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Application of β-Hydroxysulfoximines in Catalytic Asymmetric Phenyl Transfer Reactions for the Synthesis of Diarylmethanols

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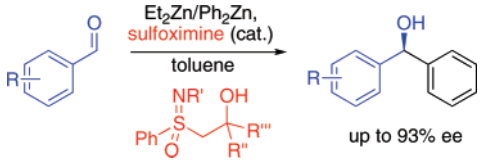

Enantiomerically enriched diarylmethanols have been prepared by catalyzed asymmetric phenyl transfer reactions onto aromatic aldehydes with use of readily available β-hydroxysulfoximines as catalysts. As the aryl source, combinations of diethylzinc with either diphenylzinc or triphenylborane have been applied affording arylphenylmethanols with up to 93% ee in good yields. Various functionalized aldehydes and heterocyclic substrates are tolerated, yielding synthetically relevant products.

Introduction

Enantiopure diarylmethanols are important intermediates for the synthesis of biologically active compounds, which show physiologically interesting properties such as antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, local-anesthetic, and anticholinergic effects.[1] Previous approaches toward enantiomerically enriched diarylmethanols involved asymmetric reductions of prochiral ketones or aryl transfer reactions onto aldehydes.[2] Our group[3] as well as several others[4] have developed various protocols for the latter transformation utilizing mixtures of diethylzinc with either diphenylzinc, triphenylborane, or boronic acids as aryl sources. Often, both yields and enantioselectivities are high. However, despite the immense progress in this area, there is still a need for improvement. For example, many catalysts are too complex to be applied on large scale and furthermore, functionalized substrates often lead to only moderate enantioselectivities.

During the past decades, sulfoximines have attracted significant attention due to their successful use as chiral auxiliaries in asymmetric synthesis[5] and ligands in enantioselective metal catalysis.[6] Their preparation is well-documented and several synthetic routes have been established. On the basis of our previous experience in addition reactions with *dialkyl*zincs,[7] we decided to test the applicability of easily accessible β-hydroxysulfoximines **2** in asymmetric phenyl transfer reactions. Sul-

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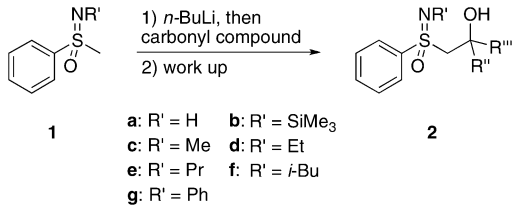
SCHEME 1



foximines of this type can be prepared in a large variety following the reaction sequence depicted in Scheme 1.[8]

Results and Discussion

The synthesis of β-hydroxysulfoximines **2** starts from the readily accessible (and commercially available) enantiopure *N*H-sulfoximine **1a**,[9] which can be silylated, alkylated, or arylated.[10] Subsequent deprotonation of the *N*-substituted sulfoximines **1b**−**g** by *n*-BuLi at −78 °C in ether and trapping of the resulting carbanion by an aldehyde or a ketone affords β-hydroxysulfoximines **2b**−**g** in good yields. By variation of the carbonyl compounds a broad range of products is accessible. For the synthesis of *N*H-β-hydroxysulfoximines **2a** silylated products **2b** are deprotected with MeOH and aqueous NH_4Cl. Generally, the diastereomeric ratios depend on the carbonyl compounds used in the trapping. In some cases single diastereomers are formed. Most of the diastereomeric mixtures are separable chromatographically or by fractional crystallization.

For the optimization of the aryl transfer reaction with respect to solvent, temperature, catalyst loading, and catalyst structure, β-hydroxysulfoximine **2ca**, 4-chlorobenzaldehyde (**3a**), and a combination of diphenylzinc and diethylzinc (in a 1:2 ratio) were used. As a result, toluene proved superior to THF, Et_2O, hexane, and 1,4-dioxane as solvent in the formation of diarylmethanol **4a**. Temperature variations indicated a maximal enantioselectivity in reactions performed at 10 °C. Albeit the yield of **4a** remained about the same, lower enantiomeric excesses were observed in reactions run at room temperature or below 0 °C. With less than 10 mol % of β-hydroxysulfoximine **2ca** the yield and the ee of **4a** were reduced. Scheme 2 summarizes the optimal conditions.

