Discovery of a New Efficient Chiral Ligand for Copper-Catalyzed Enantioselective Michael Additions by High-Throughput Screening of a Parallel Library**

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Abstract: A combinatorial library of 125 chiral Schiff base ligands **5** was synthesized with the use of solution-phase parallel synthesis and solid-phase extraction (SPE) techniques to scavenge excess reagents and reaction by-products and avoid chromatography. The synthetic methodology coupled five *N*-Boc-protected β-amino sulfonyl chlorides **1a–e** with five different amines **2f–j** to give 25 *N*-Boc sulfonamides **3**, which were in turn deprotected and coupled with five salicylaldehydes **4p–t** to give 125 ligands **5** in good yields and of sufficient purity to be used in ligand-catalyzed reactions. These ligands were tested in the copper-catalyzed conjugate addition of dialkyl zinc to cyclic and acyclic enones. A multisubstrate high-throughput screening of the library was performed with an equimolar mixture of 2-cyclohexenone and 2-cycloheptenone (**9** and **10**, respectively, 0.2 mmol total), with 5.5 mol% ligand **5** (0.011 mmol) and 5 mol% $Cu(OTf)_2$ (OTf = OSO_2CF_3) (0.010 mmol) in 1:1 toluene/hexane at $-20\,^{\circ}C$. From the screening of the library, **5bhr** was identified as the best ligand, which yielded 3-ethylcyclohexanone (**12**) and 3-ethylcycloheptanone (**13**) in 82% and 81% *ee*, respectively, and complete conversions. Under optimized conditions (2.75 mol% **5bhr**, 2.5 mol% copper(I) triflate, toluene as reaction solvent), improved results were obtained for **12** (90% *ee*, 93% yield) and for **13** (91% *ee*, 95% yield). Selected ligands **5** were also tested in the addition of Me_2Zn to 2-cyclohexenone (**9**, *ee* up to 79%), of Et_2Zn to 2-cyclopentenone (**11**, *ee* up to 80%) and to acyclic enones **16** and **17** (*ee* up to 50%).

Keywords: asymmetric catalysis · combinatorial chemistry · copper · Michael addition · zinc

Introduction

The 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an important process for C–C bond formation in organic synthesis.[1] Although organocuprates and copper-catalyzed 1,4-additions of Grignard reagents are most frequently employed,[2] a number of alternative reagents that are based on the use of other metal catalysts (such as Ni or Mn)[3] or other organometallic reagents (R_2Zn or R_3Al)[4] have been recently developed.

The importance of this reaction, the variety of reagents and fragments that can be used, and the opportunity to further react the enolate that results from the conjugate addition with other electrophiles in a highly stereoselective manner have stimulated the search for an effective control over facial discrimination during addition to prochiral substrates. Several chiral stoichiometric reagents have been described that allow enantioselective additions,[5] while the development of chiral catalysts has been slower. A prominent position in this rapidly expanding field is occupied by the copper-catalyzed, chiral-ligand-accelerated, 1,4-addition of organozinc reagents.[6] In particular, chiral phosphoramidites,[6b] phosphites,[6c–e] and bidentate P–N ligands[6f–i] were used in the addition to cyclic enones with very good enantioselectivities (*ee* up to 98%).[6b] On the other hand, chiral sulfonamides, which have proven effective in various catalytic asymmetric processes, were reported to catalyze the conjugate addition of organozinc reagents to cyclic enones[7a] with only marginal enantioselectivity ($ee \leq 31\%$).[6g, 7b]

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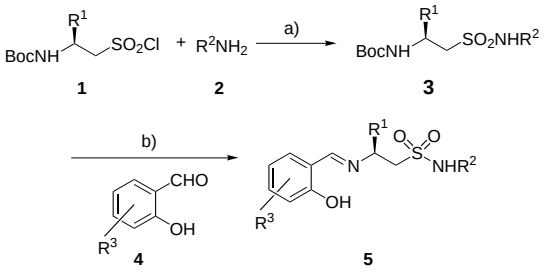
The efficiency (activity and selectivity) of a ligand for asymmetric catalysis depends on a subtle balance of electronic, geometric, and steric influences between the ligand, the metal center, and the substrates. In such a complex scenario, the development of a new effective ligand by intuition and trial-and-error is a very challenging task. The use of combinatorial methodologies for the rapid synthesis and screening of a large number of structures is an important breakthrough in this area.[8, 9] Two different basic approaches have been considered: optimization of reaction conditions (solvent, temperature, stoichiometry, various ligands, or metal ions) and the synthesis of new ligands by a modular-building-block strategy in which the stereoelectronic properties of a metal binding site (e.g., a diphosphine, a disulfonamide, or a Schiff base) are tuned by variation of substituents and side chains. In the case of screening members of a library that contains ligands for enantioselective catalysis, the identification of a hit requires a demanding selection procedure, since the screening is ultimately catalysis of a reaction and analysis of its stereochemical outcome.[9h–k] For this reason, a combinatorial system is usually chosen that allows the synthesis of discrete isolated compounds. Parallel synthesis (as opposed to "split and pool" methodology)[9l] allows one to know the identity of each ligand and keeps the ligands separated so that screening of individual complexes can be performed.

We have recently developed a new family of chiral Schiff base ligands of general structure **5** (Scheme 1, Table 1), which contain a set of different metal binding sites (a phenol, an imine, and a secondary sulfonamide), with the expectation that such a multidentate array would favor the formation of organometallic complexes with well-organized spatial arrangements, and with the goal of obtaining ligands for asymmetric catalysis capable of broad applicability. The main feature of these ligands is their modular assembly by subsequent coupling of the three components (Scheme 1), namely sulfonyl chloride **1**, amine **2**, and aldehyde **4**, which make these ligands well suited for a combinatorial development. A library of ligands **5** was synthesized in solution and tested in the copper-catalyzed conjugate addition of Et_2Zn to cyclic enones[10a] and to nitroolefins.[10b] We herein report the synthesis of an extended version of this library (125 ligands) and its screening in the copper-catalyzed conjugate addition of dialkyl zinc (Me_2Zn and Et_2Zn) to cyclic and acyclic enones.



Scheme 1. Synthesis of the library of ligands **5**. a) (Procedure A) **1** (1.2 equiv), **2** (1.0 equiv), **6** (2.0 equiv), polymer-bound **7** (0.2 equiv), CH_2Cl_2, 20 °C, 3 h; solid-phase bound **8** (3.0 equiv), 3 h, 86–88 %; (Procedure B) **1** (1.0 equiv), **2** (1.2 equiv), **6** (2.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 20 °C, 3 h; 86–88 %. b) **3** (1.0 equiv), TFA/CH_2Cl_2 (1:3), 20 °C, 30 min; evaporation; **4** (0.9 equiv), polymer-bound **7** (3.0 equiv), CH_3OH, 20 °C, 24 h, 87 %. c) For the synthesis of aldehyde **4t**, see ref. [20].

