_2CO_3) in the first step.[22] The resulting coupling products **9a–e** (Scheme 4) were obtained in good to excellent yields (53–98%). While arylated products **9a–c** and **e** were air-stable at room temperature, decomposition of **9d** was observed upon storage in air for 7–10 days. The reduction of the nitro group proceeded well for most substrates, and anilines **10** were isolated in up to 85% yield. Again, sulfoximine **9d** with $R^2 = t$Bu proved most problematic in this step, and along with the desired **10d** (22% yield) 2-aminoaniline, diphenyl disulfide and the ethyl ester of benzenesulfinic acid were isolated as by-products. The direct reductive amination of a broad range of aldehydes with anilines **10** under mild conditions with $NaBH_3CN$ gave aminosulfoximines **4** in high yields up to 92%.



Scheme 4. Preparation of aminosulfoximines **4**. a) 2-Iodonitrobenzene (2.0 equiv), CuI (10 mol%), DMEDA (20 mol%), K_2CO_3 (2.5 equiv), toluene, reflux, 16-24 h; 53–98%; b) Fe (4.5 equiv), AcOH (18 equiv), EtOH/H_2O, reflux, 4 h; 22–85%; c) aldehyde (1.0–2.5 equiv), $NaBH_3CN$ (1.0 equiv), AcOH, MeOH, 0°C to RT, 16 h; 52–92%.

Additionally, aminosulfoximine (*R*)-**4fB** could be obtained in very good yield (90%) by palladium-catalyzed Suzuki coupling of (*R*)-**4eB** and phenylboronic acid, demonstrating again the high versatility of this ligand class (Scheme 5).



Scheme 5. Palladium-catalyzed Suzuki coupling of (*R*)-**4eB** to afford (*R*)-**4fB**.

The 18 new C_1-symmetric aminosulfoximines **4** (Table 5, entries 3–20) were then tested in the synthesis of γ-butenolide **5a** from TMSOF (**2a**) with methyl pyruvate (**3a**). As reference points served the results obtained with sulfoximine (*S*)-**4aA** and known (*S*)-**4aB**[10a,b] (Table 5, entries 1 and 2). Apparently, the entire family of C_1-symmetric aminosulfoximines **4** was highly suitable and many compounds were excellent ligands for the copper-catalyzed VMAR. As long as the substitution pattern at the sulfoximine core remained unchanged (Table 5, entries 1–11) the new compounds compared well with the reference ligand (*S*)-**4aA** or even outclassed it. Interestingly, mesitylene derivative (*S*)-**4aB** was slightly better than (*S*)-**4aA** in terms of yield, diastereo- and enantioselectivity (see entries 2 vs. 1). This was

unexpected because in the previously studied Mukaiyama aldol reactions[10a,b] use of (*S*)-**4aB** gave the same enantioselectivity but a lower yield than (*S*)-**4aA**. The new sulfoximines (*S*)-**4aC** to (*S*)-**4aK**, which stemmed from aniline **10a** and the corresponding aldehydes, formed **5a** with excellent stereoselectivities (*de* and *ee* up to 99%) in very good yields (entries 3–11). The lowest *ee* (85%) was obtained in the catalysis with 2-pyrrolyl derived sulfoximine (*S*)-**4aJ** (entry 10).

Table 5. Screening of aminosulfoximines **4** in the VMAR to give γ-butenolide **5a**.[a]

Entry	Sulfoximine	Yield [%]	*de* [%][b]	*ee* [%][c]
1	(*S*)-**4aA**	88	94	95
2	(*S*)-**4aB**	89	98	97
3	(*S*)-**4aC**	99	98	96
4	(*S*)-**4aD**	83	98	95
5	(*S*)-**4aE**	83	99	97
6	(*S*)-**4aF**	86	99	96
7	(*S*)-**4aG**	81	99	97
8	(*S*)-**4aH**	86	98	95
9	(*S*)-**4aI**	89	99	97
10	(*S*)-**4aJ**	83	98	85
11	(*S*)-**4aK**	80	92	99
12	(*S*)-**4bA**	86	90	66
13	(*S*)-**4bB**	81	95	84
14	(*S*)-**4cA**	91	90	95
15	(*S*)-**4cB**	99	98	96
16	(*S*)-**4cK**	95	98	97
17	(*S*)-**4dB**	99	96	8
18	(*R*)-**4eA**	98	94	−92
19	(*R*)-**4eB**	97	97	−95
20	(*R*)-**4fB**	97	98	−96

[a] Reaction conditions: **2a** (0.22 mmol), **3a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), aminosulfoximine **4** (10 mol%), TFE (0.24 mmol), Et_2O (2 mL), RT. [b] and [c] as in Table 1.

