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Synthesis of Bisquinolone-Based Mono- and Diphosphine Ligands of the Aza-BINAP Type

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Mono- and bisphosphine ligands based on the 4,4′-bisquinolone structural framework (BIQUIP ligands) were generated by direct microwave-assisted palladium-catalyzed carbon−phosphorus cross-coupling reactions employing the corresponding heteroaryl bromides and diphenylphosphine as substrates.

Ligand design for asymmetric catalysis has been and continues to be an important area of synthetic organic chemistry. Novel classes of ligands that offer additional synthetic opportunities or provide new insights into fundamental chemical processes are constantly being pursued. In this context, atropisomeric, C_2-symmetric phosphines have played a crucial role in the development of asymmetric catalysis and are among the most effective ligand systems known today.[1–5] The most successful ligand in this class is the well-known binaphthyl bisphosphine-based BINAP ligand (Figure 1, **1**). BINAP induces very high ee's in several asymmetric transition-metal-catalyzed processes, including hydrogenations, hydrosilylations, hydrocyanations, Heck reactions, and enamine isomerizations.[2] Until now, more than 60 frameworks based on the biaryl bisphosphine theme have been developed in order to effectively tune efficiency (turnover) and selectivity (ee) but also to facilitate separation from the reaction mixture or to modify other ligand properties.[1,3]

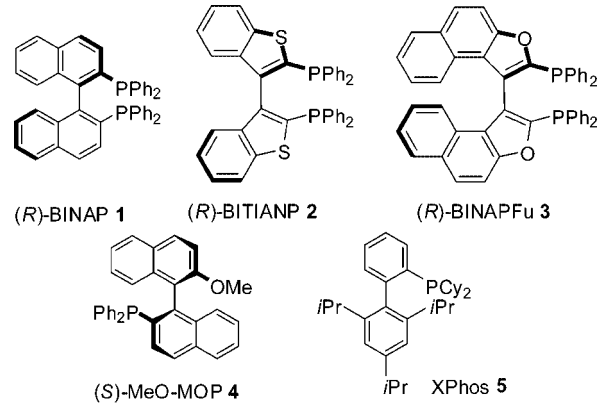

FIGURE 1. Bis- and monophosphine bi(hetero)aryl ligands.

Of more recent interest among these ligands are bisphosphines based on biheteroaryl backbones.[1,4,5] The main advantage of these systems is the possibility to synthesize ligands with a variety of electronic properties, as the electronic properties of the heteroaryl rings impact directly on the electronic properties of the phosphine ligators. In addition, a much wider variety of potential frameworks offering more flexible synthetic routes are available as compared to standard biaryl ligands. It has been demonstrated, for example, that the biheteroaryl ligands BITIANP (**2**)[4] and BINAPFu (**3**)[5] sometimes display higher catalytic activities and enantioselectivities as compared to BINAP in asymmetric hydrogenations and/or Heck reactions.

In addition to bisphosphines, monodentate chiral phosphine ligands (for example MeO-MOP **4**) and biaryl-based monophosphines in general (for example, XPhos **5**) are becoming increasingly important as ligands for those transition-metal-catalyzed reactions where bisphosphine−metal complexes cannot be used because of their low selectivity toward a desired reaction pathway.[6]

Inspired by the success of biheteroaryl phosphine ligands in asymmetric catalysis,[1,4,5] we became interested in the design and generation of both mono- and bisphosphine ligands based on the recently disclosed 4,4′-bisquinolone framework (Figure 2).[7]

The putative bisquinolone phosphine ligands of the BIQUIP type would offer several potential advantages compared to their binaphthyl counterparts (BINAP) as the electronic properties of the cyclic enamide system in the quinolone moiety are expected to exert a unique impact on the electronic properties of the phosphine ligators. In addition, the presence and proximity of soft (phosphine) and hard (carbonyl) donor groups in the ligand molecule provides the potential of hemilabile coordinating abilities in this type of hybrid ligand (Figure 2).[8] The 2(1*H*)-quinolone system itself offers several readily available diver-