Table 1. Defintion of R groups in Scheme 1.

R^1	R^2	R^3
1a: Me	**2f**: CH_2Ph	**4p**: H
1b: *i*Pr	**2g**: (*R*)-CH(Me)Cy	**4q**: 3,5-*t*Bu_2
1c: *i*Bu	**2h**: (*S*)-CH(Me)Cy	**4r**: 3,5-Cl_2
1d: CH_2Ph	**2i**: *i*Pr	**4s**: 5,6-$(CH)_4$-
1e: *t*Bu	**2j**: $CHPh_2$	**4t**: 3-Ph
	2k: *t*Bu	**4u**: 3-OMe
	2l: (*R*)-CH(*i*Pr)CH_2OH	**4v**: 5-NO_2
	2m: (*S*)-CH(*i*Pr)CH_2OH	
	2n: (*R*)-CH(Me)Ph	
	2o: (*S*)-CH(Me)Ph	

Abstract in Italian: *Una libreria combinatoriale formata da 125 leganti chirali (**5**) appartenenti alla classe delle basi di Schiff, è stata sintetizzata in soluzione, in formato parallelo, mediante una tecnica di "estrazione in fase solida" per eliminare l'eccesso dei reagenti e i sottoprodotti della reazione. La metodologia di sintesi ha previsto l'accoppiamento di 5 N-Boc β-ammino solfonil cloruri **1a–e** con 5 diverse ammine **2f–j** per formare 25 N-Boc solfonammidi **3**, che a loro volta sono state deprotette e condensate con 5 salicilaldeidi **4p–t** per fornire i 125 leganti **5**. L'efficacia di questi leganti è stata saggiata nella reazione di addizione coniugata di composti di dialchilzinco ad enoni ciclici ed aciclici, catalizzata da complessi di rame. Un saggio multi-substrato ad alta produttività è stato realizzato impiegando una miscela equimolare di 2-cicloesenone e 2-cicloeptenone (**9** e **10**, 0.2 mmol totali) in presenza di 5.5 mol % dei leganti **5** e di 5.0 mol % di $Cu(OTf)_2$ ($OTf = OSO_2CF_3$) in una miscela di toluene/esano 1:1 a −20 °C. Il saggio della libreria ha evidenziato **5bhr** quale miglior legante, che ha fornito il 3-etilcicloesanone **12** e il 3-etilcicloeptanone **13** con ee pari rispettivamente a 82 e 81 % e con conversioni complete. Nelle condizioni di reazione ottimizzate (2.75 mol % di **5bhr**, 2,5 mol % di triflato di rame (I), in toluene come solvente) si sono ottenuti migliori risultati sia per **12** (90 % ee, 93 % di resa) che per **13** (91 % ee, 95 % di resa). Una selezione dei leganti **5**, é stata infine saggiata nella reazione di addizione di Me_2Zn al 2-cicloesenone **9** (con ee fino al 79 %), e nelle reazioni di addizione di Et_2Zn al 2-ciclopentenone **11** (con ee fino al 80 %) e agli enoni aciclici **16** e **17** (con ee fino al 50 %).*

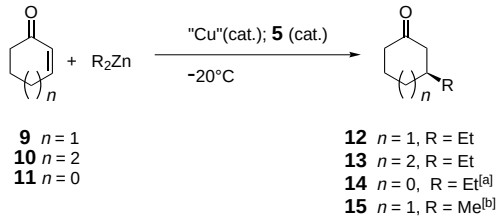
Results and Discussion

Synthesis of the library: Ligand **5** was easily obtained (Scheme 1) by condensation of salicylaldehyde with enantiomerically pure β-amino sulfonamides. Sulfonamide **3** was in turn synthesized by coupling different primary amines with sulfonyl chlorides **1a–e**, which were prepared in high yield from L-α-aminoacids (respectively Ala, Val, Leu, Phe, *t*Leu) by a straightforward synthetic protocol.[11] For the synthesis of

the ligand library, we used solution-phase parallel synthesis and solid-phase extraction (SPE) techniques to scavenge excess reagents and reaction by-products, and thus avoid chromatography.[9a, 12] For the formation of sulfonamide **3** (Scheme 1), the reaction of excess sulfonyl chloride **1** (1.2 equivalents) with amine **2** (1.0 equivalent) was run in dichloromethane in the presence of methyl trimethylsilyl dimethylketene acetal (MTDA, **6**) (2.0 equivalents)[11] and a catalytic amount (0.2 equivalents) of polymer-bound 4-dimethylaminopyridine[13] (**7**) to catalyze the coupling reaction and scavenge liberated HCl. Apart from the polymer, which was removed by filtration, the only by-products were chlorotrimethylsilane and methyl isobutyrate, which are volatile and were removed with the solvent. After all the amine had been consumed, excess sulfonyl chloride was removed by reaction with solid-phase bound (tris[2-aminoethyl]amine)[12c] (**8**) (3.0 equivalents) and subsequent filtration. In a few special cases, that is, when the sulfonyl chloride is particularly hindered (**1e**), a different methodology was employed: an excess of amine **2** (1.2 equivalents) was coupled with sulfonyl chloride (1.0 equivalent) in the presence of methyl trimethylsilyl dimethylketene acetal (MTDA, **6**) (2.0 equivalents)[11] and a catalytic amount (0.2 equivalents) of "dimethylamino pyridine" (DMAP) in solution. Once the coupling was complete (by TLC), the reaction mixture was washed with a saturated citric acid solution. The product was obtained in 88% average yield without need for further purification.

In the subsequent step, the Boc protecting group was cleaved with 25% CF_3CO_2H (TFA) in CH_2Cl_2, and the resulting amine trifluoroacetate salts (1.0 equivalent) were treated in MeOH with aldehyde **4** (0.9 equivalents) in the presence of polymer-bound 4-dimethylaminopyridine[13] (**7**) (3.0 equivalents) to yield the target Schiff base **5** in 87% overall yield (average) and of sufficient purity to be used in ligand-catalyzed reactions.

