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Tailoring Buchwald-Type Phosphines with Pyrimidinium Betaines as Versatile Aryl Group Surrogates

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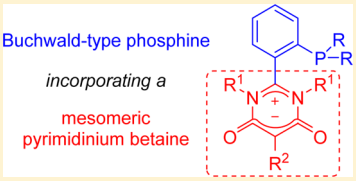
Supporting Information

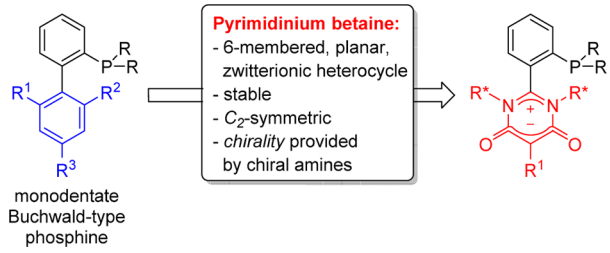
ABSTRACT: A derivatization of dialkylbiarylphosphines consisting in the formal replacement of their distal aryl group by a pyrimidinium betaine is reported. Two achiral representatives of this new class of Buchwald-type phosphines have been successfully synthesized through two strategies. The first one is based on a last stage introduction of the phosphino moiety, and the second one consists in a modular, one-pot, three-step procedure starting from an *o*-bromoaryl phosphine. The resulting phosphines have been coordinated onto gold(I) and palladium(II) centers and have been employed as supporting ligands in Pd-catalyzed Suzuki−Miyaura cross-coupling of aryl halide substrates.



Advances in transition metal catalysis are often linked to the innovative design of modulable ligands. Indeed, a suitable tailoring of the ligand architecture is crucial to ensure optimum steric protection and/or stereoelectronic control of the catalytic species and to provide low activation energy pathways for challenging transformations.[1,2] As illustrative example, monodentate, bulky, and electron-rich dialkylbiarylphosphines, first introduced in 1998 by Buchwald,[3] have revolutionized Pd-catalyzed cross-coupling[4] and have also found extensive utility in homogeneous gold catalysis,[5] often serving as a source of inspiration for many researchers. In particular, efficient chiral monodentate phosphines[6] derived from such a platform include binaphthyl-based phosphines such as MOP and KenPhos,[7] P-chirogenic [1,3]-oxaphospholines,[8] chiral P-(*o*-biaryl)-phospholanes,[9] and enantiopure 2-(imidazolidinon-2-yl)-phenylphosphines.[10] They remain relatively rare, which undoubtedly reflects a real general difficulty to convert an efficient achiral structural motif into its chiral equivalent. With this in mind, we reasoned that pyrimidinium betaines, which are the precursors of our previously reported anionic N-heterocyclic carbenes (NHCs),[11,12] present beneficial features to constitute potentially suitable chiral mimics of aryl groups. Indeed, these globally neutral, mesoionic, six-membered heterocycles are planar and stable against air and moisture and their synthesis is well documented.[13] Moreover, given that they are readily accessible from primary amines, implementation of their chiral congeners from chiral primary amines could easily be envisioned.

In a first approach, we projected the substitution of the distal aryl group of a Buchwald-type phosphine by a pyrimidinium betaine moiety, with the objective to obtain a new tunable ligand class with interesting potential (Chart 1), considering that the specific arrangement of the ligand would put the chiral groups in suitable close proximity to the metallic center, defining a precise chiral space around the latter.

Chart 1. Design and Structure of the Target Pyrimidinium Betaine-Containing Phosphine



We report here our progress toward the synthesis of an achiral representative of this new ligand class, its ability to coordinate transition metal centers, and preliminary catalytic studies demonstrating its potential as ancillary ligand.

Isopropylamine was chosen for this study since it appears to be a good achiral analogue of chiral amines possessing an asymmetric α-carbon atom such as the (*R*)- or (*S*)-1-phenylethylamine. Two strategies have been designed for the synthesis of the targeted phosphine ligands. The first one is based on a late-stage introduction of the phosphino moiety from the key intermediate **3** (Scheme 1). The latter was obtained from 2-bromobenzoic acid through a three-step sequence consisting of the amidation of 2-bromobenzoic acid leading to **1**, the subsequent activation of the amide moiety and the addition of a second amine to generate amidine **2**, and the final cyclization by coupling **2** with methylmalonyl dichloride through a double peptide-type coupling. Compound **3** is air and water stable and was fully characterized. In particular, evidence for the formation of the heterocycle was inferred from the appearance of a signal at δ = 96.9 ppm in the ^{13}C NMR spectrum assigned to the central malonate carbon atom (C_S)

