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Asymmetric Strecker Reaction of *N*-Benzhydrylimines Utilising New Tropos Biphenyldiol-Based Ligands

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Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

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The synthesis of a library of *N*-arenesulfonyl-1,3-oxazolidinyl-substituted biphenyldiols is presented. A set of two central intermediates together with easily accessible *N*-arenesulfonylamino alcohols furnish a broad variety of 1,3-oxazolidines. These are applied as chiral tropos ligands in a titanium-mediated Strecker-type reaction of *N*-benzhydrylimines. A correlation between the *ee* values in the product and the diastereomeric ratio concerning the chiral axis of the ligand is made. Those substituents in the ligand which proved to lead to a higher preference for one diastereomeric conformer of the chiral axis in related compounds now provide the most selective ligands. Two privileged ligands are identified that afford superior results in 8 of 13 screenings.

Introduction

The asymmetric hydrocyanation of imines (Strecker reaction)[1] has widely been used to furnish enantioenriched α-amino acids.[2] A number of organocatalytic[3] approaches have been developed, as well as several metal-catalysed[4] processes. Therein, the addition of cyanide to benzhydrylimines plays an important role, as conversion into amino acids is accomplished most simply in one single step.[4b] Often, trimethylsilyl cyanide has been used as a convenient source of hydrogen cyanide. Within the metal-catalysed processes, the atropos binol derivatives play an important role, but only one protocol was found utilising tropos 2,2′-biphenyldiols (BIPOL).[5] Usually, chiral ligands such as TADDOL and BINOL derivatives were required as asymmetric activators. To the best of our knowledge, there is no example of an asymmetric metal-catalysed Strecker reaction with the use of chiral tropos ligands. One major advantage of our concept, which uses tropos ligands, is the fact that resolution of enantiomeric or diastereomeric forms of the ligands is not necessary in contrast to atropos systems.[6]

In our program on the application of tropos 3,3′-oxazolidinyl-substituted 2,2′-biphenyldiols **1**, we investigated their asymmetric induction in a titanium tetraisopropoxide mediated Strecker-type reaction of *N*-benzhydrylimines. We recently disclosed the synthesis of a library of phosphite ligands **2** (Figure 1) based on chiral 1,3-oxazolidinyl-substituted biphenyldiols **1**,[7] and we now wish to report an extension of the library of the intermediate diols. Furthermore, our earlier findings concerning the asymmetric induction of the 1,3-oxazolidines onto the chiral axis of the biphenyl moiety will find application in this study.

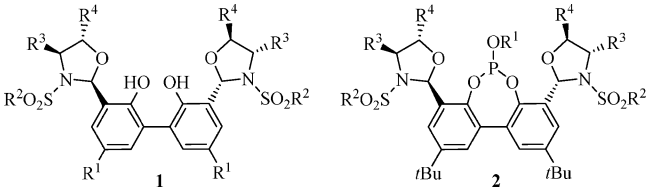

Figure 1. Biphenyldiol **1** and related phosphite **2**.

In an extensive study, we could demonstrate the influence of each substituent in phosphite **2** on the diastereomeric ratio of the conformers of **2**.[7] Besides the influence of residue R^1, the bulkiness of the R^2 and R^3 substituents clearly correlate with the preference for one diastereoisomer; particularly, a change in R^2 from a *para*-methylphenyl group to a 2,4,6-trimethylphenyl residue strongly enhanced the population of the preferred diastereomer.

In this work, the impact of those substituents, which clearly influence the diastereomeric ratio in phosphite **2**, on the selectivity induced by related biphenyldiols **1** will be investigated.

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Results and Discussion

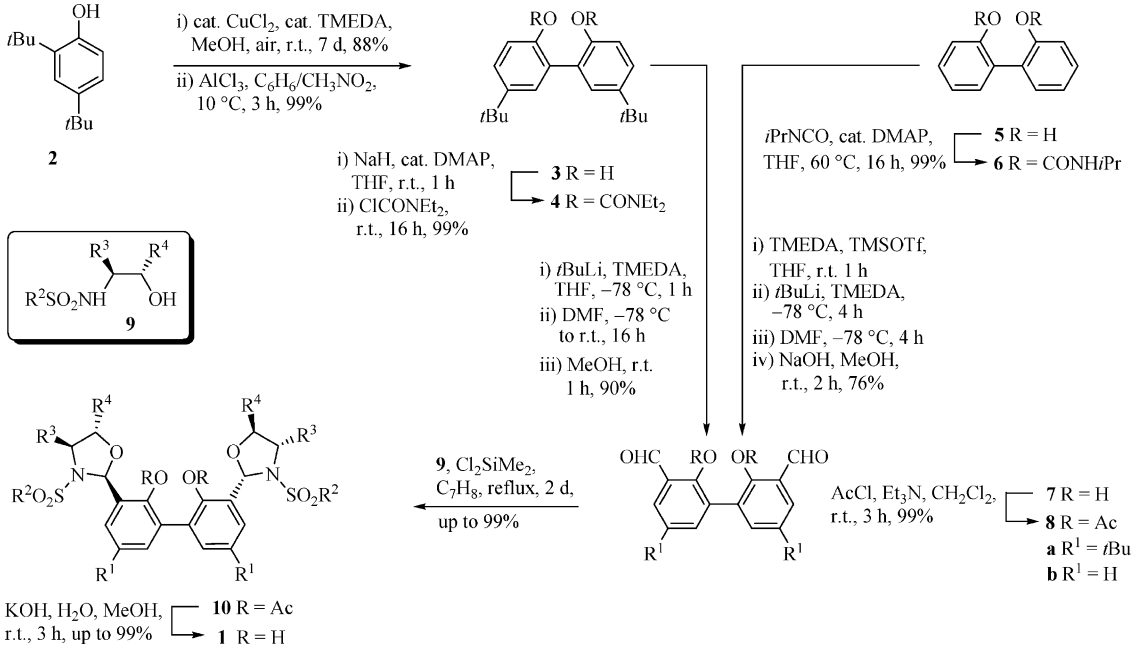
Our library of ligands **1** contains 27 members (Table 1) and can be divided into different groups according to the substitution pattern. The first distinction can be made regarding the biaryl backbone: two different R^1 substituents were introduced (these refer to the first letter added to the compound numbers **1** and **10**). A further division into subgroups can be made according to the arenesulfonyl group R^2. Four different substituents were introduced successfully, and a fifth failed (the second letter added to the compound numbers **1** and **10** divides these). Finally, ten different combinations of R^3/R^4 were introduced (distinguished by the last letter added to compound numbers **1** and **10**). Not all combinations were synthesised and it appears helpful to divide the library into three major groups (**1aax**, R^1 = *t*Bu, R^2 = Tol; **1abx**, R^1 = *t*Bu, R^2 = Mes; and **1bbx**, R^1 = H, R^2 = Mes;) and a few single members. The synthesis of ligands **1** (Scheme 1) was improved in comparison to our earlier report[7] and the number of variable sites was raised by one, namely, the 5- and 5′-position on the biaryl backbone. The library contains two different substitution patterns on the biaryl with R^1 = *tert*-butyl and R^1 = H; therefore, two different syntheses of central intermediate dialdehyde **7** were required.