Conjugate addition to cycloalkenones: At the beginning of this work, a few model ligands **5** were prepared and tested, and shown to be effective in accelerating the copper-catalyzed [5% $Cu(OTf)_2$; $Tf = SO_2CF_3$] conjugate addition of diethylzinc to cyclohexenone (**9**; Scheme 2). The copper complex



Scheme 2. Enantioselective conjugate addition of R_2Zn (R = Me, Et) to cyclic enones **9**, **10**, and **11** catalyzed by "Cu"/**5**. Screening of the library of ligands **5**. [a] This reaction was performed at 0/+10 °C. [b] This reaction was performed at 0 °C.

was preformed in situ by stirring a catalytic amount of $Cu(OTf)_2$ (0.050 equivalents) in toluene in the presence of the ligand (0.055 equivalents) at +20 °C. Diethylzinc (1.0 M in hexanes, 2.2 equivalents) and cyclohexenone (**9**) (1.0 equivalent) were then added at −20 °C and the reaction was stirred for three hours before quenching. The enantiomeric excesses of the reaction products, measured by injection of the crude reaction mixtures in a gas chromatograph (GC) equipped with a chiral capillary column, were only moderate or poor, ranging from 28% with catalytic (5.5%) **5dfp** ($R^1 = CH_2Ph$, $R^2 = CH_2Ph$, $R^3 = H$) to 48% with **5dfq** ($R^1 = CH_2Ph$, $R^2 = CH_2Ph$, $R^3 = 3,5\text{-}t\text{Bu}_2$; Scheme 2).[14] At this stage, we considered a combinatorial approach for tuning the ligand structure and improving the results.

A multisubstrate high-throughput screening[9a, 15] was also planned to optimize the ligand structure with respect to the various substrates. Cyclohexenone and cycloheptenone (**9** and **10**, respectively) were chosen, since the four peaks of the two enantiomeric pairs (reaction products **12** and **13**) did not overlap in the chromatogram and gave baseline separation (Figure 1). Cyclopentenone **11** was not included because only

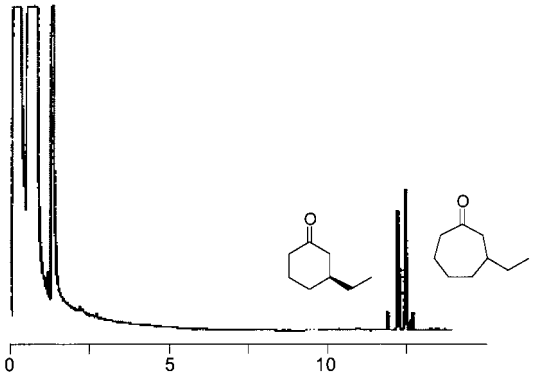


Figure 1. Multisubstrate high-throughput screening of the library: GC trace of the reaction products (**12** and **13**) that shows the resolution of the two enantiomeric mixtures.

trace amounts of addition product **14** could be detected under these reaction conditions (vide infra). The co-reactions were performed with an equimolar mixture of **9** and **10** (0.2 mmol total), with 5.5 mol% ligand **5** (0.011 mmol) and 5 mol% $Cu(OTf)_2$ (0.010 mmol) in toluene at −20 °C. The reactions were quenched after five hours, and the crude reaction mixtures were directly analyzed for conversion and enantiomeric excess (time for each analysis: 15 minutes).

For the construction of the library, the choice of the building blocks (sulfonyl chlorides, amines, and aldehydes) is crucial. A test-library of 60 compounds (one sulfonyl chloride **1d**, ten amines **2f–o**, and six aldehydes **4p–s** and **4u,v**) was built to study the influence of R^2 and R^3 by maximizing their diversity. This first set of ligands was screened in the conditions described above, and the results revealed some interesting features: 1) poor enantioselectivities (≤40% *ee*) were obtained with amines **2k**, **2l**, **2m** (irrespective of the aldehyde) and with aldehydes **4u**, **4v** (irrespective of the amine), and 2) enantioselectivities with amines **2n** and **2o** were lower than those obtained with amines **2g** and **2h**.

From this analysis, a new library of 125 terms was designed, which contained five sulfonyl chlorides (**1a–e**), five amines (**2f–j**), and five aldehydes (**4p–t**). From the screening of this library (the best 10 ligands are reported in Table 2; see

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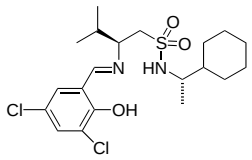
Table 2. High-throughput screening of the library of ligands **5**: $Cu(OTf)_2$ (0.05 equiv); Ligand **5** (0.055 equiv); Et_2Zn (2.2 equiv); **9** (0.1 mmol); **10** (0.1 mmol); toluene/hexane 1:1; −20 °C; 5 h. Best 10 results.

Entry	Ligand	R^1	R^2	R^3	% *ee* (**12**)	% *ee* (**13**)
1	**5bhr**	*i*Pr	(*S*)-CH(Me)Cy	3,5-Cl_2	82	81
2	**5ehq**	*t*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	80	79
3	**5biq**	*i*Pr	*i*Pr	3,5-*t*Bu_2	76	72
4	**5ejq**	*t*Bu	$CHPh_2$	3,5-*t*Bu_2	74	75
5	**5chr**	*i*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	73	74
6	**5cht**	*i*Bu	(*S*)-CH(Me)Cy	3-Ph	70	77
7	**5bit**	*i*Pr	*i*Pr	3-Ph	70	75
8	**5ejt**	*t*Bu	$CHPh_2$	3-Ph	73	73
9	**5chq**	*i*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	72	71
10	**5ehs**	*t*Bu	(*S*)-CH(Me)Cy	$(CH)_4$	71	71

Table 3. Optimization of the reaction conditions on cyclohexenone (**9**) with chiral ligand **5bhr**.

Entry	Cu [%]	*T* [°C]	Solvent	% *ee* (**12**)
1	5[a]	−20	toluene/hexane (1:1)	81
2	2.5[a]	−20	toluene/hexane (1:1)	84
3	20[a]	−20	toluene/hexane (1:1)	72
4	2.5[a]	−40	toluene/hexane (1:1)	78
5	2.5[a]	−0	toluene/hexane (1:1)	80
6	2.5[a]	−20	toluene/hexane (4:1)	88
7	2.5[a]	−20	hexane	71
8	2.5[a]	−20	toluene	88
9	2.5[b]	−20	toluene/hexane (4:1)	90
10	2.5[b]	−20	toluene	90

[a] $Cu(OTf)_2$; [b] CuOTf.

