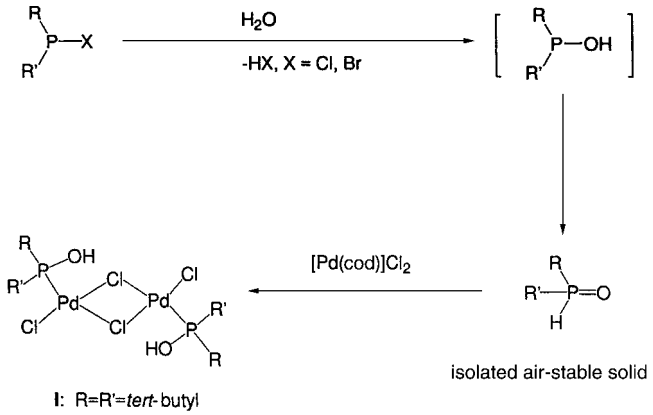
The First Phosphine Oxide Ligand Precursors for Transition Metal Catalyzed Cross-Coupling Reactions: C–C, C–N, and C–S Bond Formation on Unactivated Aryl Chlorides

George Y. Li*

Dedicated to Professor Fred Basolo on the occasion of his 81st birthday

In recent years, transition metal catalyzed cross-coupling reactions of aryl chlorides have developed into a versatile and efficient method for a variety of synthetic transformations.[1, 2] Furthermore, promising results in the Pd- (or Ni)-catalyzed C–C (Suzuki,[3–6] Kumada,[7] and Stille[8] cross-coupling) and C–N[9] bond-forming processes prompted us to search for new, inexpensive, and efficient air-stable ligands for potential industrial applications of these less expensive but readily available aryl chlorides. One potentially valuable and cost-saving approach is to apply combinatorial synthesis and screening methods for the discovery and development of efficient, air-stable novel catalysts.[10, 11] Air-stable phosphine oxides (RR′P(O)H) in the presence of transition metals undergo tautomerization to the less stable phosphinous acids (RR′POH), which subsequently and expectedly coordinate to the metal centers through phosphorus atoms to form metal–phosphinous acid compounds.[12] Deprotonolysis of the resulting phosphinous acid complex with base (e.g. NaOR, Na_2CO_3, CsF) can be anticipated to yield an electron-rich anionic compound. These results raise the interesting question of whether these phosphane-containing anionic complexes could be utilized to facilitate oxidative addition of aryl chlorides (rate-limiting step) in homogeneous catalysis[13] to generate a variety of C–C, C–N, and C–S[14] bonds in different environments by using cross-coupling reactions of aryl chlorides. Herein, we report the first examples of simple, readily accessible, air-stable phosphine oxides used as ligand precursors for the efficient transition metal catalyzed C–C, C–N, and C–S bond-forming reactions of aryl chlorides to access a variety of such architectures, as well as initial observations regarding the scope and mechanism. We also describe a general synthesis of binuclear chloride-bridged Pd^{II} monophosphinous acid complexes used as catalyst precursors for a variety of cross-coupling reactions and the X-ray crystallographic characterization of one of them.

The ligand precursors used for cross-coupling reactions were prepared either in situ or by standard sublimations (Scheme 1).[10, 11, 15] The precatalysts were synthesized by treating transition metal precursors with monophosphine oxides in a variety of solvents at either room temperature or elevated temperature. The formation of these catalyst precursors was conveniently monitored by solution ^{31}P NMR spectroscopy.[16] The catalytic cross-coupling reactions were carried out in organic solvents (e.g. toluene, DMSO, dioxane) under anhydrous/anaerobic or open-to-air conditions (catalyst loading: ~1–5 mol%).[17] The yields in Table 1 refer to products isolated by column chromatography. Known products were identified by comparison with literature data[4–9, 14] and/or with those of authentic samples. New compounds were characterized by 1D and 2D $^1H/^{13}C$ NMR spectroscopy, high-resolution mass spectrometry, and elemental analysis.[17]



Scheme 1. Synthesis of air-stable phosphine oxide ligand precursors and their corresponding phosphinous acid ligand complexes. cod = 1,5-cyclooctadiene.

