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A copper- and amine-free Sonogashira coupling reaction promoted by a ferrocene-based phosphinimine-phosphine ligand at low catalyst loading

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Abstract—A palladium(II) complex containing a ferrocene-based phosphinimine-phosphine ligand was applied to the amine- and copper-free Sonogashira coupling of aryl iodides and aryl bromides with terminal alkynes using 1 equiv of tetrabutylammonium acetate as an activator. The corresponding disubstituted alkynes were obtained in high yields and TONs using 0.1 mol% Pd-catalyst.

The Sonogashira reaction, palladium and copper co-catalyzed coupling of terminal alkynes with various organic halides, is the most straightforward and powerful method of the construction of C(sp^2)–C(sp) bonds.[1] It provides an efficient route to aryl (heteroaryl) alkynes, which are interesting intermediates for the preparation of a wide variety of target compounds with applications ranging from natural products[2] to molecular organic materials.[3]

The original protocol of the Sonogashira reaction, a dimetallic-mediated process, which is typically carried out in the presence of catalytic amounts of a palladium(II) complex as well as CuI in an amine as solvent or in large excess, has been repeatedly modified and improved to overcome several significant limitations. The most important improvement concerned the elimination of CuI, which is used as co-catalyst, since it can induce homocoupling reactions of terminal alkynes to diynes in the presence of oxygen (Glaser-type reactions). Copper-free approaches to the Sonogashira reaction must involve the use of an amine, such as piperidine or triethylamine, as solvent[4] or in large excess.[5] A copper-free coupling of aryl iodides with terminal alkynes has also been reported using an ionic liquid as solvent.[6] Recently, three amine- and copper-free methodologies for the Sonogashira reaction have been presented, the first one is based on the use of stoichiometric amounts of silver(I) oxide for aryl iodides, and tetrabutylammonium fluoride or tetrabutylammonium hydroxide for aryl bromides as activators.[7] The second one is based on the use of an oxime palladacycle and tetrabutylammonium acetate as an additive.[8] In the third one, which allows the use of aryl chlorides as coupling partners, a bulky electron-rich *ortho*-biphenylphosphane ligand is employed.[9] Interestingly, the use of a copper co-catalyst inhibits the reaction. Sonogashira cross-coupling reaction catalyzed by heterogeneous copper-free Pd-complexes have been also reported.[10]

P,N-Donor bidentate ligands exhibit hemilabile behaviour when coordinated to a soft metal centre such as palladium. The soft phosphorus atom coordinates very strongly to palladium whereas the hard nitrogen donor is weakly bound.[11] A distinguished family of hemilabile ligands results by combining a phosphine and imine

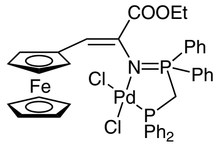

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Figure 1.

Keywords: Sonogashira reaction; Copper-free; Palladium; Catalysis; Alkynes.

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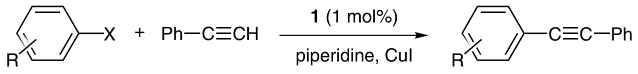
Table 1. Sonogashira reaction: reaction conditions study[a]



Entry	R	X	CuI (mol%)	T (°C)[b]	t_R (h)	Yield[c]	TON[d]
A	3-H_3CO	I	1.5	25	0.4	97	9700
B	3-H_3CO	I	1.5	80	0.25	99	9900
C	4-H_3CO	Br	1.5	25	4	<1	
D	4-H_3CO	Br	1.5	80	6	61	6100
E	4-H_3C–CO	Br	1.5	80	6	58	5800
F	4-H_3C–CO	Br	3	80	6	52	5200

[a] Reactions were run using 1 mol% of **1**, 1 mmol of aryl halide, 1.2 mmol of phenylacetylene in piperidine as solvent.

[b] The reaction mixture was placed in an oil bath at stated temperature and held there for the allotted time.

[c] Isolated product after work-up.