Next, the influence of the alkyl part of the sulfoximine fragment was investigated. Increasing the steric bulk from methyl [as in (*S*)-**4aA**] to isopropyl [as in (*S*)-**4bA**] resulted in a product with reduced *de* (90%) and a significant loss of enantioselectivity (66% *ee*; Table 5, entries 12 vs. 1). On the other hand, when the benzylic part of the ligand was smaller (having a 2,4,6-Me_3Ph instead of a 2,4,6-*i*Pr_3Ph group), the change from methyl to isopropyl at the stereogenic center was beneficial for both diastereo- and enantioselectivity (see entries 13 vs. 12). This result indicated a strong interaction between the steric environment of the stereogenic center and the backbone. A further increase in size of the alkyl substituent to a *tert*-butyl group [(*S*)-**4dB**] resulted in almost racemic **5a** (8% *ee*), albeit the yield (99%) and the *de* (96%) were excellent (entry 17). Previously, we had found very high *ee* values and yields in catalyses with *P,N*-sulfoximines having a branching at the β-position of the alkyl group,[23] and hence we expected the same positive effect for similar aminosulfoximines **4**. Indeed, when *S*-isobutyl sulfoximine (*S*)-**4cA** was utilized, product **5a** was obtained with increased yield (91%) and very high *ee* (95%), but unfortunately, the *de* (90%) was low (entry 14). To our delight this selectivity could be improved by reducing the steric bulk of the backbone of *S*-isobutyl sulfoximines and hence, use of (*S*)-**4cB** and (*S*)-**4cK** afforded **5a** with excellent *de* values (98% for both) and yields (99 and 95%, respectively; see entries 15 and 16).

Modifications on the *S*-aryl group also resulted in active catalysts but did not lead to significant improvements. Thus, from reactions with (*R*)-**4eA**, (*R*)-**4eB** and (*R*)-**4fB** γ-butenolide **5a** was isolated in very high yields and excellent stereoselectivities (Table 5, entries 18–20).

Since (*R*)-configured aminosulfoximines **4** (entries 18–20) provide products with the opposite absolute configuration both product enantiomers are accessible.

The results from this ligand screening can be summarized as follows: Most of the new aminosulfoximines **4** performed well in the VMAR; three of them (Table 5, entries 3, 15 and 17) formed **5a** in almost quantitative yield (99%), four (entries 5–7 and 9) gave rise to a product with 99% *de* and one sulfoximine (entry 11) led to almost enantiopure **5a** (99% *ee*).

Fine adjustments for single substrates: Two screening strategies had been followed up to this stage: First, a catalyst bearing sulfoximine (*S*)-**4aA** as ligand had been tested in reactions of a variety of substrate combinations (enol ethers and ketoesters), and second, various sulfoximine ligands had been screened on their applicability in the catalyzed reaction between TMSOF (**2a**) with methyl pyruvate (**3a**). In many cases, the products were obtained with very high stereoselectivities in excellent yields, but nevertheless, a few substrate combinations remained problematic and did not lead to satisfying results. It was therefore decided to focus on an additional fine-adjustment between the catalyst (ligand) structure and substrates. For this new optimization (Table 6) sulfoximines (*S*)-**4aB**, (*S*)-**4aC** and (*S*)-**4cB** were taken into consideration because before they had performed in a well-balanced manner in terms of yields and stereoselectivities. The results from the catalyses with ligand (*S*)-**4aA** were taken as reference.

Compared to the catalysis with (*S*)-**4aA** as ligand, the yield (29%) and the diastereoselectivity (52%) in the formation of γ-butenolide **5c**, obtained from 3,3,3-trifluoropyruvate (**3c**) and TMSOF (**2a**), dropped significantly when (*S*)-**4aC** was used (Table 6, entries 1 and 2). However, a minor increase in the *ee* from 4 to 11% was observed. For VMAR product **5e** the yield remained very low (13%) in the catalysis with (*S*)-**4aB** but an improvement of the *de* (95%) with unchanged enantioselectivity was observed (see entries 4 and 3). Employing ligands (*S*)-**4aB**, (*S*)-**4aC** and (*S*)-**4cB** gave γ-butenolide **5f** with excellent diastereo- and enantioselectivities (each of them 99% *de* and 97–99% *ee*), but the yields (79–85%) were slightly reduced (Table 6, entries 6–8 vs. 5). The *de* of product **5k**, stemming from 4-nitrophenylglyoxylate (**3k**) and TMSOF (**2a**), was only moderate (85%) in the catalysis with the standard ligand (*S*)-**4aA** (entry 9), but to our delight all three aminosulfoximines (*S*)-**4aB**, (*S*)-**4aC** and (*S*)-**4cB** led to significant im-

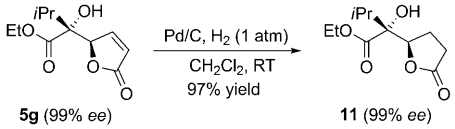
Table 6. Sulfoximine-based optimization of selected VMAR products.