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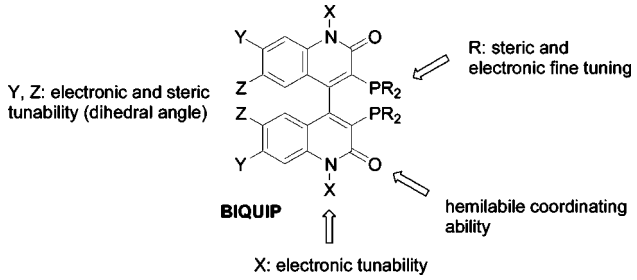


FIGURE 2. Bisquinolone-based bisphosphine ligands.

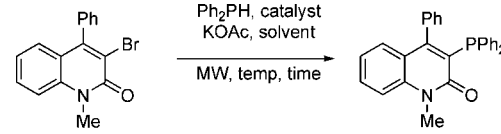
sification sites[9,10] and therefore the basicity at phosphorus can be readily adjusted by incorporating substituents with differing predefined electronic properties onto the bisquinolone core. This considerably expands the tunability of electronic properties on the ligating phosphorus and also allows some influence on the dihedral angle by variation of the Z-substituent (Figure 2).[1]

Herein, we outline a short synthetic route toward bisquinolones that utilizes Pd-catalyzed C−P cross-coupling protocols involving the corresponding 3-bromo- and 3,3′-dibromobisquinolones as starting materials.

In order to test the practicability of the planned C−P cross-coupling reactions, we initially performed optimization studies on the readily available 3-bromo-1-methyl-4-phenylquinolin-2(1*H*)-one (**6**).[9] For the transition-metal-catalyzed couplings of bromide **6** with diphenylphosphine, the reaction parameters were optimized using controlled microwave heating in sealed reaction vessels.[11] Based on our previous experience with metal-catalyzed C−P coupling protcols,[12] we were able to quickly optimize the conditions for the specific heteroaryl bromide substrate **6** (Table 1). Optimum conversion and selectivity for cross-coupling was obtained by employing equimolar amounts of the bromide substrate (**6**) and KOAc base, in combination with 3 mol % of Herrmann's palladacycle catalyst and a slight excess of diphenylphosphine (1.2 equiv). At a reaction temperature of 125−130 °C, complete conversions were achieved within 45 min using either dry THF (entry 4) or *n*-BuCl (entry 5) as solvent. From the experiment described in entry 5, a 70% yield of 3-diphenylphosphino-2-quinolone **7** was isolated by flash chromatography. The use of other solvents (entries 1−3) or different Pd or Ni catalysts (entries 6−11) provided significant amounts of dehalogenated byproduct or led to very low conversions.

For the generation of the desired BIQUIP ligands (Figure 2) it was necessary to first prepare the corresponding mono- and dibromobisquinolone derivatives **9** and **10**. In order to have ligands available with differing electronic properties in the aromatic ring we have chosen the 6,7-dimethoxy- and the 6-trifluoromethyl analogues as our initial synthetic targets.[13] The required bisquinolones **8a**,**b** were obtained following our recently reported Pd- or Ni-catalyzed methods.[7] Subsequent dibromination of dimethoxybisquinolone **8a** in DMF with *N*-bromosuccinimide (NBS) at room temperature (5 equiv, 50 min), provided the desired bisbromo derivative **10a** in 82% isolated yield (Scheme 1). Controlled monobromination using only 2.5 equiv of NBS at rt for 35 min furnished a 62% isolated yield of monobromo analogue **9a** after separation from the bisbromo derivative **10a** by flash chromatography. In sharp contrast, the electron deficient bisquinolone **8b** proved exceedingly difficult to brominate and forcing conditions had to be employed. Optimum isolated yields (68%) of the mono- bromo derivative **9b** were obtained by applying microwave-assisted NBS bromination conditions in MeCN (7 equiv NBS, 150 °C, 2.5 h).[9] Subsequent addition of an additional quantity of NBS (7 equiv)

