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Copper-catalyzed synthesis of alkynylphosphine derivatives: unprecedented use of nucleophilic phosphorus compounds[†]

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A new and smooth approach towards alkynylphosphine derivatives is described. It relies on the unprecedented catalytic coupling of secondary phosphine boranes with alkynyl bromides using the CuI/1,10-phenanthroline couple.

Phosphines play a key-role as ligands in transition metal catalysis, and as chiral controllers in asymmetric processes.¹ The design of new phosphine structures, which allow the tuning of the steric and electronic properties of the organometallic complexes employed as catalysts, is essential for the expansion of the scope of available catalytic transformations. For this purpose alkynylphosphines² are attractive building blocks in view of the rich and diverse chemistry of the alkynyl function.³ Moreover they also deserve interest as useful ligands for homogeneous catalysis because of their unique structural feature due to the linearity of the triple bond.^{4,5}

The few known methods for the preparation of alkynylphosphines involve the nucleophilic substitution reaction at the phosphorus atom of a halophosphine by a metal acetylide at low temperature.⁶ A catalytic variant, recently developed, consists in the cross-coupling reaction of terminal alkynes with chlorophosphines catalyzed by nickel, palladium or copper complexes.⁷ The application of these methods to the asymmetric series⁵ is tricky, because of the limited access to unsymmetrical halophosphines and their weak configurational stability. Thus, the emergence of complementary phosphination reactions should expand the range of available racemic and P-stereogenic derivatives. The obvious alternative, the direct C-P bond formation via oxidative coupling with terminal alkynes, as recently described for the synthesis of alkynylphosphonates,⁸ is difficult to envisage due to the highly oxidizable nature of phosphine derivatives. As part of our research program dedicated to the development of new catalytic syntheses of phosphines,9 we report here the unprecedented use of nucleophilic phosphorus compounds for the preparation of alkynylphosphines through Cu(1)-catalyzed cross-coupling



Scheme 1 Strategies for the synthesis of alkynylphosphines.

reaction between secondary phosphine boranes and 1-bromoalkynes (Scheme 1).

In the context of the fast expanding area of coppercatalyzed carbon–heteroatom cross-coupling reactions,¹⁰ the phosphorus series has been neglected.^{8,11,12} Only 3 publications report the use of phosphines as cross-coupling partners,¹¹ presumably because of the high affinity of phosphines to bound coinage metals. In order to limit the possible poisoning of the copper catalyst, we selected phosphine boranes¹³ as phosphinating agents and the readily available 1-bromoalkynes,¹⁴ recently used with success as coupling partners in the catalytic synthesis of *N*-functionalized alkynes.

To initiate our study we examined the reaction between diphenylphosphine borane **1a** and 1-bromohexyne **2a**. A preliminary screening of the conditions allowed us to select CuI (10 mol%) as the copper source, K_2CO_3 (2 equiv.) as the base, toluene as the solvent and a mild temperature of 40 °C. Under these conditions, 35% of the expected product was formed. Worthy of note is that copper is required to promote the coupling, no reaction occurring when it is omitted (Table 1, entry 1 vs. 2).

To improve the conversion, a bidentate ligand was combined with copper. The known ability of amines to favour the decomplexation^{13,15} of phosphine boranes led us to select 1,10-phenanthroline,¹⁶ a less basic ligand. Screening of various catalyst loadings and ligand/copper ratios showed that the most appropriate catalytic conditions consisted of Cu(1)I/phenanthroline in a 1 : 1 ratio (10 mol%). Once the suitable catalytic system was established, various solvents and bases were screened. Toluene proved to be optimal whereas highly coordinating polar solvents such as acetonitrile or THF prevented the reaction to occur. Among the most common bases employed for copper catalysis, K₂CO₃ afforded the best

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 Table 1
 Optimisation of the coupling reaction between 1a and 2a^a