Entry	Sulfoximine	Product[a]	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	(*S*)-**4aA**	**5c**	75	92 (99)	4/3
2	(*S*)-**4aC**	**5c**	29	52 (99)	11/n.d.
3	(*S*)-**4aA**	**5e**	20	92 (92)	93/n.d.
4	(*S*)-**4aB**	**5e**	13	95 (95)	93/n.d.
5	(*S*)-**4aA**	**5f**	92	96 (96)	96/n.d.
6	(*S*)-**4aB**	**5f**	85	99 (99)	98/n.d.
7	(*S*)-**4aC**	**5f**	79	99 (99)	99/n.d.
8	(*S*)-**4cB**	**5f**	85	99 (99)	97/n.d.
9	(*S*)-**4aA**	**5k**	96	85 (99)	91/95
10	(*S*)-**4aB**	**5k**	89	95 (99)	94/n.d.
11	(*S*)-**4aC**	**5k**	95	98 (99)	92/n.d.
12	(*S*)-**4cB**	**5k**	96	94 (99)	94/n.d.
13	(*S*)-**4aA**	**5m**	91	–	28
14	(*S*)-**4aB**	**5m**	82	–	30
15	(*S*)-**4aC**	**5m**	63	–	9
16	(*S*)-**4cB**	**5m**	84	–	26
17	(*S*)-**4aA**	**5p**	38	16 (16)	92/50
18	(*S*)-**4aB**	**5p**	17	66 (66)	94/59
19	(*S*)-**4cB**	**5p**	19	69 (69)	95/74
20[e]	(*S*)-**4aA**	**5q**	52	7 (7)	82/80
21[e]	(*S*)-**4aB**	**5q**	47	7 (7)	87/86
22[e]	(*S*)-**4aC**	**5q**	21	5 (5)	90/89
23[e]	(*S*)-**4cB**	**5q**	19	13 (13)	83/82
24[f]	(*S*)-**4aA**	**5r**	46	91 (91)	98/76
25[f]	(*S*)-**4aB**	**5r**	42	88 (88)	96/63
26[f]	(*S*)-**4cB**	**5r**	52	90 (90)	97/76
27[f]	(*S*)-**4aA**	**5s**	87	90 (90)	76/79
28[f]	(*S*)-**4aB**	**5s**	98	80 (80)	89/86
29[f]	(*S*)-**4aC**	**5s**	67	77 (77)	75/83
30[f]	(*S*)-**4cB**	**5s**	97	78 (78)	90/89
31	(*S*)-**4aA**	**7**	87	99 (99)	94/n.d.
32	(*S*)-**4aB**	**7**	57	99 (99)	89/n.d.
33	(*S*)-**4aC**	**7**	95	99 (99)	92/n.d.
34	(*S*)-**4cB**	**7**	87	99 (99)	80/n.d.

[a] Reaction conditions: Dienol silane **2** (0.22 mmol), electrophile **3** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), aminosulfoximine **4** (10 mol%), TFE (0.24 mmol), Et_2O (2 mL), RT, 2–6 h. [b], [c] and [d] as in Table 4. [e] Reaction conditions as in [a] but at −15 °C, overnight. [f] Reaction conditions as in [a] but at −20 °C, overnight.

provements (94–98% *de*, entries 10–12). Moreover, in all three cases the *ee* was raised from 91 to 92–94%. Unfortunately, this effect did not occur in the synthesis of **5m**, where (*S*)-**4aA** remained the ligand of choice (Table 6, entry 13–16). The aminosulfoximine structure had a dramatic impact in the optimization of the approach towards α,β-unsaturated ketone **5p** (entries 17–19). While only a low *de* of 16% was reached with the reference ligand (*S*)-**4aA**, it rose to 66 and 69% *de*, respectively, when (*S*)-**4aB** and (*S*)-**4cB** were applied. It is noteworthy that while the *ee* of the major diastereomer increased only slightly (94–95%) that of the minor diastereomer reached up to 74%. Unfortunately, this improvement in stereoselectivity was accompanied with a drop in yield, which was reduced to 17–19% compared to 38% in the catalysis with (*S*)-**4aA**. Yield and *de* of VMAR product **5q**, derived from TMSOT (**2c**) and methyl pyruvate (**3a**), remained problematic and could not be improved by using (*S*)-**4aB**, (*S*)-**4aC** and (*S*)-**4cB**. However, these ligands resulted in higher *ee* values for **5q** with up to 90% (entries 21–23 vs. 20). While the choice of the ligand was less relevant in the synthesis of **5r** (entries 24–26), it was important for analogous product **5s** (entries 27–30). Use of (*S*)-**4aB** and (*S*)-**4cB** as ligands led to **5s** with considerably increased yields (98 and 97%, respectively) and higher enantioselectivities (89 and 90%) at the cost of reduced *de* values (80 and 78%; see entries 28 and 30 vs. 27). For product **7** we aimed at increasing either yield or *ee* [an excellent *de* of 99% was already obtained in the catalysis with (*S*)-**4aA**; entry 31] and pleasingly we noticed that use of (*S*)-**4aC** rose the yield (95%) with almost unaffected *ee* (92%, entry 33). These reactions also indicated that a small substituent at the sulfoximine core (methyl rather than the more bulky isobutyl) was essential for high enantioselectivities (entries 31–33 vs. 34). On the other hand the diastereoselectivities were not altered by the sulfoximine ligands.

