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# Zinc Chloride-Promoted Aryl Bromide−Alkyne Cross-Coupling Reactions at Room Temperature

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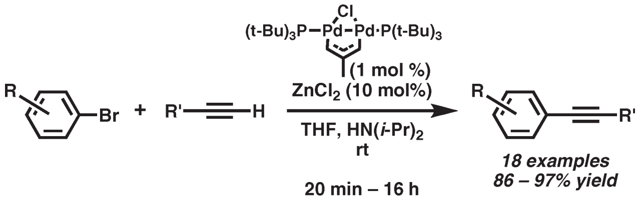

Substoichiometric amounts of $ZnCl_2$ promote the room temperature, Pd/P($t$-Bu)$_3$-catalyzed cross-coupling of aryl bromides with alkynes. Pd(I) dimer **1** is demonstrated to be a particularly active precatalyst for this reaction. The reaction is general for a wide variety of aryl bromides.

The Pd- and CuI-catalyzed cross-coupling reaction of aryl and vinyl halides with terminal alkynes, known as the Sonogashira or Hagihara−Sonogashira reaction,[1−3] is one of the most widely used and reliable methods of alkyne functionalization. Nonetheless, Cu-mediated homodimerization of alkynes and the requirement of elevated temperatures for the coupling of aryl bromides present a challenge to the efficient preparation of acetylene-containing molecular scaffolds free of chemical defects.[4,5] Recently, there have been significant advancements in overcoming the above limitations through two general strategies: the utilization of novel, highly active Pd catalysts[6] and developing methodologies that are active in the absence of copper cocatalyst.[7] However, while "copper-free Sonogashira" conditions prevent CuI-mediated homocoupling,[8] they can suffer from lower rates compared to those for reactions promoted by CuI.[9] Alternative cocatalysts that do not display this side reactivity are thus highly desirable. In this Note, we describe conditions for aryl bromide−alkyne cross-coupling reactions at room temperature, which utilize substoichiometric amounts of inexpensive $ZnCl_2$ in the presence of an active Pd catalyst.[10]

The yields for the room temperature coupling of the relatively unreactive 4-bromoanisole with phenylacetylene, both in the absence and the presence of $ZnCl_2$, for selected Pd precatalyst systems are described in Table 1. Many of these Pd catalysts have been reported previously for aryl bromide−alkyne cross-couplings. Gratifyingly, most of these previously

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(7) (a) For a review of recent advances in aryl halide−alkyne cross-coupling, see: Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871. (b) For a critical review on alternative metal-catalyzed cross-couplings of aryl halides and alkynes, see: Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954–6956.

(8) Alkynes in the presence of CuI, amine, and a stoichiometric oxidant (Pd(II) or air) rapidly and quantitatively homocouple. This is the generally accepted mechanism for reduction of some Pd(II) precatalysts in the Sonogashira reaction. See: Nguyen, P.; Yuan, Z.; Agocs, L.; Lesley, G.; Marder, T. B. *Inorg. Chim. Acta* **1994**, *220*, 289−296 and references cited therein.

(9) In our experience, this observation holds true for couplings that utilize amines as base. However, Buchwald et al. have reported that for certain coupling conditions which utilize inorganic bases, CuI inhibits reactivity (see ref 6e.).

(10) This is an optimization of a method we previously reported: Elliott, E. L.; Ray, C. R.; Kraft, S.; Atkins, J. R.; Moore, J. S. *J. Org. Chem.* **2006**, *71*, 5282–5290.