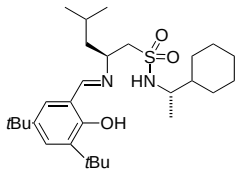


5bhr

Supporting Information for the complete layout), **5bhr** (R^1 = *i*Pr; R^2 = (S)−CH(Me)Cy; R^3 = 3,5-Cl_2) was identified as the best ligand for 2-cyclohexenone (82 % *ee*) and 2-cycloheptenone (81 % *ee*). Analysis of the results of the library screening reveals some interesting features: i) both substrates yield products in similar yields and enantioselectivities; ii) in ligand **5**, the stereocenter that bears R^1 controls the absolute configuration of the reaction product, while the stereocenter on R^2 (when present) tunes the selectivity; iii) steric hindrance is important for determining good enantioselectivities both in the case of R^1 (*i*Pr ≅ *t*Bu > *i*Bu > CH_2Ph > Me) and in the case of R^3 (3,5-Cl_2 ≅ 3,5-*t*Bu_2 > 3-Ph > naphthyl > H); iv) no simple correlation between the steric hindrance of the various substituents and the enantiomeric excesses is evident, and these data clearly show the importance of the mutual influences of the different substituents (R^1, R^2, R^3) in the fine tuning of the ligand structure. These results confirm the value of the "combinatorial approach": it would have been very difficult to identify this ligand for the two different substrates, if a rational approach had been followed.[16]

A subsequent optimization of the reaction conditions was then performed on compound **9** with the use of **5bhr** as ligand and considering the catalyst loading, reaction temperature, solvent and the source of copper (i.e., $Cu(OTf)_2$ and CuOTf; Table 3). Analysis of the results as shown in Table 3 leads to some interesting conclusions: i) the reaction enantioselectivity is only slightly influenced by the temperature (entry 2 vs entries 4 and 5); ii) high catalyst loading has a deleterious effect on the enantioselectivity (entry 2 vs entries 1 and 3); iii) the amount of toluene in the solvent mixture plays a beneficial role (entry 8 vs entries 6, 2 and 7); iv) the copper source only marginally affects the enantiomeric excess of the reaction products (entries 9 and 10 vs entries 6 and 8). Under the best conditions (2.75 mol % **5**, 2.5 mol % CuOTf, toluene, −20 °C, 5 hours), 3-ethylcyclohexanone (**12**) was obtained in 90 % *ee* with 100 % conversion and 93–95 % isolated yield. The same reaction conditions were applied to compound **10**; this gave 3-ethylcycloheptanone (**13**) in 91 % *ee* with 100 % conversion and 93–95 % isolated yield. Reaction of cyclohexenone with dimethylzinc was also attempted and, owing to the diminished reactivity of dimethylzinc relative to Et_2Zn,[7a][17] good conversions could be obtained only at +10 °C and after 24 hours. In this case, reaction with ligand **5bhr** afforded 3-methylcyclohexanone (**15**) in 79 % *ee*.

We then turned our attention to cyclopentenone, for which we obtained low conversion and almost no selectivity under the optimized conditions reported above. It is well known, in fact, that cyclopentenone gives rise to a mixture of Michael aldol products that arise from the condensation of initially formed enolates to another molecule of cyclopentenone;[7a, 18] Chan and coworkers[6e] recently reported that running the reaction between 0 °C and RT (the best results were obtained at +10 °C) greatly improved both the yield and the enantiomeric excess. Therefore, we tested the ten best ligands, which resulted from the screening of the library, in the conjugate addition to cyclopentenone at 10 °C with the use of $Cu(OTf)_2$ in toluene/hexane (4:1). Ligand **5chq** (Table 4) was recognized as the best ligand for the conversion of cyclopentenone (**11**). 3-Ethylcyclopentanone (**14**), was obtained in 72 % *ee* (entry 1), which was further increased to 80 % when the reaction was performed at 0 °C (en-



5chq

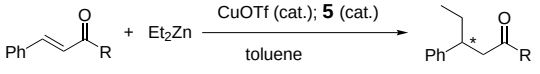
Table 4. Conjugate addition to cyclopentenone **11**. $Cu(OTf)_2$ (0.025 equiv); Ligand **5** (0.0275 equiv); Et_2Zn (2.2 equiv); toluene/hexane 4:1; +10 °C.

Entry	Ligand	R^1	R^2	R^3	% *ee* (**14**)
1	**5chq**	*i*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	72
2	**5ejq**	*t*Bu	$CHPh_2$	3,5-*t*Bu_2	70
3	**5ehq**	*t*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	50
4	**5bjq**	*i*Pr	$CHPh_2$	3,5-*t*Bu_2	46
5	**5biq**	*i*Pr	*i*Pr	3,5-*t*Bu_2	42
6	**5bhr**	*i*Pr	(*S*)-CH(Me)Cy	3,5-Cl_2	40
7	**5chr**	*i*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	34
8	**5aiq**	Me	*i*Pr	3,5-*t*Bu_2	32
9	**5ehs**	*t*Bu	(*S*)-CH(Me)Cy	$(CH)_4$	28
10	**5ehr**	*t*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	28
11[a]	**5chq**	*i*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	80
12[b]	**5chq**	*i*Bu	(*S*)-CH(Me)Cy	3,5-*t*Bu_2	76

[a] 0 °C; [b] 25 °C.

try 11). However, the isolated yield was only 25%, possibly also due to its high volatility.

Conjugate addition to linear enones: Enantioselective 1,4-addition of organometallics to linear enones is complicated by the competitive presence of s-*trans* and s-*cis* conformations;[17, 19] as a result, only a few efficient methods exist for this transformation. In the case of conjugate addition of Et_2Zn, very good results were obtained by Zhang[6i] (*ee* up to 96%) and Feringa[6b] (*ee* up to 89%). We decided to test a selection of our ligands in the conjugate addition to benzalacetone (**16**) and chalcone (**17**) (Scheme 3); the results are

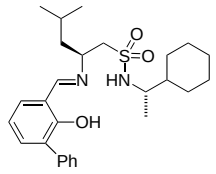


16 R = Me
17 R = Ph

18 R = Me
19 R = Ph

Scheme 3. Enantioselective conjugate addition of Et_2Zn to **16** and **17** catalyzed by CuOTf/**5**. For reaction temperatures see Experimental Section.

summarized in Table 5. Several reaction conditions were tested and under the best conditions (2.75 mol% **5**, 2.5 mol% CuOTf, toluene, +20 °C, 5 h), 4-phenylhexan-2-one (**18**) was obtained in 55% yield, and in 50% *ee*, with the use of ligand **5cht**. In the case of **17**, the reaction was sluggish and 1,3-diphenylpentan-1-one (**19**) was obtained in 14% yield and 34% *ee* (entry 7). Addition of 1.5 equivalents of chlorotrimethylsilane to trap the enolate formed during the conjugate addition reaction improved the yield (up to 65%), but gave only racemic product (entry 9).



5cht

Conclusion

In conclusion, we developed a parallel library of new Schiff base chiral ligands (**5**) and optimized their use in the enantioselective copper-catalyzed conjugate addition of dialkyl zinc reagents to various Michael acceptors by a high-throughput screening approach. Work is in progress to extend the scope of ligand **5** in other enantioselective reactions.