A variation of the phenyl source [use of Ph_3B (1.0 equiv) in combination with Et_2Zn (1.3 equiv) instead of a Ph_2Zn/Et_2Zn mixture] had no positive effect, and the results in the formation of **4a** starting from **3a** were very similar to those obtained with the original system.

SCHEME 2

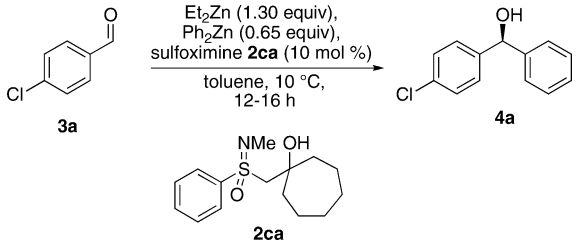
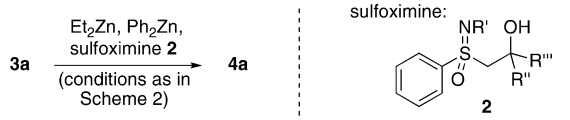


TABLE 1. Catalyst Screening in the Conversion of 3a into Arylphenylmethanol 4a[a]



entry	2[b]	R′	R″	R‴	conv of **3a** (%)[c]	ee (%)[d]
1	**ab**	H	Ph	Ph	14	10
2	**ac**	H	Me	Me	9	22
3	**ca**	Me	$(CH_2)_6$		87	−80
4	**cb**	Me	Ph	Ph	88	32
5	**cc**	Me	Me	Me	76	−46
6	**cd**	Me	*i*-Pr	Ph	86	−86
7	(*dia*)-**cd**	Me	Ph	*i*-Pr	82	−76
8[e]	**ce**	Me	H	4-Cl-Ph	49	16
9	**cf**	Me	Me	*t*-Bu	77	5
10	**cg**	Me	Ph	Bn	43	−30
11	**ch**	Me	Me	1-Naph	83	0
12	**ci**	Me	Me	2-Naph	85	−49
13	(*dia*)-**ci**	Me	2-Naph	Me	89	−78
14	**cj**	Me	$(CH_2)_4$		87	−72
15	**ck**	Me	$C_6H_4-C_6H_4$[f]		66	12
16	**cl**	Me	*c*-Hex	Ph	78	−81
17	(*dia*)-**cl**	Me	Ph	*c*-Hex	71	−68
18	**cm**	Me	4-CF_3-Ph	4-CF_3-Ph	80	−43
19	**cn**	Me	Me	Ph	87	−33
20	(*dia*)-**cn**	Me	Ph	Me	78	−80
21	**dj**	Et	$(CH_2)_4$		78	−80
22	**di**	Et	Me	2-Naph	81	−35
23	**da**	Et	$(CH_2)_6$		77	−80
24	**ej**	*n*-Pr	$(CH_2)_4$		81	−68
25	**ei**	*n*-Pr	Me	2-Naph	69	−32
26	**eh**	*n*-Pr	Me	1-Naph	74	2
27	**fj**	*i*-Bu	$(CH_2)_4$		68	−70
28	**fi**	*i*-Bu	Me	2-Naph	72	−74
29	(*dia*)-fi	*i*-Bu	2-Naph	Me	69	−74
30	**gn**	Ph	Ph	Me	64	10

[a] Method: Ph_2Zn (0.65 equiv), Et_2Zn (1.30 equiv), sulfoximine **2** (10 mol %), and aldehyde **3a** (1.0 equiv) were stirred in toluene at 10 °C for 12−16 h. [b] All sulfoximines have (*S*)-configuration at sulfur. [c] Conversion of aldehyde **3a** to diarylmethanol **4a** as determined by ^1H NMR. [d] Enantiomeric ratios were determind by HPLC analysis ,using a Chiracel OD or Chiracel ODH column. Positive values refer to (*S*) and negative ones to (*R*) enantiomers of **4a** being formed in excess. [e] See ref 11. [f] Derived from 9-fluorenone according to Scheme 1.

Following on the optimization of the reaction conditions, the dependence of the enantioselectivity on the catalyst structure under conditions depicted in Scheme 2 was investigated. The results are shown in Table 1.

From the results reported in Table 1, a number of conclusions can be drawn. First, the *N*-substituent on the sulfoximine plays an important role for both reactivity and enantioselectivity. Whereas use of *N*H-sulfoximines **2ab** and **2ac** resulted in the formation of only small product quantities (entries 1 and 2),

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(11) Only one diastereomer of **2ce** could be obtained in pure form, and the relative stereochemistry of this β-hydroxysulfoximine remained undetermined.