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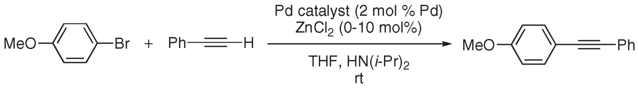
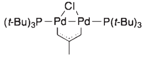
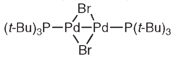
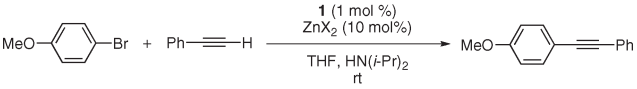
**TABLE 1. Scope of Palladium Sources with and without $ZnCl_2$**



| Entry | Pd catalyst (mol %) | % convn, 1 h[a] no added $ZnCl_2$[b] | % convn, 1 h[a] with 10 mol % $ZnCl_2$[c] |
|---|---|---|---|
| 1 | --[d] | 0 | 0 |
| 2 | $Pd(PPh_3)_4$ (2 mol %) | 0 | 0 |
| 3[6g] | $[allylPdCl]_2$ (1 mol %)<br>P(*t*-Bu)$_3$ (2 mol %) | 28 | 37 |
| 4[6d] | $Pd_2dba_3$ (1 mol %)<br>P(*t*-Bu)$_3$ • $HBF_4$ (2 mol %) | 26 | 85 |
| 5 | Pd[P(*t*-Bu)$_3$]$_2$ (2 mol %) | 27 | 90 |
| 6[8] | <br>**1** (1 mol%) | 25 | 96 |
| 7[12] | <br>(1 mol%) | 25 | 75 |

[a]Conversions by GC. [b]Reaction conditions: 4-bromoanisole (1.0 mmol), phenylacetylene (1.0 mmol), Pd catalyst (0.02 mmol), THF (1.0 mL), HN(*i*-Pr)$_2$ (0.5 mL), rt. [c]Reaction conditions: 4-bromoanisole (1.0 mmol), phenylacetylene (1.0 mmol), Pd catalyst (0.02 mmol Pd), $ZnCl_2$ (0.1 mmol), THF (1.0 mL), HN(*i*-Pr)$_2$ (0.5 mL), rt. [d]No Pd catalyst added.

**TABLE 2. Efficacy of Zinc Halides in Promotion of Cross-Coupling[a]**



| entry | $ZnX_2$ | cost[b] ($/mol) | % yield[c] 15 min | % yield[c] 24 h | % yield of diyne[c] in 24 h |
|---|---|---|---|---|---|
| 1 | none | | 2 | 84 | < 1 |
| 2 | $ZnCl_2$ | 29.71 | 87 | 100 | 0 |
| 3 | $ZnBr_2$ | 84.22 | 88 | 100 | 0 |
| 4 | $ZnI_2$ | 142.36 | 48 | 79 | 0 |
| 5 | $Zn(OTf)_2$ | 1076.05 | 85 | 100 | 0 |
| 6 | CuI[d] | 48.52 | < 1[e] | 99 | 3 |

[a]Reaction conditions: 4-bromoanisole (1.0 mmol), phenylacetylene (1.0 mmol), **1** (0.01 mmol), zinc halide (0.1 mmol), THF (1.0 mL), HN(*i*-Pr)$_2$ (0.5 mL), rt. [b]Cost for reagent grade salts (as of July 2009), Aldrich Chemical Co. [c]GC yields. [d]1 mol % CuI used in lieu of zinc halide (see text). [e]Reaction is complete after 2 h.

reported catalysts, in the presence of 10 mol % $ZnCl_2$, are effective at promoting cross-coupling at room temperature, with high yields after 1 h. The less reactive $Pd(PPh_3)_4$ (Table 1, entry 2) is an ineffective catalyst at room temperature. Pd(I) dimer **1** (Table 1, entry 6)[11] displays the highest activity in aryl bromide–alkyne cross-coupling of the catalyst systems studied. Complex **1** is a highly active catalyst that is more air-stable than other previously reported Pd/P(*t*-Bu)$_3$ precatalysts[12] (see the Supporting Information).

The necessity of a cocatalyst for rapid couplings, even in the presence of a highly active Pd catalyst, is illustrated in Tables 1 and 2. Pd catalysts which displayed high activity in the presence of $ZnCl_2$ were far less active in the absence of $ZnCl_2$ (Table 1, entries 3–7). Coupling in the presence of 1 mol % CuI (Table 2, entry 6) is complete in 2 h, but forms a significant amount of diyne byproduct. We attribute the low yield of the CuI-promoted coupling after 15 min to the solubility of CuI, which is less soluble in the reaction mixture than zinc halides.

