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

Isabelle Chataigner, Cesare Gennari,* Umberto Piarulli,* and Simona Ceccarelli

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] A number of chiral stoichiometric reagents have been described during the last few years which allow enantioselective additions,[2] while the development of chiral catalysts has been comparably slower. A prominent position in this rapidly expanding field is occupied by the copper-catalyzed, chiral-ligand-accelerated, 1,4-addition of organozinc reagents.[3] In particular, chiral phosphoramidites,[3b] phosphites,[3c–f] and aminophosphanes[3g] were used as ligands in the addition to cyclic enones with very good enantioselectivities (up to 98% *ee*).[3b] On the other hand, chiral sulfonamides, which have proved effective in various catalytic asymmetric processes, were reported to catalyze the conjugate addition of organozinc reagents to cyclic enones[4a] only with marginal enantioselectivity (up to 31% *ee*).[4b]

We have developed a new family of chiral Schiff base ligands of general structure **5**, 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. Ligands **5** were easily obtained (Scheme 1) by condensation of salicylaldehydes with enantiomerically pure β-amino sulfonamides. Sulfonamides **3** were in turn synthesized by coupling different primary amines with sulfonyl chlorides **1**, prepared in high yields from L-α-amino acids by a straightforward synthetic protocol.[5] At the beginning of this work, a few model ligands **5** were prepared and tested, which proved effective in accelerating the copper-catalyzed (5% $Cu(OTf)_2$; $Tf = F_3CSO_2$) conjugate addition of diethylzinc to

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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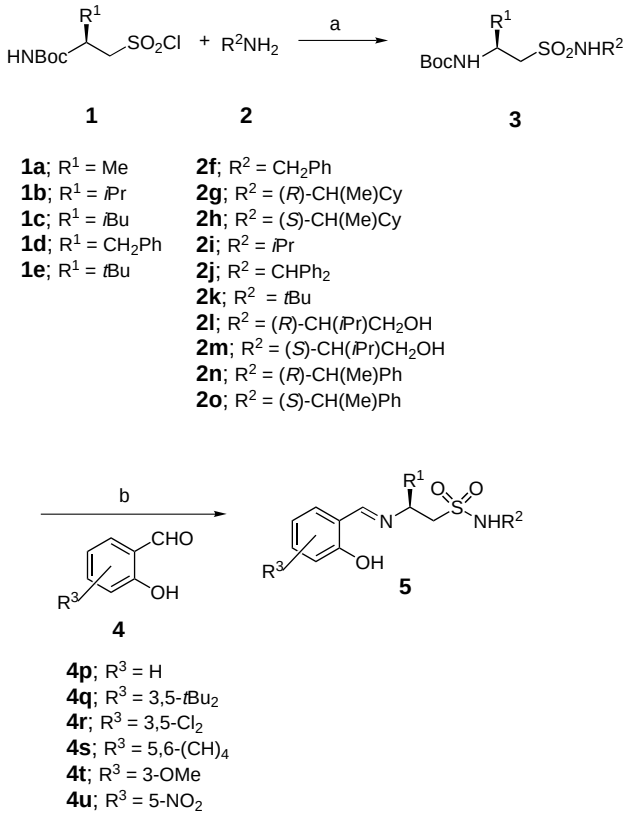
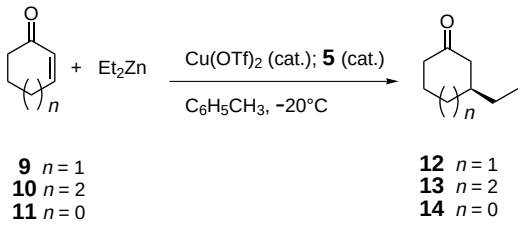


Scheme 1. Synthesis of the library of ligands **5**. a) **1** (1.2 equiv), **2** (1.0 equiv), **6** (2.0 equiv), **7** (0.2 equiv), CH_2Cl_2, 20 °C, 3 h; then **8** (3.0 equiv), 3 h, 86 %; b) **3** (1.0 equiv), TFA:CH_2Cl_2 (1:3), 20 °C, 30 min; evaporation; **4** (0.9 equiv), **7** (3.0 equiv), CH_3OH, 20 °C, 24 h, 88 %.

cyclohexenone (**9**). The enantiomeric excesses 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** ($R^1 = CH_2Ph$, $R^2 = CH_2Ph$, $R^3 = 3,5\text{-}tBu_2$) (Scheme 2).[6] At this stage, we considered a combinatorial approach for tuning the ligand structure and improving the results,[7, 8] taking advantage of the ligand synthesis scheme, a sequence of coupling steps with different monomers (Scheme 1), which is well-suited for the generation of diversity.



Scheme 2. Enantioselective conjugate addition of Et_2Zn to enones **9**–**11** catalyzed by $Cu(OTf)_2$/**5**. Screening of the library of ligands **5**.

