Axial 4,4′,6,6′-Tetrakis-trifluoromethyl-biphenyl-2,2′-diamine (TF-BIPHAM): Resolution and Applications in Asymmetric Hydrogenation
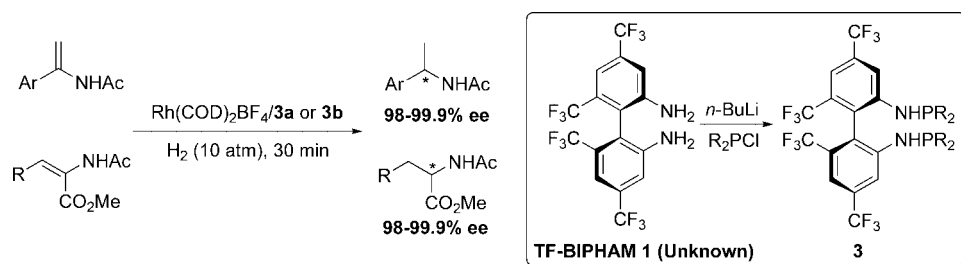
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ABSTRACT

The racemic TF-BIPHAM was resolved for the first time, and the effectiveness of the resolved diamine was demonstrated by highly enantioselective hydrogenation of α-aryl enamides and α-dehydroamino acid esters using readily accessible bis(aminophosphine) ligands.

Catalytic asymmetric reaction is one of the most powerful methods for the synthesis of enantiomerically enriched products, and ligand design based on a chiral backbone plays a crucial role in this area.[1] Among various applied chiral skeletons, atropisomeric biaryl backbones, most notably 1,1′-binaphthalene derivatives (e.g., BINOL, BINAP and BINAM), occupy an important position in asymmetric synthesis (Figure 1).[2] Inspired by the tremendous success of BINAP

in asymmetric catalysis,[3] some C_2-symmetric biphenyl diphosphines such as MeO-BIPHEP,[4] TunePhos,[5] SEGPhos,[6] and P-Phos[7] have been documented as efficient ligands in asymmetric hydrogenation. Compared to the binaphthalene counterpart, the steric and electronic properties of the atropisomeric biphenyl framework are more easily modified.[8] We are interested in the development of a new type of C_2-symmetric biphenyldiamine: the 4,4′,6,6′-Tetrakis-trifluoro-methyl-biphenyl-2,2′-diamine (abbreviated to TF-BIPHAM). Its precursor, dinitro compound, was reported early in 1949,[9] however, the racemic TF-BIPHAM was first utilized as an important intermediate for the synthesis of one less efficient chiral ligand BIFUP until 1991.[10] To the best of our

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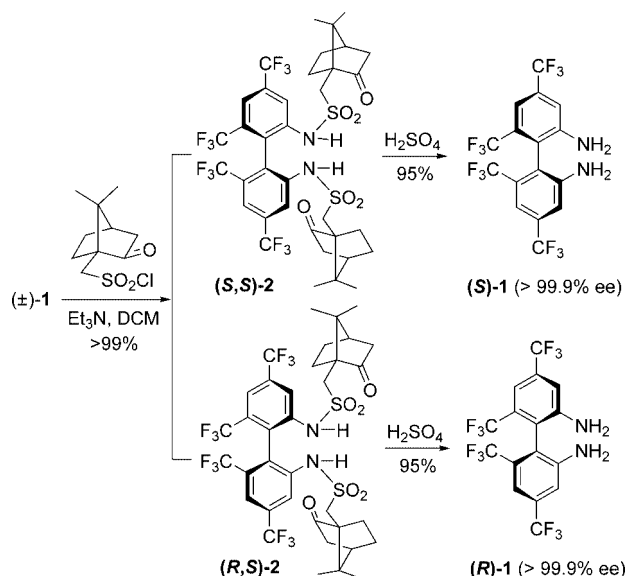(9) Bradsher, C. K.; Bond, J. B. *J. Am. Chem. Soc.* **1949**, *71*, 2659.
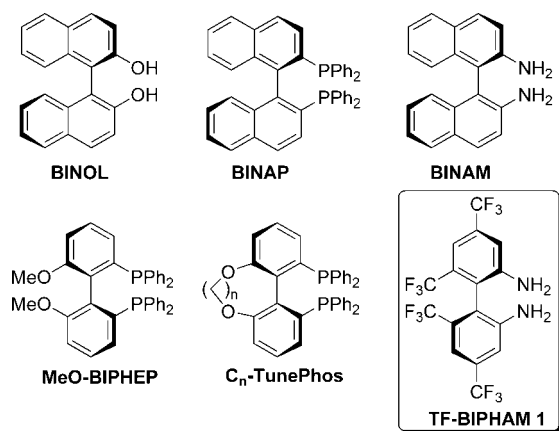
Figure 1. Some atropisomeric chiral biaryl ligands and TF-BIPHAM.