Experimental Section

General: Manipulations that involved air-sensitive compounds were carried out in an argon atmosphere with the use of Schlenk and syringe techniques. Solvents were dried with sodium (toluene), sodium/benzophenone (THF and diethyl ether), or by refluxing over CaH_2 for at least four hours prior to use. Reagents were used as received, without any further purification, and were generally purchased from Aldrich and Fluka AG. Aldehyde **4t** was prepared according to the published procedure.[20] Reactions were monitored by analytical thin-layer chromatography (TLC) with the use of Merck silica gel 60 F_{254} glass plates. Chromatograms were visualized with UV light and were stained with a cerium reagent, followed by heating. Flash chromatography[21] was performed with silica gel 60 (230–400 Mesh) purchased from Macherey Nagel. NMR spectra were recorded on Bruker instruments (AC200 and AC300). Spectral data are reported in ppm relative to tetramethylsilane. IR spectra were recorded on a Perkin–Elmer 681. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. GC chromatograms were performed on a Dani GC3800 instrument that was equipped with a FID and a chiral capillary column. HPLC chromatograms were performed on a Waters instrument that was equipped with a diode array detector and a chiral column.

General procedure for the synthesis of ligand 5

Synthesis of sulfonamide 3 (procedure A): A solution of **1** (2.5 mmol) in dichloromethane (25 mL) was treated with polymer-bound "dimethylamino pyridine" (**7**; 208 mg, 0.42 mmol), methyl trimethylsilyl dimethylketene acetal (MTDA, **6**; 0.85 mL, 4.2 mmol) and **2** (2.1 mmol). The reaction mixture was shaken at room temperature for 3.0 h. Solid-phase bound (tris[2-aminoethyl]amine) (**8**; 1.62 g, 6.25 mmol) was then added and shaking was continued for 3.0 h. The resin was drained and washed with dichloromethane (4 × 20 mL). The combined filtrates were washed with 5% citric acid, and then evaporated under reduced pressure to give sulfonamide **3** (1.80 mmol; average yield 86%).

Synthesis of sulfonamide 3 (procedure B): A solution of **1** (2.5 mmol) in dichloromethane (25 mL) was treated with **7** (61 mg, 0.5 mmol), **6** (1.01 mL, 5.0 mmol) and **2** (3.0 mmol). The reaction mixture was stirred at room temperature for 3.0 h. The organic phase was washed with 5% citric acid, and then evaporated under reduced pressure to give sulfonamide **3** (2.2 mmol; average yield 88%).

Synthesis of Schiff base 5: Each crude sulfonamide **3** was split into five portions (approx. 0.36 mmol each). Each portion was treated with 25% (v/v) trifluoroacetic acid in dichloromethane (3 mL) and stirred at room temperature for 30 min. Volatiles were removed under reduced pressure, and the residues were dissolved in methanol (4 mL). Polymer-bound **7** (540 mg, 1.08 mmol) was then added to each residue, and the suspensions were shaken for 5 min. Compound **4** (0.32 mmol) was then added and the suspensions were shaken for further 24 h. The resins were drained and washed with dichloromethane (4 × 4 mL), and the combined filtrates were then evaporated under reduced pressure. The crude residues were dissolved in dichloromethane (10 mL), washed with 5% citric acid, followed by separation of the organic phases and evaporation under reduced pressure to give Shiff base **5** (0.28 mmol; average yield 87%). The purity of ligand **5** (≥95%) was monitored by ^1H NMR analysis.

Table 5. Conjugate addition of Et_2Zn to benzalacetone **16** and chalcone **17** CuOTf (0.025 equiv); ligand **5** (0.0275 equiv); Et_2Zn (2.2 equiv); toluene; +10 °C.

Entry	Ligand	R^1	R^2	R^3	Product	Yield [%]	% *ee*
1	**5cht**	*i*Bu	(*S*)-CH(Me)Cy	3-Ph	**18** (R = Me)	55	50[a]
2	**5ejq**	*t*Bu	$CHPh_2$	3,5-tBu_2	**18** (R = Me)	55	45[a]
3	**5ehq**	*t*Bu	(*S*)-CH(Me)Cy	3,5-tBu_2	**18** (R = Me)	48	43[a]
4	**5ejt**	*t*Bu	$CHPh_2$	3-Ph	**18** (R = Me)	45	22[a]
5	**5ehr**	*t*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	**18** (R = Me)	55	18[a]
6	**5bhr**	*i*Pr	(*S*)-CH(Me)Cy	3,5-Cl_2	**18** (R = Me)	44	17[a]
7	**5cht**	*i*Bu	(*S*)-CH(Me)Cy	3-Ph	**19** (R = Ph)	14	34[b]
8	**5bhr**	*i*Pr	(*S*)-CH(Me)Cy	3,5-Cl_2	**19** (R = Ph)	13	23[b]
9[c]	**5bhr**	*i*Pr	(*S*)-CH(Me)Cy	3,5-Cl_2	**19** (R = Ph)	65	0[b]

[a] Enantiomeric excesses determined by chiral GC. [b] Enantiomeric excesses determined by chiral HPLC (Whelk-O1). [c] 1.5 equivalents of TMSCl added.

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General procedure for the screening of the library: In a flame-dried flask, under argon atmosphere, **5** (0.011 mmol) was dissolved in dry toluene (0.5 mL). $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) was added, and the resulting greenish solution was stirred at room temperature for 20 min. The reaction mixture was then cooled to $-20\,^{\circ}C$ and Et_2Zn (1.0 M solution in hexanes; 0.44 mL, 0.44 mmol) and a 1:1 mixture of **9** and **10** (10 and 11 μL, respectively, 0.1 mmol each, 0.2 mmol total) were added consecutively. The reaction mixture was stirred at $-20\,^{\circ}C$ for 5 h and was then quenched with saturated aqueous NH_4Cl (1 mL) and diluted with ethyl acetate (1 mL). The organic phase was separated and filtered through Celite. The crude reaction mixture (1 μL) was then injected into a GC instrument that was equipped with a chiral capillary column for *ee* determination [column: MEGADEX DACTBSβ, 25 m, film 0.25 μm; carrier: H_2 (70 kPa); injector: 200 °C; detector: 200 °C; oven temperature: 50 °C, 5 °C min^{-1} to 150 °C; t_R (**12**): 11.8 min (3*R* enantiomer) and 12.2 min (3*S* enantiomer); t_R (**13**): 12.4 min and 12.6 min; t_R (**9**): 14.4 min; t_R (**10**): 14.9 min].