TABLE 1. Reaction Optimization for Transition-Metal-Catalyzed C−P Cross Couplings[a]

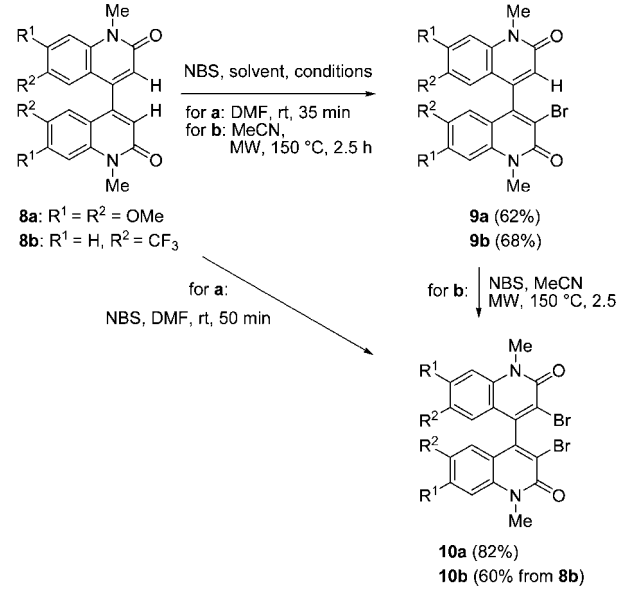


6 **7**

entry	solvent	catalyst (mol %)	*T* (°C)	time (min)	product distribution[b] (%)
1	DMF	palladacycle[c] (3)	180	35	0/**73**/27
2	dioxane	palladacycle[c] (3)	180	35	20/**51**/29
3	DMSO	palladacycle[c] (3)	180	30	0/**72**/28
4	THF	palladacycle[c] (3)	130	45	0/**88**/12
5	n-BuCl	palladacycle[c] (3)	125	45	0/**91**/9[d]
6	*n*-BuCl	$Pd_2(dba)_3$ (3.5)	125	45	18/**64**/18
7	*n*-BuCl	$PdCl_2$(dppf) (10)	125	45	6/**70**/24
8	*n*-BuCl	$Pd(OAc)_2$ (5)	125	45	42/**36**/13
9	*n*-BuCl	$Pd(PPh_3)_4$ (8)	125	45	20/**57**/23
10	*n*-BuCl	Pd/C (10)	125	45	88/**0**/12
11	DMF	$NiCl_2(PPh_3)_2$ (20)	180	30	25/**12**/63

[a] Reaction conditions: 0.25 mmol of 3-bromoquinolone **6**, catalyst (3−20 mol %), 0.25 mmol of KOAc, 1.5 mL of dry solvent, 1.2 equiv of Ph_2PH, Ar atmosphere, single-mode microwave irradiation. [b] Product distribution refers to relative peak area (%) ratios of crude HPLC−UV (215 nm) traces: starting material/product/dehalogenated product. [c] Herrmann's palladacycle, [trans-di(*μ*-acetato)bis[*o*-di-*o*-tolylphosphino)benzyl]dipalladium(II). [d] 70% isolated yield by flash chromatography.

