Synthesis, Resolution, and Applications of 2,2′-Bis(diphenylphosphino)-3,3′-binaphtho[2,1-b]furan

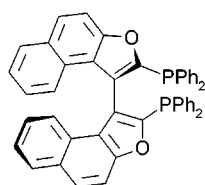**Neil G. Andersen, Masood Parvez,[†] and Brian A. Keay***

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ABSTRACT

1 BINAPFu

A short five-step synthesis of (±)-2,2′-bis(diphenylphosphino)-3,3′-binaphtho[2,1-b]furan (BINAPFu, 1) starting from 2-naphthoxyacetic acid is reported. The resolution of BINAPFu 1 was possible using our newly developed resolution procedure for phosphines wherein (1S)-camphorsulfonyl azide was used to prepare the bisphosphinimine of BINAPFu via the Staundinger reaction. BINAPFu consistently outperformed BINAP in an asymmetric Heck reaction between 2,3-dihydrofuran and phenyl triflate.

Optically active bidentate phosphine ligands have, in recent years, played a vital role in homogeneous transition metal catalyzed asymmetric synthesis,[1] thereby making the design and synthesis of novel chiral phosphine ligands an active area of research. Since the initial reports on the axially dissymmetric ligand BINAP **2** (Scheme 1),[2] a wide variety of new biaryl, bidentate ligands have appeared in the literature.[3] Moreover, many of these ligands have been applied to a variety transition metal catalyzed asymmetric
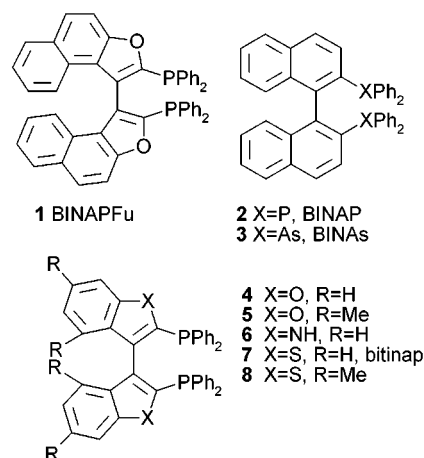
[†] To whom correspondence regarding crystallographic data should be addressed.

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Scheme 1

1 BINAPFu

2 X=P, BINAP
3 X=As, BINAs

4 X=O, R=H
5 X=O, R=Me
6 X=NH, R=H
**7** X=S, R=H, bitinap
8 X=S, R=Me

transformations with a remarkable degree of success. For example, superior catalytic activity and enantioselectivity have been observed in hydrogenations utilizing diphosphine ligands bearing aromatic rings with electron-donating methoxy and methyl substituents.[3g] As a result, the great majority of homochiral phosphine ligands reported to date are electron-rich with respect to triphenylphosphine.[3d] However, evidence has been reported to suggest that less electron rich phosphines are or would be advantageous for some transition metal mediated organic reactions. For example, Farina and co-workers reported significant rate accelerations for the Stille reaction when tri-2-furylphosphine (TFP) or triphenylarsine was employed as ligands.[4] Moreover, Shibasaki has reported superior results in a tandem Suzuki−Heck process when either TFP or triphenylarsine was utilized to complex palladium.[5] The later results subsequently lead to the development of 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (**3**, BINAs, Scheme 1) as an effective ligand for the asymmetric Heck reaction.[6] Finally, the oxidative addition of phenyl iodide has been studied with in situ generated Pd(0) complexes of triphenylphosphine and TFP showing that in DMF {Pd(dba)$_2$ + nTFP} is always more reactive than {Pd-(dba)$_2$ + nPPh$_3$} for $n \geq 2$.[7] These results in conjunction with our interests in the asymmetric palladium-catalyzed polyene cyclizations[8] led us to develop 2,2′-bis(diphenylphosphino)-3,3′-binaphtho[2,1-*b*]furan (**1**) (BINAPFu, Scheme 1) as a new bidentate phosphine ligand. We herein report a short, highly efficient synthesis of the title compound, its resolution using (*S*)-camphorsulfonyl azide, and the use of BINAPFu **1** in the Heck arylation of 2,3-dihdrofuran.

