Asymmetric Catalysis

Highly Rigid Diphosphane Ligands with a Large Dihedral Angle Based on a Chiral Spirobifluorene Backbone**

*Xu Cheng, Qi Zhang, Jian-Hua Xie, Li-Xin Wang, and Qi-Lin Zhou**

Asymmetric catalysis is undoubtedly a powerful, economically feasible tool for the synthesis of optically active organic compounds both in the laboratory and on a production scale. The design and synthesis of chiral phosphane ligands have played a significant role in the development of efficient, transition-metal-catalyzed asymmetric reactions.[1] In the last decades, a large number of chiral diphosphane ligands, such as diop,[2] binap,[3] josiphos,[4] duphos,[5] pennphos,[6] bisp,[7] p-phos,[8] and tangphos,[9] have been prepared and used in asymmetric catalysis with excellent enantioselectivities. Since there are no universal ligands and catalysts for asymmetric transformations, and most asymmetric reactions are substrate dependent, the search for chiral ligands that are more efficient in terms of high enantioselectivity and high turnover number (TON) remains one of the most important goals in asymmetric catalysis.

Although many structural features should be taken into consideration in the design of new chiral ligands, a certain degree of rigidity of the ligand and catalyst has been shown to be one of the most significant factors for obtaining high enantioselectivity.[10] For instance, in the "privileged" chiral catalysts containing a binap ligand, the highly rigid, atropisomeric, C_2-symmetric binaphthyl structure fixes the conformation of the seven-membered heterometallocyclic ring of its metal complexes and determines the orientations of the *P*-phenyl groups, which ultimately exert steric influence on the binding substrate.[11] As modifications of binap, a number of diphosphane ligands with a narrower dihedral angle have been designed, for example biphemp,[12] segphos,[13] tunaphos,[14] synphos,[15] and naphephos,[16] which have provided a better enantiocontrol in several well-established catalytic reactions.[17] In contrast, ligands with a wider dihedral angle than that of binap have rarely been explored.[18] Herein we report the synthesis of the new spirobifluorene-based diphosphane ligands (SFDPs) **1** with an extremely high rigidity and

[*] X. Cheng, Q. Zhang, Dr. J.-H. Xie, Prof. L.-X. Wang, Prof. Q.-L. Zhou
State Key Laboratory and
Institute of Elemento-organic Chemistry
Nankai University
Tianjin 300071 (China)
Fax: (+86) 222-350-6177
E-mail: qlzhou@nankai.edu.cn

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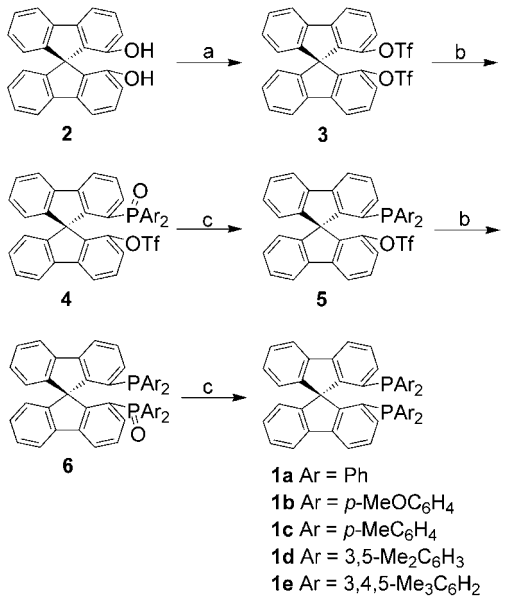
large dihedral angle based on a spirobifluorene backbone, the structural characterization of a Pd complex, and their application in ruthenium-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid, with high activity and excellent enantioselectivity.

While molecules with a 9,9′-spirobifluorene structure have been widely applied in molecular electronics,[19] light-emitting materials,[20] enantioselective molecular recognition,[21] and other areas,[22] the use of chiral ligands with a 9,9′-spirobifluorene backbone for asymmetric catalysis has not yet been reported. Recently, we reported the synthesis of optically pure 9,9′-spirobifluorene-1,1′-diol (SBFOL, **2**).[23] The diphosphane ligands **1** can be synthesized from SBFOL. Thus, (*R*)-(**2**) was first converted into the ditriflate (*R*)-**3** in quantitative yield. This compound was then directly subjected to diphosphanylation with diarylphosphanes in the presence of a nickel catalyst following the method of Cai et al.[24] for the synthesis of binap, although no coupling reaction occurred. We therefore attempted Hayashi's stepwise strategy[25] to introduce phosphanyl groups and found that it works nicely. Monophosphanylation of ditriflate (*R*)-**3** with diarylphosphane oxide in the presence of a Pd complex of dppb, followed by reduction with trichlorosilane, generated (*R*)-1-(diarylphosphanyl)-1′-trifluoromethanesulfonyloxy-9,9′-spirobifluorene ((*R*)-**5**). The second diarylphosphanyl group was introduced by repeating the above two-step protocol. The target diphosphanes (*R*)-**1** were obtained in 50–60% overall yield (Scheme 1). Following the same procedure, the diphosphanes (*S*)-**1** were also synthesized from (*S*)-9,9′-spirobifluorene-1,1′-diol.