SCHEME 1



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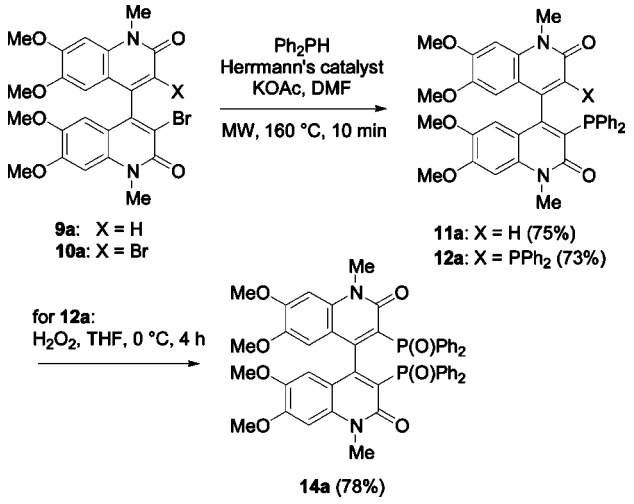
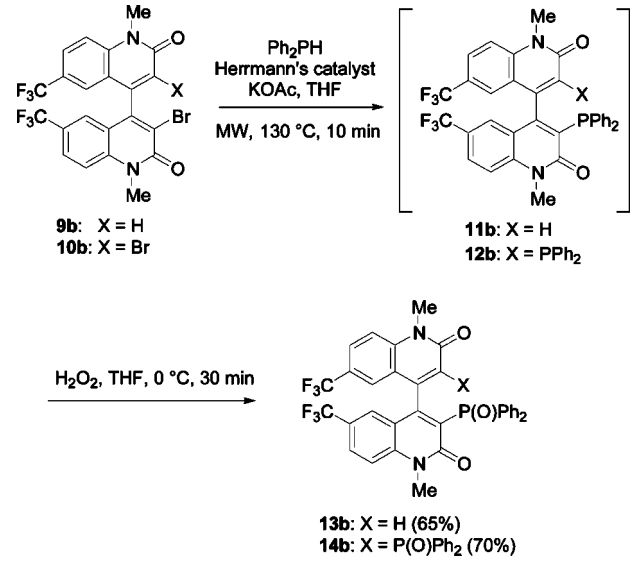
SCHEME 2



SCHEME 3



and resubjection to the microwave conditions (150 °C, 2.5 h) led to the bisbromo derivative **10b** in 60% overall yield.

With all the required four bromo precursors in hand, we continued to investigate the key mono and double C−P cross-coupling transformations leading to the desired bisquinolone phosphine ligands. Starting with dibromo bisquinolone **10a**, it was quickly realized that the initially optimized reaction conditions for the model substrate **6** (Table 1) had to be adjusted for bisquinolone **10a** mainly because of solubility issues. An extensive reoptimization revealed that for this particular substrate, DMF proved to be a very suitable solvent for bisphosphination. Thus, treatment of dibromide **10a** with 2.2 equiv of Ph_2PH, 3.5 equiv of KOAc, and 13 mol% of Herrmann's palladacycle in dry DMF at 160 °C for 10 min (MW) produced a 73% isolated product yield of bisphosphine bisquinolone ligand **12a** (Scheme 2). Under these conditions, the highest selectivities for bisphosphination could be achieved. Using lower amounts of catalyst and base resulted in incomplete conversions (monophosphination), while at higher reaction temperatures (180 °C) more dehalogenated byproducts could be observed.

Optimum results were obtained at relatively high substrate concentrations which kept oxidation to the corresponding phosphine oxides to a minimum. In order to isolate the bisphosphine ligand **12a**, an aqueous workup followed by extraction into chloroform and precipitation with methanol was performed. Standard chromatographic workup using silica gel chromatography caused partial decomposition of the material on the column. The isolated bisphosphine bisquinolone **12a** proved to be quite air stable but could be oxidized to the corresponding diphosphine oxide **14a** by stirring with an excess of aqueous H_2O_2 in THF.[14]

A byproduct (ca. 10%) in the phosphination **10a** → **12a** under certain conditions was the monophosphinated bisquinolone **11a** presumably formed by a monophosphination/monodehalogenation pathway. Since biaryl-type monophosphines are becoming increasingly important as ligands in transition-metal-catalyzed organic transformations,[6] monophosphinated bisquinolone **11a** was also synthesized directly in high yield from the monobromo bisquinolone **9a**. Thus, treatment of **9a** with 1.2 equiv of Ph_2PH, 2 equiv of KOAc and 7 mol % of Herrmann's catalyst in DMF at 160 °C for 10 min cleanly provided monophosphine **11a** in 75% isolated yield.

