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## COMMUNICATION

## Pd<sup>2+</sup> and Cu<sup>2+</sup> catalyzed oxidative cross-coupling of mercaptoacetylenes and arylboronic acids<sup>†</sup>‡

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An oxidative thiolate scavenging concept in a metal catalyzed reaction is presented and demonstrated on the aerobic Pd and Cu catalyzed cross-coupling of mercaptoacetylenes with arylboronic acids. Synthetic value of the chemistry as the complementary tool to the Sonogashira protocol has been demonstrated on a series of functionalized mercaptoacetylene substrates.

One of the foremost examples of modern synthetic methods is the chemistry that helps connect two, often highly functionalized entities, while forming a new bond between two atoms of respective subunits in the process. In this scenario, the cross-coupling reaction partners possess respective, formally electrophilic (organic halides, sulfonates etc.) and nucleophilic properties. The presence of a transition metal, which facilitates chemistry through the consequent oxidative addition/reductive elimination steps, is typically required.<sup>1</sup> The ever growing demand for sophisticated target molecules has, however, profoundly impacted the reaction conditions, encouraging the current trend of a gradual replacement of the traditionally used highly reactive organomagnesium or organozinc nucleophiles by much milder reagents such as organoboron or organotin moieties. Although in the vast majority of all cross-coupling reactions halides and, to a smaller extent, esters of inorganic acids are used,<sup>1</sup> the reaction of organosulfur compounds that falls within the same reactivity bracket was published recently.<sup>2</sup> The resulting thiolate by-products, considered to be detrimental to catalytic metals, have been in this case effectively "scavenged" by stoichiometric cuprous carboxylate additives, eventually forming highly stable Cu thiolates. Unlike in the former case however, there is an additional path, which can be explored for the adverse thiolate effects neutralization in the organosulfur cross-coupling scenario. Built around the uncomplicated thiolate oxidative transformation, this route leads, in the end, to a more chemically accommodating environment. While the basic framework of this concept has been outlined recently by introducing surprising Cu catalyzed aerobic reaction of

thioesters with aryl boronic acids,<sup>3</sup> we wanted to extend the whole concept of the aerobic transition metal catalyzed crosscoupling reaction and address the unresolved issues pertaining to the mechanism of this peculiar process. Thus, utilizing the same structural scaffold, we have examined metal catalyzed oxidative cross-coupling reaction of mercaptoacetylenes and boronic acids. Obviating the selection of mercaptoacetylenes as the cross-coupling substrates is the synthetic protocol published recently leading to their formation under neutral conditions from readily accessible terminal alkynes.<sup>4</sup>

In the cursory screening of their reactivity, the mercaptoacetylene **1** was treated with tolylboronic acid in the presence of metal catalysts under various conditions (Table 1). Surprisingly when, analogically to the published account,<sup>3</sup> Cu(1) or Cu(11) salts were used as the catalyst, no desired product was detected. Fortunately, when the situation was remedied by the addition of a Pd catalyst in a separate experiment, the desired product **2** was formed in the high yield, accompanied

Table 1 Catalyst evaluation in the aerobic cross-coupling reaction

N <sup>Bn</sup> H H H H H H H H H H H H H H H H H H H	$\begin{array}{c c} OH)_2 \\ H \\ $
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Entry	Pd cat.	Cu cat.	Ligand <sup>b</sup>	<b>2a</b> <sup><i>a</i></sup>
1	Pd(OAc) <sub>2</sub>	CuMeSal	4 eq. (2-furyl) <sub>3</sub> P	13
2	$Pd(OAc)_2$	CuMeSal	$4 \text{ eq.} (2 \text{-tolyl})_3 P$	Trace
3	$Pd(OAc)_2$	CuMeSal	$4 \text{ eq. } \text{Cy}_3\text{P}$	9
4	$Pd(OAc)_2$	CuMeSal	4 eq. Ph <sub>3</sub> P	38
5	$Pd(OAc)_2$	CuMeSal	4 eq. $(C_6F_5)_3P$	71
6	$Pd(OAc)_2$	CuMeSal	2 eq. DIPHOS	28
7	$Pd(OAc)_2$	CuMeSal	2 eq. DPEphos	30
8	$Pd(OAc)_2$	CuMeSal	_ `	65
9	Pd 4	CuMeSal	_	82
10	$Pd(dba)_2$	CuMeSal	1 eq. Ph <sub>3</sub> P	77
11	$Pd(dba)_2$	CuMeSal	1 eq. (PhO) <sub>3</sub> P	79
12	Pd(dba) <sub>2</sub>	CuMeSal	_	90
13	$Pd(dba)_2$	CuCN	_	18
14	$Pd(dba)_2$	CuI	_	12
15	$Pd(dba)_2$	CuCO <sub>3</sub>	_	Trace
16	$Pd(dba)_2$	$Cu(OAc)_2$	_	78

<sup>*a*</sup> HPLC conversion (%), Pd cat. (5 mol%), Cu cat. (10 mol%), T = 3 h. <sup>*b*</sup> The ligand equivalents are relative to the catalyst amounts.

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<sup>†</sup> Dedicated to Prof. Pavel Kočovský on the occasion of his 60th birthday.