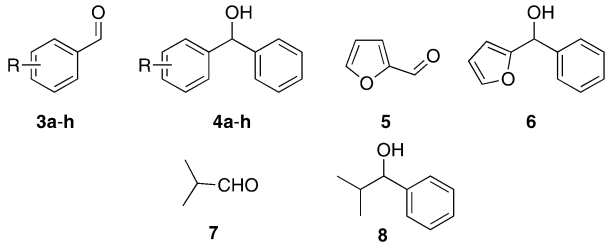
N-arylated derivative **2gn** led to a higher yield of **4a** (entry 30). The best results were obtained with *N*-alkylated catalysts (entries 3−29). This reactivity pattern was paralleled by the enantioselectivities. Also here, *N*-alkylated *β*-hydroxysulfoximines led to the best results. In the series of catalysts with R′ and R″ equal to cyclopentyl (entries 14, 21, 24, and 27) all sulfoximines led to the formation of (*R*)-**4a** (with 68−80% ee). Use of the *N*-ethyl-substituted sulfoximine **2dj** provided the product with the highest ee (80%) in this series.

As second parameter the influence of the substitution pattern at the *β* position of the *β*-hydroxysulfoximines was studied. For that purpose the lithio anion derived from *N*-methyl sulfoximine **1c** (Scheme 1) was trapped with various carbonyl compounds. Application of 4-chlorobenzaldehyde-derived sulfoximine **2ce** (entry 8) having a hydrogen and a 4-chlorophenyl substituent at the *β* carbon in the phenyl transfer reaction depicted in Scheme 2 led to disappointing results in terms of both reactivity and enantioselectivity (49% yield of **4a** with 16% ee). However, *β*-hydroxysulfoximines obtained from trappings with symmetric (cyclic and acyclic) ketones such as **2ca**, **2cb**, **2cc**, **2cj**, and **2ck** provided **4a** in good yields (up to 88%) and enantioselectivities in the range of 12−80% ee (entries 3−5, 14, and 15). In this series, the cycloheptanone-derived compound **2ca** gave the best results (87% yield, 80% ee).

When the lithio anion of *N*-methylsulfoximine **1c** was reacted with unsymmetrical ketones, diastereomeric mixtures of *β*-hydroxysulfoximines **2** resulted. Most of those were easily separated by column chromatography. Table 1 contains the results of the phenyl transfer reaction onto aldehyde **3a** of five diastereomer pairs (entries 5/6, 12/13, 16/17, 19/20, and 28/29). In all cases, the yields of **4a** obtained in catalyses with the various diastereomers were similar (ranging from 69% to 89%). Interestingly, the stereogenic center at sulfur determined the absolute configuration of the product. Thus, sulfoximines with *S* configuration at sulfur yielded predominately the *R* enantiomer of **4a**, independently of the relative configuration of the other stereogenic center. With the exception of the reactions with diastereomer pair **2fi** and (*dia*)-**2fi** (entries 28 and 29) the enantiomer ratios found for (*S*)- and (*R*)-**4a** in catalyses with diastereomeric catalysts varied (Δee up to 47%; entries 19 and 20). Overall, the best results were achieved with *β*-hydroxysulfoximines having an isopropyl and a phenyl group at the *β*-carbon. In this case, both diastereomers, **2cd** and (*dia*)-**2cd**, reacted well (86% and 82% yield) affording (*R*)-**4a** with 86% and 76% ee, respectively (entries 6 and 7). NMR experiments revealed that the more selective diastereomer [(*S*,*R*)-**2cd**] was heterochiral at both stereogenic centers.[12]

Finally, the substrate scope in phenyl transfer reactions catalyzed by *β*-hydroxysulfoximine (*S*,*R*)-**2cd** under conditions shown in Scheme 2 was investigated. As illustrated by the data presented in Table 2, various substitution patterns on the aromatic aldehydes were tolerated. Even heterocyclic 2-furaldehyde (**5**) reacted well. Generally, the yields of the corresponding diarylmethanols **4** and **6** were high (82−99%), and in three (out of 9) cases the enantioselectivities even exceeded 90% (entries 2, 7, and 8). The best result was achieved in the phenyl transfer onto 4-phenylbenzaldehyde (**3b**), which afforded the desired product **4b** with 93% ee in 95% yield (entry 2).

