Dalton Transactions

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Sequential Electrophilic P–C Bond Formation in Metal-Coordinated Chlorophosphines

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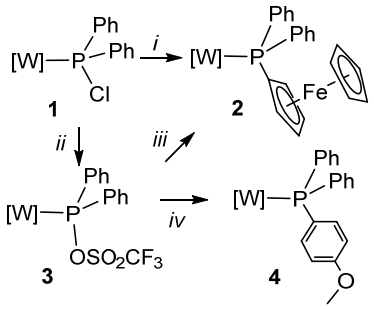
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

In the presence of chloride abstractors, metal-coordinated chlorophosphines undergo facile room-temperature electrophilic substitution reactions with unsaturated organic substrates, leading to P–C bond formation. This methodology can be applied sequentially two or three times, stepwise or in one-pot reactions, to form phosphines with three different substituents. The reactions are rapid and high-yielding, and can be applied to a wide range of organic substrates, making them valuable tools for P–C bond formation.

Tertiary phosphines, including unsymmetrical phosphines, find widespread use as ligands for transition metal catalysis,[1] and as organic catalysts[2] due to the tunability of their electronic and steric properties.[3] Phosphorus–carbon bond formation is an essential step in the synthesis of tertiary phosphines, and the development of new P–C bond forming reactions has been identified as an important goal for the future advancement of organometallic chemistry.[4] The most commonly used P–C bond forming methods involve the reaction of strong carbon-based nucleophiles, typically organolithium or Grignard reagents, with phosphorus electrophiles, usually chlorophosphines.[5] Despite their wide application, these methods have limitations, including availability and cost of organometallic reagents or their precursors, a lack of functional group tolerance,[6] and uncontrolled multiple substitutions on di- or trichloro phosphines.[5] One strategy for avoiding strong organic nucleophiles is to increase the electrophilicity of the phosphorus reagent via halide abstraction, leading to Friedel-Crafts-like electrophilic substitution reactions. Although these reactions have been known for a long time,[7] they are not as widely used, likely because they require high temperatures and are often slow and low-yielding.[8] We reasoned that the electrophilicity of the phosphenium intermediate in these reactions might be enhanced by coordination to an electron-poor metal. Previous researchers have shown that metal coordinated phosphenium ions are strongly electrophilic,[9] however, application of these complexes to P–C bond formation is very limited.[10] In two previous papers, we described two methods to enhance electrophilicity of metal coordinated chlorophosphirenes: chloride abstraction with $AlCl_3$ to form phoshirenyl cation complexes, and with silver triflate to form phosphirene triflate complexes. We showed that $W(CO)_5$ coordinated phosphirenyl cations and phosphirenyl triflates undergo facile P–C bond forming reactions with a range of substrates, and that metal coordination indeed enhances electrophilicity.[11] In this communication, we demonstrate that this reactivity is general for chlorophosphines and can be applied sequentially, and thus has wide applicability to phosphine synthesis.

We first examined PPh_2Cl, as the PPh_2 unit is ubiquitous in phosphine ligands, and new methods to add this group to organic substrates are potentially valuable. The chlorophosphine complex $[W(CO)_5\{PPh_2Cl\}]$ (**1**)[12] did not react with 1 equiv of $AlCl_3$. However, addition of 4 or more equiv led to a color change and the disappearance of **1** in the $^{31}P\{^1H\}$ NMR spectrum, but no detectable signal for a phosphenium ion, suggesting that an equilibrium mixture between **1** and a phosphenium complex or an $AlCl_3$ adduct is being formed. The reactivity of this solution towards a range of organic substrates has been tested. Two illustrative examples are described here. Addition of ferrocene resulted in immediate formation of the diphenyl ferrocenyl phosphine complex **2**, in a high yield (83%) (Scheme 1). This rapid reactivity at room temperature demonstrates the increased

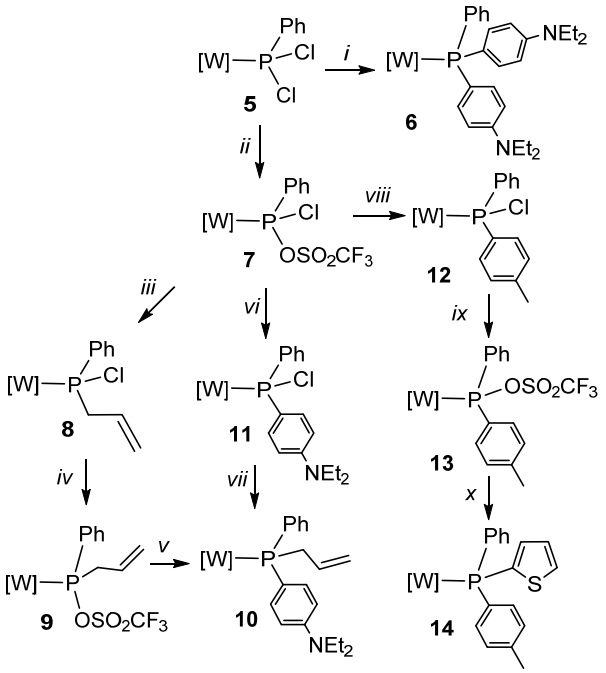


Scheme 1. Electrophilic substitution reactions of tungsten-coordinated chlorodiphenylphosphine. Reagents and conditions: CH_2Cl_2, RT, (i) $AlCl_3$, 4 equiv, Ferrocene, 2 equiv; (ii) $AgOSO_2CF_3$, 1.2 equiv, 2h; (iii) Ferrocene, 2 equiv; (iv) anisole, 10 equiv, 12h. [W] = $W(CO)_5$.