The effect of zinc halide salts in alkyne cross-coupling reactions is well-documented but underutilized.[13] Anastasia and Negishi reported that stoichiometric $ZnBr_2$ promoted room temperature coupling of alkynes with aryl iodides in the presence of $Pd(PPh_3)_4$.[14] Notably, they were able to couple the typically unreactive methyl propiolate with iodobenzene at elevated temperatures.[15] Furthermore, they demonstrated the relative inertness of zinc halide-promoted alkyne cross-couplings to air and moisture.[16]

The coupling of 4-bromoanisole with phenylacetylene with 1 mol % **1** in THF/HN(*i*-Pr)$_2$ was performed in the presence of 10 mol % of various zinc halides (Table 2, entries 2–5). Using only 10 mol % of a zinc halide salt promotes rapid cross-coupling at room temperature, indicating that stoichiometric quantities are not needed. All Zn salts display significant conversion after only 15 min. Strong inorganic bases such as $Cs_2CO_3$ and NaO*t*-Bu, when used in lieu of HN(*i*-Pr)$_2$, lead to no product formation at room temperature. Furthermore, deliberate addition of 20 mol % of a chloride source (LiCl or $Bu_4NCl$) leads to no noticeable rate enhancement.

The scope of the optimized conditions described above is summarized in Table 3. A variety of aryl bromides couple with alkynes rapidly with low catalyst loadings and at room temperature.[17] The reaction conditions tolerate many functional groups, including esters, aldehydes, and nitro groups (Table 3, entries 9–11, respectively). Heteroaryl bromides such as 2-bromothiophene are tolerated (Table 3, entry 15). Moderately hindered aryl bromides such as 2-bromotoluene couple rapidly at room temperature (Table 3, entries 6 and 12, respectively). However, very hindered aryl bromides such as 2-bromomesitylene and 9-bromoanthracene do not couple as rapidly at room temperature (Table 3, entries 11

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[11] (a) Werner, H.; Kühn, A. *J. Organomet. Chem.* **1979**, *179*, 439–445. (b) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793–795. (c) Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.* **2008**, *73*, 1440–1455. (d) Denmark, S. E.; Baird, J. D. *Tetrahedron* **2009**, *65*, 3120–3129.

[12] Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746–4748.

[13] Pioneering studies on effects of Zn salts on aryl halide–alkyne cross-couplings: (a) Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219–224. (b) Eberhard, M. R.; Wang, Z. H.; Jensen, C. M. *Chem. Commun.* **2002**, 818–819. For implementation of Zn-promoted aryl halide-alkyne cross-couplings, see: (a) Boydston, A. J.; Pagenkopf, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 6336–6338. (b) Grube, G. H.; Elliott, E. L.; Steffens, R. J.; Jones, C. S.; Baldridge, K. K.; Siegel, J. S. *Org. Lett.* **2003**, *5*, 713–716. (c) Crisp, G. T.; Turner, P. D. *Tetrahedron* **2000**, *56*, 407–415.

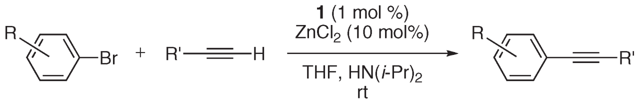
[14] Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111–3113.

[15] Reactions with methyl propiolate under our conditions lead only to decomposition/polymerization of the alkyne, regardless of the amine used. We observe that this occurs in the absence of Pd catalyst or Zn salt, indicating that even amine bases incapable of conjugate addition are capable of promoting alkyne decomposition. The method reported here is thus unsuitable for cross-couplings of propiolate esters.

[16] Our reaction conditions are insensitive to moisture, and drying of the hygroscopic zinc salts is unnecessary. However, the air sensitivity of the Pd catalysts requires these reactions be run under inert atmosphere with degassed solvents.

