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The First Catalytic Method for Heck Alkynylation of Unactivated Aryl Bromides (Copper-Free Sonogashira) in an Ionic Liquid: 1 mol-% Palladium/Triphenylphosphane/Pyrrolidine in [BMIM][BF_4] as a Simple, Inexpensive and Recyclable System

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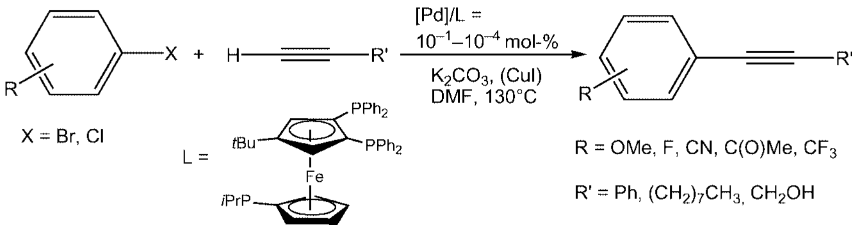
Keywords: Alkynylation / Aryl bromides / Ionic liquids / Heck reaction / Copper-free Sonogashira / Cross-coupling

Herein we report the studies of Heck alkynylation (copper-free Sonogashira) with aryl halides (I, Br, Cl) employing various metallic precursors, tertiary phosphanes and bases in [BMIM][BF_4] as the solvent. As a result, we provide the first method that allows the coupling of a large array of substrates, either activated or deactivated bromides in an ionic liquid. Furthermore, the system of highest efficiency is unexpectedly the simplest and cheaper combination that employs [$Pd(\eta^3\text{-}C_3H_5)Cl]_2/PPh_3$ at only a 1 mol-% loading with pyrrolidine as the base and in the absence of a copper salt. The coupling of sterically and electronically deactivated bromides bearing different functional groups to aryl- and alkyl acetylenes, as well as the possibility of recycling, make these results of high interest to the future development of Heck- and Sonogashira-type reactions in ionic liquids.

The development of efficient methods for the incorporation of alkynes into organic molecules is a crucial objective. Indeed, alkynes are recurring building blocks in a wide range of useful industrial intermediaries and a great number of bioactive natural products, pharmaceuticals, agrochemicals and conjugated molecules (molecular materials for optics or electronics) are built around an aryl alkyne backbone.[1] The commonly used aryl- or vinyl alkynylation process which typically employs a palladium precursor/ligand/base system in the presence of a few mol-% of a copper cocatalyst (Sonogashira reaction)[2] is recognized as extremely powerful.[3] The even more desirable *copper-free* alkynylation (Heck alkynylation)[4] is often more difficult to accomplish, but can be conducted by employing some very efficient catalytic systems.[5] Aside from their wide functional group tolerance,[6] the important features of these cross-coupling methods include the use of a reduced amount of metal when compared, for instance, to other alkynylation routes that require the stoichiometric addition of metallic reagents.

In the course of our studies aimed at the development of ubiquitous multidentate auxiliary ligands,[7,8] which could allow efficient cross-coupling reactions at low catalyst loadings ranging from 10^{-2} to 10^{-4} mol-% of palladium and phosphane auxiliary,[9–11] we reported the catalytic efficiency of new ferrocenyl triphosphane $Fc(P)_2t\text{Bu}(Pi\text{Pr})$, **1**, for the alkynylation of aryl bromides and aryl chlorides (Scheme 1).[10]



Scheme 1. Aryl alkynylation system employing Pd/**1** at 10^{-1} to 10^{-4} mol-% in DMF.