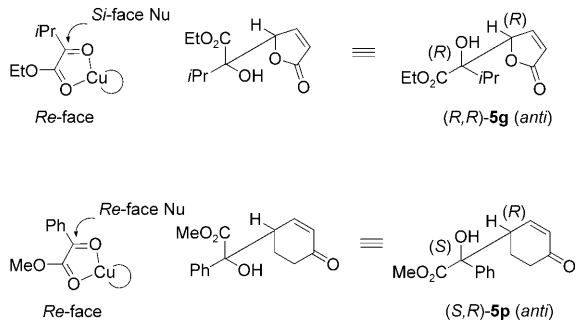
In order to demonstrate potential conversions of the new products **5** and considering that butyrolactones are common structural motifs in natural products, γ-butenolide **5g** was hydrogenated to give γ-lactone **11** (Scheme 6). As expected, the reaction proceeded smoothly, affording the reduced product with excellent *ee* (99%) in very high yield (97%).[24]



Scheme 6. Hydrogenation of γ-butenolide **5g** to give butyrolactone **11**.

Determination of the relative and absolute configuration: Previously, the absolute configuration of **5g** stemming from catalyses with *S*-configured sulfoximine **4aA** was determined as (*R*,*R*).[11] This enantiomer resulted from a preferential attack of the nucleophile from the *Si* face on the *Re* face of the electrophile (Scheme 7, top). Assuming that the reaction took place in the same manner as above, namely from the same sides of the reactants, a product with (*S*,*R*) configuration was expected for **5p** (Scheme 7, bottom).

In order to validate this hypothesis the relative and absolute configuration of **5p** was determined by means of different techniques.



Scheme 7. Simplified stereochemical models.

The relative stereochemistry[25] of **5p** was shown by X-ray single crystal structure analysis to be *anti* (Figure 1).

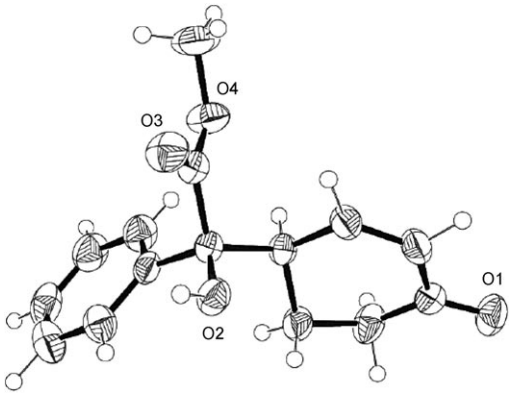


Figure 1. Structure of **5p** in the solid state.[26]

The absolute configuration (*S*,*R*) was determined by comparison of calculated and experimental CD spectra.

Computational Details

A Monte–Carlo conformational search using the AM1 Hamiltonian[28] as implemented in Spartan '02[29] provided the 62 initial geometries for the arbitrarily chosen (*R*,*S*)-enantiomer of *anti*-**5p**. Subsequent ab initio geometry optimizations were performed for isolated molecules in the gas phase employing the program Gaussian 03.[30] Accordingly, a number of 14 stationary points were located within a range of 5 kcal mol^{-1} at the MP2/6-31+G** level. Additionally, single point energy calculations taking into account the effect of the solvent (acetonitrile, $\varepsilon = 36.64$) were performed at PCM/MP2/6-31+G**//MP2/6-31+G** level. The seven most stable conformers lying within a range of 2.0 kcal mol^{-1} (Table 7) were then included in the calculation of the CD curve of *anti*-**5p**.

Table 7. Relative energies (in kcal mol^{-1}) of the seven most stable conformers of *anti*-**5p** in acetonitrile as solvent and the corresponding Boltzmann factors.

Entry	Conformer (*anti*)	ΔE [kcal mol^{-1}], CH_3CN PCM/MP2/6-31+G**//MP2/6-31+G**	w[a]
1	*anti*-**5p**	0.000	0.554731
2	*anti*-**5p-a**	0.491	0.241962
3	*anti*-**5p-b**	1.233	0.069150
4	*anti*-**5p-c**	1.328	0.058863
5	*anti*-**5p-d**	1.702	0.031301
6	*anti*-**5p-e**	1.904	0.022253
7	*anti*-**5p-f**	1.918	0.021740

[a] w is the Boltzmann factor calculated at 298 K.

Theoretical CD spectra for each of the seven conformers were obtained using the time-dependent density functional theory (TDDFT)[31] employing the B3LYP functional[32] and a valence double zeta basis set, including polarization as well as diffuse functions (6-31+G**). The rotational strengths were calculated using the origin-independent dipole-velocity formalism.[33] The solvent effect on the rotational strengths was also accounted for by employing the Polarizable Continuum Model (PCM). The calculated CD spectrum was obtained as a Boltzmann-weighted superposition of the CD curves of the single conformers. The Boltzmann factors (298 K) were calculated using the MP2/6-31+G** relative energies obtained including the solvent (Table 7). The experimental and averaged calculated[34] CD spectra are presented in Figure 2a and b, respectively. The calculated CD spectrum has a positive Cotton effect of relatively low intensity around 278 nm followed by a much stronger negative one at around 234 nm. The first calculated Cotton effect is due to transitions from a molecular orbital of π symmetry widely located on the phenyl ring with small σ and n contributions to a π^* orbital located on the C=C-C=O system of the non-aromatic six-membered ring. This band was assigned to the negative Cotton effect observed at 237 nm. The second calculated Cotton effect is negative and we correlate it with the strongly positive band observed at about 217 nm. The main contributions to this band come from $\sigma+n \rightarrow \pi^*$ transitions from HOMO−4 to LUMO and from $\pi+n \rightarrow \pi^*$ transitions from HOMO−3 to LUMO. Compared to their experimental counterparts the Cotton effects are shifted to the red. The calculated CD spectrum of the (*R*,*S*)-enantiomer of **5p** closely resembles the mirror image of the measured spectrum. Therefore, we conclude that the absolute configuration of *anti*-**5p** is very likely (*S*,*R*), a result which is in agreement with our initial assignment.