Characterization of ligand 5bhr: ^1H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta =$ 0.60–1.70 (m, 11H; cyclohexyl), 0.89 (d, $J = 6.90$ Hz, 3H; CH_3), 0.92 (d, $J = 7.00$ Hz, 3H; CH_3), 1.07 (d, $J = 6.70$ Hz, 3H; CH_3), 1.88 (m, 1H; C*H*(CH_3)$_2$), 3.10–3.26 (m, 3H; C*H*$_2$SO$_2$, C*H*(CH_3)Cy), 3.61 (m, 1H; C*H*-*i*Pr), 3.84 (d, $J = 8.90$ Hz, 1H; NH), 7.16 (d, $J = 2.50$ Hz, 1H; aromatic-H), 7.36 (d, $J = 2.50$ Hz, 1H; aromatic-H), 8.26 (s, 1H; CH=N); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 17.5$, 19.0, 19.2, 26.0, 26.2, 28.6, 28.8, 33.3, 43.6, 54.6, 57.1, 69.9, 119.3, 122.6, 122.9, 129.6, 132.4, 156.3, 165.0; IR (film): $\tilde{\nu} = 750$ (S–N), 1140, 1210, 1310 (SO_2), 1450 (CH_2, CH_3), 1630 (C=N), 2860–2960 (CH), 3280 cm^{-1} (NH); $[\alpha]_D = +67.0$ ($c = 1$ in $CHCl_3$); elemental analysis calcd (%) for $C_{20}H_{29}Cl_2N_2O_3S$ (448.4): C 53.57, H 6.47, N 6.25; found C 53.49, H 6.53, N 6.21.

Characterization of ligand 5chq: ^1H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta =$ 0.50–1.70 (m, 14H; cyclohexyl, C*H*$_2$-C*H*(CH_3)$_2$), 0.81 (d, $J = 5.9$ Hz, 3H; CH_3), 0.82 (d, $J = 6.0$ Hz, 3H; CH_3), 1.03 (d, $J = 6.8$ Hz, 3H; CH_3), 1.20 (s, 9H; *t*Bu), 1.33 (s, 9H; *t*Bu), 3.10–3.30 (m, 3H; C*H*$_2$SO$_2$, C*H*(CH_3)Cy), 3.50 (d, $J = 7.8$ Hz, 1H; NH), 3.78 (m, 1H; CH–N), 7.01 (d, $J = 2.4$ Hz, 1H; aromatic), 7.30 (d, $J = 2.4$ Hz, 1H; aromatic), 8.33 (s, 1H; CH=N); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 18.6$, 21.3, 23.2, 24.1, 25.9, 26.2, 28.4, 28.6, 29.4, 29.6, 31.4, 43.6, 45.1, 54.5, 59.4, 63.8, 117.4, 126.4, 127.6, 136.6, 140.5, 157.8, 162.3; IR (film): $\tilde{\nu} = 730$ (S–N), 1140, 1310 (SO_2), 1450 (CH_2, CH_3), 1620 (C=N), 2860–2960 (CH), 3280 cm^{-1} (NH); $[\alpha]_D = +18.0$ ($c = 1$ in $CHCl_3$); elemental analysis calcd (%) for $C_{29}H_{50}N_2O_3S$ (506.7): C 68.77, H 9.88, N 5.53; found C 68.69, H 9.92, N 5.49.

Characterization of ligand 5cht: ^1H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta =$ 0.50–1.70 (m, 14H; cyclohexyl, C*H*$_2$-C*H*(CH_3)$_2$), 0.81 (d, $J = 5.9$ Hz, 3H; CH_3), 0.82 (d, $J = 6.0$ Hz, 3H; CH_3), 1.03 (d, $J = 6.8$ Hz, 3H; CH_3), 3.10–3.30 (m, 3H; C*H*$_2$SO$_2$, C*H*(CH_3)Cy), 3.80 (d, $J = 7.8$ Hz, 1H; NH), 3.78 (m, 1H; CH-N), 7.01 (t, $J = 12.4$ Hz, 1H; aromatic), 7.25–7.68 (m, 7H; aromatic), 8.53 (s, 1H; CH=N); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 19.0$, 21.0, 23.3, 24.2, 26.0, 28.6, 43.6, 44.9, 54.6, 59.5, 63.3, 118.5, 118.9, 127.1, 128.1, 129.2, 129.8, 131.3, 133.7, 137.6, 158.2, 166.3; IR (nujol): $\tilde{\nu} = 758$ (S–N), 1136, 1310 (SO_2), 1632 (C=N), 3270 cm^{-1} (NH); $[\alpha]_D = +57.0$ ($c = 1$ in $CHCl_3$); elemental analysis calcd (%) for $C_{27}H_{38}N_2O_3S$ (470.6): C 68.91, H 8.14, N 5.95; found C 68.85, H 8.09, N 5.98.

Optimized reaction conditions

3-Ethylcyclohexanone (12)/5bhr: In a flame-dried flask, under argon atmosphere, **5bhr** (4.9 mg, 0.011 mmol) was dissolved in dry toluene (3.5 mL). $(CuOTf)_2 \cdot C_6H_6$ (2.5 mg, 0.005 mmol) was added, and the resulting yellow solution was stirred at room temperature for 20 min. The reaction mixture was then cooled to $-20\,^{\circ}C$, and Et_2Zn (1.1 M solution in toluene, 0.8 mL, 0.88 mmol) and **9** (41 μL, 0.4 mmol) were added consecutively. The reaction mixture was stirred at $-20\,^{\circ}C$ for 5 h and then quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification by flash chromatography (eluent *n*-hexane/ethyl acetate 95:5) gave pure **12** (47 mg) in 93% yield. Enantiomeric excess = 90% by chiral GC analysis [column: MEGADEX DACTBSβ, 25 m, film 0.25 μm; carrier: H_2 70 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 50 °C, 5 °C min^{-1} to 150 °C; t_R(**12**): 11.8 min (3*R* enantiomer, 5%) and 12.2 min (3*S* enantiomer, 95%)].

3-Ethylcycloheptanone (13)/5bhr: In a flame-dried flask, under argon atmosphere, **5bhr** (4.9 mg, 0.011 mmol) was dissolved in dry toluene (3.5 mL). $(CuOTf)_2 \cdot C_6H_6$ (2.5 mg; 0.005 mmol) was added, and the resulting yellow solution was stirred at room temperature for 20 min. The reaction mixture was then cooled to $-20\,^{\circ}C$, and Et_2Zn (1.0 M solution in toluene, 0.8 mL, 0.88 mmol) and **10** (45 μL, 0.4 mmol) were added consecutively. The reaction mixture was stirred at $-20\,^{\circ}C$ for 5 h and then quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification by flash chromatography (eluent *n*-hexane/ethyl acetate 95:5) gave pure **13** (53 mg) in 95% yield. Enantiomeric excess = 91% by chiral GC analysis [column: MEGADEX DACTBSβ, 25 m, film 0.25 μm; carrier: H_2 70 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 50 °C, 5 °C min^{-1} to 150 °C; t_R(**13**): 12.4 min (major enantiomer, 95.5%) and 12.6 min (minor enantiomer, 4.5%)].