The same synthetic principles as outlined in Scheme 2 for the electron-rich dimethoxyquinolone scaffolds were then applied to the electron-deficient trifluoromethyl-substituted quinolones (Scheme 3). The corresponding mono- and dibromide precursors **9b** and **10b**, respectively, were therefore subjected to the Pd-catalyzed coupling conditions. For these particular substrates, the use of THF as solvent and 130 °C as reaction temperature under otherwise identical reaction conditions proved optimal. In contrast to the electron-rich methoxy-functionalized bisquinolones **11a** and **12a** (Scheme 2), however, phosphino bisquinolones **11b** and **12b** bearing electron-withdrawing CF_3 groups in the 6,6′ positions proved to be somewhat oxidation sensitive during isolation. Typically, mixtures of the phosphines and their mono- and dioxides (for **12b**) were obtained after extractive workup. Therefore, for characterization purposes the crude reaction products were rapidly oxidized (30 min) with aqueous H_2O_2 in THF to provide the corresponding oxides **13b** and **14b** in good overall yields (Scheme 3).

In addition to our interest in the aza-BINAP analogues described above, we also wanted to explore the possibility of synthesizing aza-BINOL derivatives based on the 4,4′-bisquinolone framework. Since 1990 the enantiomeric atropisomers of 1,1′-binaphthyl-2,2′-diol (BINOL) have become the most widely used ligands both for stoichiometric and catalytic asymmetric reactions.[15] The extraordinary success of this molecule in a wide range of asymmetric transformations and in chiral recognition has led to the development of several modified BINOL analogues in order to fine-tune steric and electronic factors and for the provision of additional binding sites.[16] However, very little is known on BINOL analogues that are derived from heterobiaryl frameworks.[17]

The Pd-catalyzed formation of a phenol using 3-bromo-4-phenylquinolinone **6** as a model substrate for 3,3′-dibromobisquinolones **10** is demonstrated in Scheme 4. Following a recent protocol by Buchwald and co-workers,[18] introducing the use of 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*tert*-

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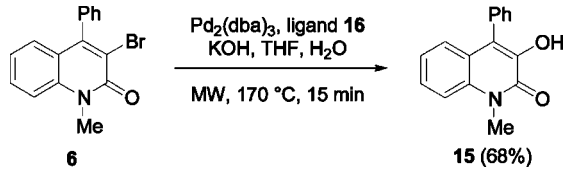
SCHEME 4



butyl X-phos, **16**) as ligand in related Pd-catalyzed couplings, we were able to synthesize 3-hydroxy-4-phenyl-1-methylquinolin-2(1*H*)-one **15** in good yield from the bromo precursor **6**. Optimum isolated yields/conversions were obtained by subjecting aryl bromide **6** in a 1:1 THF/H_2O mixture containing 4 equiv of KOH as base to microwave irradiation for 15 min at 170 °C. The use of 4 mol % of $Pd_2(dba)_3$ in combination with 8 mol % of ligand **16** resulted in the best selectivity for C−O bond formation (93%) with only 7% of dehalogenated byproduct being formed. The use of other ligand systems such as, for example, diphenylphosphinoferrocene (dppf) was significantly less effective and produced more dehalogenated byproduct under all tested reaction conditions.[19]

In conclusion, we have shown that both mono- and bisphosphine ligands derived from the 4,4′-bisquinolone framework can be readily synthesized in a two-step bromination/phosphination protocol starting from the basic biheteroaryl core. Preliminary studies confirm that these novel types of aza-BINAP phosphines containing an enamide moiety incorporated into the heteroaryl ring are indeed useful ligands in transition-metal-catalyzed transformations (see the Supporting Information).