The $[Pd_2(dba)_3]$/RR′POH precatalysts are capable of catalyzing the cross-coupling reactions of aryl chlorides and arylboronic acids to yield the desired biaryls in high yields (Table 1, entries 1–6). Entries 4–6 illustrate that the electron-rich 4-chloroanisole could be coupled with arylboronic acids quantitatively. Entries 2 and 3 demonstrate that the more sterically demanding and electron-rich substrate 2-chloroanisole was coupled with 4-methylphenylboronic acid (Table 1, entry 2) and phenylboronic acid (Table 1, entry 3). The $[Ni(cod)_2]$/RR′POH precatalyst can be employed to mediate Kumada cross-coupling reactions of aryl chlorides and RMgX at room temperature (Table 1, entries 7 and 8). The electron-rich aryl chloride is tolerated by the present system as demonstrated by 4-chloroanisole (Table 1, entry 7). Entries 9–12 reveal that the present catalysts are also effective in the C–N bond cross-coupling reactions of aryl chlorides with a variety of amines. Entries 9, 10, and 12 illustrate aminations of aryl chlorides and alkylamines. Entry 11 shows that an aryl chloride/arylamine cross-coupling reaction produces a diarylamine. Also noteworthy are the successful catalytic activities on C–S bond-forming processes of unactivated aryl chlorides. The present air-stable phosphine oxides are capable of forming precatalysts with $Pd(OAc)_2$ or $[Pd_2(dba)_3]$ to efficiently catalyze cross-coupling reactions of aryl chlorides and alkylthiols to yield novel thioethers (Table 1, entry 13). In the case of aryl bromides as substrates, the present phosphinous acids can be employed as ligands for the efficient C–S bond formations at room temperature (Table 1, entry 14).

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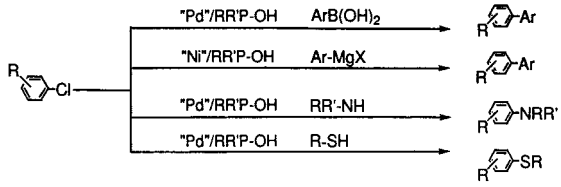
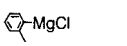
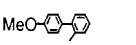
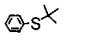
Table 1. Transition metal/phosphinous acid catalyzed cross-couplings of aryl chlorides with Ar–B(OH)$_2$, RMgX, RNH$_2$, and RSH compounds.[a]



Entry	Halide	Coupling partner	Base	Temp [°C]	Time [h]	Product	Yield [%] (isolated)
1			$CsCO_3$	100	12		88[b]
2			CsF	100	12		83[b]
3			CsF	100	12		91[c]
4			CsF	100	12		97[b]
5			CsF	100	12		99[c]
6			CsF	100	12		99[b,d]
7			none	RT	12		93[e]
8			none	RT	12		96[e]
9			NaO*t*Bu	100	12		51[b]
10			NaO*t*Bu	100	12		61[b]
11			NaO*t*Bu	100	12		44[b]
12			NaO*t*Bu	100	12		67[b]
13			NaO*t*Bu	100	24		26[f]
14			NaO*t*Bu	RT	24		49[f]

[a] General reaction conditions (not optimized): aryl halide (1.0 equiv), boronic acid (or RMgX, RNH$_2$, RSH) (1–1.5 equiv), CsF (or NaO*t*Bu) (1.0–3.0 equiv), [Pd$_2$(dba)$_3$] (0.5–2.5 mol%; dba = *trans*,*trans*-dibenzylideneacetone), 1.0–5.0 mol% ligand. [b] [Pd$_2$(dba)$_3$]/(*t*Bu)$_2$P(O)H as precatalyst. [c] [Pd$_2$(dba)$_3$]/(*t*Bu)$_2$PCl/H$_2$O as precatalyst. [d] [Pd$_2$(dba)$_3$]/(*t*Bu)$_2$P(O)H or [Pd$_2$(dba)$_3$]/(2,4-(OMe)$_2$C$_6$H$_3$)$_2$P(O)H as precatalyst. [e] [Ni(cod)$_2$]/(*t*Bu)$_2$P(O)H as precatalyst. [f] [Pd$_2$(dba)$_3$]/(*t*Bu)$_2$PCl/H$_2$O as precatalyst.

