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ABSTRACT

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As balanced electron-rich P,C-chelating ligands, phosphine-phosphonium-ylides are considered for their ability to *in situ* promote palladium-catalysed direct sp²-C–H arylation. Using methyl phosphonium salts of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ("methyl-BINAPIUM") as ylide precursors under optimized reaction conditions, arylation of benzoxazole was found to proceed in moderate to high yield to give functional 2-aryl benzoxazoles. A strong anion effect of the non-salt free ylide was evidenced (TfO⁻ > I⁻ > PF₆⁻ ≈ salt-free). This first example of phosphonium ylides as ligands in catalytic C–H activation extends the prospect of their general implementation in homogeneous transition metal catalysis.

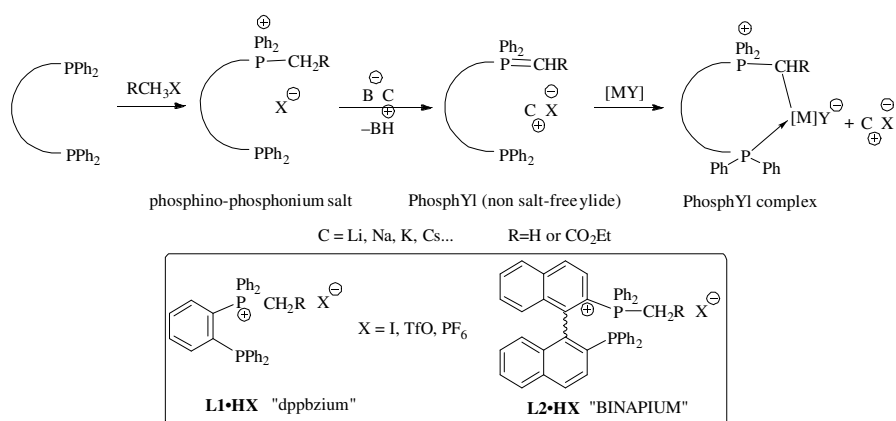
Transition-metal-catalyzed direct C–H bond functionalization have experienced tremendous developments over the past decade, allowing novel key step approaches in the synthesis of natural products and therapeutic agents [1]. These reactions have required catalysts with high kinetic reactivity to ensure broad substrate scope, lower reaction temperature and catalyst loading, short time and favourable product distributions. Ligand development has also played a central role. While the efficiency of phosphine and N-heterocyclic carbenes (NHCs) as σ-donating ligands of catalytic transition metal centers has been widely exemplified [2,3], general guidelines for the design of suitable ligand scaffolds to promote C–H arylation are still lacking. In this context, however, beyond electron-balanced monodentate phosphoramidites [4] or imidazolium ylides [4b], bidentate amino/imino-amides, such as mono-protected amino acids (MPAAs), were shown to behave as LX *N,N*-ligands in enantioselective sp³-C–H arylation, or through reverse polarity from aryl boronates [5]. Noteworthy is the recently reported use of a P,C-ligand for Pd-catalysed 2-arylation of benzoxazoles (actually a phosphine-NHC ligand in a labile PNC pincer framework) [6]. Such ligands enable access to a structurally diverse range of valuable products *via* C–H bond activation with superior chemo-, regio- and enantio-selectivity. But the potential of ligands in improving catalyst efficiency of C–H bond activation remains to be further explored. As a new prospect of our continuing studies on direct sp²-C–H bond activation [7], we envisaged the implementation of particular P,C-ligands, *i.e.* phosphino-phosphonium ylides [8], hereafter referred to as

"PhosphYls" (Scheme 1). These ligands were shown to be stronger σ-donating ligands than NHCs [8b].

By design, suitable PhosphYls are of limited structural variety, as they must be derived from monoalkyl-triarylphosphoniums, with a single type of acidic P⁺CH unit with low steric hindrance and moderate pK_a value, such as those of the P⁺CH₃ moiety, to allow selective deprotonation and efficient coordination (Scheme 1). Under these requirements, the simplest PhosphYls are ylides of phosphonium salts of *o*-bis(diphenylphosphino)benzene (dppbz) such as L1•HX, which were shown to provide catalysts for malonate C-allylation (Pd) [9], asymmetric alkene hydrogenation or ketone hydrosilylation (Rh) [10], and theoretical olefin metathesis (Ru) [11]. Alternative PhosphYls satisfying the above requirement are methylenephosphorane derivatives of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), such as the methyl-BINAPIUM ylide L2 [12], used in Rh-catalysed hydrogenation and hydrosilylation [13], or its methoxycarbonyl-stabilized versions, Yliphos (R = CO₂Et, Scheme 1) used in Pd-catalysed C-allylation [14] (not to be confused with YPhos, ylide-phosphines acting as strongly donating P ligands in Pd or Au catalysts) [15]. As the low pK_a values of Yliphos favours partial de-coordination of the stabilized free ylide [17], exploratory investigations prompted the choice of the *rac*-methyl-BINAPIUM ylide L2 as a benchmark PhosphYL. On the tracks of pioneering works [16] and recent advances in Pd-catalysed C–H arylation of heterocycles [17], the transformation was chosen as a model to further evaluate the ability of PhosphYls to form *in situ* catalysts.