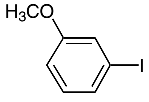
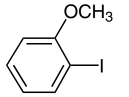
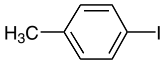
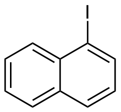
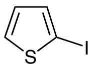
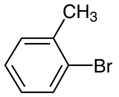
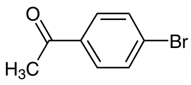
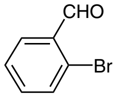
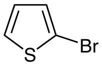
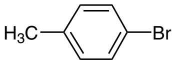
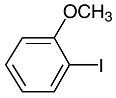
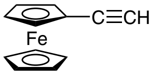
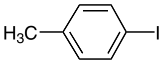
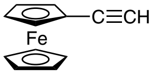
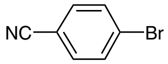
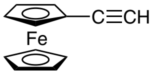
[d] TON (turnover number) = mol product mol Pd^{-1}.

groups (phosphine-imine ligands), which have been attracting considerable attention in the past few years as an important class of P,N-ligands.[12] In spite of the fact that iminophosphoranes have been shown to coordinate to transition metals via the approximately sp^2-hybridized nitrogen atom to give stable complexes,[13] functionalized iminophosphoranes that contain a phosphino group as a second donor site have received very little attention as ligands for homogeneous catalysis.[14]

Some years ago, we reported[15] the preparation and structural characterization of the palladium(II) complex **1** (Fig. 1), containing a ferrocene-based phosphinimine-phosphine ligand. We wish now to report its efficient use in an easy, quick, amine- and copper-free methodology for the Sonogashira reaction.

As a starting point for the development of the methodology, we chose as model reactions the coupling between the 'deactivated' 3-methoxy-iodobenzene and 4-methoxy-bromobenzene and the 'activated' 4-bromoacetophenone with phenylacetylene in the presence of catalyst **1** (1 mmol% of Pd) in piperidine as solvent. As illustrated by Table 1, the coupling reaction between 3-methoxy-iodobenzene and phenylacetylene provided an excellent yield (87%) in the presence of CuI as co-catalyst (1.5 mol%) at 25 °C. The transformation of the related 4-methoxy-bromobenzene and 4-bromoacetophenone necessitated a reaction temperature of 80 °C and longer reaction time (entries d and e). Increasing the co-catalyst loading to 3 mol% had a negligible effect on the yield (entry f). These results demonstrate clearly the applicability of the complex **1** in the Sonogashira cross-coupling reaction, however, the success of these examples remains linked to the use of CuI as co-catalyst. The use of *N*-methylpyrrolidinone

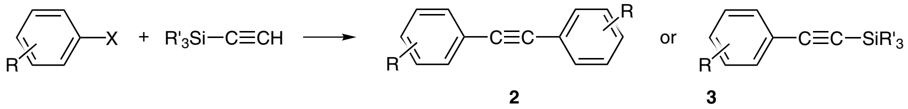
Table 2. Amine- and copper-free Sonogashira coupling of aryl- and heteroaryl halides catalyzed by **1**[a]

Entry	Halide	Alkyne	Yield (%)[b]
a		Ph–C≡CH	99
b		Ph–C≡CH	98 (96)
c		Ph–C≡CH	>99 (99)
d		Ph–C≡CH	96 (94)
e		Ph–C≡CH	>99 (97)
f		Ph–C≡CH	84 (83)
g		Ph–C≡CH	94 (92)
h		Ph–C≡CH	72 (70)
i		Ph–C≡CH	96 (90)
j		Ph–C≡CH	99
k			>99 (97)
l			>99 (98)
m			65 (64)

[a] Reactions were run using 0.1 mol% of **1**, 1 mmol of aryl halide, 1.2 mmol of phenylacetylene in NMP as solvent in the presence of TBAOAc (1.5 mmol) at 110 °C for 1 h.

[b] Conversion determinated by GC using decane as internal standard and based on starting halide. In brackets, isolated product yields after workup, which gave satisfactory spectroscopic data (^{1}H and ^{13}C NMR and MS).