Our design of BINAPFu **1** was based on previous studies reported with other 2,2′-bis(diphenylphosphino)-3,3′-biheteroaryl systems **4**−**8** (Scheme 1). In 1996, bisbenzofuran **4** was prepared and found to be configurationally unstable at room temperature.[9] Interestingly, compound **5** was mentioned in a patent,[10] but it has not been reported as a ligand in any organic reaction. Similarly, bisindole **6** has been prepared and resolved but not used in any reactions.[11] Bisbenzothiophenes **7** and **8** have been prepared, resolved, and found to be configurationally stable.[9] Both compounds **7** (bitinap) and **8** provided good ee's in Ru(II)-catalyzed hydrogenations,[9] while **8** has recently been used in asymmetric Heck reactions.[12] We wanted to design a 3,3′-bifuryl ligand that would have the diphenylphosphino groups at-

tached to the C-2 position and be configurationally stable under a variety of reaction conditions (>150 °C). Semiempirical calculations (PM3) indicated that BINAPFu **1** should be configurationally stable; thus a synthesis and resolution of (±)-**3** was undertaken.

We envisaged that the biaryl bond in BINAPFu could be formed via a low-valent titanium-mediated dimerization of naphthoketone **10**. Hence, commercially available and inexpensive 2-naphthoxyacetic acid (**9**) was converted to ketone **10** using a simple, high-yielding two-step procedure (Scheme 2). McMurry coupling of **10** in DME and subse-
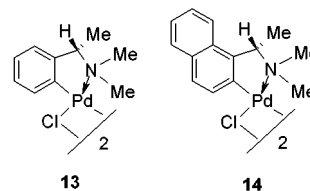

Scheme 2[a]
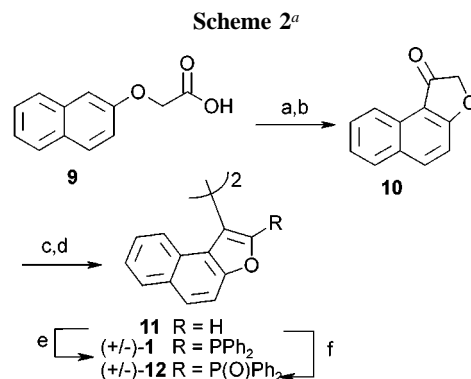
quent DDQ oxidation of the resulting olefin cleanly afforded the desired biaryl precursor **11**. Dilithiation of binaphthofuran **11** with 2 equiv of *t*-BuLi in diethyl ether followed by treatment with chlorodiphenylphosphine furnished (±)-BINAPFu **3** in 91% yield. The product can be easily isolated from the reaction mixture by crystallization, and in contrast to BINAP **1**,[3d] we have found it to be remarkably resistant to air oxidation in both solution and crystalline forms.

With (±)-BINAPFu **1** in hand, attention was then focused on resolution of the two optical isomers. Unfortunately, a number of reported methods for phosphine resolution[13−16] failed to resolve the BINAPFu ligand. However, a minor variation of our novel phosphine resolution procedure,[17] using (1*S*)-camphorsulfonyl azide as the resolving agent, efficiently

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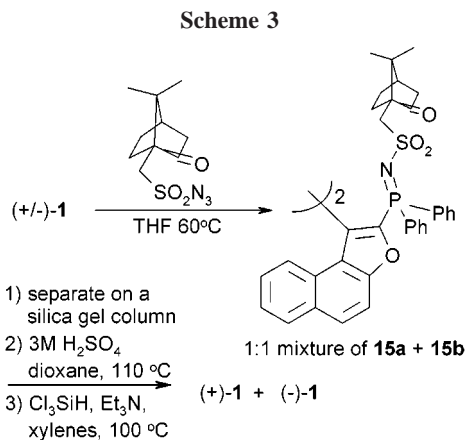
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(14) Treatment of (±)-**1** with homochiral *ortho*-palladated resolving agents **13** or **14** efficiently provided the desired diastereomeric complexes in a 1:1 ratio as evidenced by ^{31}P NMR analysis.[15] Unfortunately, numerous attempts to separate the above complexes by crystallization from a variety of solvent systems failed. Alternatively, protonation of the weakly basic phosphoryl oxygens of bisphosphine oxide **12** was explored as a possible resolution procedure. However, treatment of (±)-**12** with either (−)-dibenzoyltartaric acid or (1*S*)-(+)-camphorsulfonic acid under a wide variety of conditions failed to furnish the desired diastereomeric complexes.[16]

