# Di-µ-Hydroxy-bis(*N*,*N*,*N'*,*N'*-tetramethylenediamine)copper(II) Chloride {[Cu(OH)·TMEDA]<sub>2</sub>Cl<sub>2</sub>} Catalyzed Tandem Phosphorous–Carbon Bond Formation–Oxyfunctionalization: Efficient Synthesis of Phenacyl Tertiary Phosphine-Boranes

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**Abstract:** A novel  $[Cu(OH) \cdot TMEDA]_2Cl_2$  catalyzed tandem reaction has been developed for the synthesis of a series of sterically and electronically divergent phenacyl tertiary phosphine-boranes.

**Key words:** phosphine-boranes, terminal alkynes, phenacyl tertiary phosphine-borane, copper iodide, methyl propiolate

The functionalization of substituted aryl terminal alkynes and olefins by an activated-hydrogen-containing heteroatom is of fundamental importance in terms of synthetic value as well as atom economy.<sup>1</sup> Among such processes, the construction of carbon–phosphorus bonds has an intriguing potential due to their use as ligands in transitionmetal-catalyzed reactions.<sup>2</sup> In particular, phosphineboranes are the requisite precursors for the synthesis of tunable ligands. Recently, efficient approaches have been reported for the regioselective addition to terminal alkynes. Many of these protocols are via a metalcatalyzed P–H activation, particularly by palladium,<sup>3</sup> rhodium,<sup>4</sup> and organolanthanide<sup>5</sup> followed by their subsequent addition to terminal alkynes leading to stereodefined vinyl phosphine-borane derivatives.

An excellent regio- and stereocontrolled thermally activated hydrophosphination of simple alkynes with secondary phosphine-borane has also been reported on the gram scale, leading to β-addition vinyl phosphine-borane adducts.<sup>6</sup> Recently, we have demonstrated a mild and efficient protocol for phosphorous-carbon bond formation with a substoichiometric amount of copper for the synthesis of scalemic tertiary phosphine-boranes.<sup>7</sup> Herein, we report to the best of our knowledge, the first [Cu(OH)·TMEDA]2Cl2 catalyzed tandem phosphorouscarbon bond formation-oxyfunctionalization of terminal aryl-substituted alkynes and aryl olefins resulting in the synthesis of phenacyl tertiary phosphine-boranes. At the outset, we explored this transformation using phosphineborane  $(\pm)$ -1b (1.1 equiv) and phenyl acetylene (2a, 1 equiv) in the presence of 10 mol% of CuI in acetonitrile, stirring at ambient temperature. To our surprise, the antic-

SYNLETT 2009, No. 7, pp 1180–1184 Advanced online publication: 26.03.2009 DOI: 10.1055/s-0028-1088120; Art ID: D00309ST © Georg Thieme Verlag Stuttgart · New York ipated vinyl phosphine-borane product was not formed; instead the phenacyl tertiary phosphine-borane **3b** was isolated in 30% yield. A control reaction conducted without CuI was unsuccessful. After exploring several copper salts<sup>8</sup> and reaction conditions<sup>9</sup> it was found that 10 mol% of [Cu(OH)·TMEDA]<sub>2</sub>Cl<sub>2</sub> and 20 mol% of Et<sub>3</sub>N as a base in an open system,<sup>10</sup> stirring at ambient temperature in acetonitrile, afforded the phenacyl tertiary phosphineborane **3b** in an 80% yield (Scheme 1).<sup>11</sup>



## Scheme 1

The structure of phenacyl tertiary phosphine-borane **3b** was determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and mass spectrometry and was finally established by X-ray crystallography (Figure 1).