[17] "Room temperature" in this context refers to the absence of *external* heating. In reality, many of these reactions, particularly with electron-poor aryl bromides, can be quite exothermic.

**TABLE 3. Aryl Bromide−Alkyne Cross-Couplings Promoted By Catalytic $ZnCl_2$[a]**



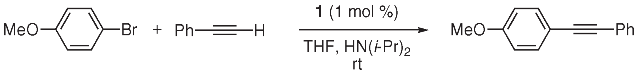
| entry | R | R′ | time | yield (%)[b] |
|---|---|---|---|---|
| 1 | H | Ph | 30 min | 93 |
| 2 | 4-OMe | Ph | 1 h | 86 |
| 3 | 4-OMe | TMS | 2 h | 89 |
| 4 | 4-OMe | Bu | 2 h | 88 |
| 5[c] | 2-OMe | Ph | 2 h | 83 |
| 6 | 2-Me | Ph | 1 h | 92 |
| 7 | 4-COMe | Ph | 20 min | 94 |
| 8 | 3-(COOMe) | Ph | 30 min | 97 |
| 9 | 4-CHO | Ph | 20 min | 94 |
| 10 | 4-$NO_2$ | Ph | 20 min | 96 |
| 11 | 2,4,6-$(Me)_3$ | Ph | 16 h | 76 (90) |
| 12 | 2-Ph | Ph | 2 h | 93 |
| 13 | 1-naphthyl | Ph | 1 h | 94 |
| 14 | 9-anthracyl | Ph | 5 h | 86 |
| 15 | 2-thienyl | Ph | 1 h | 91 |
| 16[d] | 4-Br | Ph | 3 h | 88 |
| 17 | 4-OTf | Ph | 30 min | 92 |
| 18 | 3-OTf | Ph | 30 min | 93 |

[a] Reaction conditions: aryl bromide (3.0 mmol), alkyne (3.0 mmol), **1** (0.03 mmol), $ZnCl_2$ (0.3 mmol), THF (7.0 mL), HN(*i*-Pr)$_2$ (3 mL), rt. [b] Yields are an average of two runs. Yields in parentheses are GC yields. [c] The alkyne was added over 2 h and stirred at rt for an additional 2 h. [d] 2.0 equiv (6.0 mmol) of phenylacetylene was used. The product is 1,4-bis(2-phenylethynyl)benzene.

and 14, respectively) but still give acceptable yields. Aryl chlorides are unreactive at room temperature. Both 3- and 4-bromophenyltriflate exclusively couple with the bromide over the triflate under the standard reaction conditions, rapidly and in good yield (Table 3, entries 17 and 18).[18] No triflate coupling products are detectable by GC. This orthogonal reactivity has the potential for the rapid, iterative preparation of unsymmetrical, conjugated architectures.

The exact role of the zinc halide salt is unknown at this time. However, previous mechanistic studies under similar conditions propose an in situ zinc acetylide formation via "soft" deprotonation of a zinc halide−alkyne complex.[19] Recently, it was reported that trace copper in commercially available iron salts acts as the active catalyst in C−O and C−N bond formation reactions previously thought to be iron-catalyzed.[20] To address the possibilty that trace copper in our zinc salts is responsible for the rate enhancement in our reactions, trace metal copper analysis was performed by ICP-MS.[21] The coupling of 4-bromoanisole with phenylacetylene in the presence of trace amounts of CuI (0.005 mol %, 50 ppm) was compared to the use of 10 mol % $ZnCl_2$; the results are summarized in Table 4. To our surprise, even small amounts of CuI can enhance the rate of coupling (Table 4, entry 2). However, couplings were faster in the presence of 10 mol % $ZnCl_2$ (Table 4, entry 4), which, after accounting for trace Cu contaminants in $ZnCl_2$, contains 1/100th the amount of Cu compared to entries 3 and 4. There does not appear to be a significant rate enhancement when trace CuI is added in the presence of 10 mol % $ZnCl_2$. Thus, we conclude that trace copper does not appear to be the active catalyst. Mechanistic studies to delineate the role of the zinc halide are currently underway.