These interesting results prompted us to extend the study of the reactivity of our Pd/ferrocenyltriphosphane system for alkynylation into room temperature ionic liquids (IL), especially into imidazolium salts. Because of their negligible

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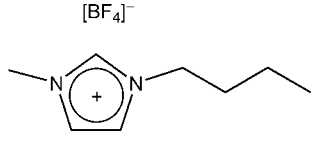
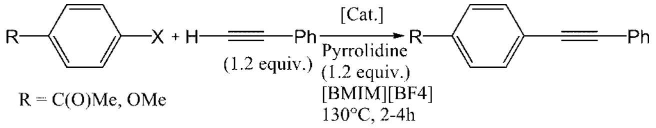
vapour pressure, ease of handling and potential for recycling, these novel solvents have shown great promise. As a reaction medium, their high compatibility with transition metals and limited miscibility with common solvents enable easy separation of organic products and possibly retention of the catalyst at the resting-state in the ionic phase.[12] Apart from the pioneering work recently reported by Ryu and coworkers,[13a] and by Alper and Park,[13b] which were the first groups to disclose catalytic systems for the coupling of aryl iodides in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), aryl alkynylation in ionic liquids is still underdeveloped.[12,13] Herein we report our studies on the Heck alkynylation (copper-free Sonogashira) reaction with aryl halides (I, Br, Cl) by employing various metallic precursors, tertiary phosphanes and bases in [BMIM][BF_4] as the solvent[14] (Scheme 2). As a result, we provide the first method that allows the coupling of a large array of substrates, either activated or deactivated bromides. Furthermore, the system of highest efficiency is unexpectedly the simplest and cheaper combination that employs [Pd(η^3-C_3H_5)Cl]$_2$/PPh_3 at only a 1 mol-% loading with pyrrolidine as the base and in the absence of a copper salt.



Scheme 2. 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]).

Because our original goal was to extend the previously reported methodology by employing palladium combined with tridentate ferrocenyl polyphosphane **1** to valuable alkynylations in ionic liquids, we first explored different conditions summarised in Table 1. On the basis of previous reports,[13] we anticipated that a significant advance in this methodology would be the efficient coupling of terminal alkynes with aryl chlorides or bromides. The relative reactivity of the aryl halides is well-established as Ar–I >> Ar–Br > Ar–Cl,[3b,15] and chloride and bromide substrates are more attractive starting materials with regard to sustainable chemistry and economic concerns. Therefore, 4-bromoacetophenone (electron-poor *activated* substrate) and 4-bromoanisole (electron-rich *deactivated* substrate) were chosen as benchmarks for the preliminary screening. With regard to terminal alkyne candidates, phenylacetylene and alkynylsilanes are among the most studied in organic solvents; the former, which we chose as a benchmark, appeared generally as a more demanding substrate.[1b,16] As the inorganic base K_2CO_3 that we originally used[10] was not suitable in this reaction because of solubility troubles, we chose to examine the effect of pyrrolidine as an organic amine base.[17] Preliminary experiments indicated that the coupling of aryl iodides to phenylacetylene is easy and gives satisfactory results in [BMIM][BF_4], which is similar to reactions conducted in [BMIM][PF_6].[13a,13b] Then, *we were delighted to discover and show for the first time that the coupling of aryl bromides is also possible* in the absence of a copper cocatalyst, and within only a few hours, by employing the catalytic systems in Table 1. Whereas the alkynylation of 4-bromoacetophenone was not effective in the absence of a palladium/ligand system, when 0.5 mol-% of [Pd(allyl)Cl]$_2$ (1 mol-% Pd, no auxiliary ligand) was employed as the catalyst, less than 10% of coupling product was obtained (Table 1, Entries 1 and 2). The alkynylation reactions with the use of catalytic system Pd/**1**, which is remarkably active in DMF,[10] were not as promising as we expected: only 52% yield of 4-(2-phenylethynyl)acetophenone and 31% of

Table 1. Screening of catalytic systems.