Figure 1 X-ray crystal structure of **3b**<sup>1,2</sup>

Encouraged by this result, the scope of this new reaction was investigated with substituted phenylacetylene and phosphine-boranes. The results are summarized in Table 1. Various phosphine-boranes were coupled with a wide range of substituted phenylacetylenes irrespective of the steric and electronic nature of aromatic nucleus and further oxidation led to the corresponding phenacyl tertiary phosphine-boranes in moderate to good yields. For example, under the standard conditions, 3,4-dimethoxy phenylacetylene (2c) reacted with  $(\pm)$ -1b leading to the desired product 5a in 90% yield where as 2-amino-5-nitro phenylacetylene 2e with  $(\pm)-1b$  furnished the desired product 7b, albeit in moderate yield (65%). The 2-methoxy-5-tert-butylphenylacetylene (2d) also underwent phosphination–oxygenation with  $(\pm)$ -1b and the resulting product 6b was isolated in 80% yield. The heteroatomcontaining 3-pyridylacetylene and (±)-1b was subjected to an identical protocol, and the anticipated product **11a** resulted in 80% yield but, with 2-pyridylacetylene, the expected product was not formed. Interestingly, 1,3-diethinylbenzene (2f) also underwent coupling-oxygenation with 2.2 equivalents of  $(\pm)$ -1a and the corresponding 1,3substituted tertiary phosphine-borane 8a was isolated in 85% yield. Surprisingly, a fast and efficient hydrophosphination-oxidation reaction was brought about using activated alkenes. Thus, phosphine-boranes  $(\pm)$ -1b were allowed to react with styrene 2i under the same set of conditions resulting in phenacyl tertiary phosphine-borane 3b in 85% isolated yield. It was also observed that the phosphine-borane had coupled to the terminal carbon of acetvlene or olefin, and oxidation occurred at the benzylic carbon maintaining complete regioselectivity leading to the observed product. Under identical conditions, we also examined the reaction of phosphine-boranes (±)-1a-d, with Michael acceptor such as methyl propiolate. Only

β-addition products **13a**–**d** were isolated with *E*-selectivity<sup>6a</sup> (Scheme 2).



#### Scheme 2

The reaction mechanism remains to be explored but the postulated catalytic cycle is shown in Scheme 3. The monomeric Cu(II) catalyst **B** activates sequentially alkyne and secondary phosphine-borane leading to the formation of mixed Cu(II)–alkyne–phosphine-borane species **D** followed by reductive elimination and subsequent hydrolysis results in the observed product.<sup>13,14</sup>

In conclusion, we have succeeded in developing a Cu(II)– TMEDA catalyzed tandem phosphorous–carbon bond formation–oxyfunctionalization protocol for the synthesis of a series of sterically and electronically divergent phenacyl tertiary phosphine-boranes. Further work is under way to broaden the scope of this reaction.



Scheme 3

 Table 1
 Cu-Catalyzed Hydrophosphination and Oxygenation of Aryl-Substituted Terminal Alkynes and Olefins<sup>a</sup>

Acetylene $R^2 =$	Product, <sup>b</sup> yield (%) <sup>c</sup>
	BH <sub>3</sub>
	Ph-P
	R <sup>1</sup>
2a	<b>3a</b> $R^1 = Me, 85\%$
	<b>3c</b> $R^1$ = Ph, 80% <b>3d</b> $R^1$ = MeO, 75%
	BH <sub>3</sub>
	Ph-P
OMe	R <sup>1</sup>
2b	$\sim$ OMe 4a R <sup>1</sup> = Me. 72%
	<b>4b</b> $R^1 = t$ -Bu, 78%
	<b>4с</b> К <sup>2</sup> = Рп, 85% ВН <sub>3</sub>
OMe	
OMe	
2c	OMe
	<b>5a</b> R <sup>*</sup> = <i>t</i> -Bu, 90% BH <sub>3</sub>
MeO	
	Ph <sup>-</sup> / R <sup>1</sup>
2d	<b>6a</b> $R^1 = Me, 78\%$
	<b>6b</b> R <sup>1</sup> = <i>t</i> -Bu, 80%
H₂N	
	Ph-P
	n'
NO <sub>2</sub>	NO <sub>2</sub>
2e	<b>7a</b> $R^1 = Me, 61\%$ <b>7b</b> $R^1 = t$ -Bu, 65%
	H <sub>3</sub> B B
2f	$Ph' R^1 Ph' R^1$
	<b>8a</b> R <sup>1</sup> = Me, 85% BH <sub>2</sub>
	Ph-P-R
2g	
	<b>9a</b> $R^{*} = MeO, 75\%$ BH <sub>3</sub>
OMe	
	Ph <sup>-</sup> r R <sup>1</sup>
	$10_{2} R^{1} = Me \ 85\%$
2h	$100 R^{-1} = tBu, 80\%$
	<b>10c</b> $R^{1} = Ph, 82\%$ <b>10d</b> $R^{1} = MeO, 75\%$

 Table 1
 Cu-Catalyzed Hydrophosphination and Oxygenation of Aryl-Substituted Terminal Alkynes and Olefins<sup>a</sup> (continued)



<sup>a</sup> All reactions were carried out with terminal alkyne (1 mmol), phosphine-borane (1.1 mmol) using 10 mol% of  $[Cu(OH) \cdot TMEDA]_2Cl_2$  and 20 mol% of  $Et_3N$  in MeCN (5 mL) at ambient temperature and stirring for 6 h.