**TABLE 4. Effects of Trace CuI in Cross-Coupling[a]**



| entry | $ZnCl_2$ (mol %) | CuI (mol %) | % yield[b] | | |
|---|---|---|---|---|---|
| | | | 1 h | 2 h | 24 h |
| 1 | −[c] | −[c] | 2 | 5 | 19 |
| 2 | −[c] | 0.005 | 5 | 10 | 56 |
| 3 | 10 | 0.005 | 24 | 56 | 100 |
| 4 | 10 | −[c] | 30 | 58 | 100 |

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylacetylene (1.1 mmol), **1** (0.01 mmol), zinc halide (0.1 mmol) and/or CuI ($5 \times 10^{-5}$ mmol), THF (10.0 mL), HN(*i*-Pr)$_2$ (3.0 mL), rt. Details are in the Supporting Information. [b] GC yields, average of two runs. [c] Not added.

In conclusion, we have developed optimized conditions for a general and convenient aryl bromide−alkyne cross-coupling method in which rates of coupling are significantly enhanced by addition of catalytic $ZnCl_2$, without promoting diyne byproduct formation. These conditions present a superior alternative to other "copper-free Sonogashira" cross-couplings, by enhancing the rate of coupling via addition of an inexpensive cocatalyst that is less susceptible to alkyne homocoupling.

## Experimental Section

**General Procedure for the Preparation of Substituted Alkynes with Catalytic $ZnCl_2$ (Table 3, entry 2): 4-Methoxydiphenylacetylene.** In a glovebox, a 20 mL vial with stirbar and PTFE/silicone septum-lined cap was charged with, in order, 4-bromoanisole (0.561 g, 3 mmol, 1 equiv), $ZnCl_2$ (41 mg, 0.3 mmol, 0.1 equiv), THF (7 mL), HN(*i*-Pr)$_2$ (3 mL), and Pd(I) dimer **1** (21 mg, 0.03 mmol, 0.01 equiv). The solution was stirred to dissolve the solids, and then phenylacetylene (0.306 g, 3 mmol, 1 equiv) was added. The vial was capped, removed from the glovebox, and stirred at room temperature for 1h. The solution was diluted with EtOAc and passed through a plug of silica gel (10 g) and eluted with 100 mL of EtOAc to remove salts. The solution was evaporated, and the residue was purified by column chromatography ($SiO_2$, 6:1 hexane:EtOAc) to give the product in 90% yield (0.562 g). Pale yellow solid, mp 58−59 °C (lit.[22] mp 58−61 °C); $^1H$ NMR (500 MHz; $CDCl_3$) $\delta$ 7.53−7.51 (m, 2H), 7.50−7.47 (m, 2H), 7.36−7.32 (m, 3H), 6.90−6.88 (m, 2H), 3.83 (s, 3H); $^{13}C$ NMR (126 MHz; $CDCl_3$) $\delta$ 159.7, 133.2, 131.6, 128.4, 128.1, 123.7, 115.5, 114.1, 89.5, 88.2, 55.4.

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(18) (a) For examples of reverse selectivity (triflates preferential to halides), see: Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922–8925. Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742–1744. (b) Pd/P(*t*-Bu)$_3$ is selective for aryl chlorides over aryl triflates in Suzuki cross-couplings: Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

(19) Fassler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843–5845.

(20) See ref 7b and the following: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5587.

(21) The amounts of Cu (in ppm) of the zinc salts we used were as follows: $ZnCl_2$ (0.97 ppm); $ZnBr_2$ (1.10 ppm); $ZnI_2$ (1.23 ppm); $Zn(OTf)_2$ (0.62 ppm).

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**Supporting Information Available:** Synthetic procedures, spectroscopic characterization of compounds, and preparation and handling of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.