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Scheme 1. Phosphine-phosphonium salts and ylides thereof (PhosphYls) as LX-chelating ligands of late transition metals M (e.g. Ru, Rh, Pd).

Indeed, while their electron-donating ability is expected to facilitate the step of the aryl halide oxidative addition, their bulky chelating characters appear appropriate for steric protection of the Pd center.

With the view to accessing functional hetero-aromatic systems without resorting to an *ortho*-directing group, the reaction of the benzoxazole substrates **1** with various aryl halides **2** was considered [7]. The target 2-aryl-benzoxazole products **3** indeed exhibit versatile properties [18], going from antibacterial [19], cholesterol ester transfer protein inhibition [20], adenosine receptor antagonism [21], amyloidogenesis inhibition [22], and thioflavine-like binding affinity to β -amyloid plaques [23], to fluorescence in the solid state [24].

As a soluble Pd(II) salt widely used in C-H activation catalysis also exhibiting propensity to form Pd-C(sp³) bonds [25], Pd(OAc)₂ was envisaged as catalyst precursor, to which non-salt-free PhosphYls could be added, after *in situ* deprotonation of parent phosphoniums. Considering the possible effect of the anion X⁻ in non-salt-free ylides, well known in the Wittig reaction [26], several phosphonium salts **L2•HX** were compared (X= I, TfO, PF₆).

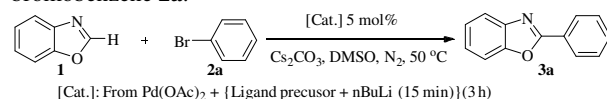
Benzoxazole **1** and bromobenzene **2a**, or 4-bromoanisole **2b**, were selected as the model reactants. From a preliminary screening under various conditions, the following conditions were adopted: DMSO as a solvent, Cs₂CO₃ as a base and Pd(OAc)₂ as catalyst precursor at 50 °C for 14 h (Table 1). At the outset, commercially available monodentate phosphines, PPh₃, PCy₃, PtBu₃, were first selected as standard reference ligands, giving **3a** in 48%, 45% and 37% yield, respectively (entries 1-3). Bidentate phosphines BINAP, dppm, *o*-dppbz, dppe and dppf also gave medium yields of 53%, 44%, 51%, 47% and 36%, respectively (entries 4-8). Under the same conditions, using the methylphosphonium salt **L1•HX** (X = I, TfO, PF₆) of *o*-dppbz as pro-ligand (non-salt-free PhosphYls **L1/HX** or **L2/HX** were separately prepared by deprotonation of **L1•HX** or **L2•HX** with nBuLi in DMSO solution during 15 min at room temperature), the coupling product **3a** was isolated in 53%, 59% and 43% yield, respectively (entries 9-11). These results are similar to those obtained by bidentate phosphines, and then it was decided to change the *o*-dppbz backbone to the BINAP backbone. The use of the BINAPIUM ylide generated from **L2•HI** gave **3a** in an improved yield of 65% (entry 12). The same ylide **L2** generated from **L2•HOTf** gave **3a** in a much higher yield of 93%, revealing

a dramatic counterion effect (entry 13). This was confirmed by the result of **L2•HPF₆**, giving **3a** in a twice lower yield of 50% (entry 14), thus showing a correlation of the yield with the association effect between the anion and the Pd and/or P⁺ centers [27].

A systematic screening of the reaction conditions was then undertaken (Table 1). In the absence of any potential P-ligand, the reaction was found to proceed with 16% yield only (entry 15). It was also found that both the solvent and base are of critical importance. By reducing the amounts of Cs₂CO₃ from 1.0 equiv. to 0, the yields in **3a** are reduced to 41%, 33% and 0% respectively (entries 16-18). Upon replacement of Cs₂CO₃ by weaker bases, such as Et₃N or PPh₃, product was not observed (entries 19 and 20). The use of a stronger base, such as NaHMDS, ^tBuOK or MeONa, gave lower yields in the range of 27%-39% (entries 21-23). When the same bases were used in THF instead of DMSO, the yields dropped to 12%-20% (entries 24-26). Other solvents, such as THF, DMF, MeCN, EtOH or NMP, also resulted in a dramatic decrease of the yield (< 15%, details see the Supporting information).