Entry	Aryl halide	Catalytic system, [Cat.][a]	[Cat.] ratio [mol-%]	Yield [%][b]
1	4-Bromoacetophenone	None	/	0
2		[Pd(allyl)Cl]$_2$, no ligand	1	<10
3		[Pd(allyl)Cl]$_2$/**1**	1	52
4		[Pd(allyl)Cl]$_2$/3 PPh_3	1	100 (88)
5		[Pd(allyl)Cl]$_2$/dppe	1	96
6		[Pd(allyl)Cl]$_2$/dppf	1	86
7		[Pd(allyl)Cl]$_2$/**1**	0.1	47
8		[Pd(allyl)Cl]$_2$/3 PPh_3	0.1	91
9		$Ni(NO_3)_2(PPh_3)_2/PPh_3$	5	0
10		$Ni(SCN)_2(PPh_3)_2/PPh_3$	5	0
11	4-Bromoanisole	[Pd(allyl)Cl]$_2$/**1**	1	31
12		[Pd(allyl)Cl]$_2$/3 PPh_3	1	61 (55)
13		[Pd(allyl)Cl]$_2$/dppe	1	15
14		[Pd(allyl)Cl]$_2$/dppf	1	51

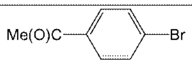
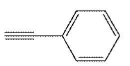
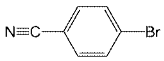
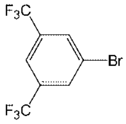
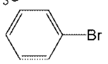
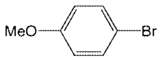
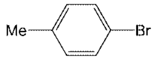
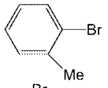
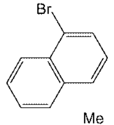
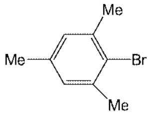
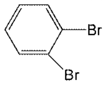
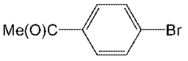
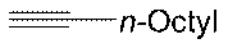
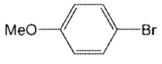
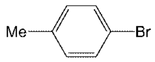
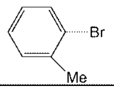
[a] Reaction conditions: 1.0 equiv. aryl bromide, 1.2 equiv. phenylacetylene, 1.2 equiv. pyrrolidine, 3 mL [BMIM][BF_4], 130 °C; catalyst: 0.5 mol-% [Pd(allyl)Cl]$_2$ and 1 mol-% **1**, or dppe (1,2-bis[diphenylphosphanyl]ethane), or dppf (1,1′-bis[diphenylphosphanyl]ferrocene), or 3 mol-% PPh_3. [b] Yields determined after 2 h for 4-bromoacetophenone and 4 h for 4-bromoanisole (GC), isolated yields are in brackets, which is the average of several consistent runs.

(4-methoxyphenyl)phenylacetylene were obtained in short-time reactions. In an effort to comparatively evaluate the properties of cheap and robust classical phosphane ligands (typically PPh_3, dppe and dppf), we eventually identified the superior effectiveness of the catalytic system that combines 1 mol-% Pd with 3 mol-% PPh_3; by using this system, 4-bromoacetophenone (Entry 4) was selectively and quantitatively alkynylated in two hours. Under similar conditions, with the employment of dppe or dppf as auxiliary ligands, 96% and 86% of coupling product were obtained, respectively, with some secondary products being formed.[18]

Consistently, the alkynylation of 4-bromoanisole is effected in [BMIM][BF_4] at 130 °C in 4 h with a 61% conversion with the use of Pd/PPh_3 (Entry 12), 15% with Pd/dppe (Entry 13), 51% with Pd/dppf (Entry 14) and 31% with Pd/**1** (Entry 11). We noticed as well that the coupling of 4-bromoacetophenone is efficiently achieved with only one-tenth the catalyst concentration that was originally employed (Entries 7 and 8). Finally, the ionic nickel complexes bearing triphenylphosphane proved to be completely inactive in this reaction.[18]

From these screening results we selected the simple catalytic system combining 1 mol-% palladium/3 mol-% triphenylphosphane in [BMIM][BF_4] for the detailed studies presented in Table 2.[18] In addition to the quantitative conversion of 4-bromoacetophenone (Entry 1), good to excellent conversions were obtained in 2 to 4 h for the coupling of phenylacetylene with the electronically activated 4-bro-

Table 2. Scope of the copper-free alkynylation of aryl bromides with 1 mol-% of Pd/PPh_3 in [BMIM][BF_4].[a]