Scheme 1. Resolution of TF-BIPHAM

knowledge, the resolution and applications of this potential chiral backbone in asymmetric catalysis have not been reported so far.

Herein, we report the first resolution of racemic TF-BIPHAM, and the development of a class of efficient bis(aminophosphine) ligands using the resolved diamine. These bis(aminophosphine) ligands exhibit excellent to almost perfect enantioselectivity in Rh-catalyzed asymmetric hydrogenation of enamides and α-dehydroamino acid esters.[11]

The preparation of racemic TF-BIPHAM was carried out by following the reported method in >80% yield from the commercially available 2,4-bis(trifluoromethyl)-bromobenzene in 3 steps.[10,12] After several unsuccessful attempts to resolve the racemic TF-BIPHAM through inclusion crystallization,[13] we were able to obtain the two optical diamines through highly efficient chromatography resolution of the corresponding diastereomeric disulfonamide derived from inexpensive (1S)-camphor-10-sulfonyl chloride and then hydrolyzation of each pure diastereomer with sulfuric acid (Scheme 1).[14] The two disulfonamides of (±)-TF-BIPHAM showed unusually large separation factors on TLC plates, which allowed their separation by simple column chromatography. Removal of the (1S)-camphor-10-sulfonyl moieties

under mild condition furnished each enantiomer in high overall yield. The enantiomeric excess, determined by chiral HPLC (Chiralpak AS-H column, hexane/isopropanol 95:5, 1 mL/min), was found to be >99.9% ee in each case. The (S)-configuration of the (−)-enantiomer was determined by the X-ray analysis of the corresponding diastereomer (S,S)-2 (Figure 2).[15,16]
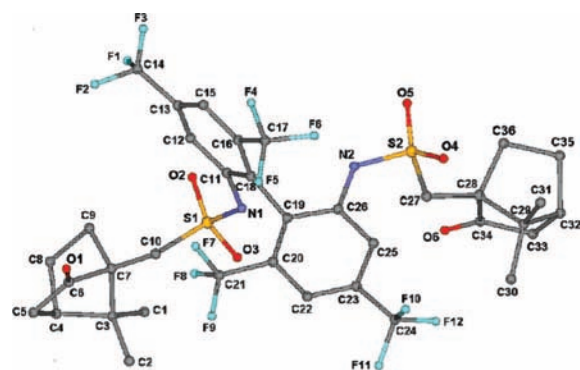
Figure 2. X-ray Crystal Structure of (S,S)-2.

With enantiopure **1** in hand, we extended its application to the synthesis of a new type of C_2-symmetric bis(aminophosphine) ligands **3**. As shown in Scheme 2, the chiral ligands **3** were conveniently obtained in good yields by lithiation of (S)-**1** with n-BuLi and then reaction with R2PCl. Ligands **3** are stable enough to be purified by column chromatography in air. The enhanced stability of the ligands could be possibly attributed to the four strong electron-withdrawing trifluoromethyl groups attached to the biphenyl backbone.