<sup>b</sup> All products were fully characterized.

<sup>c</sup> Unoptimized isolated yields.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (8) Other copper salts evaluated for this transformation are CuOTf, CuOAc, CuCl, CuCl<sub>2</sub>, Cu(Piv)<sub>2</sub>, [Cu(MeCN)<sub>4</sub>]PF<sub>6</sub>, and Cu(acac)<sub>2</sub>. Except CuCl<sub>2</sub> (30%), none gave target compound.
- (9) Various solvents and bases were screened for the optimization of yield of **3b**. Halogenated solvents (CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, DCE) and toluene failed to give the product. In addition to MeCN, only the aprotic solvent DMF was successful albeit in low yield (40%). Bases such as K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and KO*t*-Bu did not yield the observed product.
- (10) We have performed the reaction under aerobic conditions and under inert atmosphere. In both cases the product formation was observed but in open air a slightly better yield was obtained. Further, using an oxygen balloon, the reaction did not proceed. These experiments imply that the dissolved air is essential for the product formation. At present, we have no satisfactory explanation for this phenomenon and it clearly needs further work.

#### (11) **Typical Procedure**

Secondary phosphine-borane ( $\pm$ )-**1b** (198 mg, 1.1 mmol) and phenyl acetylene (**2a**, 198 mg, 1.0 mmol) were dissolved in MeCN (5 mL). To this reaction mixture, [Cu(OH)·TMEDA]<sub>2</sub>Cl<sub>2</sub> (38 mg, 10 mol%) and Et<sub>3</sub>N (20 mg, 20 mol%) were added sequentially. The resulting reaction mixture was stirred 6 h at ambient temperature. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl solution and

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extracted with EtOAc (2 × 10 mL) and washed with brine solution. The combined extracts were dried over anhyd Na<sub>2</sub>SO<sub>4</sub> and filtered, and evaporation under reduced pressure resulted in a crude residue. The residue was subjected to SiO<sub>2</sub> column chromatography, and it furnished the phenacyl tertiary phosphine-borane **3b** in 80% yield (262 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.18$  (d, J = 14.3 Hz, 9 H), 3.55–3.85 (m, 2 H), 7.36–7.53 (m, 6 H), 7.76–7.89 (m, 4 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 25.4$ , 29.8, 30.1, 128.1, 128.2, 129.0, 131.3, 131.4, 133.4, 133.5, 133.6, 195.9. IR (KBr): 2925, 2855, 2386, 1668, 1143, 1068, 996, 738 cm<sup>-1</sup>. MS–FAB: m/z = 297 [M – 1]<sup>+</sup>. HRMS (ESI-MS): m/z calcd for C<sub>18</sub>H<sub>24</sub>PBONa: 321.1415; found: 321.1415.

(12) The crystal belongs to the monoclinic crystal system, space group is Cc with a = 11.6520 (7) Å, b = 22.6559 (14) Å, c = 7.5701 (5) Å,  $\beta = 117.933$  (1), V = 1765.58 (19) Å<sup>3</sup>,  $\rho_{calc} = 1.122$  mg m<sup>-3</sup>,  $\lambda = 0.71073$ Å,  $\mu$ (Mo K $\alpha$ ) = 0.152 mm<sup>-1</sup>,  $F_{000} = 640$ , T = 294 (2) K. Data collection yielded 8337 reflection resulting in 3095 unique, averaged reflection, 3041 with I > 2σ(I), θ range: 1.80–25.00°. Fullmatrix least-squares refinement led to a final R = 0.0293, wR = 0.0770 and GOF = 1.013. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 714891 contains the supplementary crystallographic data for the structure **3b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.

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