 $<sup>\</sup>ddagger$  Electronic supplementary information (ESI) available: All the relevant synthetic details as well as  $^1H$  and  $^{13}C$  spectra for all compounds. See DOI: 10.1039/c1cc10505a

by the expected obligatory oxidative by-product **3** in a 1:1 ratio.<sup>5</sup>

In order to glean additional information about the process and support the oxidative thiolate scavenging notion, the same reaction was carried out under an inert atmosphere. No product(s) were formed in this case, which further corroborates the whole concept. An equally critical role in the cross-coupling scenario was played by the thiosalicylamide scaffold; the reaction of a simple *p*-tolylmercaptophenylacetylene did not lead to the expected products leaving the substrate unaffected. Underscoring the vital role of copper in the reaction scheme, experiments with catalytic or stoichiometric amount of a Pd catalyst failed to furnish any products in the absence of Cu ions. An unavoidable issue critical to the mechanism of the present reaction is the question of the metal catalyst's oxidative state. While the reaction can be catalyzed by a variety of the Pd complexes [various triarylphosphine, trialkylphosphine complexes, Pd(OAc)<sub>2</sub>] and Cu salts [(CuCN, CuI, Cu 3-methylsalycilate, Cu(OAc)<sub>2</sub>]<sup>6</sup> regardless of their respective oxidation state, the presence of air suggests that the metals function as transformation catalysts in their oxidized states-Pd<sup>2+</sup> and Cu<sup>2+</sup> respectively. In the light of the fact that low valent palladium complexes generally facilitate cross-coupling reactions of various substrates through the oxidative addition step ( $Pd^0$  to  $Pd^{2+}$ ), the higher oxidation state in the present case is rather unusual, contradicting the common mechanistic scenario.7 To distinguish between the two oxidation states of the Pd catalyst, the cyclic complex 4 (Fig. 1), known to remain, under the relatively mild reaction condition in the 2+ oxidation state was selected as the metal source.8

The ensuing cross-coupling experiment provided, again, the same set of products in excellent yields pointing thus at the likely catalytically active  $Pd^{2+}$  oxidation state.

Based on the experiments above, we have proposed the mechanism starting with the formation of arylcopper from arylboron by transmetallation with Cu.<sup>9</sup> The resultant intermediate subsequently adds, assisted by pre-coordinated  $Pd^{2+}$ , in *trans* fashion across the alkyne triple bond.<sup>8,10</sup> The subsequent  $\beta$ -mercapto elimination of the Pd intermediate results in the desired disubstituted acetylene **3** accompanied by the corresponding metal thiolate.<sup>11</sup> The eventual oxidative arylation of the thiolate finally leads to the requisite arylthioether, liberating the metal(s) back to the catalytic cycle in the process (Scheme 1).

Although understanding of oxidative cross-coupling concept has been the ultimate goal of the present study we want to illustrate our insights into the process by the synthesis of chemically valuable targets. Substituted alkynes belong, undeniably, in this group. Their importance for modern chemistry is best illustrated by numerous methods developed recently,<sup>12,13</sup>





Scheme 1 Tentative mechanism of the Pd and Cu catalyzed coupling.

 Table 2
 Oxidative coupling of mercaptoacetylenes with arylboronic acids



Entry	1 (R)	Boronic acid (Ar)	$2^{a}$	<b>3</b> <sup><i>a</i></sup>
a	Ph	4-Tolyl	83	86
b	Ph	4-(CHO)C <sub>6</sub> H <sub>4</sub>	84	80
с	COOEt	$2-(CH_3O)C_6H_4$	64	75
d	$4-(CH_3CO)C_6H_4$	3-HOC <sub>6</sub> H <sub>4</sub>	93	87
e	$2-BrC_6H_4$	Indole-5-yl	82	78
f	2-Cl-5-NO2-PhCOOCH2-	Thianthrene-1-yl	79	64
g	$4-(CH_3CO)C_6H_4$	$3-(NH_2CO)C_6H_4$	85	95
ĥ	N-Methyl phthalyl	3-BrC <sub>6</sub> H <sub>4</sub>	81	80
i	N-Methyl phthalyl	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	82	70
j	COOEt	$4-ClC_6H_4$	78	69

<sup>*a*</sup> Yield of isolated products (%) General procedure: mercaptoacetylene 1 (0.5–1.0 mmol), corresponding boronic acid (2.2–3.0 eq.), CuMeSal (3 mol%) and Pd(dba)2 (1 mol%) were placed into a reaction flask (10 ml). DMF (2–4 mL) was added and the resulting reaction mixture was stirred for 8–20 h at 45–50 °C in the presence of air. Reaction progress was followed by HPLC.

peaking in the invention of such a stalwart tool in the synthetic toolbox as a Pd catalyzed Sonogashira protocol,  $^{12a}$  which utilizes organic halides and terminal alkynes as the substrates. In the light of the "mirror-like" reactivity arrangement, our chemistry can thus be viewed as the complementary synthetic tool for the construction of the alkyne moieties. In order to demonstrate the scope of our chemistry and show its synthetic advantages, a variety of functionalized substrates was examined under the reaction conditions. The results are summarized in Table 2.

In an effort to exemplify the complementarity of our chemistry with the Sonogashira protocol, compound **2**, prepared by the present procedure (entry **2e**), was subjected to Sonogashira coupling conditions. The resultant substituted bis acetylene moiety **5**, formed in good yield, undoubtedly substantiates the synthetic advantages (Scheme 2).

Overall, the aerobic Pd and Cu catalyzed cross-coupling of mercaptoacetylenes with arylboronic acids has been presented



Scheme 2 Synthetic comparison of the present chemistry with a Sonogashira protocol.

which illustrates an oxidative thiolate scavenging concept in a metal catalyzed reaction. Distinctly different from the published protocols which are, due to the robust catalysts, air tolerant,<sup>14</sup> the present chemistry goes one step further, requiring air for the successful reaction outcome.<sup>13</sup> The synthetic value of the chemistry as the complementary tool to the Sonogashira protocol has been demonstrated on a series of functionalized mercaptoacetylene substrates. The coupling mechanism, likely involving the addition/elimination step, has been proposed and corroborated by published accounts and control experiments.

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