The catalytic performance of ligands **3** were initially tested in the Rh(I)-catalyzed hydrogenation of aryl enamide sub-

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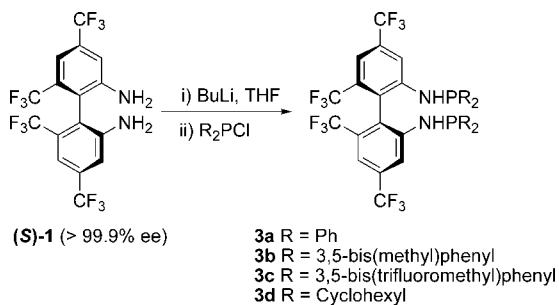
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Scheme 2. Synthesis of the C_2-Symmetric Bis(aminophosphine)s from the Resolved TF-BIPHAM

(S)-1 (> 99.9% ee)

3a R = Ph
3b R = 3,5-bis(methyl)phenyl
3c R = 3,5-bis(trifluoromethyl)phenyl
3d R = Cyclohexyl

strate **4a**.[11] As shown in Table 1, the catalytic activity of

Table 1. Screening Studies of Asymmetric Hydrogenation of Enamide **4a**[a]

entry[b]	ligand	solvent	temp (°C)	PH_2 (atm)	ee (%)[c,d]
1	3a	PhMe	rt	10	97.4
2[e]	3a	PhMe	rt	3	97.0
3[f]	3a	PhMe	rt	50	97.5
4	3b	PhMe	rt	10	97.9
5	3c	PhMe	rt	10	10.7
6	3d	PhMe	rt	10	5.8
7	3a	PhMe	5	10	**99.2**
8	3b	PhMe	5	10	**99.5**
9	3a	Acetone	5	10	98.7
10	3a	EtOAc	5	10	99.1
11	3a	DCM	5	10	97.3
12	3a	MeOH	5	10	97.0
13	3a	THF	5	10	97.5

[a] Unless otherwise noted, the reactions were carried out with a S/C = 200:1. [b] In all cases, full conversion was achieved. [c] Enantiomeric excesses were determined by GC using a Chiral Select 1000 capillary column. [d] Absolute configuration of the products was determined by comparing the GC retention times with the reported data in the literature. [e] Reaction time = 10 h. [f] Reaction time = 20 min.

ligands **3a** and **3b** was found to be superior to that of ligands **3c** and **3d** (Table 1, entries 1 and 4−6). These results demonstrated the importance of the steric and electronic effects of the ligands on the enantioselectivities: when the phenyl group on the phosphorus atom of ligand **3a** was replaced by more steric hindered but electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group, the enantioselectivity decreased significantly; ligand **3d** containing cyclohexyl group on the phosphorus atom, displayed a similarly negative effect on the enantioselectivity. The hydrogen pressure has influence only on the reaction rate not on the enantioselectivity (Table 1, entries 1−3). A preliminary screening of solvent effects showed that there was no significant difference among the tested solvents (Table 1, entries 7−13). Reducing the temperature to 5 °C in toluene led to complete reaction with >99% ee within 30 min (Table 1, entries 7 and 8).

Encouraged by these results, we then applied ligands **3a** and **3b** in the Rh(I)-catalyzed hydrogenation of other α-aryl enamides under the optimized conditions (Table 2). It appears

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of Enamides **4**[a]

entry	substrate	Ar	ee (%)[b,c]
1	4a	Ph	99.5 (99.2)
2	4b	m-Me-Ph	99.4 (99.3)
3	4c	p-Me-Ph	99.7 (99.1)
4	4d	m-Cl-Ph	99.2 (99.3)
5	4e	p-Cl-Ph	98.2 (97.8)
6	4f	m-Br-Ph	99.8 (99.2)
7	4g	p-Br-Ph	99.9 (99.6)
8	4h	m-MeO-Ph	99.6 (99.4)
9	4i	p-MeO-Ph	99.5 (99.0)
10	4j	o-F-Ph	97.6 (95.5)
11	4k	p-F-Ph	99.2 (99.0)
12	4l	p-CF$_3$−Ph	99.0 (99.3)
13	4m	2-naphtyl	99.3 (99.0)
14	4a	Ph	99.0