3-Methylcyclohexanone (15)/5bhr: In a flame-dried flask, under argon atmosphere, **5bhr** (6.4 mg, 0.014 mmol,) was dissolved in dry toluene (3.5 mL). $Cu(OTf)_2$ (4.7 mg, 0.013 mmol) was added, and the resulting greenish solution was stirred at room temperature for 20 min. The reaction mixture was then cooled to $+10\,^{\circ}C$, and Me_2Zn (2.0 M solution in toluene, 0.57 mL, 1.14 mmol) and **9** (50 μL, 0.52 mmol) were added consecutively. The reaction mixture was stirred at $+10\,^{\circ}C$ for 24 h and then quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification by flash chromatography (eluent *n*-hexane/ethyl acetate 8:2) gave pure **15** (45 mg) in 78% yield. Enantiomeric excess = 79% by chiral GC analysis [column: MEGADEX DMEPEβ, 25 m, film 0.25 μm; carrier: H_2 70 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 70 °C, 1 °C min^{-1} to 200 °C; t_R(**15**): 13.4 min (10.5%) and 13.6 min (89.5%)].

3-Ethylcyclopentanone (14)/5chq: In a flame-dried flask, under argon atmosphere, **5chq** (5.6 mg, 0.011 mmol) was dissolved in dry toluene (3.5 mL). $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) was added, and the resulting greenish solution was stirred at room temperature for 20 min. The reaction mixture was then cooled to 0 °C, and Et_2Zn (1.0 M solution in hexanes, 0.88 mL, 0.88 mmol) and **11** (34 μL, 0.4 mmol) were added consecutively. The reaction mixture was stirred at 0 °C for 5 h and then quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4, and the solvent evaporated by distillation at ambient pressure. Purification by flash chromatography (eluent *n*-pentane/diethyl ether 8:2) gave pure **14** (11 mg) in 25% yield. Enantiomeric excess = 80% by chiral GC analysis [column: MEGADEX DACTBSβ, 25 m, film 0.25 μm; carrier: H_2 70 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 50 °C, 1.0 °C min^{-1} to 150 °C; t_R(**14**): 22.9 min (3*S* enantiomer, 90%) and 23.7 min (3*R* enantiomer, 10%)].

4-Phenylhexan-2-one (18)/5cht. In a flame-dried flask, under argon atmosphere, **5cht** (6.6 mg, 0.014 mmol) was dissolved in dry toluene (2.5 mL). $(CuOTf)_2 \cdot C_6H_6$ (3.1 mg, 0.0062 mmol) was added, and the resulting yellow solution was stirred at ambient temperature for 1 h. The reaction mixture was then cooled to $+10\,^{\circ}C$, and Et_2Zn (1.1 M solution in toluene, 1.0 mL, 1.1 mmol) and **16** (73.1 mg, 0.5 mmol) were added consecutively. The reaction mixture was stirred for 20 h and quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4, and the solvent evaporated under reduced pressure. Purification by flash chromatography (eluent *n*-hexane/ethyl acetate 9:1) gave pure **18** (48 mg) in 55% yield. Enantiomeric excess = 50% by chiral GC analysis [column: MEGADEX DMEPEβ, 25 m, film 0.25 μm; carrier: H_2 101 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 100 °C, 1.5 °C min^{-1} to 200 °C; t_R(**18**): 14.4 min (25%) and 14.7 min (75%)].

1,3-Diphenylpentan-1-one (19)/5cht. In a flame-dried flask, under argon atmosphere, **5cht** (6.3 mg, 0.014 mmol) was dissolved in dry toluene (2.5 mL). $(CuOTf)_2 \cdot C_6H_6$ (3.1 mg, 0.0062 mmol) was added, and the resulting yellow solution was stirred at ambient temperature for 1 h. The reaction mixture was then cooled to $-20\,^{\circ}C$, and Et_2Zn (1.1 M solution in toluene, 1.0 mL, 1.1 mmol) and **17** (104 mg, 0.5 mmol) were added consecutively. The reaction mixture was stirred for 20 h and quenched with saturated aqueous NH_4Cl (1 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4, and the solvent evaporated under reduced pressure. Purification by flash chromatography (eluent *n*-hexane/ethyl acetate 95:5) gave pure **19** (16 mg) in 14% yield. Enantiomeric excess = 34% by chiral HPLC analysis: [Lichrocart 250–4 [(*R*,*R*) Whelk 01]; gradient: *n*-hexane to 20% *i*-PrOH in *n*-hexane in 40 min. UV diode array detector (254 nm); t_R(**19**): 9.5 min (33%), 10.5 min (67%)].

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[1] a) "Conjugate Addition Reactions in Organic Synthesis": P. Perlmutter, *Tetrahedron Organic Chemistry Series, Vol. 9* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1992**; b) Y. Yamamoto, Methoden Org. Chem. (*Houben–Weyl*) *4th ed. 1952–*, Vol. E21b/4, **1995**, Chapter 1.5.2.1.

[2] B. H. Lipshutz, *Organometallics in Synthesis* (Ed.: M. Schlosser), Wiley, Chichester, **1994**, Chapter 4, pp. 283–382.

[3] a) A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479–4491; b) C. L. Gibson, *Tetrahedron: Asymmetry* **1996**, *7*, 3357–3358; c) A. H. M. de Vries, R. Imbos, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 1467–1473; d) A. H. M. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, 8, 1377–1378; e) M. Alami, S. Marquais, G. Cahiez, *Org. Synth.* **1993**, *72*, 135–146.

[4] a) J. Westermann, K. Nickisch, *Angew. Chem.* **1993**, *105*, 1429–1431; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1368–1370; b) J. Kabbara, S. Flemming, K. Nickisch, H. Neh, *Synlett* **1994**, 679–680; c) S. M. W. Bennett, S. M. Brown, J. P. Muxworthy, S. Woodward, *Tetrahedron Lett.* **1999**, *40*, 1767–1770; d) A. Alexakis, J. Vastra, P. Mangeney *Tetrahedron Lett.* **1997**, *38*, 7745–7748; e) J. F. G. A. Jansen, B. L. Feringa, *J. Org. Chem.* **1990**, *55*, 4168–4175.