TABLE 2. Substrate Scope in the Catalyzed Aryl Transfer onto Aldehydes[a]



entry	aldehyde	R	product	yield (%)	ee (%)
1	**3a**	4-Cl	**4a**	82	86
2	**3b**	4-Ph	**4b**	95	93
3	**3c**	4-CH_3	**4c**	90	86
4	**3d**	2,4,6-$(CH_3)_3$	**4d**	99	80
5	**3e**	2-Cl	**4e**	88	84
6	**3f**	4-F	**4f**	89	85
7	**3g**	4-$N(CH_3)_2$	**4g**	84	91
8	**3h**	4-OCH_3	**4h**	86	90
9	**5**		**6**	96	87
10	**7**		**8**	45	33

[a] Use of 10 mol % of *β*-hydroxysulfoximine **2cd** as catalyst under conditions shown in Scheme 2.

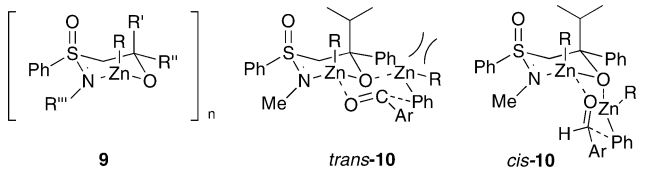


FIGURE 1. Possible intermediates of the asymmetric phenyl transfer reaction onto aromatic aldehydes.

To our surprise and in contrast to our previous findings with other catalyst systems,[3] both electronic and steric factors had only a minor effect on the efficiency (in terms of yield and ee) of the phenyl transfer onto aldehydes **3**. Thus, regardless of the electronic nature of the substituent R on the aldehyde, the yield and the enantioselectivity was always in the same ee range. Even the presence of ortho-substituents did not hamper the addition reaction significantly (entries 4 and 5). Unfortunately, aliphatic aldehyde **7** did not react well, affording the corresponding product with only 33% ee in 45% yield. Although this result is significant in itself, it is in accord with the common reactivity pattern of catalyzed aryl transfer reactions.[2] Alternatively, **8** could be prepared by alkyl transfer onto benzadehyde or reduction of the corresponding carbonyl compounds, which both are known to proceed with high enantioselectivities.[7]

With respect to the mechanism the situation is complex. Following the general reaction path elucidated by Noyori for amino alcohol-catalyzed dialkyzinc addition reactions to aldehydes,[7d−f] and taking into account our previous findings on related zinc alkoxide formations,[7a,b] we assume that the *β*-hydroxysulfoximines are deprotonated upon reaction with the Et_2Ph/Ph_2Zn mixtures. The resulting chelates **9** would then be the actual catalysts. (For clarity reasons, in the graphics zinc alkoxides with the *R*-configuration at sulfur are shown in Figure 1.) In the absence of substrates, those chelates will be aggregated. A complication arises from the fact that mixtures of zinc reagents are applied. Theoretical studies have been

(12) This assignment is based on the assumption that the H-bond of the hydroxyl group in *β*-hydroxysulfoximine **2cd** bridges toward the sulfoximine nitrogen. This scenario would be consistent with the bonding mode observed in the majority of related *β*-hydroxysulfoximines as determined by NMR spectroscopy and X-ray structure analysis. For details, see: (a) Reference 5. (b) Felder, M. Dissertation, University of Marburg, 1995.

performed on amino alcohol-based systems,[13] and they give guidelines on the Et/Ph positional preferences in such zinc alkoxides. However, they also reveal that various catalyst/substrate aggregates are possible and that some of them are close in energy. Consequently, we can only speculate on possible intermediates. Two of those are shown in Figure 1.

By using heterochiral β-hydroxysulfoximine **2cd** [here shown as (*R*,*S*)-**2cd**] as the model, a cis arrangement as in *cis*-**10** appears more likely than the corresponding trans aggregate, *trans*-**10**, since it minimizes steric interactions between the bulky phenyl substituent at the ligand and the R group at the organozinc. Furthermore, the remote position of the *N*-alkyl substituent of the sulfoximine would explain its low effect on the observed enantioselectivity of the aryl transfer process. Finally, following arrangement *cis*-**10** the expected enantiomer of the product would result.