[a] In all cases, full conversion was achieved. [b] Enantiomeric excesses were determined by GC or HPLC. The absolute configuration of the products was determined by comparing the retention times with the reported data in the literature. [c] Data in parentheses was achieved by using **3a** as the chiral ligand. [d] S/C = 1000.
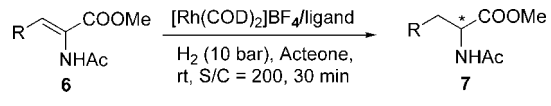
that the position and the electronic property of the substituents on the aromatic rings had a very limited effect on the enantioselectivities. In all cases, ligands **3a** and **3b** exhibited similar excellent enantioselectivities. Further optimization showed that high yield and enantioselectivity remained when the reaction was performed with as low as 0.1 mol% of catalyst loading. (Table 2, entry 14).

Remarkable enantioselectivity and catalytic activity were also observed in the Rh(I)-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters with ligand **3b**.[11] As shown in Table 3, a wide array of substituted phenylalanine derivatives were formed with excellent enantioselectivities regardless of the position and the electronic property of the substituents on the phenyl ring (Table 3, entries 2, 4−12). Hydrogenation of **6a** and **6k** with the reduced catalyst loading (0.1−0.02 mol%) still afforded the corresponding products in full conversion with 99% ee. (Table 3, entries 3 and 14).

(15) Crystal data for (S,S)-**2**: $C_{36}H_{36}F_{12}N_2O_6S_2$, $M_r = 884.79$, $T = 150$ K, Orthorhombic, space group $P2_12_12_1$, $a = 13.8439(5)$, $b = 14.6436(6)$, $c = 37.6480(14)$ Å, $V = 7632.2(5)$ Å^3, $Z = 8$, 13 657 unique reflections, final $R_1 = 0.0886$ and $wR_2 = 0.1961$ for 11 145 observed [$I > 2\sigma(I)$] reflections. Higher parameters R_1 and wR_2 may be ascribed to the poor data quality. CCDC 692522 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223−336−033; or deposit@ccdc.cam.ac.uk).

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Table 3. Rh-Catalyzed Asymmetric Hydrogenation of (Z)-Acetamido-3-arylacrylic Acid Methyl Esters[a]

entry	substrate	R	ligand	ee (%)[b]
1	**6a**	Ph	**3a**	97.4
2	**6a**	Ph	**3b**	99.0
3[c]	**6a**	Ph	**3b**	99.1
4	**6b**	o-Me-Ph	**3b**	99.0
5	**6c**	p-Me-Ph	**3b**	99.0
6	**6d**	o-Cl-Ph	**3b**	98.7
7	**6e**	m-Cl-Ph	**3b**	98.6
8	**6f**	p-Cl-Ph	**3b**	98.1
9	**6g**	o-MeO-Ph	**3b**	99.0
10	**6h**	m-MeO-Ph	**3b**	98.5
11	**6i**	p-MeO-Ph	**3b**	98.0
12	**6j**	p-F-Ph	**3b**	98.5
13	**6k**	H	**3b**	99.8
14	**6k**	H	**3b**	99.9

[a] In all cases, full conversion was achieved. [b] Enantiomeric excesses were determined by GC or HPLC. The absolute configuration of the products was determined by comparing the retention times with the reported data in the literature. [c] S/C = 1000, 12 h. [d] S/C = 5000, 12 h.

In comparison with the literature results achieved by similar bis(aminophosphine) ligands such as BDPAB,[17] H_8–BDPAB[18] derived from chiral 1,1′-binaphthyl-2,2′-diamine (BINAM), and MABP derived from chiral 6,6′-dimethyl-biphenyl-2,2′-diamine,[19] our catalyst system shows comparable reactivities but higher enantioselectivities.

In conclusion, the chiral TF-BIPHAM was resolved through a rapid and reliable procedure for the first time, which diversifies the family of chiral biphenyl backbones. The effectiveness of TF-BIPHAM was demonstrated by highly enantioselective hydrogenation of α-aryl enamides and α-dehydroamino acid esters using readily accessible bis(aminophosphine) ligands. Further application of the resolved chiral diamine in asymmetric catalysis is ongoing in our laboratory and will be reported in due course.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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