Entry	Aryl bromide	Alkyne	*t* [h]	Enyne yield [%][b]	Secondary products and remarks[c]
1			2	> 99	–
2			4	80	10% Ar–Ar, 10% Ar–pyrrolidine
3			4	92	8% Ar–H addition to enyne
4			2	82	18% Ar–X
5			20	95	5% Ar–X
6			20	86	14% 4-(phenylethenyl)toluene
7			20	99	–
8			4	98	–
9			48[d]	>99	–
10			24[e]	98	58% monosubstituted, 42 % disubstituted
11			4	96	4% decyne addition to enyne
12			4 20	40 76	60% Ar–X, 4% Ar–X, 15% of enyne isomerization, 5% of phenyldecyne
13			4	76	20% Ar–X, 4% decyne addition to enyne
14			4	65	30% Ar–X, 5% decyne addition to enyne

[a] Reaction conditions: 1.0 equiv. of aryl bromide, 1.2 equiv. of phenylacetylene, 1.2 equiv. of pyrrolidine, 3 mL [BMIM][BF_4], 130 °C; catalyst: 0.5 mol-% [Pd(allyl)Cl]$_2$, 3 mol-% PPh_3. [b] Yields determined by GC (external standard), isolated yields obtained after column chromatography reach 90–95% of these values. [c] Secondary products identified by GC–MS. [d] 1.6 equiv. of phenylacetylene and pyrrolidine. [e] 3 equiv. of phenylacetylene and pyrrolidine. Ar-X = unconverted halide.

mobenzonitrile (80% in 4 h, Entry 2), 3,5-bis(trifluoromethyl)bromobenzene (92%, 4 h, Entry 3) and with the unactivated bromobenzene (82%, 2 h, Entry 4). However, the most remarkable results were obtained with longer times for the electronically and/or sterically *deactivated* substrates: in 20 h, 4-bromanisole was converted in 95% yield (Entry 5), 4-bromotoluene in 86% yield (Entry 6) and 2-bromotoluene in 99% yield (Entry 7). Whereas cross-coupling reactions with aryl halides in which one or both the *ortho* positions are substituted generally suffer from additional complications of steric origin,[1b] 2-bromonaphthalene and bromomesitylene were quantitatively converted into the corresponding enyne in 4 and 48 h, respectively (Entries 8 and 9).[18] Interestingly, we verified that a double alkynylation was possible starting from a dibromoaryl (98% conversion in enynes, with 60% monosubstitution and 40% disubstitution; Entry 10). Finally, the coupling of aryl bromides with a demanding (long chain) aliphatic terminal alkyne, namely 1-decyne, was also explored with success: in only 4 h, 4-bromoacetophenone was converted in 96% yield (Entry 11), the electronically and/or sterically deactivated 4-bromotoluene and 2-bromotoluene yielded 76% and 65%, respectively, of the expected alkynylation product. For 4-bromoanisole, a 20 h reaction time gave 76% conversion into the desired enyne. Table 2 also summarises some of the secondary products encountered in these reactions. Our attempts to activate aryl chlorides with the Pd/PPh$_3$ system remained unsuccessful as even 4-chloroacetophenone was not converted.

Recycling of our catalytic system was also carried out (Table 3). After extraction, the resulting IL phase was kept under air for several days (Table 3 for Entries 3–4, cycles 2 were run after 78 days standing!) and was reused without any pretreatment (no washing with water). Because of the importance of the phosphane ligand, and to limit the negative effect of some possible leaks of monophosphane within the extraction process, the recycling tubes were refilled with 3 mol-% triphenylphosphane. The ionic phase was reused successfully for different substrates with a slight loss in its activity[19] for activated 4-bromoacetophenone (Table 3, Entry 1), electronically deactivated 4-bromotoluene (Entry 2), and electronically and sterically deactivated (*ortho*-substituted) 2-bromotoluene (Entry 3). Recycling of strongly deactivated 4-bromoanisole gave a more disappointing result.