The synthesis of *tert*-butyl derivative **7a** commenced with oxidative coupling of di-*tert*-butylphenol **2** in 88% yield[8] and selective removal of the *ortho*-*tert*-butyl groups in excellent 98% yield[9] after recrystallisation. Biphenol **3** was then converted into carbamate **4** nearly quantitatively. In contrast to our previously reported synthesis,[7] we now applied the Snieckus protocol[10] for double *ortho* lithiation of carbamate **4**, as this proved more reliable on a multigram scale. The slight drawback of the diethylcarbamoyl group, namely, the more harsh conditions of its removal, does not

Table 1. Synthesis of 1,3-oxazolidinyl-substituted ligands **1**.

Entry	R^1	R^2	R^3	R^4	Product **10**[a] Yield [%]	Product **1**[a] Yield [%]
1	*t*Bu	Tol[b]	Me	H	**10aaa** (99)	**1aaa** (78)
2	*t*Bu	Tol	Et	H	*ent*-**10aab** (83)	*ent*-**1aab** (99)
3	*t*Bu	Tol	*i*Pr	H	**10aac** (97)	**1aac** (99)
4	*t*Bu	Tol	*i*Bu	H	**10aad** (99)	**1aad** (95)
5	*t*Bu	Tol	*s*Bu[g]	H	**10aae** (90)	**1aae** (93)
6	*t*Bu	Tol	*t*Bu	H	**10aaf** (99)	**1aaf** (95)
7	*t*Bu	Tol	Ph	H	*ent*-**10aag** (93)	*ent*-**1aag** (94)
8	*t*Bu	Tol	Bn	H	**10aah** (84)	**1aah** (94)
9	*t*Bu	Tol	$(CH_2)_2SCH_3$	H	**10aai** (99)	**1aai** (72)
10	*t*Bu	Tol	Me	Ph	**10aaj** (0)	**1aaj** (0)
11	*t*Bu	Mes[c]	Me	H	**10aba** (78)	**1aba** (99)
12	*t*Bu	Mes	Et	H	*ent*-**10abb** (50)	*ent*-**1abb** (94)
13	*t*Bu	Mes	*i*Pr	H	**10abc** (96)	**1abc** (99)
14	*t*Bu	Mes	*i*Bu	H	**10abd** (76)	**1abd** (96)
15	*t*Bu	Mes	*s*Bu	H	**10abe** (82)	**1abe** (96)
16	*t*Bu	Mes	*t*Bu	H	**10abf** (83)	**1abf** (99)
17	*t*Bu	Mes	Ph	H	*ent*-**10abg** (73)	*ent*-**1abg** (99)
18	*t*Bu	Mes	Bn	H	**10abh** (46)	**1abh** (99)
19	*t*Bu	Mes	Me	Ph	**10abj** (0)	**1abj** (0)
20	*t*Bu	Trip[d]	Et	H	*ent*-**10acb** (0)	*ent*-**1acb** (0)
21	*t*Bu	Tbp[e]	Et	H	*ent*-**10adb** (99)	*ent*-**1adb** (81)
22	*t*Bu	Tbp	*s*Bu	H	**10ade** (94)	**1ade** (93)
23	*t*Bu	As[f]	Ph	H	*ent*-**10aeg** (0)	*ent*-**1aeg** (0)
24	*t*Bu	As	Me	Ph	**10aej** (90)	**1aej** (96)
25	H	Mes	Me	H	**10bba** (88)	**1bba** (76)
26	H	Mes	Et	H	*ent*-**10bbb** (83)	*ent*-**1bbb** (81)
27	H	Mes	*i*Pr	H	**10bbc** (72)	**1bbc** (86)
28	H	Mes	*i*Bu	H	**10bbd** (70)	**1bbd** (80)
29	H	Mes	*s*Bu	H	**10bbe** (84)	**1bbe** (90)
30	H	Mes	*t*Bu	H	**10bbf** (65)	**1bbf** (65)
31	H	Mes	Ph	H	*ent*-**10bbg** (58)	*ent*-**1bbg** (84)
32	H	Mes	Bn	H	**10bbh** (0)	**1bbh** (0)

[a] The alphabetical keys refer to R^1 (first letter), R^2 (second letter) and R^3/R^4 (third letter). [b] Tol = 4-methylphenyl. [c] Mes = 2,4,6-trimethylphenyl. [d] Trip = 2,4,6-triisopropylphenyl. [e] Tbp = 4-*tert*-butylphenyl. [f] As = 4-methoxyphenyl. [g] (*S*) configured, derived from isoleucine.



Scheme 1. Synthesis of the 1,3-oxazolidinyl-substituted ligands **1** (see Table 1 for substituent key).

play any role here, as in this particular case the formyl group assists in the hydrolysis by a neighbouring group effect. Hence, the carbamate is cleaved under the basic conditions of methanolic workup to furnish dialdehyde **7a** in 90% yield. The synthesis of unsubstituted dialdehyde **7b** started from commercially available 2,2′-dihydroxybiphenyl (**5**) by a similar route. Nearly quantitative conversion into isopropyl carbamate **6**, followed by the *ortho* lithiation sequence developed in our group[11] gave desired aldehyde **7b** in good yield.

Acetylation of the hydroxy groups, in both cases in 99% yield, afforded starting materials **8** for the synthesis of the 1,3-oxazolidines. It is noteworthy that not only the first steps were conducted up to a 1-mol scale, but the lithiations can also be performed on a 50-mmol scale for stockpiling of the intermediates. The key step of our synthesis, the formation of the chiral 2,4-*cis*-1,3-oxazolidines, proceeds in the presence of 3 equiv. of *N*-sulfonylamino alcohol **9** and 5 equiv. of dichlorodimethylsilane[12] in refluxing toluene. Depending on the substituents in amino alcohol **9**, yields up to 99% of product **10** could be isolated (Table 1). It turned out that an excess amount of amino alcohol **9** and the silane, as well as high concentrations and prolonged reaction times are beneficial to the yield. In some cases, conversion was nearly complete after 1 d, whereas in one case (Table 1, Entry 18) the reaction was run over 5 d and still afforded only 46% yield. In several cases, significant amounts of intermediate monooxazolidine **11** were isolated, which could be recycled (Scheme 2). The acetyl group in the salicylic aldehyde moiety that was cleaved upon workup was reinstalled to give **12**, and its reaction with an excess amount of amino alcohol **9** afforded additional quantities of the product. In general, the reactivity decreases with increasing steric demand of the arenesulfonyl group. With a tosyl- or 4-*tert*-butylbenzenesulfonyl group excellent yields were obtained (Table 1, Entries 1–9, 21–22), whereas the more bulky mesitylene sulfonyl group (compounds **9xbx**; Table 1, Entries 11–18, 25–31) led to moderate-to-excellent yields, depending on the substituents R^3 and R^4; in one case (Table 1, Entry 32), no product could be isolated. The most bulky triisopropylbenzenesulfonyl group did not give any desired products **8** (Table 1, Entry 20). To our surprise, the reaction of norpseudoephedrine with a *para*-methoxybenzenesulfonyl group attached to it readily proceeded, but the same sulfonyl substituent on phenyl glycine did not lead to any product (compare Table 1, Entries 10, 19, 23 and 24).