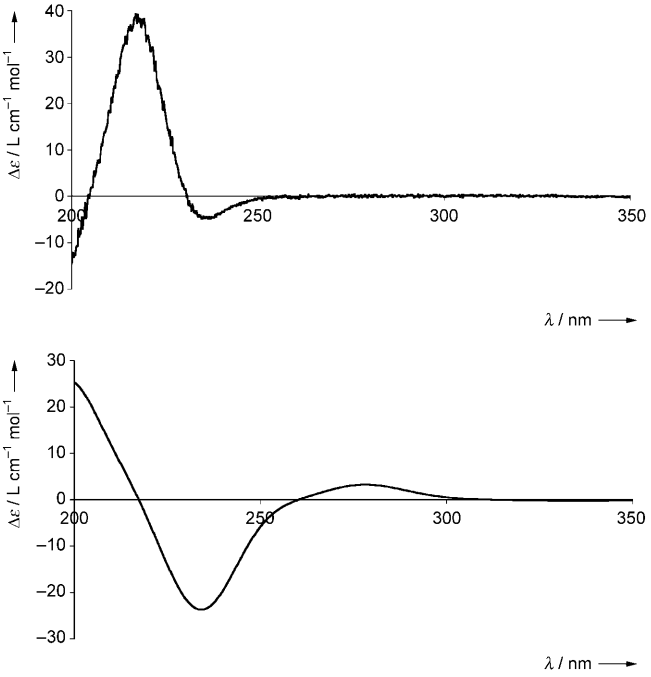


Figure 2. a) Experimental CD spectrum of *anti*-**5p**. b) Averaged calculated CD spectrum of (*R*,*S*)-**5p**.

Conclusion

In this full account we describe an efficient vinylogous Mukaiyama-type aldol reaction. The catalytic system which consists of $Cu(OTf)_2$ and a C_1-symmetric aminosulfoximine tolerates numerous electrophiles/nucleophiles combinations and affords the corresponding products with high stereoselectivities in excellent yields. A detailed study of the variation of the ligand backbone revealed that the applied sulfoximines are highly modular and that they can perfectly be adjusted to substrate requirements. The relative and absolute configuration of two products was assigned by combined experimental and theoretical means.

Experimental Section

The analytical data for all other new compounds can be found in the Supporting Information.

General procedure for the Cu-catalyzed VMAR: A dry Schlenk tube under argon atmosphere was charged with $Cu(OTf)_2$ (0.02 mmol, 0.1 equiv) and the aminosulfoximine (0.02 mmol, 0.1 equiv). Dry Et_2O (2.0 mL, 0.1 M) was added and the green solution was stirred at RT for 30 min. Subsequently, 2,2,2-trifluoroethanol (0.24 mmol, 1.2 equiv), electrophile **3** (0.2 mmol) and cyclic dienol silane **2** (0.22 mmol, 1.1 equiv) were added and the Schlenk tube was sealed. After complete consumption of starting material (2–6 h, TLC control), the solvent was evaporated under reduced pressure, and the crude reaction mixture was analyzed by ^1H NMR to determine the diastereomeric excess. Afterwards the product was purified by flash column chromatography.

(*R*,*R*)-Methyl 2-hydroxy-2-(5-oxo-2,5-dihydrofuran-2-yl)butanoate (5b): Prepared from methyl 2-oxo-butyrate (**3b**) and TMSOF (**2a**). The product was purified by flash column chromatography (pentane/EtOAc 1:1) to give the title compound as single diastereomer. Yield: 79% (light yellow oil); *de* = 98% (99% after chromatography); optical rotation: $[\alpha]_D = 102.0$ ($c = 1.8$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.4$ Hz, 3H, CH_3), 1.81–2.02 (m, 2H, CH_2), 3.29 (brs, 1H, OH), 3.84 (s, 3H, CH_3), 5.15 (dd, $J = 2.1$ Hz, 1.6 Hz, 1H, CH), 6.21 (dd, $J = 5.8$ Hz, 2.1 Hz, 1H, CH), 7.34 (dd, $J = 5.8$ Hz, 1.6 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.5$ (CH_3), 28.2 (CH_2), 53.3 (CH_3), 78.5 (C), 85.8 (CH), 123.3 (CH), 152.1 (CH), 172.3 (C), 173.1 (C); IR ($CHCl_3$): $\tilde{\nu} = 3485$ (m), 3099 (w), 2961 (m), 2883 (w), 1754 (s), 1665 (m), 1602 (w), 1448 (m), 1309 (w), 1246 (s), 1162 (s), 1098 (m), 1052 (w), 1035 (w), 1012 (w), 892 (m), 845 (m), 812 (m), 757 (m), 693 (w); MS (EI): *m*/*z* (%): 141 (11) $[M-C_2H_3O_2]^+$, 117 (23), 84 (55), 57 (100), 55 (11); HRMS: *m*/*z*: calcd for $C_7H_9O_3$: 141.0552, found 141.0550 $[M-C_2H_3O_2]^+$; HPLC: $t_R = 13.6$ min [minor], $t_R = 15.4$ min [major] (Chiralpak AD column, flow rate 1.0 mL min^{-1}, heptane/*i*PrOH 90:10, $\lambda = 210$ nm, 20°C); *ee* = 97%.

