Synthesis of Chiral Self-Assembling Monodentate Ligands for Combinatorial Homogeneous Catalysis Based on an A-T Base-Pair Model

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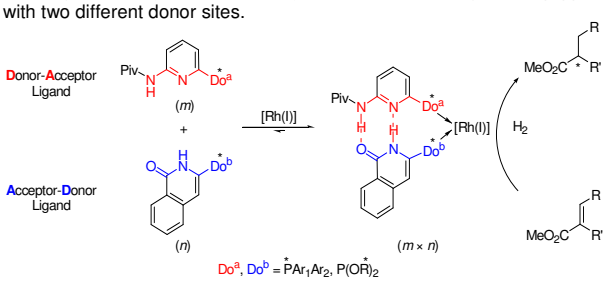
Introduction

Combinatorial methods have recently been introduced to homogeneous metal complex catalysis as a means to accelerate the catalyst discovery process.[1] Many elegant solutions for high throughput screening have been developed.[2] However, so far the combinatorial approach to catalyst discovery and optimization suffers from the limited access to structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, due to the complexity of bidentate ligand synthesis. In many cases, the covalent connection of two donor atoms to an appropriate ligand backbone necessitates a number of non-trivial synthetic operations, which often make the ligand more expensive than the noble metal source itself and thus render the ligand synthesis unsuited for automation. A particular challenge is the synthesis of nonsymmetric bidentate ligands equipped with two different donor sites.

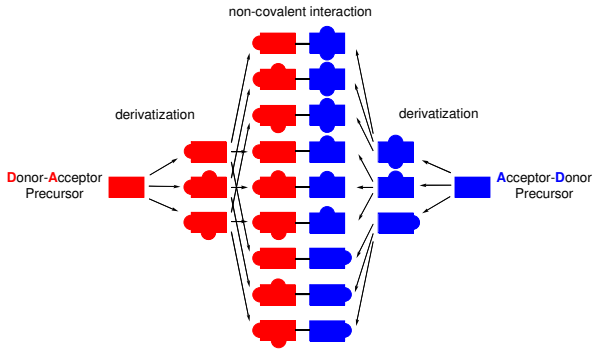


Scheme 1: Self-assembly of chiral monodentate to chiral bidentate ligands through complementary hydrogen-bonding for combinatorial asymmetric catalysis.

We recently introduced an alternative to the classical covalent bidentate ligand synthesis, which relies on self-assembly of monodentate ligands through complementary hydrogen-bonding to give defined heterodimeric bidentate ligands on the basis of an A-T base pair analogue, the aminopyridine-isoquinolone system (Scheme 1).[3,4] On the basis of this platform an achiral bidentate phosphine ligand library was generated and screened for regioselectivity control in the course of the rhodium-catalyzed hydroformylation of terminal alkenes.

Results

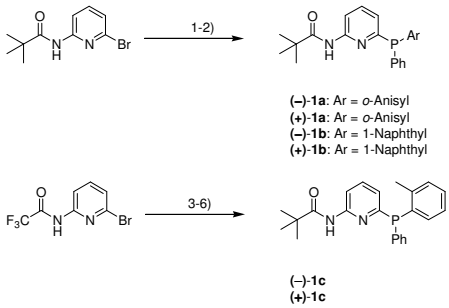
We herein report on the synthesis of a new library of **chiral** aminopyridine and **chiral** isoquinolone systems equipped with phosphine and phosphonite donors.[5]



Scheme 2: Rapid generation of ligand diversity based on a modular approach.

