Coordination Chemistry and Mechanisms of Metal-Catalyzed C−C Coupling Reactions, 13[‡]

A Copper-Free Procedure for the Palladium-Catalyzed Sonogashira Reaction of Aryl Bromides with Terminal Alkynes at Room Temperature

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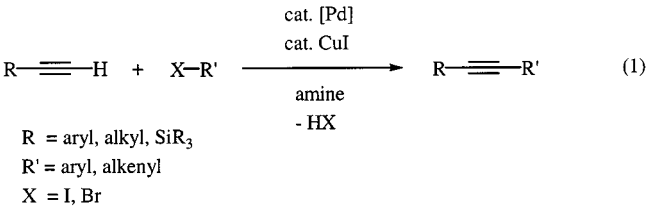
Keywords: Alkynes / Arenes / Catalysis / C−C coupling / Palladium

The catalyst system $Pd_2(dba)_3/P(tBu)_3$ was found to promote the Sonogashira reaction of aryl bromides at room temperature *and* without CuI as the co-catalyst in high yield. The catalyst system was identified from a library of 58 potential ligands by the application of a color assay. The reaction conditions allow the use of only 0.5 mol-% palladium and ligand with reagent grade chemicals.

Introduction

The preparation of arylalkynes and conjugated enynes is most conveniently achieved by the palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl halides.[1] This reaction is now generally referred to as the Sonogashira reaction and is carried out in the presence of catalytic amounts of a palladium complex and copper(I) iodide in an amine as the solvent and the base [Equation (1)].[2] Therefore, this reaction has been used extensively in organic synthesis[3] and in the preparation of liquid crystalline materials and conducting polymers.[4] Furthermore, internal alkynes can be easily used for the selective formation of thermodynamically disfavored *cis*-alkenes by catalytic reduction with molecular hydrogen.[5]

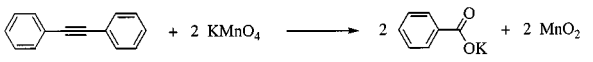


(1)

In order to simplify the reaction protocol for the Sonogashira reaction, we wanted to develop a general catalytic system for various types of substrates. We had an efficient, novel system in our minds which had to meet certain requirements: (i) less reactive substrates like deactivated aryl bromides, e.g. 4-bromoanisole, should be converted in high yield;[6] (ii) the amounts of palladium catalyst and ligand as the major cost factors should be lowered from typically 2−5 mol-% and should be in a 1:1 ratio;[2] (iii) copper(I) iodide as the co-catalyst makes the system more complicated and can render it useless for certain applications including technically feasible transformations.[7] Activity should therefore be obtained with a palladium catalyst only; (iv) room temperature activity is highly desirable for the transformation of sensitive substrates; (v) oxygen promotes the undesired Glaser-type homocoupling of the alkynes to symmetrical diynes **1**[8] as well as the precipitation of catalytically inactive palladium black.[9] Nevertheless, nondegassed, reagent-grade chemicals should be used.

1 **2**

In order to evaluate a large variety of potential catalysts, we used a ligand library of phosphanes, arsanes and imidazolium salts in combination with $Pd_2(dba)_3$ as the palladium(0) precursor.[10,11] As a convenient screening assay, we chose the oxidation of the product alkyne by $KMnO_4$ [Equation (2)]. In the case of product formation, a bleaching of the lilac color through reduction of manganese(VII) to manganese(IV) should be observed.



(2)

The bleaching of the $KMnO_4$ solution can only be correlated with the catalyst activity if the product is the only reagent which is oxidized. Therefore, the product had to be purified from the catalyst and the reactants. To achieve this easily, the product was immobilized on a functionalized polystyrene Wang-resin.[12] This was accomplished by reacting phenylacetylene with a deactivated, heterogenized aryl bromide **3**. Its preparation by ether formation of

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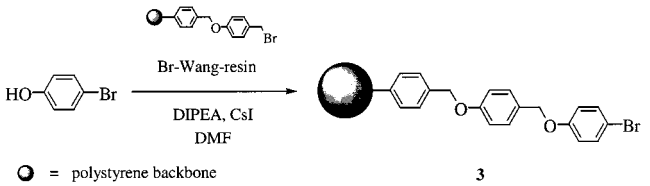
4-bromophenol with 4-bromomethylphenoxymethyl polystyrene (bromo Wang-resin) in the presence of CsI and DIPEA follows the reaction outlined in Scheme 1.[11,13]



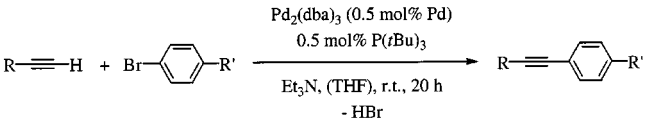
Scheme 1. Preparation of the immobilized, 4-bromoanisole type aryl bromide **3**

Testing of the ligand library revealed P(tBu)$_3$ and P(Cy)$_3$ [Cy = cyclohexyl] to be hits in combination with $Pd_2(dba)_3$ in a 1:1 ratio as catalysts for the Sonogashira reaction of **3** with phenylacetylene in triethylamine Et_3N as the base and the solvent.[11] The imidazolium salts tend to promote the homocoupling of the alkyne and thus the formation of the by-products **1** and **2** rather than catalyzing the desired Sonogashira reaction. Optimization in larger scale experiments reveals P(tBu)$_3$ to be more active than P(Cy)$_3$.