General procedure for the *N*-arylation of sulfoximines:[22] A dry large Schlenk tube under argon atmosphere was charged with sulfoximine **8**, 2-iodonitrobenzene (2.0 equiv), K_2CO_3 (2.5 equiv), CuI (0.1 equiv) and toluene (0.5 M). After addition of DMEDA (0.2 equiv) the Schlenk tube was sealed with a stopper and heated to reflux for 16–20 h. The reaction mixture was cooled to RT, diluted with CH_2Cl_2 and treated with aqueous HCl (2.0 M). After extracting the aqueous layer with CH_2Cl_2 (three times) the combined organic extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography.

(*S*)-*N*-(2-Nitrophenyl)-*S*-isopropyl-*S*-phenylsulfoximine [(*S*)-9b] Prepared from (*S*)-*S*-isopropyl-*S*-phenylsulfoximine [(*S*)-**8b**, 6.33 mmol]. The product was purified by flash column chromatography (pentane/EtOAc 4:1) to give the title compound. Yield: 93% (red-brown oil); optical rotation: $[\alpha]_D = -25.4$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.39 (d, $J = 6.8$ Hz, 3H, CH_3), 3.44 (sept., $J = 6.8$ Hz, 1H, CH), 6.85 (ddd, $J = 8.2$ Hz, 7.0 Hz, 1.6 Hz, 1H, Ar-H), 7.10–7.20 (m, 2H, Ar-H), 7.49–7.57 (m, 2H, Ar-H), 7.59–7.65 (m, 2H, Ar-H), 7.91–7.97 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.8$ (CH_3), 16.0 (CH_3), 58.2 (CH), 120.3 (Ar-CH), 123.6 (Ar-CH), 124.4 (Ar-CH), 129.4 (2 Ar-CH), 130.2 (2 Ar-CH), 132.4 (Ar-CH), 133.6 (Ar-CH), 134.7 (Ar-C), 139.9 (Ar-C), 144.6 (Ar-C); IR (neat): $\tilde{\nu} = 1601$ (s), 1521 (s), 1478 (s), 1447 (m), 1355 (s), 1287 (s), 1199 (s), 1164 (m), 1097 (s), 1041 (w), 1015 (s), 855 (m), 750 (s), 721 (s), 692 (m); MS (EI): *m*/*z* (%): 304 (27) $[M]^+$, 227 (2), 181 (12), 125 (100), 77 (18); HRMS for $C_{15}H_{16}N_2O_3S$: calcd for 304.0882, found 304.0882.

General procedure for the reduction of the nitro group:[10a,b] A round-bottom flask was charged with nitrosulfoximine **9** and iron turnings (4.5 equiv) in EtOH/H_2O (2:1, 0.05 M). After addition of glacial acetic acid (18 equiv) the reaction mixture was heated to reflux for 4 h, then cooled to RT and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (three times) and the combined organic extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography.

(*S*)-*N*-(2-Aminophenyl)-*S*-isopropyl-*S*-phenylsulfoximine [(*S*)-10b]: Prepared from nitrosulfoximine (*S*)-**9b** (5.71 mmol). The product was purified by flash column chromatography (pentane/EtOAc = 1:2) to give the title compound. Yield: 70% (beige solid); m.p. 117–120°C; optical rotation: $[\alpha]_D = -14.4$ ($c = 0.9$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.43 (d, $J = 6.8$ Hz, 3H, CH_3), 3.44 (sept., $J = 6.8$ Hz, 1H, CH), 4.01 (brs, 2H, NH_2), 6.44 (ddd, $J = 7.8$ Hz, 5.8 Hz, 3.1 Hz, 1H, Ar-H), 6.68–6.71 (m, 2H, Ar-H), 6.84–6.89 (m, 1H, Ar-H), 7.46–7.61 (m, 3H, Ar-H), 7.82–7.87 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.1$ (CH_3), 16.3 (CH_3), 57.3 (CH), 114.7 (Ar-CH), 118.5 (Ar-CH), 121.6 (Ar-CH), 122.0 (Ar-CH), 129.3 (2 Ar-CH), 130.2 (2 Ar-CH), 132.0 (Ar-C), 133.1 (Ar-CH), 135.5 (Ar-C), 140.5 (Ar-C); IR (KBr): $\tilde{\nu} = 3424$ (s), 3336 (s), 1606 (s), 1497 (s), 1445 (m), 1342 (w), 1290 (s), 1248 (s), 1176 (s), 1093 (s), 1040 (m), 1012 (s), 757 (s), 690 (m), 566 (s); MS (EI): *m*/*z* (%): 274 (55) $[M]^+$, 213 (20), 182 (11), 137 (17), 125 (34), 107 (100), 78 (27); elemental analysis calcd (%) for $C_{15}H_{18}N_2OS$: C 65.66, H 6.61, N 10.21; found C 65.69, H 6.65, N 10.18.