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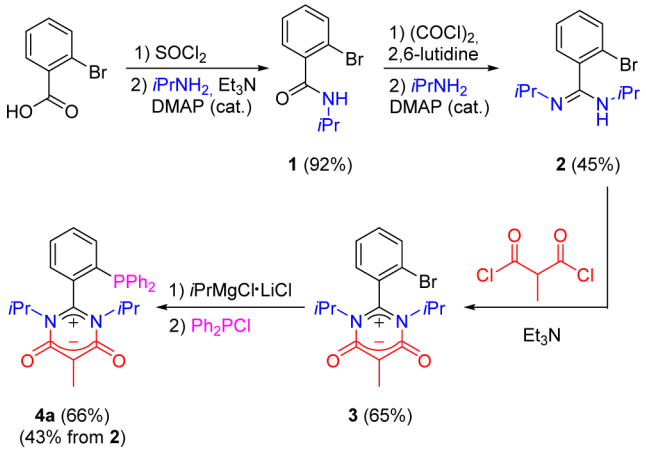
Scheme 1. Synthesis of Phosphine 4a Based on the Final Introduction of the Phosphino Moiety



characteristic of pyrimidinium betaine rings. Whereas first tests of Br/Li exchange on **3** using *n*BuLi or *t*BuLi led to intractable mixtures, we were pleased to find that Br/Mg exchange smoothly occurred using Knochel's isopropylmagnesium chloride lithium chloride complex *i*PrMgCl·LiCl, giving clean and quantitative transmetalation in less than 30 min (conversion determined after hydrolysis of the crude product).[14] Further addition of chlorodiphenylphosphine provided the phosphine **4a** in 66% yield after column chromatography.

Phosphine **4a** is fully air stable in the solid state and moderately sensitive toward oxidation in solution. Its formulation was confirmed by spectroscopic and analytical methods. The ^{31}P signal of the phosphorus atom appears at δ = −17.8 ppm in the ^{31}P{^{1}H} NMR spectrum. The molecular structure of **4a** was confirmed by an X-ray crystal structure determination (Figure 1). As previously observed,[11] the pyrimidinium betaine ring is almost perfectly planar and consists of two independent π systems, namely, a four-π-electron amidinium moiety on which a six-π-electron malonate backbone is grafted via the N1−C2 and N2−C4 bonds, whose average length (1.45 Å) falls in the range of prototypical single

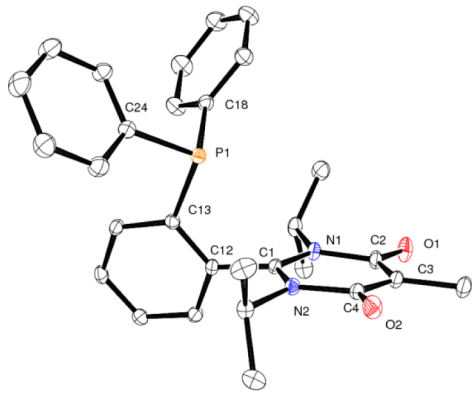
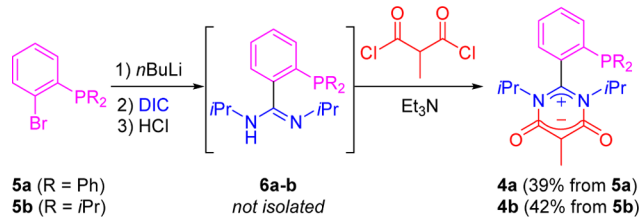


Figure 1. Molecular structure of **4a** (ellipsoids drawn at the 30% probability level). Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): C1−N1 1.337 (2), C1−N2 1.335(2), N1−C2 1.452 (2), N2−C4 1.451 (2), C2−C3 1.393(2), C3−C4 1.399(2), C2−O1 1.230(2), C4−O2 1.236(2), P1−C13 1.838 (2), P1−C18 1.831(2), P1−C24 1.839(2), N1−C1−C12−C13 100.16.

C sp^2−N sp^2 bonds (1.45−1.47 Å).[15] The 2-(diphenylphosphino)phenyl and heterocycle moieties are roughly orthogonally arranged around their C1−C12 connection (dihedral angle N1−C1−C12−C13: 100.16°), as expected for a Buchwald-type phosphine. Most notably, the observed conformation of **4a** in the solid state, with the lone pair of the phosphorus atom pointing toward the upper side of the pyrimidinium betaine and the C−H bonds of the isopropyl substituents pointing toward the 2-(diphenylphosphino)phenyl group, may result from the minimization of the steric constraint, validating our first hypothesis.