Finally, removal of the acetyl groups under mild conditions in usually very high yields afforded desired diol ligands **10**. The sometimes decreased yield in this deprotection step might be due to partial hydrolysis of the oxazolidines, as in some cases amino alcohol **9** was detected.

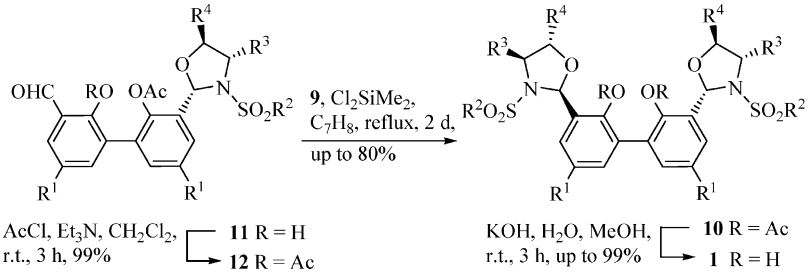
The *N*-arenesulfonylamino alcohols (Table 2) were prepared as shown in Scheme 3.[12] The synthesis of **9aj**, **9bj** and **9ej** from norephedrine is a three-step sequence with inversion of the stereocentre at C-1 by oxidation and diastereoselective reduction.[13]

Table 2. Synthesis of amino alcohols **9**.

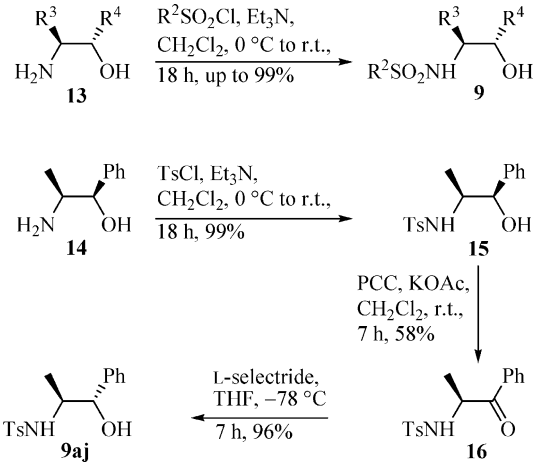
Entry	R^2	R^3	R^4	Product **9**[a] Yield [%]
1	Tol	Me	H	**9aa** (92)
2	Tol	Et	H	*ent*-**9ab**[12]
3	Tol	*i*Pr	H	**9ac** (95)
4	Tol	*i*Bu	H	**9ad** (96)
5	Tol	*s*Bu	H	**9ae** (90)
6	Tol	*t*Bu	H	**9af** (99)
7	Tol	Ph	H	*ent*-**9ag** (95)
8	Tol	Bn	H	**9ah** (92)
9	Tol	$(CH_2)_2SCH_3$	H	**9ai** (90)
10	Tol	Me	Ph	**9aj** (57, 3 steps)
11	Mes	Me	H	**9ba** (97)
12	Mes	Et	H	*ent*-**9bb**[14]
13	Mes	*i*Pr	H	**9bc** (86)
14	Mes	*i*Bu	H	**9bd** (87)
15	Mes	*s*Bu	H	**9be** (89)
16	Mes	*t*Bu	H	**9bf** (99)
17	Mes	Ph	H	*ent*-**9bg** (99)
18	Mes	Bn	H	**9bh** (95)
19	Mes	Me	Ph	**9bj**[15]
20	Trip	Et	H	*ent*-**9cb**[16]
21	Tbp	Et	H	*ent*-**9 db** (97)
22	Tbp	*s*Bu	H	**9de** (87)
23	As	Ph	H	*ent*-**9eg**[15]
24	As	Me	Ph	**9ej**[15]

[a] The alphabetical keys refer to R^2 (first letter) and R^3/R^4 (second letter).

With a set of 27 ligands in hands, we then turned our focus on exploring their application in asymmetric catalysis. Because titanium forms strong bonds to oxygen-containing ligands and because titanium tetraisopropoxide is readily available as a precursor for the active complex, we sought titanium-mediated reactions. It was our hope that two of the isopropoxide residues might be easily replaced by our diol ligands **1** for entropic reasons. Furthermore, the titanium atom provides additional ligation sites, which can be occupied by a substrate molecule. In our expectation, the

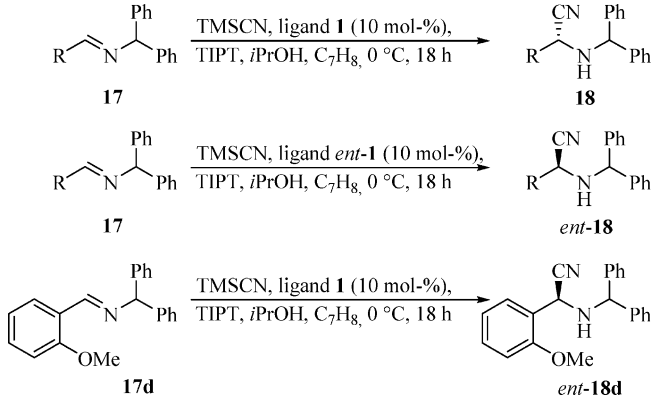


Scheme 2. Conversion of intermediates **11** into 1,3-oxazolidines **10**.



Scheme 3. Synthesis of amino alcohols **9** (see Table 2 for substituent key).

steric demand of the remaining isopropoxy ligands should lead to enhanced asymmetric induction of the 1,3-oxazolidines onto the chiral axis. This would be in good agreement with our previous observations on the diastereomeric ratio in phosphites **2** derived from oxazolidines **1** (Scheme 4).[7]



Scheme 4. Titanium-mediated Strecker reactions of *N*-benzhydrylimines **17** (see Table 3 for substituent key).

First, we turned our attention to the development of ideal reaction conditions. With trimethylsilyl cyanide as the reagent it was reported by other researchers[4] that slow addition of protic additives is beneficial to the reaction rate and enantioselectivity. Our own findings support these observations with a 2-propanol solution as the superior additive. The addition of alcohol should liberate hydrogen cyanide, which is the active cyanating agent. Additionally, the remaining alkoxide might bind to the TMS cation, which would therefore make it less prone to catalyse the reaction competitively to the titanium. The optimum was found to be an addition period of 18 h; slower additions did not improve the enantioselectivity. However, the addition must not be quicker than the Ti-catalysed reaction of the hydrogen cyanide with the imine to suppress a nonselective reaction mediated by free hydrocyanic acid. Another important fact for this reaction is to prove ligand acceleration. Indeed, without any ligand nearly no conversion was observed. Second, we investigated the ideal reaction conditions: (1) the solvent of choice is toluene; (2) the best enantiocontrol is obtained at 0 °C, as higher and lower temperatures led to a decrease in the *ee* values;[17] (3) the catalyst complex is formed in situ at room temperature, and elevated temperatures and the addition of amines[4e] are not required to assist the complex formation − both led to poor selectivity and reaction rate. With the optimum setup for the enantioselective Strecker-type reaction, we then turned our attention to the screening of ligands. The conversion in all reactions was nearly complete after 18 h; only traces of starting material were detected by HPLC. Only the naphthaldimines required a prolonged reaction time of 72 h; the addition of 2-propanol was also carried out over the same duration. For each substrate, Table 3 shows the best ligand and the isolated yield after chromatography at full conversion.