In summary, we have synthesized various β-hydroxysulfoximines and proved their catalytic applicability in asymmetric phenyl transfer reactions onto aldehydes. In contrast to many other systems, the efficiency of the phenyl transfer shows only a minor dependence on electronic and steric factors of the substrate. The corresponding products have been obtained with up to 93% ee in good yields. Albeit this enantioselectivity cannot compete with the existing methodology,[3,4] the straightforward catalyst synthesis (with only two steps from a commercially available and readily accessible intermediate) renders this protocol synthetically interesting.

Experimental Section

General Procedure for the Synthesis of β-Hydroxysulfoximines 2. *N*-Substituted sulfoximines were prepared according to literature procedures.[10] One equivalent of *n*-butyllithium (1 M in hexane) was added to a stirred solution of sulfoximine **1** in ether at −78 °C, and the reaction mixture was allowed to warm to 0 °C. The resulting suspension was stirred at this temperature for 0.5 h. Then the carbonyl compound (1.10 equiv in ether) was added slowly. The reaction mixture was stirred at ambient temperature overnight and then quenched with water. After stirring for 0.5 h, the phases were separated and the ether phase was extracted with aqueous 3 N HCl. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield the products, which were purified by column chromatography (EtOAc−pentane). In most cases a separation of the diastereomeric mixture was possible either by fractional crystallization or chromatography on silica gel.

Synthesis of (*S*)-1,1-Diphenyl-2-(*S*-phenylsulfonimidoyl)ethanol (2ab). 2ab was prepared according to the general procedure with a 75% yield as a white solid. R_f (pentane:EtOAc 1:1) 0.47; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (br s, 2H), 7.11 (m, 3H), 7.18−7.34 (m, 7H), 7.46 (m, 3H), 7.59 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.9, 76.4, 125.9, 126.0, 127.2, 127.4, 127.9, 128.1, 128.2, 129.0, 132.8, 143.0, 143.8, 144.5; mp 158−161 °C; IR (KBr) ν 3274, 1495, 1450, 1426, 1404, 1216, 1179, 760, 708, 681, 560, 489 cm^{-1}; MS (EI, 70 eV) *m*/*z* 338 ([M + 1]$^+$, 2%), 218 (43%), 217 (100%), 196 (21%), 169 (28%), 125 (45%), 105 (72%). Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.00; H, 5.83; N, 4.08; $[\alpha]^{25}_D$ −45.2 (*c* 0.68, $CHCl_3$).

General Procedure for the Phenyl Transfer onto Aldehydes. In a glovebox a 10 mL vial was charged with diphenylzinc (35.5 mg, 0.16 mmol). The vial was sealed with a septum and removed from the glovebox. Freshly distilled toluene was added (1.25 mL). After the addition of $ZnEt_2$ (1M in heptane, 0.33 mL, 0.33 mmol), the mixture was stirred for 30 min at room temperature. Another vial was charged with β-hydroxysulfoximine **2** (10 mol %, 0.025 mmol), sealed with a septum, and flushed with argon. Toluene (1.0 mL) was added to dissolve **2** and the solution was transferred via syringe into the first vial. The resulting mixture was stirred for 0.5 h at room temperature, then cooled to 10 °C and stirred for an additional 10 min at this temperature. A third vial was charged with aldehyde **3** (0.25 mmol), closed with a septum, and flushed with argon, then the substrate was dissolved in toluene (1.0 mL). After cooling to 10 °C the solution was transferred via syringe into the other reaction vial. The resulting mixture was stirred for 12−16 h at 10 °C. Then the reaction was quenched with water and the mixture extracted with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The product was purified by column chromatography to give the desired alcohol **4**.

(*S*)-4-(Chlorophenyl)phenylmethanol (4a).[14] **4a** was obtained from aldehyde (**3a**) (35 mg, 0.25 mmol) according to the general procedure in a yield of 45 mg (82%, 0.206 mmol, 86% ee). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (br s, 1H), 5.78 (s, 1H), 7.23−7.45 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 75.7, 126.6, 127.9, 128.7, 128.7, 133.3, 142.3, 143.5; HPLC (Chiralcel OB-H, 25 °C, 230 nm, 90:10 heptane/*i*-PrOH, 0.5 mL/min) t_R = 27.7 (*R*), 34.8 min (*S*).

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Supporting Information Available: General synthetic procedures, characterization data of all products, and copies of ^{1}H and ^{13}C NMR spectra of compounds **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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