electrophilicity of the metal-coordinated phosphorus center, as the comparable reaction with metal-free PPh_2Cl required 24h at 105 °C to achieve 59% yield.[13] Ferrocene also reacts with **1** in the presence of 1 equiv of $AlCl_3$, however, the reaction is much slower, requiring 48h to go to completion. To probe the lower reactivity limit, the reaction with the weakly activated substrate anisole was attempted, but led to reversion to the precursor, suggesting that anisole is interacting with $AlCl_3$. These observations suggest that $AlCl_3$ does not abstract Cl, but interacts with it, enhancing its leaving group ability. A similar mechanism

has been described in a related chlorophosphirane system.[14] The limited functional group tolerance of the $AlCl_3$ methodology led us to consider silver triflate as an alternative. Compound **1** reacts with silver triflate to form diphenyl phosphine triflate complex **3**. Reaction of **3** with ferrocene afforded **2**, in an excellent yield (92%). Reaction with anisole in CH_2Cl_2 at room temperature for 12h afforded the regiospecific *para*-substituted anisolyl diphenyl phosphine complex **4**, in 82% yield. This reaction shows that the triflate methodology is appropriate for cases where the $AlCl_3$ is incompatible with the substrate.

Successful mono-substitution reactions led us to consider the possibility of sequential multiple substitutions. We next explored the reactivity of dichloro phenyl phosphine complex $[W(CO)_5\{PPhCl_2\}]$ (**5**).[15] Addition of $AlCl_3$ to **5** resulted in a color change, the disappearance of **5** in the $^{31}P\{^1H\}$ NMR spectrum, but no detectable signal for a phosphenium ion. Addition of activated substrates to this solution leads to disubstitution, regardless of stoichiometry, illustrated here in the reaction with *N*,*N*-diethylaniline. Addition of 1 equiv of substrate and 1 equiv of $AlCl_3$ leads to a 50:50 mixture of **5** and the bis(*N*,*N*-diethyl anilinyl) phenyl phosphine complex **6**. Addition of 2 equiv of substrate and excess $AlCl_3$ leads to **6** as the only major product. Greater control can be achieved by using silver triflate as the chloride abstractor. Reaction of **5** with 1.2 equiv of $AgOSO_2CF_3$ for 3h at room temperature selectively abstracts one chloride and forms the chloro phenyl triflate phosphine complex **7** (Scheme 2), which reacts with substrates to give monosubstituted products. For example, reaction of **7** with allyl

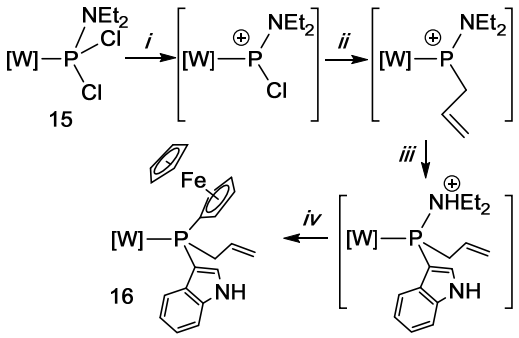


Scheme 2. Sequential electrophilic substitution reactions of tungsten-coordinated dichlorophenylphosphine. Reagents and conditions: CH_2Cl_2, RT, (i) $AlCl_3$, *N*,*N*-diethylaniline, 1 equiv; (ii) $AgOSO_2CF_3$, 1.2 equiv, 3h; (iii) allyl trimethylsilane, 3 equiv; (iv) $AgOSO_2CF_3$, 1.2 equiv, 12h; (v) *N*,*N*-diethylaniline, 2 equiv; (vi) *N*,*N*-diethylaniline, 2 equiv; (vii) allyl trimethylsilane, 3 equiv, $AlCl_3$, 1 equiv; (viii) toluene, 15 equiv, 36h; (ix) $AgOSO_2CF_3$, 1.2 equiv, 2h. (x) thiophene, 2 equiv. [W] = $W(CO)_5$.

trimethylsilane leads to the allyl phenyl chloro phosphine complex **8** (Scheme 2). Compound **8** can then be converted to allyl phenyl phosphine triflate complex **9** via addition of $AgOSO_2CF_3$, and then to the allyl-anilinyl-phenyl phosphine complex **10** via addition of *N*,*N*-diethylaniline. Compound **10** can also be obtained from **7** by altering the sequence of addition. Reaction of **7** with *N*,*N*-diethylaniline leads to the *para*-substituted anilinyl phenyl chloro phosphine complex **11**. Addition of $AlCl_3$ to **11** in the presence of allyl trimethylsilane then leads to **10**.