[5] a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806; b) N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204; c) B. L. Feringa, A. H. M. de Vries, *Advances in Catalytic Processes, Vol. 1* (Ed.: M. P. Doyle), JAI, Greenwich, Connecticut **1995**, pp. 151–192; d) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061.

[6] Although the mechanistic path for this reaction has not yet been completely clarified, it is likely that mixed (Cu–Zn) organometallic species are involved in the catalytic step. For a brief review, see: a) N. Krause, *Angew. Chem.* **1998**, *110*, 295–297; *Angew. Chem. Int. Ed.* **1998**, *37*, 283–285; b) L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, *Tetrahedron*, **2000**, *56*, 2865–2878, and references therein; c) A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, F. Mazé, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011–4027, and references therein; d) O. Pamies, G. Net, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **1999**, *10*, 2007–2014; e) M. Yan, A. S. C. Chan, *Tetrahedron Lett.* **1999**, *40*, 6645–6648; f) I. H. Escher, A. Pfalz, *Tetrahedron*, **2000**, *56*, 2879–2888, and references therein; g) Y. Nakagawa, K. Matsumoto, K. Tomioka, *Tetrahedron* **2000**, *56*, 2857–2863, and references therein; h) G. Delapierre, T. Constantieux, J. M. Brunel, G. Buono *Eur. J. Org. Chem.* **2000**, 2507–2511; i) X. Hu, H. Chen, X. Zhang, *Angew. Chem.* **1999**, *111*, 3720–3723; *Angew. Chem. Int. Ed.* **1999**, *38*, 3518–3521.

[7] a) M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* **1996**, *37*, 5141–5144; b) V. Wendisch, N. Sewald, *Tetrahedron: Asymmetry* **1997**, *8*, 1253–1257.

[8] For reviews on the combinatorial development of new catalysts see: a) C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann./Recl.* **1997**, 637–647; b) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885–1889; c) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg *Angew. Chem.* **1999**, *111*, 2648–2689; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494–2532, and references therein.

[9] a) C. Gennari, S. Ceccarelli, U. Piarulli, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Org. Chem.* **1998**, *63*, 5312–5313; b) G. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712–7713; c) S. R. Gilbertson, X. Wang, *Tetrahedron* **1999**, *55*, 11609–11618; d) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707; e) B. M. Francis, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 987–991; *Angew. Chem. Int. Ed.* **1999**, *38*, 937–941; f) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281; g) A. M. Porte, J. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **1998**, *120*, 9180–9187; h) M. T. Reetz, K. M. Kühling, A. Deege, H. Hinrichs, D. Belder, *Angew. Chem.* **2000**, *112*, 4049–4052; *Angew. Chem. Int. Ed.* **2000**, *39*, 3891–3893; i) M. T. Reetz, K.-E. Jaeger, *Chem. Eur. J.* **2000**, *6*, 407–412; j) M. T. Reetz, M. H. Becker, H.-W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872–1875; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758–1761; k) K. Mikami, R. Angelaud, K. Ding, A. Ishii, *Chem. Eur. J.* **2001**, *7*, 730–737; for the screening of a pooled stereoselective polymerization catalyst library, see: l) J. Tian, G. W. Coates, *Angew. Chem.* **2000**, *112*, 3772–3775; *Angew. Chem. Int. Ed.* **2000**, *39*, 3626–3629.

[10] a) I. Chataigner, C. Gennari, U. Piarulli, S. Ceccarelli, *Angew. Chem.* **2000**, *112*, 953–956; *Angew. Chem. Int. Ed.* **2000**, *39*, 916–918; b) S. Ongeri, U. Piarulli, R. F. W. Jackson, C. Gennari, *Eur. J. Org. Chem.*, in press.

[11] a) M. Gude, U. Piarulli, D. Potenza, B. Salom, C. Gennari, *Tetrahedron Lett.* **1996**, *37*, 8589–8592; b) C. Gennari, M. Gude, D. Potenza, U. Piarulli, *Chem. Eur. J.* **1998**, *4*, 1924–1931.

[12] a) R. M. Lawrence, S. A. Biller, O. M. Fryszman, M. A. Poss, *Synthesis* **1997**, 553–558; b) D. L. Flynn, J. Z. Crich, R. V. Devraj, S. L. Hockerman, J. J. Parlow, M. S. South, S. Woodard, *J. Am. Chem. Soc.* **1997**, *119*, 4874–4881; c) R. J. Booth, J. C. Hodges, *J. Am. Chem. Soc.* **1997**, *119*, 4882–4886; d) J. J. Parlow, D. A. Mischke, S. S. Woodard, *J. Org. Chem.*, **1997**, *62*, 5908–5919; e) J. J. Parlow, D. L. Flynn, *Tetrahedron* **1998**, *54*, 4013–4031.

[13] Polymer-bound "4-dimethylaminopyridine" is commercially available from the Aldrich Chemical Company.

[14] The absolute configuration shown in Scheme 2 for **12** (3*S*) was determined by ^{13}C NMR spectroscopy after derivatization with (1*R*,2*R*)-1,2-diphenylethylenediamine, according to: a) A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2431–2434; the absolute configuration of **13** is unknown. The absolute configuration of **14** (3*S*) was determined by optical rotation, see: b) G. H. Posner, M. Hulce, *Tetrahedron Lett.* **1984**, *25*, 379–382; the absolute configuration for **15** was not determined.

[15] X. Gao, H. B. Kagan, *Chirality* **1998**, *10*, 120–124.

[16] One of the referees pointed out that a "positional scanning" approach would have been highly productive here. For instance, starting with ligand **5dfp** (28% *ee*), a positional scan would have led to **5dhp** (44% *ee*), then to **5dhq** (65% *ee*), and finally **5ehq** (80% *ee*); this is comparable to the best ligand **5bhr** (82% *ee*). For the positional scanning approach in the development of new catalysts, see: a) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed.* **1996**, *35*, 1668–1671; b) Y. Hoshino, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 10452–10453.

[17] A. Alexakis, C. Benhaïm, X. Fournioux, A. van den Heuvel, J. Levêque, S. March, S. Rosset, *Synlett* **1999**, 1811–1813.

[18] E. Keller, J Maurer, R. Naasz, T. Schader, A. Meetsma, B. L. Feringa, *Tetrahedron: Asymmetry* **1998**, *9*, 2409–2413.

[19] a) S. M. W. Bennett, S. M. Brown, A. Cunningham, M. R. Dennis, J. P. Muxworthy, M. A. Oakley, S. Woodward, *Tetrahedron*, **2000**, *56*, 2847–2855, and references therein; b) Y. Takaya, M. Ogasawara, T. Hayashi, *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.

[20] a) G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Sartori, G. Terenghi, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1862–1865; b) N. A. Bumagin, V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437–14450.

[21] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

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