Table 3. Efficiency of the recycled ionic liquid phase of the catalytic system.[a]

Entry	Aryl bromide	Cycle 1 yield [%]	Cycle 2 yield [%]	Cycle 3 yield [%]
1	4-Bromoacetophenone	>99	80	78
2	4-Bromotoluene	86	99	73
3	2-Bromotoluene	>99	72	61
4	4-Bromoanisole	95	61	20

[a] Reaction conditions identical to Table 2 for each cycle.

In summary, herein is provided the first catalytic method for Heck alkynylation of aryl bromides in an ionic liquid. The system Pd/3 PPh$_3$ (1 mol-%) in [BMIM][BF$_4$] is efficient for the coupling of a variety of activated and deactivated aryl bromides: *para* and/or *ortho* mono- and disubstituted substrates, with the two demanding aromatic (phenylacetylene) and aliphatic (long chain 1-decyne) terminal acetylenes. The recycling possibility has been shown and ongoing studies are aimed at the optimisation of the reaction. The simplicity and accessibility of the system (low price for ligand, organic base and IL)[20] make these results of high interest to the future development of Heck- and Sonogashira-type coupling reactions in ionic liquids.

Experimental Section

Representative Catalytic Experiment for the Heck Alkynylation Reaction in [BMIM][BF$_4$]: The solid mixture of [Pd(allyl)Cl$_2$] (6.3 mg, 0.03416 mmol of Pd), triphenylphosphane (26.9 mg, 0.10256 mmol) and 4-bromoacetophenone (680 mg, 3.416 mmol) was degassed for 15 min in a 20 mL Schlenk tube equipped with a magnetic stirring bar and a reflux condenser. Under an atmosphere of argon, [BMIM][BF$_4$] (3 mL) was added. The mixture was then degassed under reduced pressure for another 10 min. The Schlenk tube was heated in an oil bath at 110 °C to give an orange solution. Once out of the oil bath, pyrrolidine (292 mg, 0.35 mL, 4.099 mmol, $d = 0.87$) and then phenylacetylene (419 mg, 0.45 mL, 4.099 mmol, $d = 0.93$) were added to the ionic liquid solution. The resulting mixture was heated at 130 °C for 2 h under an atmosphere of argon. The product was extracted from the ionic liquid phase by the addition of diethyl ether (6×5 or 10 mL) and decanting off the ether from the IL phase (GC yield 88%). After evaporation, the residue was purified by silica gel chromatography (diethyl ether/hexane, 1:9) to give 620 mg (isolated yield 82%) of 4-(2-phenylethynyl)acetophenone.

Recycling Experiment for the Heck Alkynylation Reaction in [BMIM][BF$_4$]: After extraction with diethyl ether, the resulting dark coloured ionic liquid was kept under air for several days or weeks with no particular precaution. The recovered ionic liquid was reused without any pretreatment (no water washing), but degassed under reduced pressure for 15 min. The tube was refilled with triphenylphosphane (26.9 mg), the aryl halide was added and the mixture degassed for 15 min. The reaction was carried out and worked up under the same conditions employed for the first run.

Supporting Information (see footnote on the first page of this article): Experimental details, GC chromatograms, mass spectra, elemental analyses and NMR spectroscopic data for coupling products and identification of secondary products.

Acknowledgments

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[17] The amines piperidine and *i*Pr$_2$NH are efficient bases that promote alkynylation of aryl iodides in [BMIM][PF$_6$], see ref.[13]

[18] See Supporting Information.

[19] These results are reminiscent of the recycling experiments that were reported with less demanding aryl iodides (see ref.[13]). The loss of activity reported here is of great importance with regard to the genuine nature of the catalyst resting state in the IL (molecular, colloidal); a question that has, so far, not been tackled in the few alkynylation reports. Our results of activity suggest a molecular nature for the catalyst. The IL phase would therefore be (upon recycling) a reservoir of palladium atoms in a colloidal form. Ongoing research in our groups is aimed at addressing this question.

[20] By now, [BMIM][BF$_4$] is generally less expensive than [BMIM][PF$_6$], see for instance: http://www.solvionic.com.

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