Experimental Section

4,4′-Bis(3-bromo-6,7-dimethoxy-1-methylquinolin-2(1*H*)-one) (10a) (Scheme 1). A mixture of 109 mg (0.25 mmol) of 4,4′-bis(6,7-dimethoxy-1-methylquinolin-2(1*H*)-one) (**8a**), 222.4 mg (1.25 mmol, 5.0 equiv) of *N*-bromosuccinimide (NBS), and 0.6 mL of DMF in a vial equipped with a magnetic stirring bar was stirred for 50 min at room temperature. The reaction was quenched by addition of ice−water and was filtered. The resulting crude product mixture was purified by automated flash chromatography using EtOAc/CH_3CN as eluent to give 122 mg (82%) of **10a** as a yellow solid: mp 319−320 °C (ethanol); IR (KBr) ν_{max} 1642, 1251, 1166, 645 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.63 (s, 6H), 3.96 (s, 6H), 4.05 (s, 6H), 6.45 (s, 2H), 6.91 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 31.8, 56.3, 56.5, 97.7, 107.5, 111.5, 115.6, 135.2, 145.2, 146.1, 153.0, 158.2; MS (positive APCI) *m*/*z* 594 (100, M), 596 (65, M + 2), 592 (55, M − 2), 595 (30, M + 1); HRMS ($APCI^+$) calcd for $C_{24}H_{23}N_2O_6Br_2$ $[M + H]^+$ 592.99174, found 592.99168.

4,4′-Bis(3-diphenylphosphanyl-6,7-dimethoxy-1-methylquinolin-2(1*H*)-one) (12a, BIQUIP) (Scheme 2). A mixture of 61.2 mg (0.103 mmol) of 4,4′-bis-(3-bromo-6,7-dimethoxy-1-methylquinolin-2(1*H*)-one) (**10a**), 12.6 mg (0.013 mmol, 13 mol %) of Herrmann's palladacycle, and 35.4 mg (0.36 mmol, 3.5 equiv) of KOAc in a 2 mL Pyrex microwave vial was equipped with a magnetic stirring bar and sealed. After flushing with Ar, 0.8 mL of anhydrous DMF and 39.2 μL (0.23 mmol, 2.2 equiv) of Ph_2PH were added with shaking. The resulting mixture was stirred for 5 min at room temperature under Ar and then heated for 10 min at 160 °C via single-mode microwave irradiation. After being cooled to ambient conditions, the mixture was diluted with 5 mL of water and extracted with 3 × 15 mL of $CHCl_3$. The combined organic extracts were washed with saturated aqueous KCl solution and dried over $MgSO_4$ for 2 h. After filtration and evaporation, the remaining crude mixture was dissolved in a few drops of $CHCl_3$ and after addition of excess MeOH, the yellowish precipitate was filtered and dried to give 60.6 mg (73%) of bisphosphine **12a** as yellow crystals: mp 278−279 °C (ethanol); IR (KBr) ν_{max} 1633, 1253 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.21 (s, 6H), 3.78 (s, 6H), 4.07 (s, 6H), 6.39 (s, 2H), 6.86 (s, 2H), 6.96−7.57 (m, 20H); ^{31}P NMR (90 MHZ, $CDCl_3$) δ −10.06 (1 signal); ^{13}C NMR (90 MHz, $CDCl_3$) δ: 30.2, 56.3, 97.4, 106.2, 109.1, 113.4, 121.0, 126.0, 129.1, 129.6, 136.9, 142.7, 145.8, 148.1, 153.5, 161.4; MS (positive APCI) *m*/*z* 804 (100, M), 805 (60, M + 1), 806 (18, M + 2), 620 (35, M − 184); HRMS ($APCI^+$) calcd for $C_{48}H_{43}N_2O_6P_2$ $[M + H]^+$ 805.25909, found 805.25890.

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Supporting Information Available: Experimental procedures and characterization data of compounds **7**−**11** and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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