A crystal of the complex [$PdCl_2$((*R*)-**1a**)] suitable for X-ray diffraction was grown and analyzed.[26] As can be seen from Figure 1, the complex has a square-planar configuration and the eight-membered heterometallocyclic ring formed by the chelate coordination of SFDP to palladium is highly rigid. The perpendicular spirobifluorene structure is distorted: in [$PdCl_2$((*R*)-**1a**)], the P-Pd-P bite angle is 96.7°, which is



Scheme 1. Synthesis of ligands **1**: a) Tf_2O, pyridine, CH_2Cl_2, −15 °C, 3 h; b) $Pd(OAc)_2$ (5 mol%), dppb (5 mol%), iPr_2EtN, Ar_2POH, DMSO, 100 °C, 1 h; c) $HSiCl_3$, iPr_2EtN, toluene, 110 °C, 8 h.

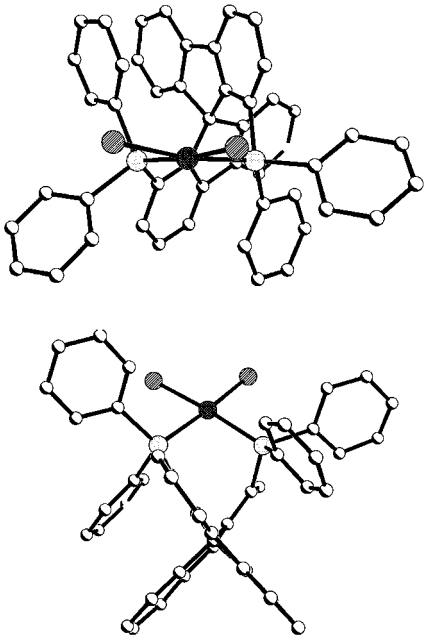
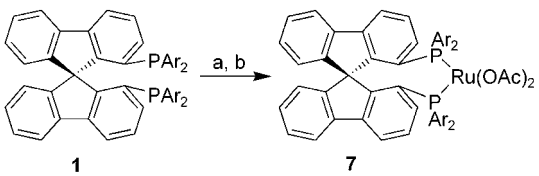


Figure 1. Crystal structure of [$PdCl_2$((*R*)-**1a**)]. Solvent and hydrogen atoms have been omitted for clarity.

greater than that of [$PdCl_2$((*R*)-binap)] (92.7°).[11c] In addition, one *P*-phenyl group on each phosphorus atom lies parallel to the fluorene ring of the bifluorene moiety; the distances between the centers of the *P*-phenyl rings and the benzo rings of bifluorene are 3.5 and 3.6 Å, respectively, thereby indicating π–π stacking interactions between the *P*-phenyl rings and the fluorenes, as also observed in [$PdCl_2$((*R*)-binap)].[11c] The Pd–P (2.28 and 2.30 Å) and Pd–Cl (2.33 and 2.36 Å) bond lengths in [$PdCl_2$((*R*)-**1a**)] are in the typical range for dichloropalladium complexes bearing diphosphane ligands.[27]

The efficiency of the chiral SFDP ligands in the enantioselective, ruthenium-catalyzed hydrogenation of α,β-unsaturated carboxylic acids, which is a very useful reaction in organic and industrial synthesis, was investigated.[28] The catalysts **7** were prepared as red powders from [{$RuCl_2(C_6H_6)$}$_2$] and **1** in DMF followed by the addition of NaOAc (Scheme 2).[29] The catalysts [$Ru(OAc)_2$((*R*)-**1**)] ((*R*)-**7**) show a single resonance signal in their ^{31}P NMR spectra ($\delta = 64$–67 ppm).

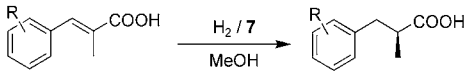
Although significant progress has been achieved in asymmetric hydrogenation of α-arylacrylic acid and other α,β-unsaturated carboxylic acids,[8,30] the asymmetric hydrogenation of cinnamic acid derivatives is still a challenge.[30c,31] The catalyst [$Ru(OAc)_2$((*R*)-**1a**)] ((*R*)-**7a**) was initially tested in the hydrogenation of α-methylcinnamic acid at a substrate-



Scheme 2. Preparation of catalysts [$Ru(OAc)_2$((*R*)-**1**)] ((*R*)-**7**)): a) [{$RuCl_2(C_6H_6)$}$_2$] (0.56 equiv.), DMF; b) NaOAc (10 equiv.), MeOH.

to-catalyst (S/C) ratio of 400 in MeOH under 6 atm of H_2 at room temperature over 48 h. The hydrogenation product α-methylhydrocinnamic acid was obtained in 93% yield with 60% *ee* (Table 1, entry 1). This result is better than that

Table 1: Asymmetric hydrogenation of α-methylcinnamic acid derivatives.[a]