Table 3. Enantioselective Strecker reaction of *N*-benzhydrylimines **17**.

Entry	R	Product **18** Yield [%][a]	*ee*[b] (abs. config.)[c]	Ligand **1**
1	Ph	**18a** (94)	89 (*R*)	**1abf**
2	4-OMePh	*ent*-**18b** (92)	68 (*S*)	*ent*-**1abg**
3	3-OMePh	**18c** (83)	59 (*R*)	**1bbd**
4	2-OMePh	**18d** (67)	48 (*S*)	**1aaf**
5	4-ClPh	**18e** (87)	84 (*R*)	**1abc**
6	3-ClPh	**18f** (87)	20(*R*)	**1abd**
7	2-ClPh	**18g** (93)	62 (*R*)	**1abe**
8	4-MePh	**18h** (92)	80 (*R*)	**1bba**
9	3-MePh	**18i** (83)	72 (*R*)	**1abc**
10	2-MePh	**18j** (91)	85 (*R*)	**1abc**
11	1-naphthyl[d]	*ent*-**18k** (34)	55 (*S*)	*ent*-**1abb**
12	2-naphthyl[d]	*ent*-**18l** (99)	72 (*S*)	*ent*-**1adb**
13	*t*Bu	**18m** (86)	63 (*R*)	**1abe**

[a] Isolated yield after chromatography; only traces of starting material were left in the crude reaction mixture by HPLC. [b] Determined by chiral HPLC. [c] Determined by comparison with literature values of the optical rotation.[4b,18,19] [d] Prolonged reaction time and duration of the addition of the 2-propanol solution: 72 h.

The results from the first substrate, *N*-benzhydrylbenzaldimine (**17a**), are shown in Figure 2. The best results were obtained from ligands **1abc** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Pr) (87%*ee*) and **1abf** (R^1 = *t*Bu, R^2 = Mes, R^3 = *t*Bu)

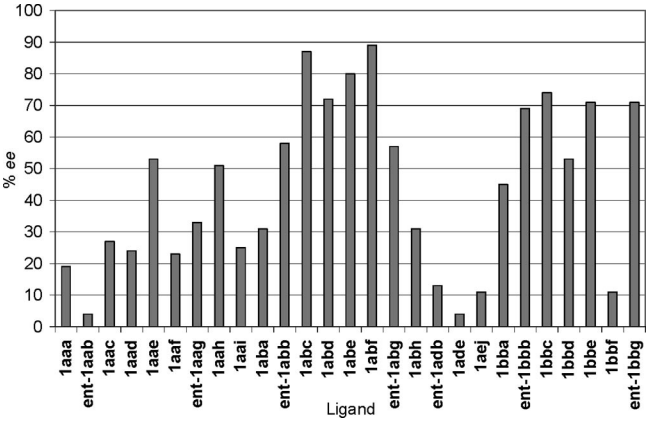


Figure 2. Enantiomeric excess of nitrile **18a**.

(89%*ee*), other good *ee* values were obtained with ligands **1abe** (R^1 = *t*Bu, R^2 = Mes, R^3 = *s*Bu) (80%*ee*) and **1bbc** (R^1 = H, R^2 = Mes, R^3 = *i*Pr) (74%*ee*).

As a general trend, those ligands bearing the more bulky mesitylene sulfonyl group in the 1,3-oxazolidine moiety (compounds **1xbx**) seem to afford superior results. This is in good agreement with our expectation that the induction onto the chiral axis of the ligand should be higher with sterically more-demanding sulfonyl substituents. Additionally, the more branched side groups on C-4 of the oxazolidine give better enantioselectivity. Secondly, the R^1 group on the biaryl backbone of the ligand seems to have some influence; those derivatives with a *tert*-butyl substituent (compounds **1axx**) display a trend to higher *ee* values.

Next, we examined the substrate scope of the reaction. A number of *ortho*-, *meta*- and *para*-substituted *N*-benzhydrylbenzaldimines were subjected to the Strecker-type reaction. Further substrates were derived from 1- and 2-naphthaldehyde and pivaldehyde. The results (Supporting Information, Figures S1–S12) demonstrate: (1) a strong dependence of the enantioselectivity from the substitution pattern in the substrate, (2) a preference for the mesitylene sulfonyl group as R^2 in the ligand (only two exceptions), (3) moderate-to-good enantioselectivity at nearly complete conversion for all substrates and (4) a superior lead structure exists, which still requires a ligand library.

The first variation in the substrate was the introduction of a methoxy group, which provided a more electron-rich imine (Supporting Information, Figures S1–S3). In the reaction of *para*-substituted imine **17b**, the best selectivity (68%*ee*) was achieved with three different ligands, [**1abf** (R^1 = *t*Bu, R^2 = Mes, R^3 = *t*Bu), **1abg** (R^1 = *t*Bu, R^2 = Mes, R^3 = Ph) and *ent*-**1bbb** (R^1 = H, R^2 = Mes, R^3 = Et)]. Again, the more bulky arenesulfonyl group at the oxazolidine moiety performed superiorly, but in contrast, the smaller R^3 substituents furnish the better results; ligand **1abf** is the exception to this trend and proved to behave differently with other substrates as well (vide infra). *meta*-Methoxybenzaldimine **17c** gave moderate selectivity (59%*ee*), but with this substrate, the same trends as those of the parent benzaldimine were observed: the more bulky the residues, the better the *ee*. As indicated earlier, ligands **1abf** and **1bbf** (R^3 = *t*Bu) are an exception, as they provide very poor enantiomeric excesses. The next result, the reaction of *ortho*-methoxybenzaldimine **17d**, was even more surprising to us. The general trend for all other substrates that the mesitylene sulfonyl group as R^2 gave the best selectivity is reversed: the tosyl-substituted ligands provided superior results, and ligand **1aaf** (R^1 = *t*Bu, R^2 = Tol, R^3 = *t*Bu) gave a moderate 48%*ee* as the highest selectivity. However, the low enantiocontrol in this set might be due to a mismatched correlation of the induction within the ligand structure (chiral axis vs. oxazolidine moieties) for this substrate; this is a plausible explanation for the unexpected reversal of the general trend.

The next set of reactions was carried out on the more electron-poor chloro-substituted imines (Supporting Information, Figures S4–S6). With *para*-chlorobenzaldimine **17e**, ligand **1abc** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Pr) furnished the product in good 84%*ee*, whereas **1abe** (R^1 = *t*Bu, R^2 = Mes, R^3 = *s*Bu) gave 75%*ee*. These results again follow the general trend: the more bulky substituents provided better selectivity; also, the unsubstituted biaryl backbone (ligands **1bxx**) gave only moderate results (decrease in *ee* around 20%). Once more, ligands **1abf** and **1bbf** did not follow this rule. The set of reactions with *meta*-chloro substrate **17f** displayed a similar trend, but the best *ee* obtained was only 20% [compounds **1abd** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Bu) and **1bbe** (R^1 = H, R^2 = Mes, R^3 = *s*Bu)]; several ligands afforded just racemates. Better enantioselectivity was obtained from the reactions of *ortho*-chlorobenzaldimine **17g** [ligand **1abe** (R^1 = *t*Bu, R^2 = Mes, R^3 = *s*Bu) 62%*ee*, ligands *ent*-**1bbb** (R^1 = H, R^2 = Mes, R^3 = Et) 51%*ee* and **1bbc** (R^1 = H, R^2 = Mes, R^3 = *i*Pr) 56%*ee*]. The other reactions furnished results within the general rule. Surprisingly, with substrate **17g**, ligand **1aej** (R^1 = *t*Bu, R^2 = As, R^3 = Me, R^4 = Ph) afforded the product in 60%*ee*, and in all other reactions this oxazolidine performed much worse.