Although quite efficient, the latter synthetic pathway suffers from its high number of steps and purifications. We thus decided to develop a more straightforward, modular procedure in view of a future rapid optimization of the ligand structure for catalytic applications (Scheme 2). Starting from the readily

Scheme 2. One-Pot, Two-Step Synthesis of Phosphines 4a,b[a]



[a]DIC: *N*,*N*′-diisopropylcarbodiimide.

available (2-bromophenyl)phosphines **5a,b**,[16] the amidines **6a,b** were obtained by bromine−lithium exchange using *n*BuLi followed by nucleophilic addition onto *N*,*N*′-diisopropylcarbodiimide (DIC) and final reprotonation with HCl. The amidines **6a,b** were used directly in the next cyclization step with methylmalonyl dichloride. Noteworthy, the protonation step was found to be crucial for the procedure since the direct coupling between basic amidinates and methylmalonyl dichloride led to considerable amounts of decomposition products, probably due to undesired deprotonation of the malonyl moiety. The target phosphines **4a,b** were isolated in 39% and 42% yields, respectively, after simple-column chromatography.[17] Being quick and operationally simple, the strategy appears quite promising for the development of a library of chiral monodentate phosphines, especially as chiral carbodiimides are easily obtained from the corresponding chiral amines in two steps.[18]

To estimate the coordination ability of phosphines **4a,b**, we next prepared their gold(I) and palladium(II) complexes (Scheme 3).

Mixing ligand **4a** and AuCl(tht) in CH_2Cl_2 at room temperature led to the complete formation of complex **7** in less than 30 min as judged by ^{31}P{^{1}H} NMR with a downfield shift of the phosphorus atom from δ = −17.8 ppm in the free phosphine to δ = 21.9 ppm in the complex. In the solid state, complex **7** exhibits the typical linear coordination geometry of gold(I) complexes [P1−Au1−Cl1: 177.87(2)°] (Figure 2), adopting a conformation where the AuCl unit lies above the pyrimidinium betaine ring. More specifically, the gold center Au1a is positioned above the ipso carbon C1a of the amidinium ring. The Au1−C1 distance of 3.145 Å is smaller than the sum of the van der Waals radii (~3.36 Å)[19] and lies in the range of typical Au−C$_{ipso}$ distances in neutral Buchwald-type phos-

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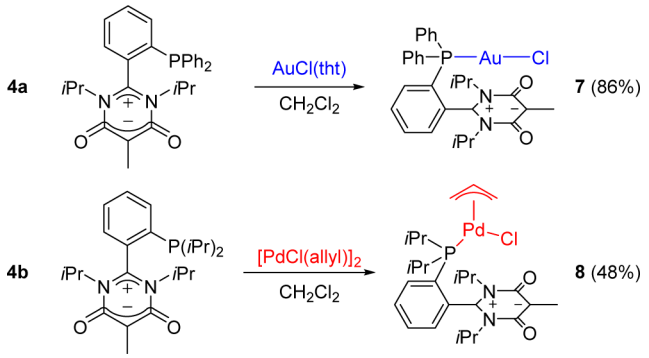
Scheme 3. Preparation of the Gold(I) and Palladium(II) Complexes 7 and 8[a]



[a]tht = tetrahydrothiophene.

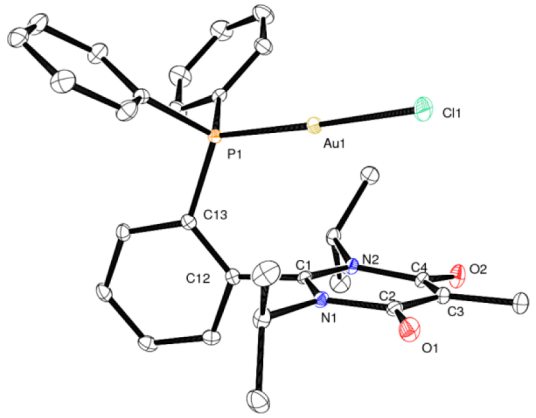


Figure 2. X-ray structure of complex **7** (ellipsoids displayed at 30% probability). Solvent molecule and hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Au1–P1 2.2280(12), Au1–Cl1 2.2796(13), Au1–C1 3.145, P1–Au1–Cl1 177.87(2), Au1–P1–C12–C1 12.68.

phine/gold(I) complexes (3.12–3.25 Å),[20] suggesting a weak attractive interaction between both atoms. The Au1–P1 coordination bond is twisted relative to the C1–C12 bond [dihedral angle Au1–P1–C12–C1: 11.09°], while a slight distortion from planarity of the heterocycle is observed.