Table 1

Ligand effect in Pd-catalysed 2-phenylation of benzoxazole **1** with bromobenzene **2a**.^a



Entry	Ligand	X	Base (equiv.)	Solvent	Yield (%) ^b
1	PPh ₃	-	Cs ₂ CO ₃ (2.0)	DMSO	48
2	PCy ₃	-	Cs ₂ CO ₃ (2.0)	DMSO	45
3	P ^t Bu ₃	-	Cs ₂ CO ₃ (2.0)	DMSO	37
4	BINAP	-	Cs ₂ CO ₃ (2.0)	DMSO	53
5	dppm	-	Cs ₂ CO ₃ (2.0)	DMSO	44
6	<i>o</i> -dppbz	-	Cs ₂ CO ₃ (2.0)	DMSO	51
7	dppe	-	Cs ₂ CO ₃ (2.0)	DMSO	47
8	dppf	-	Cs ₂ CO ₃ (2.0)	DMSO	36
9	L1	I	Cs ₂ CO ₃ (2.0)	DMSO	53
10	L1	TfO	Cs ₂ CO ₃ (2.0)	DMSO	59
11	L1	PF ₆	Cs ₂ CO ₃ (2.0)	DMSO	43
12	L2	I	Cs ₂ CO ₃ (2.0)	DMSO	65
13	L2	TfO	Cs ₂ CO ₃ (2.0)	DMSO	93
14	L2	PF ₆	Cs ₂ CO ₃ (2.0)	DMSO	50
15	-	-	Cs ₂ CO ₃ (2.0)	DMSO	16
16	L2	TfO	Cs ₂ CO ₃ (1.0)	DMSO	41
17	L2	TfO	Cs ₂ CO ₃ (0.5)	DMSO	33
18	L2	TfO	-	DMSO	N.R.
19	L2	TfO	NEt ₃ (2.0)	DMSO	N.R.

20	L2	TfO	PPh ₃ (2.0)	DMSO	N.R.
21	L2	TfO	NaHMDS (2.0)	DMSO	39
22	L2	TfO	^t BuOK (2.0)	DMSO	35
23	L2	TfO	CH ₃ ONa (2.0)	DMSO	27
24	L2	TfO	NaHMDS (2.0)	THF	20
25	L2	TfO	^t BuOK(2.0)	THF	12
26	L2	TfO	CH ₃ ONa (2.0)	THF	15
27 ^c	L2	-	Cs ₂ CO ₃ (2.0)	DMSO	46
28 ^{c,d}	L2	-	Cs ₂ CO ₃ (2.0)	DMSO	80

^a Reactions performed using 1.0 equiv. of **1**, 1.2 equiv. of **2a**, 5 mol% of Pd(OAc)₂, 5 mol% of PhosphYL **L1** or **L2**, on a 0.4 mmol scale in 2 mL of dry solvent, N₂, 50 °C, 14 h.

^b Isolated yields.

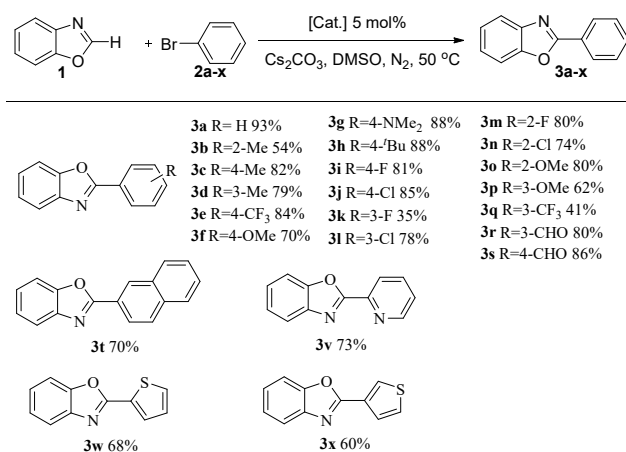
^c 5 mol% of salt-free ylide was used (preparation of salt-free ylide described in Supporting information).

^d 5 mol% of LiOTf was added.