Next, we turned our attention to methyl-substituted substrates (Supporting Information, Figures S7–S9) by assuming that these should electronically be very close to unsubstituted *N*-benzhydrylbenzaldimine **17a**, but behave differently for steric reasons. The reaction of *para*-methyl-substituted imine **17h** was the most selective in the presence of ligand **1bba** (R^1 = H, R^2 = Mes, R^3 = Me) (80%*ee*); *ee* values above 70%*ee* were observed for ligands *ent*-**1bbb** (R^1 = H, R^2 = Mes, R^3 = Et), **1bbd** (R^1 = H, R^2 = Mes, R^3 = *i*Bu), **1bbe** (R^1 = H, R^2 = Mes, R^3 = *s*Bu) and *ent*-**1bbg** (R^1 = H, R^2 = Mes, R^3 = Ph). In good agreement with the results from the *para*-methoxy substrate, the slightly less bulky residues R^3 furnished higher enantioselectivities, but this time the unsubstituted biaryl backbone performed better. *meta*-Methylbenzaldimine **17i** displayed behaviour according to the general trend, and the best result was obtained for ligand **1abc** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Pr) (72%*ee*). The results from *ortho*-methyl substrate **17j** are comparable to those of the same ligand that gave the best selectivity, and it afforded a good enantiomeric excess of 85%.

We then focused on 1- and 2-naphthaldimines (Supporting Information, Figures S10 and S11). Moderate-to-good selectivities were observed for both substrates, and the ligand performance was found to follow the general trend. 1-Naphthaldehyde-derived substrate **17k** gave only 55%*ee* [ligand *ent*-**1abb** (R^1 = *t*Bu, R^2 = Mes, R^3 = Et)], whereas isomeric imine **17l** afforded the product in 72%*ee*. Surprisingly, the latter result was obtained with ligand **1adb** (R^1 = *t*Bu, R^2 = Tbp, R^3 = Et), which bears a medium-sized 4-*tert*-butylbenzenesulfonyl group. Finally, we were interested in the pivaldimine as an entirely different substrate (Supporting Information, Figure S12). We were pleased to find that moderate-to-good enantioselectivities could be achieved in the reaction of imine **17m**, as often those ligands affording good selectivity with aromatic imines perform much worse with nonaromatic derivatives. Once again, ligand **1abe** (R^1 = *t*Bu, R^2 = Mes, R^3 = *s*Bu) furnished

product **18m** in the best *ee* of this set (63%). Two further ligands produced *ee* values greater than 50% [oxazolidines **1abc** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Pr) and **1abd** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Bu)].

To conclude the results from this screening, a general trend concerning the relation between substitution pattern in the ligand and *ee* in the product is observed to result from two leading ligands: **1abc** (R^1 = *t*Bu, R^2 = Mes, R^3 = *i*Pr) and **1abe** (R^1 = *t*Bu, R^2 = Mes, R^3 = *s*Bu). In 8 out of 13 screening sets, one or both oxazolidines afforded the best or slightly lower second best *ee* in the product. By comparing the substrates, it can be noted that substitution of the phenyl ring in the *meta* position leads to lower enantioselectivities with a particularly strong effect of chlorine. The reactions of naphthyl- and *tert*-butyl imines **17** proceed with moderate *ee* values.

The absolute configuration in product **18** in all cases is (*R*) when (2*S*,4*S*)-configured oxazolidines **1** were used as ligands, and (*S*) with their optical antipodes *ent*-**1**; the exception is *ortho*-methoxybenzaldimine **17d**. Figure 3 might explain the observed selectivity where the *Si* face of the substrate is more open to the approaching nucleophile; the *Re* face is slightly shielded by the − in this view rear − 1,3-oxazolidine moiety. A possible explanation for the behaviour of substrate **17d** is a different binding mode of the substrate. Steric reasons seem not to play a role here, as *ortho*-methylbenzaldimine **17j** affords products with good *ee* values and the usually privileged ligands afford the best results. Similar observations are made with *ortho*-chloro substrate **17g**. The oxygen atom of the methoxy group probably coordinates to the metal centre as well and, thus, the substrate is a bidentate ligand to the titanium. The complex should be significantly different from that shown in Figure 3 and, hence, lead to the unexpected results. Such coordination is only possible for the oxygen atom of an *ortho*-methoxy group and therefore here is the sole exception.

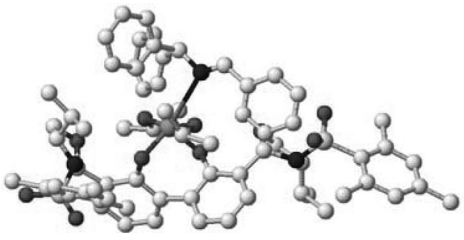


Figure 3. Model for a substrate–catalyst complex.

From X-ray-crystallographic analysis (Figure 4) we know that the chiral axis in free (2*R*,4*R*)-configured ligand *ent*-**1aab** (R^1 = *t*Bu, R^2 = Tol, R^3 = Et) adopts the (*S*) configuration. Together with our earlier findings in phosphites **2** that more bulky *N*-arensulfonyl groups in the oxazolidine moiety strongly enhance the preference for the energetically favoured diastereomer,[7] we can explain the general trend that ligands **1xbx** afford superior results. On the one hand, in the unfavoured diastereomer of **1** the oxazolidine moieties point towards each other and the metal centre. Therefore, the product-determining face discrimination becomes more unselective. On the other hand, given that the oxazolidine moiety shields one face of the substrate, the reaction must be more efficient with more bulky substituents in the 1,3-oxazolidine.

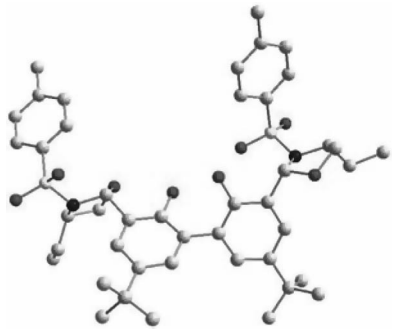


Figure 4. X-ray-crystallographic structure of ligand *ent*-**1aab**.