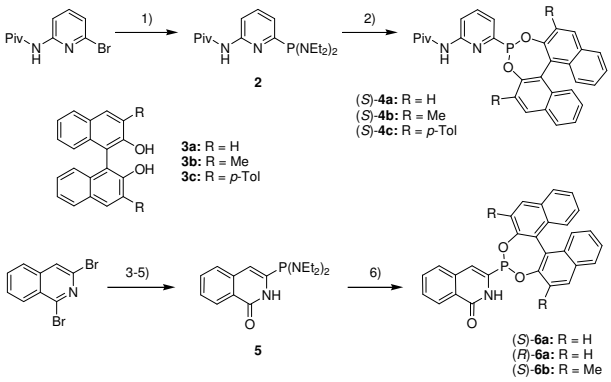
Following our concept, only a few highly convergent synthetic steps are necessary to create a large and structurally diverse bidentate ligand library (Scheme 2). Thanks to the non-covalent interaction of the two monodentate counterparts, even unsymmetrical chelating ligands are easily accessible.

Chiral monodentate phoshines **1a-c** were synthesized in racemic form and separated via chiral HPLC (Scheme 3). Up to 250 mg of each enantiomer could be obtained by this procedure.



Scheme 3: Preparation of chiral aminopyridinyl phosphines **1a-c**: 1) *n*BuLi (2 equiv), thf, –100 °C, then ClP(Ar)Ph, –100 °C to rt (50-52%); 2) Resolution via preparative HPLC (Chiralpak AD-H); 3) *n*BuLi (2 equiv), thf, –100 °C, then ClP(*o*-Tol)Ph, –100 °C to rt (41%); 4) MeOH/K_2CO_3, 60 °C, 4 h (88%); 5) Resolution via preparative HPLC (Chiralpak AD-H); 6) Pivaloylchloride, NEt_3, CH_2Cl_2, 0 °C to rt (89%).

Chiral monodentate aminopyridinyl phosphonites **4a-c** were obtained by reaction of the common precursor **2** with various enantiomerically pure BINOL-derivatives **3a-c**. In a similar manner, chiral isoquinolone-phosphonites **6a-b** were generated by substitution of intermediate **5** with **3a-b** (Scheme 4).



Scheme 4: Preparation of chiral monodentate aminopyridinyl phosphonites **4a-c** and isoquinolones **6a-b**: 1) *n*BuLi (2 equiv), thf, –100 °C, 90 min then $ClP(NEt_2)_2$ (1 equiv), –100 °C to rt (52%); 2) **3a-c** (1 equiv), toluene, 95 °C (quant.); 3) KO*t*Bu, $TMS(CH_2)_2OH$, 0 °C to rt, 90 min (96%); 4) *n*BuLi (1 equiv), thf, –100 °C, 90 min then $ClP(NEt_2)_2$ (1 equiv), –100 °C to rt (quant.); 5) TBAF (1.1 equiv), thf, 3 h (53%); 6) **3a** (1 equiv), toluene, reflux (80%); **3b** (0.8 equiv), *m*-xylene, reflux (70%).

Conclusion

In conclusion, by simply mixing equimolar amounts of aminopyridine- and isoquinolone-moieties in the presence of a metal source, unsymmetrical bidentate ligands can be generated through self-assembly *via* hydrogen-bonding without the need of a further synthetic step. Thus, a library of bidentate phosphine/phosphonites as well as diphosphonite ligands was obtained employing a few simple synthetic operations. The successful application of this library in the rhodium-catalyzed asymmetric hydrogenation is presented on the poster of M. Weis and C. Waloch entitled *Self-Assembly of Bidentate Ligands for Combinatorial Homogeneous Catalysis: Asymmetric Rhodium-Catalyzed Hydrogenation.*

References

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Acknowledgments

This work was supported by the Fonds der Chemischen Industrie, the DFG (International research training group GRK 1038: "Catalysts and catalytic reactions for organic synthesis"), the Alfried Krupp Award for young university teachers of the Krupp foundation (to BB) and BASF AG (high throughput screening). We thank G. Leonhardt-Lutterbeck for technical and G. Fehrenbach and Dr. R. Krieger for analytical assistance. MW and CW are grateful to the FCI for Kekulé fellowships.