Several features of these phosphinous acid ligands are noteworthy and provide both informative parallels and contrasts to the corresponding phosphane ligands[5, 8, 9, 14] in the cross-coupling reactions of aryl chlorides. Air-stable phosphine oxides (RR′P(O)H) can be employed in the present process as ligand precursors to produce electron-rich phosphane-containing anionic complexes in the presence of bases. We found that [Pd(cod)Cl$_2$] reacts smoothly with phosphine oxides (RR′P(O)H), in dioxane solution, affording a new binuclear derivative shown in Scheme 1. Well-characterized examples of this type of Pd^{II} complex are extremely rare.[12] Complex **I** was isolated and characterized by X-ray crystallography (see Supporting Information) and the structure is shown in Figure 1. As expected, the core structure of complex **I** is based on P–Pd coordination with phosphinous acid ligands (RR′POH). Important features of the structure of **I** include the O1–P1 and P1–Pd1 bond lengths of 1.5922 and 2.2434(6) Å, respectively. The O1–P1 distance is about 0.105 Å longer than the P=O double bond length in RRP(O)H and to a first approximation can be interpreted as a O–P single bond. Also noteworthy is the facile preparation of these air-stable phosphine oxide ligand precursors which can be generated as libraries by using polymer-supported synthesis [Eqs. (1) and (2)].[10, 11]

Figure 1. Structure of the dichloro(di-*tert*-butylphosphinous acid)palladium(II) dimer (ORTEP view; 50% probability). The 12 methyl groups are omitted for clarity. Selected interatomic distances [Å] and angles [°]: Pd1-P1 2.2434(6), Pd1-Cl2 2.2917(6), Pd1-Cl1 2.3188(6), Pd1-Cl1* 2.4500(6), Cl1-Pd1* 2.4500(6), P1-O1 1.5922(17); P1-Pd1-Cl2 90.36(2), P1-Pd1-Cl1 95.39(2), Cl2-Pd1-Cl1 174.23(2), P1-Pd1-Cl1* 179.109(19), Cl2-Pd1-Cl1* 88.76(2), Cl1-Pd1-Cl1* 85.48(2), Pd1-Cl1-Pd1 94.52(2), O1-P1-C5 100.47(10), O1-P1-C1 102.65(10), C5-P1-C1 116.54(10), O1-P1-Pd1 111.10(7).

(1)

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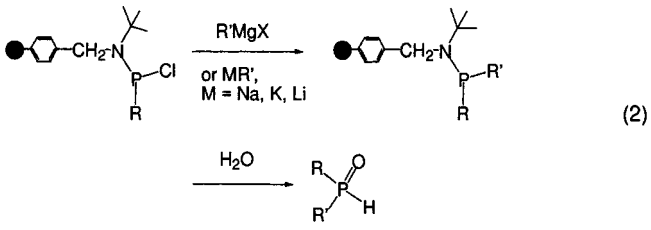

(2)

In conclusion, these results demonstrate that air-stable phosphine oxides (RR′P(O)H) are ideal ligand precursors for the formation of phosphinous acid (RR′POH)–metal complexes for the rapid and regioselective oxidative addition of unactivated aryl chlorides in the presence of bases, and that such processes can be incorporated into efficient catalytic cycles for a variety of C–C, C–N, and C–S bond-forming processes. Noteworthy are the efficiency for unactivated aryl chlorides, as well as the simplicity, low cost, air-stability, and ready accessibility by using polymer-supported synthesis of these ligand precursors.

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[16] A reaction of $[Pd_2(dba)_3]$ (100 mg, 0.109 mm) and $(t\mathrm{Bu})_2\mathrm{PH(O)}$ ((36.0 mg, 0.218 mmol), $^{31}P\{^1H\}$ NMR: $\delta = 69.8$ (d, $^1J(P,H) =$

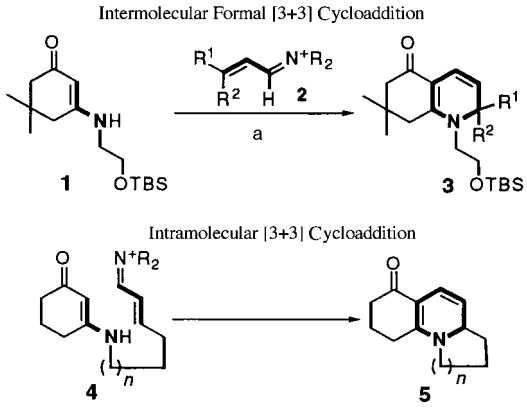
434.2 Hz)) in 1,4-dioxane (6.0 mL) at room temperature for 6 h generated a brown mixture exhibiting a ^{1}H-coupled ^{31}P NMR resonance at $\delta = 123.4$ (singlet).