Conclusions

In this report, the synthesis of an extended ligand library is disclosed. A set of 27 1,3-oxazolidine-substituted biphenyldiol ligands was synthesised in good-to-excellent yields on a multigram scale. These chiral tropos ligands were used in a titanium-catalysed hydrocyanation of imines. A privileged structure is identified with the bulky mesitylene sulfonyl group and sterically more-demanding alkyl side chains in the oxazolidine moiety. Both are expected, in agreement with our earlier findings, to enhance the diastereomeric ratio concerning the chiral biaryl axis in the ligand. A broad range of substrates was investigated, and moderate-to-good enantioselectivities were observed. Substituents in the *meta* position of *N*-benzhydrylbenzaldimine afford products with lower *ee* values. Our results demonstrate that a ligand library may contain a privileged member, but the design of fine-tunable ligands with several variable sites is still a powerful tool in asymmetric catalysis to cover a broad substrate range.

Experimental Section

General: Reactions were carried out in flame-dried glassware under an atmosphere of argon, where appropriate. Toluene was distilled from Na/benzophenone and THF from K/benzophenone; CH_2Cl_2 was dried with CaH_2. TMEDA and NEt_3 were distilled from CaH_2 and stored under an atmosphere of argon in the dark. DMF was stirred over CaH_2, distilled under reduced pressure and stored over 4 Å molecular sieves. 2-Propanol was distilled from CaH_2 and stored over 4 Å molecular sieves. TIPT was distilled and stored under an atmosphere of argon. All other reagents were used as supplied by the commercial sources. Flash-column chromatography (FCC) was carried out by using Merck 60 silica gel (40–60 μm, 230–400 mesh ASTM), and monitored by thin-layer chromatography (TLC) on Merck 60 F_{254} TLC plates. NMR spectra were recorded with Bruker ARX 300 and ARX 400 spectrometers. Chemical shifts are relative to TMS (δ = 0.00 ppm). Calibration was performed by using the signals of TMS (δ = 0.00 ppm, ^{1}H

NMR spectra) and $CDCl_3$ (δ = 77.0 ppm, ^{13}C NMR spectra). Peak assignments were made by using routine 2D spectra; diastereotopic methylene protons are named H_A and H_B. IR spectra were recorded with a Nicolet 5DCX, Bruker IFS 28 or Varian 3100 Excalibur Series with Specac Golden Gate Single Reflection ATR. Mass spectra were recorded with a Bruker Micro-TOF and a Waters Micromass Quatro-LC (both ESI) or a Finnigan MAT 8200 (EI) spectrometer. Optical rotations were measured with a Perkin–Elmer 341 apparatus. Melting points were measured with a Stuart Melting Point Apparatus SMP3 (Bibby Sterlin Ltd) and are uncorrected. Combustion analyses were carried out with a Vario EL III (Elementar-Analysensysteme GmbH). HPLC measurements were performed with a Waters 600E Multisolvent Delivery System and 996 PDA detector or Knauer Smartline UV detector 2600, Pump 1000 and Manager 5000. As stationary phases were used: Chira Grom 1 and Chira Grom 2 (2.0 × 250 mm) by Grom, and Eurocel (4.6 × 250 mm) by Knauer.

5,5′-Di-*tert*-butyl-2,2′-bis(diethylcarbamoyloxy)biphenyl (4): To a solution of **3** (18.49 g, 62.0 mmol, 1.0 equiv.) and DMAP (397 mg, 3.25 mmol, 0.05 equiv.) in THF (100 mL) was cautiously added a suspension (60% wt.) of sodium hydride in mineral oil (9.10 g, 228.0 mmol, 3.5 equiv.) at 0 °C. After gas evolution had ceased, the mixture was warmed to r.t. and diethylcarbamoyl chloride (20.5 mL, 162.5 mmol, 2.5 equiv.) was added. The solution was stirred at r.t. for 16 h, followed by the careful addition of aqueous HCl (2 M, 50 mL). The phases were separated, and the aqueous phase was extracted with TBME (3 × 30 mL). The combined organic layer was dried with sodium sulfate, and the solvent was evaporated. The remaining oil was filtered through a plug of silica, and the solvent was removed in vacuo. After 2 d, white crystals had formed, which were filtered and washed with cold *n*-pentane. The mother liquor was subjected to FCC to give a combined amount of a white solid (30.75 g, 62.0 mmol, 99%), m.p. 73 °C. R_f = 0.54 (*n*-pentane/diethyl ether, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, ^3J = 8.5 Hz, ^4J = 2.5 Hz, 2 H, 4-H), 7.29 (d, ^4J = 2.5 Hz, 2 H, 6-H), 7.16 (d, ^3J = 8.4 Hz, 2 H, 3-H), 3.19 (br. s, 4 H, CH_2), 3.08 (br. s, 4 H, CH_2), 1.31 (s, 18 H, *t*Bu), 1.01 (br. s, 6 H, CH_3), 0.81 (br. s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3 (CO), 147.2 (C-2), 147.1 (C-5), 131.1 (C-1), 128.3 (C-4), 125.6 (C-6), 122.5 (C-3), 41.6 (br., CH_2), 41.35 (br., CH_2), 34.2 (quart. *t*Bu), 31.2 (*t*Bu), 15.0 (br., CH_3), 13.8 (br., CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2966 (s), 2873 (s), 1714 (s), 1472 (m), 1418 (m), 1211 (s), 1159 (s), 807 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 496 (1) $[M]^+$, 100 (100). $C_{30}H_{44}N_2O_4$ (496.68): calcd. C 72.55, H 8.93, N 5.64; found C 72.61, H 9.10, N 5.33.

5,5′-Di-*tert*-butyl-2,2′-dihydroxybiphenyl-3,3′-dicarbaldehyde (7a): To a solution of TMEDA (20.8 mL, 139.5 mmol, 3.0 equiv.) in THF (300 mL) at –78 °C was added a solution of *tert*-butyllithium (1.5 M in pentane, 100 mL, 150.0 mmol, 3.2 equiv.). The mixture was stirred at this temperature for 15 min before a solution of **3** (23.064 g, 46.50 mmol, 1.0 equiv.) in THF (75 mL) was added over 20 min (syringe pump). The reaction mixture was held at –78 °C for 90 min. Then, DMF (15.5 mL, 200 mmol, 4.3 equiv.) was added dropwise into the solution over 20 min, and the reaction mixture was warmed to r.t. over 16 h. Subsequently, methanol (30 mL) was added and stirring was continued for 2 h. Then, aqueous HCl (2 M, ca. 100 mL) was added until acidic pH was achieved (change of colour to bright yellow). The phases were separated, and the aqueous phase was extracted with TBME (3 × 100 mL). The combined organic layer was dried with sodium sulfate, and the solvent was evaporated. The remaining solid was suspended in *n*-pentane and the residual yellow precipitate (18.860 g, 41.86 mmol, 90%) was filtered off. The characterization of compound **7a** was reported earlier by us.[7]