Compound **7** also reacts with the unactivated substrate toluene to afford the *para*-substituted tolyl phenyl chloro phosphine complex **12** (Scheme 2). This reaction demonstrates that **7** is more electrophilic than **3**, and is capable of activating very unreactive substrates. The higher reactivity can be attributed to electronegative Cl substituent, which increases electrophilicity at P. In the subsequent step, compound **12** was converted to the corresponding triflate **13**, and reacted with thiophene, to form the phenyl-*p*-tolylthienylphosphine complex **14.**

Sequential formation of two P–C bonds from **5** led us to consider the sequential introduction of three P–C bonds to the trichloro phosphine complex $[W(CO)_5\{PCl_3\}]$.[16] Unfortunately, this complex was unreactive toward $AlCl_3$, $AgOSO_2CF_3$ and all other chloride abstractors we tried. Furthermore, there was no reaction with any organic substrate in the presence of $AlCl_3$. This suggests that the Cl substituents lack sufficient π-donation to stabilize a transient dichloro phosphenium ion. Since amino substituents are well-known to effectively stabilize the low-valent phosphorus species through π-donation,[17] we next considered the *N*,*N*-diethylaminodichloro phosphine complex $[W(CO)_5\{P(NEt_2)Cl_2\}]$ (**15**).[18] Reaction of **15** with 1 equiv of $AlCl_3$ resulted in immediate formation of a red solution. Using this solution, we have demonstrated a one-pot sequential triple P–C bond formation using three different substrates (Scheme 3). First, allyl trimethylsilane was used to add an allyl group. This was followed by addition of indole (1.3 equiv), followed by ferrocene (1.0 equiv), to give the indolyl allyl ferrocenyl phosphine complex **16** in 79% yield (Scheme 3). In this reaction



Scheme 3. A one-pot sequential triple electrophilic substitution reaction. Reagents and conditions: CH_2Cl_2, RT. (i) $AlCl_3$, 1 equiv, 15 min; (ii) allyl trimethylsilane, 1 equiv, 10 min; (iii) indole, 1.3 equiv; (iv) ferrocene, 1 equiv, 12h. [W] = $W(CO)_5$.

sequence, the regeneration of $AlCl_3$ as a by-product of the first step promotes the second substitution step by abstracting chloride, while the HCl generated in the second step promotes the third substitution step by protonating the amino group. Compound **16** has been characterized by X-ray crystallography, and an ORTEP diagram of the structure in shown in Figure 1.

In summary, we have demonstrated that in the presence of $AlCl_3$ or after treatment with $AgOSO_2CF_3$, tungsten-coordinated chlorophosphines undergo facile and regioselective electrophilic substitution reactions with various unsaturated substrates. These reactions can be applied sequentially in a controlled fashion to dichloro phosphines and aminodichlorophosphines. The two chloride abstractors $AlCl_3$ and $AgOSO_2CF_3$ are complementary, and most potential substrates are compatible with one or the other. As a result, functional group compatibility is wide. Further,

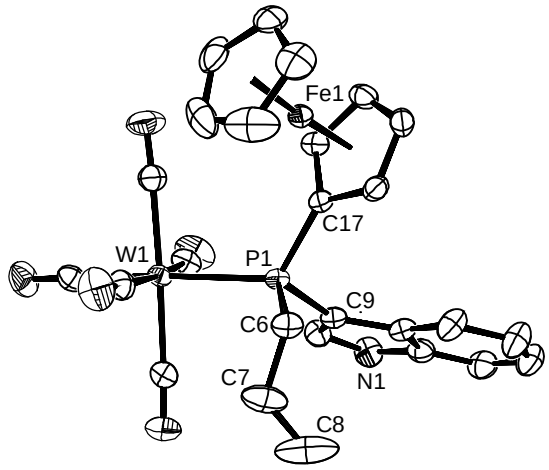


Figure 1. ORTEP diagram showing the molecular structure of **16**. Thermal ellipsoids are shown at the 50% probability level, and H atoms have been omitted.

these reactions all occur at room temperature or lower. A systematic investigation on the reactivity of these metal-coordinated chlorophosphines with other functionalized aromatic substrates, and other organic substrates such as alkenes, alkynes, and ketones is currently underway. Because reactions are rapid and high-yielding, and can be applied to a wide range of organic substrates, they are potentially valuable tools for P–C bond formation and phosphine ligand synthesis. We are also now extending this methodology to lower cost metals like iron, and catalytically active metals like palladium.

This work was financially supported by the University of Regina. We thank Bob McDonald and Mike Ferguson (University of Alberta) for X-ray data collection.

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† Electronic Supplementary Information (ESI) available: Experimental details and compound characterization data. A CIF file containing crystallographic data for 1**6**. See DOI: 10.1039/b000000x/

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