Table 3. Amine- and copper-free Sonogashira reaction of trialkylsilyl-protected acetylenes



Entry	R	X	R′	t_R (h)	Product	Yield (%)[a]
a	4-H$_3$CO	I	Me	1	2	76 (72)
b	4-H$_3$C	I	Me	1	2	97 (93)
c	2-Thienyl	I	Me	2	2	85
d	4-H$_3$C	I	*i*-Pr	1	3	99 (93)
e	2-H$_3$CO	I	*i*-Pr	1	3	99 (85)
f	4-H$_3$CCO	Br	*i*-Pr	1.5	3	97 (75)
g	4-CN	Br	*i*-Pr	1.5	3	95

[a] Conversion determinated by GC using decane as internal standard and based on starting halide. In brackets, isolated product yields after workup, which gave satisfactory spectroscopic data (^{1}H and ^{13}C NMR and MS).

(NMP) as solvent and tetrabutylammonium acetate (TBAOAc) as additive, allows that this alkynylation process can be performed under very convenient amine- and copper-free conditions.

The coupling reaction between 2-methoxy-iodobenzene and phenylacetylene led to a product yield of 85% when NMP was used as solvent in the presence of TBAOAc as additive at 25 °C for 27 h using 1 mol% of **1**. Increasing the reaction temperature to 110 °C improved the yields to 99% after 1 h. Under these conditions coupling of 4-bromoacetophenone with phenylacetylene provided the product in 99% yield. With this in mind, we investigated the effects of decreasing the catalyst loading. We found that reduction of the catalyst loading to 0.1 mol% led in the reaction of 2-methoxy-iodobenzene and 4-bromoacetophenone with phenylacetylene to a product yield of 99% and 94%, respectively.

With our optimized reaction conditions in hand, we screened a range of aromatic and heteroaromatic iodides and bromides in the coupling reaction with phenyl- and ferrocenylacetylene (Table 2). The results show that the procedure is applicable to a range of aryl iodides and activated aryl bromide substrates, with good product yields being obtained. The method is found to be relatively insensitive to the steric hindrance of the starting halide (entries b, f and k), and it also shows good functional group compatibility. For example, 2-bromobenzaldehyde is not destroyed during the course of the reaction (entry h).

In an effort to explore the scope of the method, we have screened the coupling of representative aryl iodides and aryl bromides with trialkylsilyl-protected acetylenes, which are known to be much more difficult to couple as compared to phenylacetylene in Sonogashira copper-free protocols. While we found that the use of trimethylsilylacetylene was inefficient due to the significant desilylation of the product that takes place under our reaction condition to give symmetrically disubstituted alkynes **2** (Table 3 entries a–c), the use of triisopropylsilylacetylene was a suitable surrogate and the monoarylacetylenes **3** were obtained (entries d–g) in excellent yields.

In conclusion, we have shown that the readily available palladium(II) complex, is an efficient and versatile catalyst for amine- and copper-free Sonogashira reactions of aryl(heteroaryl) iodides and aryl(heteroaryl) bromides with a variety of terminal alkynes. The catalyst system is highly active using very low loading conditions (0.1 mol% of Pd).

Typical experimental procedure. In a 25 mL flask was placed N-methylpyrrolidinone (8 mL), 4-iodotoluene (545 mg, 2.5 mmol), phenylacetylene (312 mg, 3 mmol), tetrabutylammonium acetate (1130 mg, 3.75 mmol) and the catalyst **1** (2.1 mg, 2.5 10^{-3} mmol). The resulting solution was placed in a sand bath pre-heated to 110 °C and stirred for 1 h. After this time, the solution was poured into 5% v/v hydrochloric acid (20 mL) and then extracted with diethyl ether (4 × 15 mL). The combined organic layers were washed with brine (20 mL) and water (20 mL) before being dried over anhydrous MgSO$_4$. After filtration the solvent was removed and the crude product was chromatographed on a silica gel column, using 1:12 EtOAc/hexanes as eluent to give 4-methyl-1-phenylethynyl benzene (475 mg, 90%).

Acknowledgements

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