2,2′-Bis(isopropylcarbamoyloxy)biphenyl (6): To a solution of 2,2′-dihydroxybiphenyl (**5**; 55.80 g, 300.0 mmol, 1.0 equiv.) and DMAP (1.098 g, 9.00 mmol, 0.03 equiv.) in THF (75 mL) was added isopropyl isocyanate (69 mL, 700.0 mmol, 2.3 equiv.), and the mixture was stirred at 60 °C for 24 h. The solution was washed with aqueous HCl (2 M, 145 mL), and the aqueous phase was extracted with TBME (3 × 50 mL). The combined organic layer was dried with sodium sulfate, and the solvent was removed in vacuo. Crude carbamate **6** was purified by FCC (*n*-pentane/diethyl ether, 1:1) to yield **6** (106 g, 99%) as a white solid, m.p. 123 °C, R_f = 0.29 (*n*-pentane/diethyl ether, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.34 (m, 2 H, aromatic), 7.30–7.22 (m, 6 H, aromatic), 5.23 (d, ^3J = 6.7 Hz, 2 H, NH), 3.67 (oct., ^3J = 6.6 Hz, 2 H, CH), 1.05 (br. d, ^3J = 5.7 Hz, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (CO), 148.5 (C-2), 130.9 (CH), 130.7 (C-1), 128.6 (CH), 125.3 (CH), 122.8 (CH), 43.0 (CH), 22.5 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3290 (br), 2975 (m), 1724 (s), 1698 (s), 1530 (s), 1238 (s), 1204 (s), 1172 (s), 1099 (s), 1029 (s), 762 (s) cm^{-1}. MS (ESI): *m*/*z* (%) = 379.162 (100) $[M + Na]^+$; calcd. 379.163. $C_{20}H_{24}N_2O_4$ (356.42): calcd. C 67.40, H 6.79, N 7.86; found C 67.39, H 6.55, N 7.90.

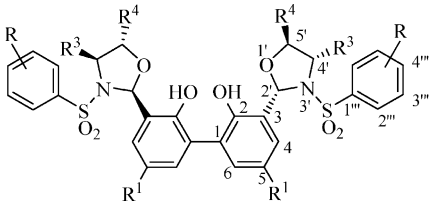
2,2′-Dihydroxybiphenyl-3,3′-dicarboxaldehyde (7b): To a stirred solution of **5** (8.900 g, 25.00 mmol, 1.0 equiv.) in THF (200 mL) was added TMEDA (8.9 mL, 60.0 mmol, 2.4 equiv.) and TMSOTf (9.05 mL, 50.00 mmol, 2.00 equiv.) at 0 °C. The mixture was stirred at r.t. for 30 min and then cooled to –78 °C. Again, TMEDA (8.9 mL, 60.0 mmol, 2.4 equiv.) was added, followed by a solution of *tert*-butyllithium (1.5 M in pentane, 100 mL, 150.0 mmol, 6.0 equiv.). The mixture was stirred at –78 °C for 4 h and, subsequently, DMF (11.7 mL, 150.0 mmol, 6.0 equiv.) was added dropwise. The reaction mixture was warmed to r.t. before methanol (30 mL) and a solution of NaOH (2 M in water, 80 mL) were added. The solution was stirred at r.t. for 3 h; then, aqueous HCl (2 M, ca. 150 mL) was added until acidic pH (change of colour to bright yellow). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 80 mL). The combined organic layer was dried with sodium sulfate, and the solvent was removed in vacuo. The remaining solid was suspended in TBME and the residual yellow precipitate (4.590 g, 18.97 mmol, 76%) was filtered off. M.p. 158 °C. R_f = 0.45 (CH_2Cl_2/MeOH, 500:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 11.43 (s, 2 H, OH), 9.96 (s, 2 H, CHO), 7.63 (dd, ^3J = 8.0 Hz, ^4J = 1.9 Hz, 2 H, 4-H), 7.61 (dd, ^3J = 7.7 Hz, ^4J = 1.9 Hz, 2 H, 6-H), 7.11 (t, ^3J = 7.9 Hz, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6 (CHO), 159.1 (C-2), 138.8 (C-6), 133.7 (C-4), 125.1 (C-1), 120.9 (C-3), 119.5 (C-5) ppm. IR (ATR): $\tilde{\nu}$ = 3535 (m), 3023 (br), 2871 (m), 1628 (s), 1612 (s), 1423 (s), 1386 (s), 1293 (s), 1219 (s), 1064 (s), 727 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 242 (100) $[M]^+$. $C_{14}H_{10}O_4$ (242.23): calcd. C 69.42, H 4.14; found C 69.32, H 4.13.

2,2′-Diacetoxy-5,5′-di-*tert*-butylbiphenyl-3,3′-dicarboxaldehyde (8b): To a stirred solution of **6b** (4.590 g, 18.97 mmol, 1.0 equiv.) in dichloromethane (80 mL) was added triethylamine (5.9 mL, 42 mmol, 2.2 equiv.) and acetyl chloride (3.0 mL, 42 mmol, 2.2 equiv.) at 0 °C. The mixture was stirred at r.t. for 2 h. Then, TBME (80 mL) was added, and subsequently, the suspension was filtered through a plug of silica. The filtrate was concentrated under vacuum to give acetate **8b** (6.182 g, 18.97 mmol, 99%) as a white solid, m.p. 90 °C. R_f = 0.17 (*n*-pentane/diethyl ether, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 2 H, CHO), 7.96 (dd, ^3J = 8.0 Hz, ^4J = 1.9 Hz, 2 H, 4-H), 7.56 (dd, ^3J = 7.7 Hz, ^4J = 1.9 Hz, 2 H, 6-H), 7.50 (t, ^3J = 7.6 Hz, 2 H, 5-H), 2.12 (s, 6 H, Ac-CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2 (CHO), 168.7 (Ac-CO), 148.6 (C-2), 136.6 (C-6), 131.6 (C-4), 131.0 (C-1), 128.5 (C-3), 126.2 (C-5), 20.3 (Ac-CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2975 (m), 1670 (m), 1604 (m), 1455 (s), 1309 (s), 1227 (m), 1153 (s), 1081 (s), 952 (s), 669 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 326 (15) $[M]^+$, 242 (100). $C_{18}H_{14}O_6$ (326.30): calcd. C 66.26, H 4.32; found C 66.24, H 4.45.

General Procedure for the Synthesis of Oxazolidines 10: To a stirred solution of **8** (1.0 equiv.) and *N*-sulfonyl-2-amino-1-alkanol **9** (3.0 equiv.) in toluene (10.0 mL per mmol) was added dichlorodimethylsilane (5.0 equiv.). The solution was heated at reflux under an atmosphere of argon for 48 h and then cooled to r.t. Then, the mixture was poured into saturated aqueous potassium carbonate solution (10 mL per mmol) and washed. After phase separation, the aqueous phase was extracted with TBME (3 × 5 mL per mmol), and the combined organic layers were dried with sodium sulfate. The solvents were removed in vacuo, and the residue was purified by FCC with mixtures of *n*-pentane and diethyl ether. The characterisation of one representative example is given, for further compounds, see Supporting Information.

General Pattern for the Numbering of Atoms: The atoms are numbered for the assignment as shown. The substituents R^3 are labelled as 1′′ etc. Assignments have been made by using DEPT, COSY, HSQC, and HMBC spectra.