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 avoid chromatography.[8, 9] For the formation of sulfonamides **3** (Scheme 1), the reaction of excess sulfonyl chlorides **1** (1.2 equiv) with amines **2** (1.0 equiv) was run in dichloromethane in the presence of methyl trimethylsilyl dimethylketene acetal (MTDA, **6**) (2.0 equiv)[5] and a catalytic amount (0.2 equiv) of polymer-bound "4-dimethylaminopyridine"[10] (**7**) to catalyze the coupling reaction and scavenge the liberated HCl. Apart from the polymer, which is removed by filtration, the only by-products were trimethylsilyl chloride and methyl isobutyrate. These are volatile and are removed with the solvent. After all the amine had been consumed, the excess sulfonyl chloride was removed by reaction with solid-phase-bound [tris(2-aminoethyl)amine][9c] (**8**) (3.0 equiv) and subsequent filtration. The *tert*-butyloxycarbonyl (Boc) protecting group was then cleaved with 25 % CF_3CO_2H (TFA) in CH_2Cl_2, and the resulting amine trifluoroacetate salts (1.0 equiv) were treated in MeOH with aldehydes **4** (0.9 equiv) in the presence of **7**[10] (3.0 equiv) to yield the target Schiff bases **5** in 76 % overall yield (average); these were pure enough to be used in the ligand-catalyzed reactions.

A multisubstrate[8, 11] high-throughput screening of the library was realized by performing the conjugate addition reactions on an equimolar mixture of 2-cyclohexenone (**9**) and 2-cycloheptenone (**10**, each 0.1 mmol), using 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 5 h, and the crude reaction mixtures were directly analyzed for conversion and enantiomeric excess by gas chromatography using a chiral capillary column, under conditions where the four peaks of the two enantiomeric pairs show baseline separation (time for each analysis: 15 min).

In 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**–**u**) was built to study the role of R^2 and R^3 by maximizing their diversity. This first set of ligands was screened under the conditions described above, and the results revealed some interesting features. 1) Poor enantioselectivities (≤ 40 % *ee*) were obtained with amines **2k**–**m** (irrespective of the aldehyde), and with aldehydes **4t** and **4u** (irrespective of the amine). 2) Enantioselectivities with amines **2n** and **2o** were lower than those obtained with amines **2g** and **2h**. 3) The stereocenter bearing R^1 controls the absolute configuration of the reaction product, while the stereocenter on R^2 (when present) tunes the selectivity.

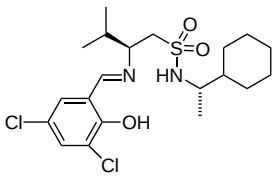
From this analysis a new library of 100 terms was designed, containing five sulfonyl chlorides (**1a**–**e**), five amines (**2f**–**j**), and four aldehydes (**4p**–**s**). From the screening of this library, **5bhr** ($R^1 = iPr$; $R^2 = (S)$-CH(Me)Cy; $R^3 = 3,5\text{-}Cl_2$) was identified as the best ligand for 2-cyclohexenone (82 % *ee*) and 2-cycloheptenone (81 % *ee*). 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" or a "positional scanning"[12] approach were followed. The data in Table 1 clearly show the importance of the mutual influences of the substituents R^1–R^3 in the fine tuning of the ligand structure.

Optimization of the reaction conditions was performed on the single enones **9**–**11** using the best ten ligands shown in Table 1, and taking into consideration the catalyst loading, the concentration, the reaction temperature, and the solvent.

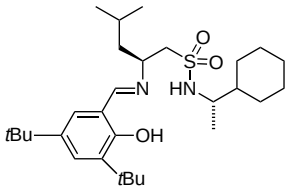
Table 1. High-throughput screening of the library of ligands **5**: best ten results.

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-tBu_2	80	79
3	**5biq**	*i*Pr	*i*Pr	3,5-tBu_2	76	72
4	**5ejq**	*t*Bu	$CHPh_2$	3,5-tBu_2	74	75
5	**5chr**	*i*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	73	74
6	**5chq**	*i*Bu	(*S*)-CH(Me)Cy	3,5-tBu_2	72	71
7	**5aiq**	Me	*i*Pr	3,5-tBu_2	69	76
8	**5ehs**	*t*Bu	(*S*)-CH(Me)Cy	$(CH)_4$	71	71
9	**5bjq**	*i*Pr	$CHPh_2$	3,5-tBu_2	70	69
10	**5ehr**	*t*Bu	(*S*)-CH(Me)Cy	3,5-Cl_2	71	67

Under the best conditions (2.75 mol% **5**, 2.5 mol% $Cu(OTf)_2$, toluene/hexane 80/20, 5 h), **5bhr** was identified as the best ligand for cyclohexenone **9** and cycloheptenone **10**



5bhr



5chq

(at −20 °C), giving **12** in 90% *ee* and **13** in 85% *ee*, with 100% conversion in both cases and 93–95% yield (isolated product). Compound **5chq** (Figure 1) was recognized as the best ligand for cyclopentenone (**11**) (at 0 °C), giving **14** in 80% *ee* albeit in a low yield (25%).

In conclusion, we have developed a parallel library of new Schiff base chiral ligands **5** and optimized their use in the enantioselective conjugate addition of Et_2Zn to cyclic enones by a high-throughput screening approach. Work is in progress to extend the scope of ligands **5** in other enantioselective reactions.

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The Melting Point Alternation in α,ω-Alkanediols and α,ω-Alkanediamines: Interplay between Hydrogen Bonding and Hydrophobic Interactions**

Venkat R. Thalladi, Roland Boese,* and Hans-Christoph Weiss

Dedicated to Professor Paul Rademacher on the occasion of his 60th birthday

Hydrogen bonding and hydrophobic interactions are ubiquitous in biological structures, be they lipids, proteins, or nucleic acids.[1] The interference between these two kinds of interactions in such natural systems is obvious, but hard to study and difficult to perceive owing to their inherent complexity. An understanding of such interference has important implications in biological and material phenom-

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