$Pd_2(dba)_3$/P(tBu)$_3$ has also proven to be very efficient for other palladium catalyzed C−C bond formation reactions.[14]

In order to evaluate the scope of the new catalyst system, we performed the reaction of various aryl bromides with phenylacetylene or trimethylsilylacetylene (Table 1). Yields are generally high after 20 h for all types of substrates. Steric effects as in 2-bromotoluene influence the yield only slightly (Entry 8, Table 1) but changing the solvent from Et_3N to THF results in lower yields (Entries 10−17, Table 1).[15] Dropwise addition of the alkyne suppresses the formation of the undesired by-products **1** and **2**.[15c]

Table 1. The Sonogashira reaction catalyzed by $Pd_2(dba)_3$ and P(tBu)$_3$ (1.0 equiv. of aryl bromide, 1.2 equiv. of alkyne, 1.5 equiv. of Et_3N; THF or Et_3N, T = 22 °C, t = 20 h)



Entry	R	R′	Et_3N[a]	Yield [%][b]	TON[c]
1	C_6H_5	$C(O)CH_3$	pure	>99	200
2	C_6H_5[d]	$C(O)CH_3$	pure	44	88
3	$Si(CH_3)_3$	$C(O)CH_3$	pure	100	200
4	C_6H_5	F	pure	78	156
5	C_6H_5	Cl	pure	78	156
6	$Si(CH_3)_3$	H	pure	92	184
7	C_6H_5	CH_3	pure	71	142
8	C_6H_5	2-CH_3	pure	68	136
9	C_6H_5	OCH_3	pure	51	102
10	C_6H_5	$C(O)CH_3$	1.5 equiv.	79	158
11	$Si(CH_3)_3$	$C(O)CH_3$	1.5 equiv.	99	198
12	C_6H_5	F	1.5 equiv.	71	142
13	C_6H_5	Cl	1.5 equiv.	68	136
14	$Si(CH_3)_3$	H	1.5 equiv.	88	176
15	C_6H_5	CH_3	1.5 equiv.	61	122
16	C_6H_5	2-CH_3	1.5 equiv.	59	118
17	C_6H_5	OCH_3	1.5 equiv.	42	84

[a] Solvent and base: (i) pure = 2 mL Et_3N, no THF. − (ii) 1.5 equiv. = 1.5 equiv. Et_3N, 2 mL THF. − [b] GC-yield using diethylene glycol-di-*n*-butyl ether as the internal standard. − [c] mol product/mol Pd. − [d] t = 2 h.

In summary, we have found that the catalyst system $Pd_2(dba)_3$/P(tBu)$_3$ promotes the Sonogashira reaction of aryl bromides at room temperature *and* without CuI as the co-catalyst in high yield. The catalyst formed under reaction conditions is highly active, even allowing the use of only 0.5 mol-% palladium and ligand. Both Et_3N and THF can be used as the solvent in combination with Et_3N as the base. Furthermore, reagent grade chemicals can be employed.

The most active catalyst system was identified from a library of 58 potential ligands by the application of a color-assay. The assay was based on the bleaching of a $KMnO_4$ solution through reduction to insoluble MnO_2 induced by the desired product of the reaction.

Experimental Section

Preparation of 4-(Phenylethinyl)acetophenone:[11] $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) was weighed into a Schlenk tube under an atmosphere of nitrogen. After the addition of Et_3N [2.0 mL; or 415 μL (3.000 mmol) in 2.0 mL THF] and P(tBu)$_3$ (2.0 mg, 0.010 mmol), 4-bromoacetophenone (398.0 mg, 2.000 mmol) was added. The mixture was stirred for 2 min and the reaction started at ambient temperature by the dropwise addition of phenylacetylene (263 μL, 2.400 mmol) in 0.5 mL of Et_3N or THF from a syringe over a period of 20 min. After 20 h the reaction was quenched with water and extracted three times with 5 mL of Et_2O. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude pale yellow product was redissolved in acetone and crystallized in a freezer at −30 °C.

Yield: 430.1 mg (98%). − ^{1}H (400 MHz, $CDCl_3$, 22 °C, TMS): δ = 2.57 (s, 3 H, CH_3), 7.33−7.35 (m, 3 H), 7.52−7.54 (m, 2 H), 7.58 (d, $^3J_{HH}$ = 8.2 Hz, 2 H), 7.91 (d, $^3J_{HH}$ = 8.2 Hz, 2 H). − $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$, 22 °C, TMS): δ = 26.5 (CH_3), 88.6, 92.6, 122.6, 128.1, 128.2, 128.4, 131.6, 131.7, 136.1, 197.2 (CO). − $C_{16}H_{12}O$ (220.27): calcd. C 87.25, H 5.49; found C 87.08, H 5.29.

After submission of this manuscript a related catalyst system was published.[16]

Acknowledgments

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