General procedure for the reductive amination with $NaBH_3CN$:[10a,b] A round-bottom flask was charged with aniline **10** in MeOH (0.1–0.5 M). The corresponding aldehyde was added (1.0–2.5 equiv) and the reaction mixture was cooled to 0°C. After addition of $NaBH_3CN$ (1.0 equiv) and 3–6 drops of glacial acetic acid the reaction mixture was stirred at RT for 16–20 h. The reaction mixture was quenched with 10% aqueous K_2CO_3 and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (three times) and the combined organic extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography. **Caution**: After column chromatography most of the aminosulfoximines **4** are obtained as oils, which suddenly solidify with *strong* foaming on the rotary evaporator or at high vacuum.

(*S*)-*N*-[2-(9-Anthracenylmethyl)aminophenyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-4aD)]: Prepared from aniline (*S*)-**10a** (0.50 mmol) and anthracene-9-carboxaldehyde (1.00 mmol, 2.00 equiv). The product was purified by flash column chromatography (pentane/EtOAc 4:1) to afford an inseparable mixture of the product and the corresponding alcohol. A second flash column chromatography (CH_2Cl_2/EtOAc 20:1) of the crude product yielded the pure title compound. Yield: 68% (yellow solid); m.p. 144–146°C; optical rotation: $[\alpha]_D = -161.7$ ($c = 1.5$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.92$ (s, 3H, CH_3), 4.91 (brs, 1H, NH), 5.17 (d, $J = 11.9$ Hz, 1H, C*H*H), 5.25 (d, $J = 11.9$ Hz, 1H, CH*H*), 6.54 (ddd, $J = 7.8$ Hz, 6.7 Hz, 2.3 Hz, 1H, Ar-H), 6.95–7.06 (m, 3H, Ar-H), 7.29–7.36 (m, 2H, Ar-H), 7.45–7.61 (m, 5H, Ar-H), 7.68 (dt, $J = 8.5$ Hz, 1.6 Hz, 2H, Ar-H), 8.07 (dd, $J = 8.6$ Hz, 1.1 Hz, 2H, Ar-H), 8.38 (d, $J = 8.9$ Hz, 2H, Ar-H), 8.51 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.2$ (CH_2), 45.8 (CH_3), 109.8 (Ar-CH), 117.0 (Ar-CH), 121.3 (Ar-CH), 122.9 (Ar-CH), 124.6 (2 Ar-CH), 125.1 (2 Ar-CH), 126.2 (2 Ar-CH), 127.6 (Ar-CH), 128.3 (2 Ar-CH), 129.0 (2 Ar-CH), 129.3 (2 Ar-CH), 130.4 (Ar-C), 130.6 (2 Ar-C), 131.3 (Ar-C), 131.6 (2 Ar-C), 133.0 (Ar-CH), 139.2 (Ar-C), 142.7 (Ar-C); IR (KBr): $\tilde{\nu} = 3047$ (m), 2362 (s), 2342 (m), 1650 (w), 1581 (s), 1501 (s), 1420 (s), 1326 (m), 1253 (s), 1188 (m), 1122 (m), 1092 (m), 1019 (s), 960 (m), 878 (m), 837 (m), 737 (s), 687 (s), 614 (m), 523 (s); MS (EI): *m*/*z* (%): 436 (20) $[M]^+$, 296 (100), 295 (81), 246 (13), 191 (84), 140 (34), 125 (33), 119 (32), 97 (33), 77 (21); elemental analysis calcd (%) for $C_{28}H_{24}N_2OS$: C 77.03, H 5.54, N 6.42, found C 76.88, H 5.73, N 6.08.

General procedure for the reductive amination with $NaBH_4$:[10a,b] A round-bottom flask was charged with aniline **10** in MeOH (0.1 M), the corresponding aldehyde (1.2 equiv) and glacial acetic acid (1.0 equiv). After stirring at RT for 3 h $NaBH_4$ (2.5 equiv) was added in small portions at 0°C and the reaction mixture was stirred additional 16 h at RT. For work-up see the protocol described for the reductive amination with $NaBH_3CN$.

