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

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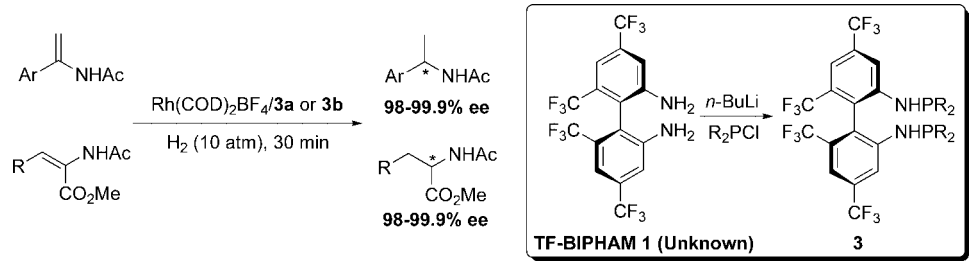
ABSTRACT



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-trifluoromethyl-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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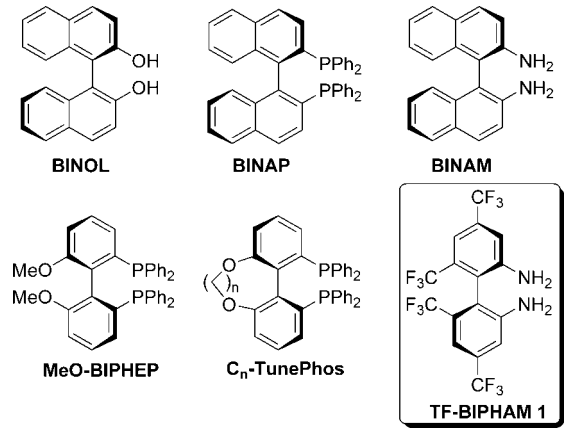


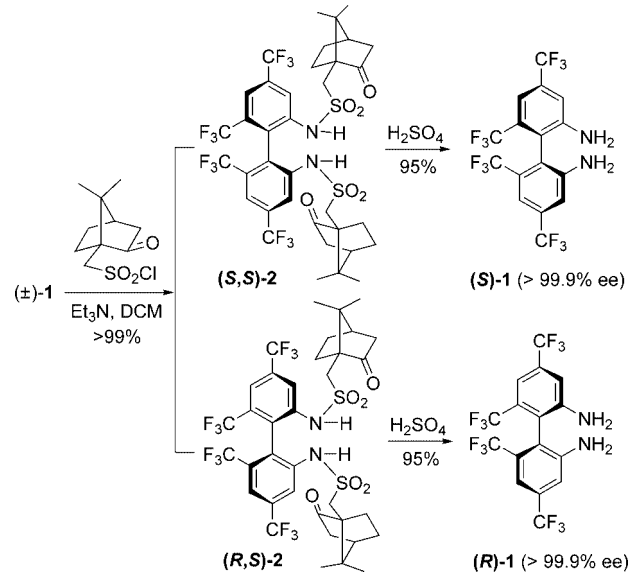
Figure 1. Some atropisomeric chiral biaryl ligands and TF-BIPHAM.

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 (1*S*)-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 (1*S*)-camphor-10-sulfonyl moieties

Scheme 1. Resolution of TF-BIPHAM



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]

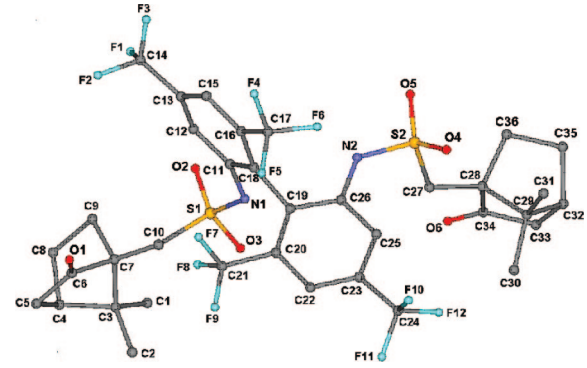


Figure 2. X-ray Crystal Structure of (*S*,*S*)-**2**.

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 R_2PCl. 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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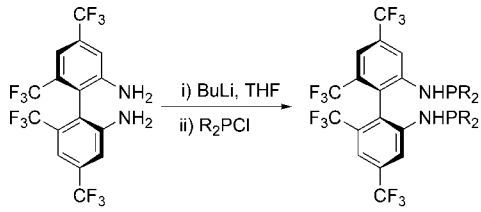
Scheme 2. Synthesis of the C_2-Symmetric Bis(aminophosphine)s from the Resolved TF-BIPHAM

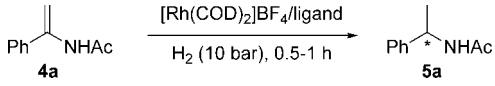


(*S*)-1 (> 99.9% ee)

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]



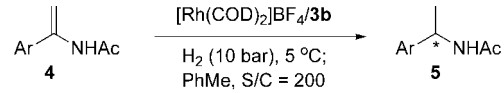
entry[b]	ligand	solvent	temp (°C)	PH_2 (atm)	ee (%)[c,d]
1	**3a**	PhMe	rt	10	97.4
2[e]	**3a**	PhMe	rt	3	97.0
3[f]	**3a**	PhMe	rt	50	97.5
4	**3b**	PhMe	rt	10	97.9
5	**3c**	PhMe	rt	10	10.7
6	**3d**	PhMe	rt	10	5.8
7	**3a**	PhMe	5	10	**99.2**
8	**3b**	PhMe	5	10	**99.5**
9	**3a**	Acetone	5	10	98.7
10	**3a**	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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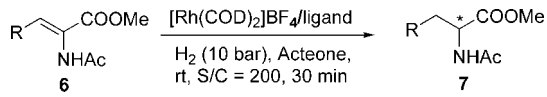
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-Acetamido-3-arylacrylic Acid Methyl Esters[a]



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.

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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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