| Ph | ВН ₃ ╱Р~н — [∩] Н С ^{Ph} 1а | Br <u>2a</u> ul/1,10-phenan Base, toluer | -n-Bu throline | B │ Ph │ Ph │ P | H ₃ | −n-Bu |
|--------|---|--|------------------------|-----------------------------|--------------------|-----------------------|
| Entry | Catalytic system | Base (equiv.) | $T/^{\circ}\mathrm{C}$ | Time/h | Conv. (%) | $\mathbf{3a}^{b}$ (%) |
| 1 | CuI | $K \cdot CO \cdot (2)$ | 40 | 16 | 61 | 35 |
| 1) | Cui | $K_2CO_3(2)$ | 40 | 16 | 0 | 0 |
| 2 | - CuI/L 1 · 1 | $K_2CO_3(2)$ | 40 | 3.5 | 100 | 100 |
| , 1 | $CuI/L 1 \cdot 1$ $CuI/L 1 \cdot 1$ | $K_2CO_3(2)$ | 40 | 2.5 | 01 | 100 91 |
| + | CuI/L 1 . 1 CuI/L 1 . 1 | $V_{2}CO_{3}(2)$ | 40 | 5.5 | 91 | 01 |
|) | Cul/L 1 : 1 | $\mathbf{K}_{3}\mathbf{PO}_{4}(2)$ | 40 | 3.5 | 99 | 80 |
| 5 | CuI/L 1 : 1 | $K_2CO_3(1)$ | 40 | 5 | 46 | 46 |
| 7 | CuI/L 1 : 1 | $K_2CO_3(2)$ | 20 | 5.5 | 100 | 100 |
| | | | | | | |

^{*a*} Reaction conditions: **1a** (50 mg, 0.25 mmol), **2a** (1 equiv.), CuI (10 mol%), L = 1,10-phenanthroline (10 mol%), base (1 or 2 equiv.), toluene (4 mL). ^{*b*} Measured from the crude product by ³¹P NMR.

results (Table 1, entry 3 vs. 4 or 5). Under optimized conditions, the complete conversion of **1a** into **3a** was reached after only 3.5 h at 40 °C (entry 3).¹⁷ Interestingly, a 1 mol% catalyst loading was also suitable to reach full conversion providing that the reaction time was extended to 38 h. Reducing the amount of base from 2 to 1 equiv. had a detrimental effect on the conversion (entry 6), probably because of the weak solubility of K_2CO_3 in toluene. It is worth noting that with the CuI/phenanthroline couple, the reaction proceeded even at room temperature leading to a full conversion after only 5.5 h (entry 7). The purification was performed by silica gel flash chromatography, affording phosphine borane **3a** in 74% yield (Table 2, entry 1). Importantly, the reaction was scaled-up to gram-scale with similar yields.

The scope and limitations of this reaction were then evaluated by testing a range of alkynyl bromides as coupling partners with diphenylphosphine borane **1a** (Table 2). Like **2a**, alkyl bromoalkyne **2b** readily underwent the cross coupling reaction at 40 °C (entry 2), whereas a temperature of 60 °C was more suitable for the bulky silylated 1-bromoalkyne **2c** (entry 3) and for aryl 1-bromoalkynes **2d–e** (entries 4 and 5). By contrast electron-deficient 1-bromoalkynes ($\mathbf{R} = CO_2Me$, 4-NO₂Ph) failed to react under the defined conditions.

We next examined the scope of secondary phosphine boranes. It is important to recall that, due to its higher reactivity compared to phosphines bearing alkyl substituents, diphenylphosphine is often the only phosphine used in coupling reactions. This is a strong limitation in term of diversity. Interestingly, under the conditions previously defined, diethylphosphine borane 1b, selected as a model of alkylphosphines, was cleanly converted into the coupling products 3f-i (full conversion after 38 hours, Table 2, entries 6-9). In the case of methylphenylphosphine borane 1c, K₃PO₄ was preferred to ensure a complete conversion (20 h at 60 °C). The corresponding alkynylphosphines 3j-k were isolated in 50-52% yields (entries 10 and 11). This result is of interest since it opens the way to the development of an enantioselective version of the reaction through the use of a chiral ligand associated to a copper(1) salt. The mild conditions used (20 to 60 °C) strongly contrast with the harsh conditions (110 °C, 15 h) required for the copper-catalyzed cross-coupling of aryl

 Table 2
 Scope of the copper-catalyzed cross-coupling reaction of secondary phosphine boranes with alkynyl bromides^a