13   **14**

afforded a 1:1 mixture of diastereomeric phosphinimines **15a** and **15b** which were separable by column chromatography (Scheme 3). The diastereomerically pure phosphinimines **15a**

Scheme 3

1) separate on a silica gel column
2) 3M H$_2$SO$_4$ dioxane, 110 °C
3) Cl$_3$SiH, Et$_3$N, xylenes, 100 °C

1:1 mixture of **15a** + **15b**

(+)-**1** + (−)-**1**

and **15b** were subsequently converted to their respective phosphine oxides (−)-**12** and (+)-**12** by treatment with 3 M H$_2$SO$_4$ in dioxane (100 °C). Trichlorosilane reduction of (+)-**12** and (−)-**12** in xylenes provided enantiopure (+)-**1** and (−)-**1**, respectively (Scheme 3). The absolute stereochemistry of BINAPFu **1** was unequivocally established by obtaining a single-crystal X-ray structure analysis on diselenide **16**, prepared from enantiopure (−)-**1** (Figure 1).[18]
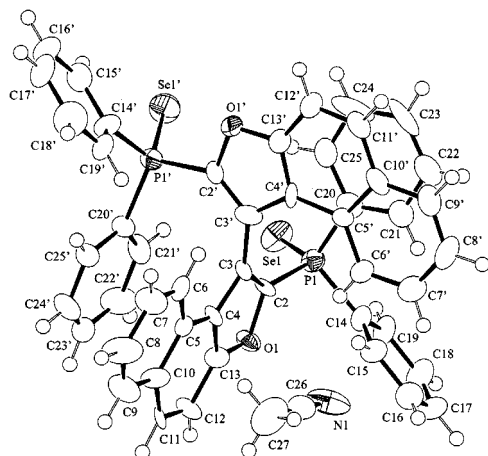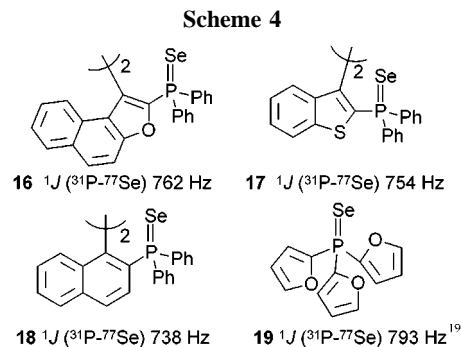
Figure 1. ORTEP diagram of selenide **16** drawn with 30% probability ellipsoids. Hydrogens are represented as spheres of arbitrary size.

Allen and Taylor have reported[19] that an increase in the $^1J(^{31}P-^{77}Se)$ coupling constant of phosphorus selenides

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indicates an increase in the s-character of the phosphorus lone pair orbital (i.e., less basic phosphine). A comparison of the $^1J(^{31}P-^{77}Se)$ coupling values for **16** with selenium derivatives **17**−**19** (Scheme 4) shows that the phosphorus

Scheme 4

16 $^1J(^{31}P-^{77}Se)$ 762 Hz

17 $^1J(^{31}P-^{77}Se)$ 754 Hz

18 $^1J(^{31}P-^{77}Se)$ 738 Hz

19 $^1J(^{31}P-^{77}Se)$ 793 Hz [19]

atoms in **1** are less basic than those in bitinap **7** and BINAP **2** (Scheme 1) but are more basic than the phosphorus atom in tri-2-furylphosphine.[19]

With (+)-**1** and (−)-**1** in hand, we compared the efficacy of BINAPFu in the asymmetric Heck arylation of 2,3-dihydrofuran and compared the results to those obtained with BINAP **1** (Table 1). In our hands, Hiyashi's reaction conditions reported with BINAP[20] and Proton Sponge