The yield in **3a** was decreased from 93% (entry 13) with the salted ylide (**L2**/LiOTf) to 46% (entry 27) with the salt-free ylide, similar to the 50% yield (entry 14) obtained with the pseudo-salt-free ylide **L2**/LiPF₆ (contrary to TfO⁻, PF₆⁻ is totally inert with respect to the Pd and P⁺ centers). Under the same conditions, 1 equiv. of LiOTf was added to the salt-free ylide **L2**, the yield in **3a** was restored to 80%, thus demonstrating the key role of LiOTf (entry 28). The effect of LiOTf could be attributed to the interaction ability of the TfO⁻ anion with the P⁺ and/or the Pd(II) centers, by either electrostatic contact or coordination bonding [27].

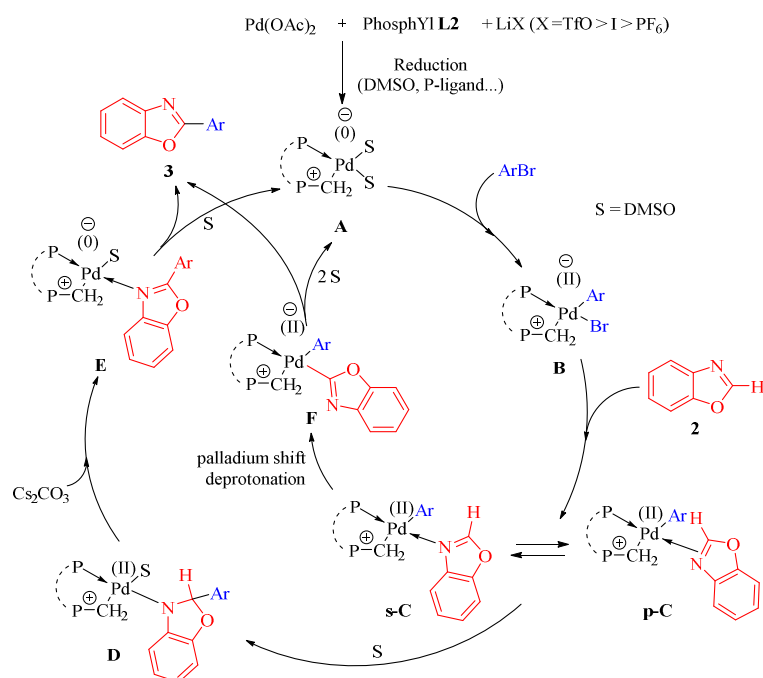
With the optimized reaction conditions in hand, the scope of the substrates was examined (Scheme 2). Benzoxazole **1** reacted smoothly with bromobenzene **2a** and its derivatives **2b-2t** to give the anticipated products **3a-3t** in moderate to high yields (35%-93%). Aryl bromides with a methyl group at the *para*- or *meta*-position (**2c-2d**) gave the corresponding products **3c** and **3d** in 82% and 79% yields, respectively. When the methyl group was attached at the *ortho*-position, a lower 54% yield was obtained, revealing the steric hindrance of the reacting position. The electron-withdrawing substituent CF₃ at the *para*-position of **2e** allowed isolation of the aryl-benzoxazole **3e** in a slightly higher yield (84%), while electron-donating OMe counterpart has the opposite effect on the corresponding product **3f** (70%). Nevertheless, both weakly electron-withdrawing (F, Cl) and strongly electron-donating (NMe₂, ^tBu) substituents gave higher yields (81%-88%), showing that the limiting step is not, at least not always, an S_NAr-like oxidative addition process of the C-Br bond to the electron-rich Pd center (a favored by electron-withdrawing substituents on the aryl ring) [28]. For substituent F, however, the classical trend is restored through the relative reactivity of the *para* and *ortho* aryl bromide derivatives **2i** and

2m (giving **3i** and **3m** in 81% and 80% yields) vs. the *meta* derivative **2k** (giving **3k** in 35% yield). This trend is also observed for the CF₃ substituent, giving 41% yield in **3q** for the *meta* position, vs. 84% yield in **3e** for the *para* position. For a non-fluorinated electron-withdrawing substituent, the position effect of the formyl group remains consistent but much less dramatic, giving 80% yield in **3r** for the *meta* position, vs. 86% yield in **3s** for the *para* position. For the donating OMe substituent, a remarkable counter-effect of the position is observed: while *para*- and *meta*-bromoanisoles led to the expected products **3f** and **3p** in 70% and 62% yields, respectively, the more hindered *ortho*-bromoanisole **2o** gave **3o** with a significantly higher yield of 80%, revealing an assistance of the OMe group. The isosteric, but non-coordinating *ortho*-bromotoluene **2b** gives **3b** in 54% yield only. 2-Bromonaphthalene and brominated heterocycles such as 2-bromopyridine, 2-bromothiophene, and 3-bromothiophene were also found to be suitable substrates, affording the corresponding products **3t** and **3v-3x** in 60%-73% yields.