2,2′-Diacetoxy-5,5′-di-*tert*-butyl-3,3′-bis[(2*S*,4*S*)-4-methyl-3-(4-methylbenzenesulfonyl)-1,3-oxazolidinyl]biphenyl (10aaa): After FCC, the product was obtained in 99% yield. M.p. 110–113 °C. R_f = 0.17 (*n*-pentane/diethyl ether, 1:1). $[\alpha]_D^{20}$ = –109.4 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.79 (m, 4 H, 2′′′-H), 7.70 (br. s, 2 H, 4-H), 7.36–7.34 (m, 4 H, 3′′′-H), 7.32 (br. s, 2 H, 6-H), 6.30 (s, 2 H, 2′-H), 3.90 (sext., ^3J = 6.3 Hz, 2 H, 4′-H), 3.76 (dd, ^2J = 8.8 Hz, ^3J = 7.0 Hz, 2 H, 5′-H_A), 3.39 (dd, ^2J = 8.9 Hz, ^3J = 7.0 Hz, 2 H, 5′-H_B), 2.44 (s, 6 H, Ts-CH_3), 1.91 (s, 6 H, Ac-CH_3), 1.42 (d, ^3J = 5.8 Hz, 6 H, 1′′-H), 1.33 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (Ac-CO), 148.2 (C-5), 144.6 (C), 144.1 (C-4′′′), 134.7 (C-1′′′), 131.2 (C), 129.8 (C-3′′′), 129.6 (C), 129.2 (C-6), 127.9 (C-2′′′), 125.7 (C-4), 89.1 (C-2′), 71.7 (C-5′), 55.5 (C-4′), 34.7 (quart. *t*Bu), 31.3 (*t*Bu), 21.5 (Ts-CH_3), 20.5 (Ac-CH_3), 19.6 (C-1′′) ppm. IR (ATR): $\tilde{\nu}$ = 2965 (m), 2873 (w), 1765 (s), 1351 (s), 1192 (m), 1163 (s), 1094 (m), 903 (s), 815 (s), 666 (s) cm^{-1}. MS (ESI): *m*/*z* (%) = 883.326 (100) [M + Na]$^+$; calcd. 883.327. $C_{46}H_{56}N_2O_{10}S_2$ (861.07): calcd. C 64.16, H 6.56, N 3.25; found C 64.19, H 6.52, N 2.98.

General Procedure for the Synthesis of Ligands 1: To a stirred solution of oxazolidine **10** (1.0 equiv.) in MeOH (20 mL per mmol) was added water (0.5 mL per mmol) and potassium hydroxide (3.0 equiv.). The yellow solution was stirred at r.t. for 2 h. The same volume of saturated aqueous ammonium chloride solution was added, followed by the same amount of dichloromethane. After phase separation, the aqueous layer was extracted with dichloromethane (3 × 10 mL per mmol), and the combined organic layer was dried with sodium sulfate. The solvent was removed in vacuo, and the residue was purified by FCC on silica (*n*-pentane/diethyl ether). The characterisation of one representative example is given, for further compounds, see Supporting Information.

5,5′-Di-*tert*-butyl-3,3′-bis[(2*S*,4*S*)-4-methyl-3-(4-methylbenzenesulfonyl)-1,3-oxazolidinyl]biphenyl-2,2′-diol (1aaa): After FCC, the product was obtained in 78% yield, m.p. 106–109 °C. R_f = 0.08 (*n*-pentane/diethyl ether, 1:1). $[\alpha]_D^{20}$ = –155.4 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, ^3J = 8.2 Hz, 4 H, 2′′′-H), 7.60 (d, ^4J = 2.6 Hz, 2 H, 4-H), 7.33 (d, ^3J = 8.1 Hz, 4 H, 3′′′-H), 7.28 (d, ^4J = 2.4 Hz, 2 H, 6-H), 7.26 (s, 2 H, OH), 6.48 (s, 2 H, 2′-H), 4.04 (sext., ^3J = 6.3 Hz, 2 H, 4′-H), 3.84 (dd, ^2J = 8.6 Hz, ^3J = 7.0 Hz, 2 H, 5′-H_A), 3.56 (dd, ^2J = 8.8 Hz, ^3J = 5.9 Hz, 2 H, 5′-H_B), 2.43 (s, 6 H, Ts-CH_3), 1.43 (d, ^3J = 6.3 Hz, 6 H, 1′′-H), 1.34 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2 (C-2), 144.2 (C-4′′′), 143.3 (C-5), 134.5 (C-1′′′), 129.9 (C-3′′′), 129.7 (C-6), 128.0 (C-2′′′), 126.0 (C-3), 125.5 (C-4), 123.4 (C-1), 90.0 (C-2′), 71.8 (C-5′), 55.5 (C-4′), 34.3 (quart. *t*Bu), 31.5 (*t*Bu), 21.5 (Ts-CH_3), 20.2 (C-1′′) ppm. IR (ATR): $\tilde{\nu}$ = 2972 (m), 2875 (w), 1344 (s), 1161 (s), 1095 (m), 815 (s), 667 (s) cm^{-1}. MS (ESI): *m*/*z* (%) = 799.305 (100) [M + Na]$^+$, calcd. 799.306. $C_{42}H_{52}N_2O_8S_2$ (777.00): calcd. C 64.92, H 6.75, N 3.61; found C 64.88, H 6.60, N 3.38.

General Procedure for the Titanium-Mediated Addition of TMSCN to Imines: A 10-fold reactor was charged with ligand **1** (0.05 mmol, 0.1 equiv.) and flushed with argon. The ligand was dissolved in toluene (3.0 mL) before a solution of Ti(O*i*Pr)$_4$ (0.1 M in toluene, 0.50 mL, 0.05 mmol, 0.1 equiv.) was added. The catalyst mixture was stirred at r.t. for 30 min and then the imine (0.50 mmol, 1.0 equiv.) was added. After cooling to 0 °C, TMSCN (0.13 mL, 1.00 mmol, 2.0 equiv.) was added. A solution of 2-propanol (1.0 M in toluene, 1.00 mL, 1.00 mmol, 2.0 equiv.) was added over 18 h at 0 °C by means of a syringe pump. The reaction mixture was passed through a silica plug with mixtures of *n*-pentane/diethyl ether, concentrated and analysed by chiral HPLC (λ = 210 nm). For each substrate, one representative example was purified by FCC with mixtures of *n*-pentane/diethyl ether.

Experimental Data for the Crystal Structure of *ent*-1aab: X-ray crystal structure analysis for **HOP2807**:[20] formula $C_{45}H_{58}Cl_2N_2O_8S_2$, *M* = 889.95, colourless crystal 0.35 × 0.15 × 0.05 mm, *a* = 14.064(1) Å, *b* = 12.017(1) Å, *c* = 14.757(1) Å, β = 109.35(1)°, *V* = 2353.2(3) Å^3, $\rho_{calcd.}$ = 1.256 g cm^{-3}, μ = 2.489 mm^{-1}, empirical absorption correction (0.476 ≤ *T* ≤ 0.886), *Z* = 2, monoclinic, space group $P2_1$ (No. 4) λ = 1.54178 Å, *T* = 223 K, $\omega/2\theta$ scans, 5242 reflections collected, (+*h*, –*k*, ±*l*), [(sinθ)/λ] = 0.62 Å^{-1}, 5038 independent (R_{int} = 0.025) and 3741 observed reflections [$I \geq 2\sigma$ (*I*)], 595 refined parameters, *R* = 0.047, *w*R^2 = 0.134, Flack parameter 0.00(2), max. residual electron density 0.20 (–0.42) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

Supporting Information (see footnote on the first page of this article): Complete results of all asymmetric Strecker reactions and full characterisation of all new compounds.

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