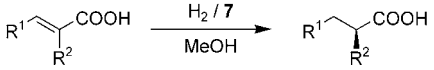
Entry	R	Cat.	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H	(*R*)-**7a**	48	93	60
2	H	(*R*)-**7b**	48	89	45
3	H	(*R*)-**7c**	30	91	70
4	H	(*R*)-**7d**	24	93	87
5	H	(*R*)-**7e**	18	91	94
6	*p*-Me	(*R*)-**7e**	22	93	90
7	*m*-Me	(*R*)-**7e**	20	93	97
8	*o*-Me	(*R*)-**7e**	22	91	95
9	*p*-OMe	(*R*)-**7e**	25	91	94
10	*m*-OMe	(*R*)-**7e**	20	92	94
11	*o*-OMe	(*R*)-**7e**	24	90	94
12	*p*-Cl	(*R*)-**7e**	10	91	94
13	*m*-Cl	(*R*)-**7e**	12	94	92
14	*o*-Cl	(*R*)-**7e**	9	90	93
15	*m*-Br	(*R*)-**7e**	12	90	95
16	*o*-Br	(*R*)-**7e**	12	93	95
17	*p*-CF_3	(*R*)-**7e**	9	90	92
18	*o*-CF_3	(*R*)-**7e**	8	94	92
19	*o*-NO_2	(*R*)-**7e**	30	93	92
20	2-naphth	(*R*)-**7e**	18	95	93

[a] Conditions: [substrate] = 0.25 mol L^{-1} in MeOH, S/C = 400, p_{H_2} = 6 atm, *T* = 25–28 °C. [b] Conversions were quantitative for all reactions. All hydrogenated products were fully characterized (see Supporting Information). [c] *ee* was determined by HPLC analysis of the respective anilide with a chiral column (see Supporting Information). The predominant configuration of α-methylhydrocinnamic acid is *S*. All other saturated acids have positive rotations.

obtained with [Ru(OAc)$_2$((*R*)-binap)] (48 h, 29% yield, 30% *ee*).[30c] A systematic investigation of the effect of the substituents in ligands **1** showed that the introduction of 3,4,5-trimethylphenyl groups in (*R*)-**1e** dramatically increased the activity and enantioselectivity of the catalyst (18 h, 94% *ee*; Table 1, entry 5). A variety of α-methylcinnamic acid derivatives were hydrogenated under these mild conditions using catalyst (*R*)-**7e** with excellent enantioselectivities. The results summarized in Table 1 represent the highest enantioselectivity yet achieved in the asymmetric hydrogenation of α-methylcinnamic acid.[30c,31]

The asymmetric hydrogenation of tiglic acid and its derivatives was also examined with catalyst **7**. The results are summarized in Table 2. In contrast to the hydrogenation of α-methylcinnamic acid, all catalysts **7** provided high enantioselectivities (Table 2, entries 1–5). It was found that the highly enantioselective hydrogenation can be performed even when the S/C ratio is increased to 10000 (Table 2, entry 7). Different tiglic acid derivatives can be hydrogenated with catalyst **7d** with excellent enantioselectivities (Table 2, entries 8–12). These results are comparable to, or better than, those obtained with [Ru(OAc)$_2$(binap)][30a] and other catalysts.[30c,32]

Table 2: Asymmetric hydrogenation of tiglic acid derivatives.[a]



Entry	R^1	R^2	Cat.	*t* [h]	Yield [%]	*ee* [%][b]
1	Me	Me	(*R*)-**7a**	16	92	96
2	Me	Me	(*R*)-**7b**	16	85	96
3	Me	Me	(*R*)-**7c**	16	91	94
4	Me	Me	(*R*)-**7d**	16	92	97
5	Me	Me	(*R*)-**7e**	12	85	97
6[c]	Me	Me	(*R*)-**7d**	30	90	98
7[d]	Me	Me	(*R*)-**7d**	100	94	98
8	Et	Me	(*R*)-**7d**	24	94	96
9	*n*Pr	Me	(*R*)-**7d**	30	91	96
10	*n*Pr	Et	(*R*)-**7d**	40	82	94
11	*n*Bu	Me	(*R*)-**7d**	35	92	96
12	*i*Bu	Me	(*R*)-**7d**	40	88	97

[a] Conditions: see footnote [a] in Table 1. [b] *ee* was determined by HPLC analysis of the respective anilide with a chiral column (AD-H); the predominant configuration is *S* for all products. [c] [substrate] = 0.625 mol L^{-1}, S/C = 1000. [d] [substrate] = 6.25 mol L^{-1}, S/C = 10000, 50 °C.

In conclusion, SFDP, a new type of highly rigid diphosphane ligands with a large dihedral angle, has been synthesized based on a chiral spirobifluorene backbone. Their ruthenium complexes are highly efficient catalysts for asymmetric hydrogenation of α,β-unsaturated carboxylic acids. The excellent activity and enantioselectivity of these ruthenium complexes in the hydrogenation of α-methylcinnamic acid derivatives and tiglic acid derivatives indicate that these highly rigid ligands might be more widely applicable in asymmetric catalytic reactions.

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