Scheme 2. Substrate scope. All reactions were carried out using **1** (0.4 mmol), **2** (0.48 mmol), Pd(OAc)₂ (5 mol%), **L2**/LiOTf (5 mol), Cs₂CO₃ (2 equiv.) in DMSO (2.0 mL) at 50 °C for 14 h. Isolated yields.

On the basis of the previous literature reports and above experimental results, a tentative mechanism is proposed in Scheme 3. The PhosphYL ligand **L2** could first coordinate *in situ* to the Pd(II) center, prior to or after *in situ* reduction of Pd(II) (e.g. by the phosphine end of **L2** or DMSO) to Pd(0) in a zwitterionic palladate complex **A** similar to previously invoked. [12a,29].



Scheme 3. Putative mechanism for PhosphYI-Pd-catalysed 2-arylation of benzoxazole: alternative to the depicted Pd(0)/Pd(II) cycle, a Pd(II)/Pd(IV) cycle might also be envisaged.

Then, oxidative-addition of PhBr would give the Pd(II) intermediate **B**, from which the bromide anion would give the amido Pd(II) complex **D**. Deprotonation of **D** would afford the zwitterionic palladate intermediate **E**, which would release the arylbenzoxazole product **3** while regenerating the catalytic pivot **A**. Alternative processes could also be envisaged [9], *e.g.* via a Pd(II)/Pd(IV) cycle instead of the Pd(0)/Pd(II) cycle or through a transient isonitrile-phenolate resulting for the opening of the oxazole ring of **1** [7]. Nevertheless, the conversion $\sigma/\pi\text{-C} \rightarrow \mathbf{3} + \mathbf{A}$ could also proceed *via* a Pd-C-oxazolyl intermediate **F** from which the products would be directly released by reductive elimination, as invoked in the quinoline series [9,30]. The propositions remain, however, quite speculative, as preliminary attempts did not allow isolation of any pre-catalytic **L2**/Pd complex (mixture of several unidentified species were observed by $^{31}\text{P}/^1\text{H}$ NMR spectra).

In conclusion, the disclosed C-H arylation allows 2-arylbenzoxazoles to be produced in moderate to high yields over a night at 50 °C. The use of the particular PhosphYI BINAPIUM ylide **L2** proves to be superior to the use of classical phosphine ligands. The *in situ* catalytic system happens to be general for arylbromide substrates and specific hetero-unsaturated C-H substrates, *i.e.* benzoxazole. It is indeed found to be ineffective for related benzothiazole and imidazole substrates under standard conditions, but is thus selective. Considering the adjustable steric and electronic features of the ylide structure and the variety of ways to generate it from phosphonium precursors, prospects of optimization are open, in particular for extending the substrate scope. In this context, the axially chiral BINAPIUM backbone allows envisaging applications in enantioselective catalysis from prochiral substrates, *e.g.* in Cammidge-like coupling of 1-halophthalenes with dissymmetric bulky (hetero)cycles [31]. Beyond the scope of the present report of *in situ* catalysis investigations, further efforts in coordination chemistry will be

undertaken with the view to elucidating the actual structure of the catalyst. Finally, further extension of the potentialities of generic PhosphYI ligands in transition metal catalysis of other organic transformations deserves continuing investigations.

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Table 1. Drugs/therapies combined with bisphosphonates in osteosarcoma

BPs	Drug/therapy combined with BPS	Effects	References
Zoledronate	Paclitaxel, Doxorubicin Gemcitabine	Increased sensitivity to paclitaxel, doxorubicine and gemcitabine	[77]
Zoledronate	Cisplatin	Sensitization to cisplatin	[78]
Zoledronate	TRAIL	Enhanced sensitivity to TRAIL	[79]
Zoledronate	PF4942847 (HSP90 inhibitor)	Synergistic inhibitory effect on tumor cell proliferation, metastasis development	[80]
Zoledronate	OGX-11 (clusterin inhibitor)	Synergistic activity	[81]
Zoledronate	Ursolic acid	Increased cell apoptosis	[82]
Zoledronate	RAD001 (Everolimus)	Potentiated mTOR inhibition and abolishes the resistance of osteosarcoma cells to RAD001	[83]
Minodronate	p38 inhibitor Doxorubicin	Increased efficacy of p38 inhibitor and Doxorubicin	[84]
Zoledronate Pamidronate	Radiation	Radiosensitization	[85-87]
Zoledronate	Photochemotherapy	Enhanced effect	[88]