[17] See Supporting Information for full synthetic details and characterization of new compounds. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157421. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Novel and Highly Stereoselective Intramolecular Formal [3+3] Cycloaddition Reaction of Vinylogous Amides Tethered with α,β-Unsaturated Aldehydes: A Formal Total Synthesis of (+)-Gephyrotoxin**

Lin-Li Wei, Richard P. Hsung,* Heather M. Sklenicka, and Aleksey I. Gerasyuto

We have been exploring reactions of β-diketo equivalents **1** with α,β-unsaturated iminium salts **2** for the construction of heterocycles such as **3** (Scheme 1).[1–3] These reactions involve a sequence consisting of a Knoevenagel condensation followed by a six π-electron electrocyclic ring-closure,[4] thereby constituting a stepwise formal [3+3] cycloaddition[5–7] in which two σ bonds are formed, along with a new stereocenter adjacent to the heteroatom. This cycloaddition protocol can be classified as a sequential anionic–pericyclic strategy for which the significance in natural product synthesis has been elegantly summarized by Tietze and Beifuss.[8] Our recent work on the use of vinylogous amides in this formal cycloaddition[1] has allowed us to envision an intramolecular version of this reaction. Since the vinylogous amide **1**, which contains a functionalized tether, provided the formal cycloadduct **3** in good yields,[1] it is conceivable that the vinylogous amides **4**, which are tethered with an α,β-unsaturated iminium ion, may lead to piperidinyl heterocycles **5**, attractive as intermediates in the syntheses of natural alkaloids (Scheme 1). We report herein the first stereoselective intramolecular formal [3+3] cycloaddition reaction by using vinylogous amides that are tethered with iminium ions, and its application in a formal total synthesis of (+)-gephyrotoxin.[9–11]



Scheme 1. [3+3] Cycloaddition reactions of vinylogous amides and α,β-unsaturated iminium salts. Reagents and conditions: a) EtOAc/toluene 1:2, 150 °C, 15–30 h, 76–80%; TBS = *tert*-butyldimethylsilyl.

Based on our previous studies, the formation of the α,β-unsaturated iminium salt prior to the addition of a β-diketo nucleophile is crucial to the regio- and chemoselectivity of the intermolecular formal cycloaddition reaction.[1, 2a] Conditions and protocols that generate α,β-unsaturated iminium salts in the presence of the β-diketo nucleophile lead to low yields of the desired products, and/or to synthetically less useful by-products resulting from various competing reaction pathways.[7b–e] However, the enal precursor to α,β-unsaturated iminium ions in the intramolecular variant also contains a vinylogous amide. Thus, controlling the extent of iminium ion formation before competing reactions take place is a major challenge.

To demonstrate the feasibility of an intramolecular formal [3+3] cycloaddition, the vinylogous amides **6** and **7** were prepared[12, 13] and treated with piperidine (2.0 equiv) and Ac_2O (2.0 equiv) in EtOAc/toluene (1:2; concentration of vinylogous amides: 0.03–0.30 M) at 85 °C for 1 h (Scheme 2). These are the standard reaction conditions that have been consistently employed for the formation of iminium salts.[1, 2] Subsequent heating at 150 °C in a sealed tube led to the isolation of the desired heterocycles **8** and **9** in yields of 80 and 68%, respectively. Furthermore, the chiral vinylogous amide **10**[12] led to the desired tricycle **11** in 55% yield as a single diastereomer under the same reaction conditions. The stereochemistry of **11** was assigned by NOESY experiments.

These examples suggest that our initial concern regarding the extent of iminium salt formation was not necessary; under conditions that do not promote the formation of iminium ions, these reactions were essentially arrested. This control study suggests that even a low concentration of the iminium species is sufficient to promote this intramolecular formal [3+3] cycloaddition reaction. On the other hand, under the same standard reaction conditions, the vinylogous amide **12** did not provide the desired cycloadduct **13** in useful yields (Scheme 2). We were, however, able to observe the formation of **13** by ^{1}H NMR spectroscopy; thus our inability to isolate **13** from **12** may be a result of the instability of **13** under the reaction conditions and/or under the work-up conditions. This prompted us to explore other protocols suitable for generating iminium salts.

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