Table 1. Asymmetric Heck Results with BINAPFu and BINAP

ligand	solvent	°C	% sm	% yield of products		
				22 (% ee)	**23**	**24** (ee %)
1. (*R*)-**2**	C$_6$H$_6$a	30^c	99	0.7 (−)		
2. (*R*)-**1**	C$_6$H$_6$a	30^c	83	1.2 (−)	3	13 (93)
3. (*R*)-**2**	C$_6$H$_6$a	30^d	70	27 (86)	0.1	3 (51)
4. (*R*)-**1**	C$_6$H$_6$a	30^d	67	21 (>97)	0.5	11 (75)
5. (*R*)-**2**	dioxane^a	30^d	54	43 (73)	2	2 (46)
6. (*R*)-**1**	dioxane^a	30^d	29	61 (>97)	2	9 (57)
7. (*R*)-**2**	dioxane^a	100^d	0	90 (57)	2	10 (64)
8. (*R*)-**1**	dioxane^a	100^d	0	94 (74)	1	5 (69)
9. (*R*)-**2**	DME^b	85^d	0	55 (48)	13	32 (72)
10. (*R*)-**1**	DME^b	85^d	0	95 (73)	1	4 (64)
11. (*R*)-**2**	dioxane^b	100^d	0	73 (41)	9	17 (26)
12. (*R*)-**1**	dioxane^b	100^d	0	90 (77)	1	10 (40)
13. (*R*)-**2**	DMF^b	90^d	0	55 (35)	5	41 (47)
14. (*R*)-**1**	DMF^b	90^d	0	94 (71)	2	3 (39)
15. (*R*)-**2**	dioxane^b	100^c	0	93 (54)	4	3 (23)
16. (*R*)-**1**	dioxane^b	100^c	0	66 (79)	2	33 (44)

^{a} 3 mol % Pd(OAc)$_2$ for 9 d. ^{b} 1.5 mol % Pd$_2$dba$_3$ for 7 d. ^{c} Proton sponge used as base. ^{d} (*i*-Pr)$_2$NEt used as base.

afforded low product conversion. BINAPFu gave similar results under otherwise identical conditions (entry 2). Hunig's base was found to increase the conversion in benzene (entries 3 and 4). Changing the solvent to 1,4-dioxane further increased the amount of product obtained (entries 5 and 6). In accordance with Hayashi's findings, use of $Pd(OAc)_2$ as the precatalyst was essential for achieving product of high enantiomeric excess. At low temperature (30 °C), in dioxane using Hunig's base, BINAPFu provided a 61% yield of **22** in >97% ee (entry 6) while BINAP only provided **22** in 43% yield with a 73% ee (entry 5). To increase the conversion to product, we turned our attention to trying the reaction at higher temperatures. Repeating the reaction at 100 °C in dioxane for 9 d[21] provided a 94% yield of **22** in 74% ee with BINAPFu (entry 8). BINAP under otherwise identical conditions gave a 90% yield of **22** but a much lower ee of 57% (entry 7). Unlike the low-temperature reactions, we found that changing the Pd source from $Pd(OAc)_2$ to Pd_2-dba_3 did not significantly change the enantioselectivity of the reaction (entries 9−14). At high temperatures (85−100

°C) in a variety of solvents, the BINAPFu ligand provided the major product **22** with significantly improved optical purity relative to the reactions performed with BINAP. Hence, the Heck arylation of 2,3-dihydrofuran may be performed over 9 d with BINAPFu at 30 °C to ensure a high % ee of **22** (>97%) with a diminished yield of 61% (entry 6) or refluxed in dioxane to provide **22** with a 74% ee in 94% yield (entry 8). It is interesting to note that in all the reactions performed to date, the conjugated product **23** was always observed with BINAP and BINAPFu. Compound **23** has not been reported as a product of this reaction, and we are now examining the mechanism of its formation.

In conclusion, we have shown that enantiopure BINAPFu can be easily prepared and outperforms BINAP in the Heck reaction between phenyl triflate and 2,3-dihydrofuran. Further structural modifications of BINAPFu are currently underway in order to improve the enantioselectivity of the high-temperature Heck arylation reaction.

Supporting Information Available: Experimental procedures for the preparation of (+)-**1** and (−)-**1**, a general experimental procedure for the Heck reaction, and characterization data for compounds **1**, **10**−**12**, **15a**, and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Compound **14**: monoclinic $P2_1$ (No. 4); a = 9.842(4) Å, b = 21.045(5) Å, c = 10.347(3) Å, β = 108.64(3)°, V = 2031(1) Å3; Z = 2; R = 0.0406; Rw = 0.0915; Flack parameter = 0.006(19). Bijvoet analysis was performed. A refinement of the inverted structure was carried out which converged with R = 0.0465, Rw = 0.1043; Flack parameter = 0.20(2) and was therefore rejected as the absolute configuration present in the crystal.

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