Complex [(**4b**)PdCl(allyl)] (**8**) was obtained through a classical complexation procedure, namely by reaction of phosphine **4b** with the $[PdCl(allyl)]_2$ dimer, and was isolated in 48% yield after crystallization. Interestingly, whereas both ^{1}H and ^{13}C NMR spectra display only one well-defined set of signals for complex **8**, one small singlet at $\delta = -3.3$ ppm assigned to free **4b** is observed in the ^{31}P NMR spectrum besides the signal at $\delta = 60.8$ ppm for **8**. This suggests the occurrence of an equilibrium between free **4b** and complex **8**, as confirmed by a 2D ^{31}P–^{31}P EXSY experiment revealing the existence of cross-peaks between the two signals. In the solid-state structure, the PdCl(allyl) moiety was found opposite the pyrimidinium betaine, probably due to a strong steric repulsion between this bulkier metallic fragment (compared to the AuCl fragment) and the isopropyl substituents of the nitrogen atoms (Figure 3). Complex **8** displays a distorted square planar coordination geometry typical of η^3-allyl palladium(II) complexes. Here again, the preferred conformation of the isopropyl groups on nitrogen atoms, where the C–H bonds

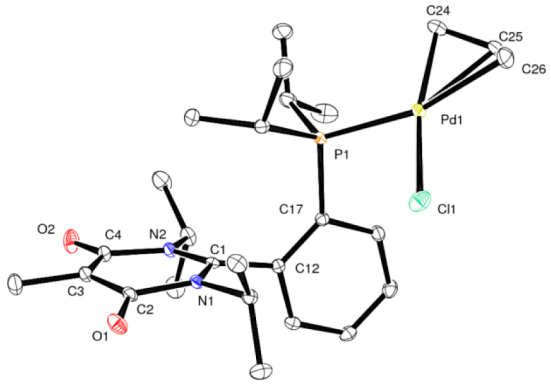
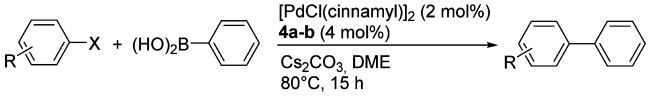


Figure 3. X-ray structure of complex **8** (ellipsoids displayed at 30% probability). Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd1–P1 2.3148(4), Pd1–Cl1 2.3808(5), Pd1–C24 2.112(2), Pd1–C25 2.1567(18), Pd1–C26 2.2053(19), P1–Pd1–Cl1 90.819(16), P1–Pd1–C24 103.21(6), C24–Pd1–C26 67.92(9), C26–Pd1–Cl1 97.45(7).

point toward the aryl group, is the result of the minimization of the steric energy.

In a preliminary evaluation of the catalytic activities of phosphines **4a,b** as supporting ligands in the Suzuki–Miyaura coupling of substituted aryl halogenides with phenyl boronic acid, classical conditions were chosen (DME as the solvent, Cs_2CO_3 as the base, and a reaction temperature of 80 °C) (Table 1). The catalyst was generated *in situ* by mixing

Table 1. Pd-Catalyzed Suzuki–Miyaura Coupling between Phenyl Boronic Acid and Several Aryl Halides Using 4a,b as Supporting Ligands[a]



entry	ligand	X	R	yield (%)[b]
1	**4a**	Br	4-Me	96
2	**4b**	Br	4-Me	97
3	**4a**	Br	4-OMe	88
4	**4b**	Br	4-OMe	90
5	**4b**	Br	2-Me	90
6	**4a**	Cl	4-NO_2	57
7	**4b**	Cl	4-NO_2	63
8	**4b**	Cl	4-COMe	26
9	**4b**	Cl	4-Me	<10% conv[c]

[a]Reaction conditions: aryl halide (0.5 mmol), phenyl boronic acid (1.5 equiv), Cs_2CO_3 (2.0 equiv), $[PdCl(cinnamyl)]_2$ (2 mol %), ligand (4 mol %), DME (0.5 mL), 80 °C, 15 h. [b]Yields refer to the average of isolated yields of two runs after chromatography. [c]Conversion determined by GC.

$[PdCl(\eta^3\text{-cinnamyl})]_2$ (2 mol %) and phosphines **4a,b** (4 mol %). Generally, the electron-rich phosphine **4b** was found to be slightly more efficient than the triarylphosphine **4a** (entries 1–4, 6, 7). While both systems gave very good isolated yields of 4-methyl- and 4-methoxybiphenyl, switching to the more challenging aryl chlorides allowed an estimate of the limits of their catalytic efficiency. While 4-nitrochlorobenzene and 4-chloroacetophenone were coupled with phenyl boronic acid in moderate isolated yields (entries 6–8), only low conversion was observed for the nonactivated 4-chlorotoluene (entry 9).

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In summary, we have validated an efficient modular synthetic strategy to a new class of Buchwald-type phosphines, incorporating a mesoionic pyrimidinium betaine ring in their structure. Coordination on gold(I) and palladium(II) centers has been achieved, whereas our preliminary tests of the latter complexes in Pd-catalyzed cross-coupling are testimony to the potential of these phosphines in homogeneous catalysis. In a logical extension of the present conceptual approach, the next challenge will now be to access the chiral congeners of these ligands from commercially available chiral amines and to implement them in asymmetric catalysis. This work is currently under way in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental section, full characterization data for all new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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