| BH₃ [→] P→H R ^{1→} H R ² 1a-c | | BrR (1 equiv.) 2a-e Cul (10 mol%) 1,10-phenanthroline (10 mol%) K ₂ CO ₃ (2 equiv.), toluene, 60 °C | | | BH | ₃ ─────R | |
|--|------------------------------|---|--|--|----------|--------------------|------------------------|
| | | | | | %) °C | $R^{1^{-1}}$ R^2 | 3a-k |
| Entry | 2 (R) | | Alkynylph | osphine | 3 | Time/h | Yield ^b (%) |
| 1 | 2a (n-Bu) | I | BH ₃ Ph ₂ P | n-Bu | 3a | 5 | 74 ^{<i>c</i>} |
| 2 | 2b (C ₁₀ H | 21) | BH ₃ Ph ₂ P | -(CH ₂) ₉ CH ₃ | 3b | 16 | 69 ^{<i>c</i>} |
| 3 | 2c (TIPS) |) | Ph ₂ P — | TIPS | 3c | 16 | 55 |
| 4 | 2d (Ph) | | $Ph_2P \xrightarrow{BH_3}$ | ⊟—Ph | 3d | 5 | 69 |
| 5 | 2e (<i>o</i> -Me | O–Ph) | BH ₃ Ph ₂ P | — <i>o</i> -Anisyl | 3e | 20 | 59 |
| 6 | 2a | | $Et_2P \xrightarrow{BH_3}$ | n-Bu | 3f | 38 | 60 |
| 7 | 2b | | Et ₂ P | -(CH ₂) ₉ CH ₃ | 3g | 38 | 58 |
| 8 | 2c | | $Et_2P \xrightarrow{BH_3}$ | TIPS | 3h | 38 | 58 |
| 9 | 2d | | $Et_2P \overset{BH_3}{=}$ | Ph | 3i | 38 | 59 |
| 10 | 2a | | Ph ⁻ Ph ⁻ Me | n-Bu | 3j | 21 | 50 ^d |
| 11 | 2d | | BH3 Ph-== Me | — Ph | 3k | 20 | 52 ^{<i>d</i>} |

^{*a*} Reaction conditions: **1a–c** (0.75 or 0.96 mmol), **2a–e** (1 equiv.), CuI (10 mol%), 1,10-phenanthroline (10 mol%), K₂CO₃ (2 equiv.), toluene (12 or 16 mL), 60 °C. ^{*b*} Isolated yields. ^{*c*} Reaction was run at 40 °C. ^{*d*} K₃PO₄ (2 equiv.) was used.

iodides with diphenylphosphine.¹¹ To account for this result, we propose that both the use of an activated phosphine (phosphine borane complex) and of an alkyne derivative, which might be functioning as a π -Lewis base to copper, favour the process.¹⁸

Despite the recent progress achieved in copper-catalyzed coupling reactions regarding the scope and the smoothing of the reaction conditions, the mechanistic fundamentals are still poorly documented in the literature. According to some recent theoretical and experimental studies,¹⁹ ligand-bound copper(1)-nucleophiles are the reactive intermediates involved in the catalytic arylation of *N*- and *O*-nucleophiles. In our case, a working hypothesis could involve the initial formation of a copper(1) phosphide species as nucleophile. Since the phosphorus atom in phosphine borane is tetrahedral, its deprotonation has to take place prior to the complexation to copper. In order to validate this hypothesis, we performed the reaction under stoichiometric conditions. Deprotonation of **1a** was achieved with *n*-BuLi (1 equiv.) and the resulting lithiated anion ($\delta_P = -31$ ppm) was first treated with CuI (1 equiv.) at 0 °C



Scheme 2 Tentative mechanistic cycle for the copper-catalyzed synthesis of alkynylphosphine derivatives.

then with 1,10-phenanthroline (1 equiv.). The ³¹P NMR spectrum revealed the instant formation of a new phosphorus derivative ($\delta_{\rm P} = -22$ ppm), which was attributed to the copper phosphide species [Ph2P(BH3)Cuphen] based on the ¹H and ¹³C NMR spectra. All attempts to grow crystals from this complex failed. 1-Bromoalkyne 2a (1.4 equiv.) was added to this complex at 0 °C and the reaction medium was subsequently heated at 40 °C. A ³¹P NMR spectrum registered after 2 h of heating showed the expected signal corresponding to alkynylphosphine **3a** ($\delta_{\rm P} = 5$ ppm). Based on this result, and by analogy to related catalytic syntheses of N-functionalized alkynes,²⁰ a tentative mechanism is shown in Scheme 2: (i) formation of Cu(1) phosphide species 4, (ii) oxidative addition to 1-bromoalkyne 2, (iii) reductive elimination leading to cross-coupling product 3 and regeneration of the copper catalyst.

In conclusion we have developed a new and efficient access to various alkynylphosphine derivatives, through coppercatalyzed cross-coupling reaction between alkyl, aryl and alkylaryl phosphine boranes and various 1-bromoalkynes. Worthy of note are the mild conditions (20 to 60 °C) required in this coupling reaction, and the first use of a nucleophilic phosphorus derivative in the catalytic synthesis of alkynylphosphines. Preliminary mechanistical studies are consistent with the involvement of a copper phosphide as an intermediate. The reaction mechanism and the extension of this methodology to the asymmetric series are currently under investigation.

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