(*S*)-*N*-[2-(2,4,6-Triisopropylbenzyl)aminophenyl]-*S*-isobutyl-*S*-phenylsulfoximine [(*S*)-4cA]: Prepared from aniline (*S*)-**10c** (1.46 mmol) and 2,4,6-triisopropylbenzaldehyde (1.75 mmol, 1.20 equiv). The product was purified by flash column chromatography (pentane/EtOAc 10:1) to

afford an inseparable mixture of the product and the corresponding alcohol. A second flash column chromatography (CH_2Cl_2) of the crude product yielded the pure title compound. Yield: 66% (beige solid); m.p. 100–102°C; optical rotation: $[\alpha]_D = -115.7$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.7$ Hz, 3H, CH_3), 1.04 (d, $J = 6.7$ Hz, 3H, CH_3), 1.37–1.48 (m, 18H, 6 CH_3), 2.24–2.44 (m, 1H, CH), 2.99–3.16 (m, 2H, C*H*H and CH), 3.27 (dd, $J = 14.1$ Hz, 6.0 Hz, 1H, CH*H*), 3.40–3.53 (m, 2H, 2 CH), 4.35 (d, $J = 11.4$ Hz, 1H, C*H*H), 4.46 (d, $J = 11.3$ Hz, 1H, CH*H*), 4.70 (br s, 1H, NH), 6.52 (t, $J = 7.4$ Hz, 1H, Ar-H), 6.85 (d, $J = 7.7$ Hz, 1H, Ar-H), 6.93–7.07 (m, 2H, Ar-H), 7.22 (s, 2H, Ar-H), 7.48–7.56 (m, 2H, Ar-H), 7.56–7.63 (m, 1H, Ar-H), 7.91 (d, $J = 7.5$ Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.8$ (CH_3), 23.0 (CH_3), 24.3 (CH_3), 24.4 (CH_3), 24.5 (CH), 25.0 (4 CH_3), 29.6 (2 CH), 34.5 (CH), 40.9 (CH_2), 65.8 (CH_2), 109.4 (Ar-CH), 116.5 (Ar-CH), 120.8 (Ar-CH), 121.2 (2 Ar-CH), 122.5 (Ar-CH), 128.9 (2 Ar-CH), 129.5 (2 Ar-CH), 130.5 (Ar-C), 131.5 (Ar-C), 133.0 (Ar-CH), 139.0 (Ar-C), 142.6 (Ar-C), 148.1 (2 Ar-C), 148.2 (Ar-C); IR ($CHCl_3$): $\tilde{\nu} = 3398$ (m), 3058 (m), 2961 (s), 2872 (s), 2362 (w), 2336 (w), 1587 (m), 1502 (s), 1426 (m), 1256 (s), 1182 (w), 1119 (m), 1018 (m), 750 (s), 688 (w), 543 (m); MS (EI): *m/z* (%): 504 (74) $[M]^+$, 307 (62), 288 (100), 217 (12), 201 (8), 182 (6), 126 (21), 78 (9); elemental analysis calcd (%) for $C_{32}H_{44}N_2OS$: C 76.14, H 8.79, N 5.55, found C 75.69, H 8.74, N 5.56.

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[21] Here, the absolute configuration of **8e** was unambiguously assigned as (*R*) by debromination of **8e** and comparison of the optical rotation and CSP-HPLC elution order of the resulting **8a** with those data of independently prepared samples of *rac*- and (*S*)-**8a**; a) for the synthesis of **8e** see: G. Y. Cho, H. Okamura, C. Bolm, *J. Org. Chem.* **2005**, *70*, 2346–2349; b) Correction: G. Y. Cho, H. Okamura, C. Bolm, *J. Org. Chem.* **2010**, *75*, 522.

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[24] X-ray crystal structure of **11** is included in the Supporting Information.

[25] By X-ray crystal structure analysis the relative stereochemistry of two further derivatives (**5d** and **5r**) has been determined to be *anti*. For details see Supporting Information.

[26] X-ray structure determination of compound **5p**: A colourless platelike crystal (ca. $0.5\times0.5\times0.2$ mm) suitable for single crystal structure determination was obtained from diethyl ether. The compound ($C_{15}H_{16}O_4$) crystallizes in monoclinic space group $P2_1$ (4) with cell constants $a=8.519(2)$, $b=8.800(2)$, $c=8.940(2)$ Å, and $\beta=102.62(1)°$. A volume of $V=654.0(3$ Å^3, a molecular weight of $M=260.29$ g mol^{-1}, and $Z=2$ result in a density of $\rho_{calcd}=1.322$ g cm^{-3}. A total number of 4985 reflections was collected at room temperature (298 K) on an Eraf-Nonius CAD4 diffractometer employing graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda=1.54179$ Å, $\mu=0.787$ mm^{-1}, no absorption correction) in the range $-10\le h\le 10$, $-10\le k\le 10$, $-10\le l\le 10$ ($\theta_{max}=68.02°$). The structure was solved using direct methods as implemented in Xtal3.7 package of crystallographic routines, a) employing GENSIN, b) to generate structure-invariant relationships and GENTAN, c) for the general tangent phasing procedure. 2377 observed reflections ($I>2\sigma(I)$, $R_{int}=0.06$) were included in the final full-matrix leas-squares refinement of 172 parameters on *F*, converging at $R(R_w)=0.067$ (0.083, $w=1/35.0\sigma^2(F)$), a goodness of fit of 1.289, and a residual electron density of $-0.39/0.25$ e Å^{-3}. The coordinates of the hydrogen atoms were calculated for idealized positions and their U_{eq} were fixed at 1.5 times the value for the corresponding heavy atom. No hydrogen parameters were refined. CCDC-742721 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[34] The averaged calculated CD spectrum of **5p** has been obtained as previously described in the Supporting Information associated with ref. [11].

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