Palladium-Catalysed Heck Alkynylation of Aryl Bromides in an Imidazolium Ionic Liquid: An Unexpected Subsequent Alkyne Hydrogenation Reaction

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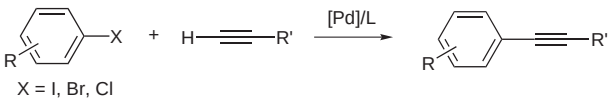
Dedicated to Professor Richard Heck for his decisive contribution to modern palladium-catalysed synthetic chemistry

Abstract: The copper-free palladium-catalysed alkynylation of aryl bromides with phenylacetylene in the imidazolium ionic liquid [BMIM][BF_4], in the presence of triphenylphosphine ligand and pyrrolidine as a base, was found effective and significantly more chemoselective employing deactivated substrates. When activated aryl substrates were used, unexpected side reactions were observed, especially the subsequent hydrogenation of the alkyne function in some coupling products. In other cases, amine arylation reactions occurred, as illustrated by the formation of pyrrolidinyl-4-nitrobenzene, for which an X-ray diffraction structure is reported.

Key words: catalysis, palladium, alkynes, arylation, cross-coupling

Conjugated alkynes are important building blocks in modern chemistry and their preparation is a crucial industrial and synthetic goal.[1] This important class of molecules has found application in diverse areas ranging from natural products chemistry to materials science.[2] The most attractive ways to form aryl/alkyne molecules of conjugated enyne-type remains palladium-catalysed reactions in the presence of stabilising ligands and/or co-catalysts such as copper salts (Scheme 1).



Scheme 1 Palladium-catalysed alkynylation of aryl halides.

In 1975, R. Heck was the first to describe the alkynylation of aryl-, vinyl- and heterocyclic halides using aromatic or aliphatic terminal alkynes.[3] The reactions were conducted in the presence of catalytic amounts of $Pd(OAc)_2(PPh_3)_2$, in amine solvents at 100 °C. The major limitation of the system, early underlined by Heck, was that '…halides with strongly electron-donating substituents, or halides which are otherwise made relatively unreactive (…), do not react well.'[3] Following this seminal work, a great number of studies have been conducted. The current leading procedures allow the aryl alkynylation under a variety of experimental conditions: in the presence of copper salt,[4] at low[5] or high temperature,[6] with ultra-low catalyst loadings,[7] from aryl chlorides,[7,8] etc. Nevertheless, only a few reports address the problem of extending the Heck alkynylation in the attractive solvents that are ambient-temperature ionic liquids (ILs).[9–11] Due to their low vapour pressure, ease of handling and potential for recycling, these solvents have shown great promise.[12] As reaction media, their compatibility with transition metals and limited miscibility with classical organic solvents enables easy organic-products separation, and possibly immobilisation of the catalytic species. To the best of our knowledge, only aryl iodides, which are less demanding but more expensive, have been employed in the studies concerning palladium-catalysed alkynylation of aryl halides in ambient-temperature ILs. We report herein our results of Heck alkynylation from aryl bromides in the imidazolium ambient-temperature ionic liquid, 1-*n*-butyl-3-methylimidazolium tetrafluoroborate, called [BMIM][BF_4] (Figure 1).[13]

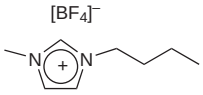


Figure 1 Imidazolium salt [BMIM][BF_4].

In the search of convenient catalysts usable in the coupling of a wide array of functionalised aryl halides (comprising deactivated bromides or chlorides) we found that under certain conditions the simple system combining 0.5 mol% $[Pd(allyl)Cl]_2$ with 3 mol% PPh_3 in the presence of 1.2 equivalents of pyrrolidine was very efficient to activate aryl bromides. Bromide substrates being significantly more difficult to activate as compared with aryl iodides, we were greatly satisfied of the scope of reaction detailed in Table 1. The catalytic methodology we propose is particularly appealing due to its accessibility and simplicity. The components are all commercially available at costs among the lowest of their category (PPh_3, [BMIM][BF_4], pyrrolidine) and only 1 mol% of palladium metal is required. However, to our surprise, we noticed that the chemoselectivity of the alkynylation reaction employing phenylacetylene in [BMIM][BF_4] was substantially higher with the more demanding bromide substrates (see entries 1–3 in Table 1). Within 20 hours, excellent conversion of the strongly electronically deactivated 4-

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bromoanisole (electron-rich) was obtained (entry 1), as well as of the electronically and sterically deactivated 2-bromotoluene (entry 2). Even the extremely demanding trisubstituted aryl halide 2-bromomesitylene was quantitatively converted with a total selectivity, albeit within a longer period of time (48 h, entry 3). The hindered 2-bromonaphthalene was also converted in high yield in only four hours (Table 1, entry 4, first row). The situation appeared somewhat different with the less demanding substrates (Table 1, entries 5–9). We eventually carried out the Heck alkynylation reactions in 20 hours, under conditions similar to the other substrates; within this reaction time fairly good to moderate conversions were obtained for 4-bromotoluene (80%, entry 5), bromobenzene (31%, entry 6), 4-bromobenzonitrile (70%, entry 7), 4-bromonitrobenzene (10%, entry 8) and 3,5-bis(trifluoromethyl)bromobenzene (69%, entry 9). Concurrently to these couplings a number of side reactions occurred, for which the nature and yield of side products are detailed in Table 1 (footnote, MS identification).

The most intriguing reaction is the hydrogenation of the enyne coupling product, repetitively observed in long-term reactions (20 h) employing the substrates 2-bromonaphthalene (29%, entry 4, row 2), 4-bromotoluene (20%), bromobenzene (54%), 4-bromobenzonitrile (20%), and 3,5-bis(trifluoromethyl)bromobenzene (11%).

Nevertheless, the selectivity for desired enyne was greatly enhanced upon shortening of the reaction time down to 2–

Table 1 Alkynylation of Aryl Bromides with 1 mol% of [Pd/3PPh$_3$] in [BMIM][BF$_4$][14]

Entry	R group or aryl substrate	R′	Time (h)	Enyne yield (%)	Side-product yield (%)
1	4-MeO	Ph	20	95	–
2	2-Me	Ph	20	99	–
3	2,4,6-Me	Ph	48	>99	–
4	2-Bromo naphthalene	Ph	4	98	–
	2-Bromo naphthalene	Ph	20	61	29[a]
5	4-Me	Ph	20	80	20[b]
6	H	Ph	20	31	68[c]
	H	Ph	2	82	–
7	4-CN	Ph	20	70	30[d]
8	4-NO$_2$	Ph	20	10	90[e]
	4-NO$_2$	Ph	2	58	42[f]
9	3,5-CF$_3$	Ph	20	69	31[g]
	3,5-CF$_3$	Ph	4	92	8[h]
10	4-MeCO	*n*-Oct	4	96	–
11	4-Me	*n*-Oct	4	66	10[i]
12	2-Me	*n*-Oct	4	65	–
13	4-MeO	*n*-Oct	4	40	–
	4-MeO	*n*-Oct	20	76	15[i]

[a] MS: *Z*- and *E*-aryl/alkyne hydrogenation isomers: 19%, *m/z* (%) = 230 (100) [M$^+$], 229 (96), 228 (50), 226 (20), 215 (28), 114 (20), 101 (14); 10%, *m/z* (%) = 230 (100) [M$^+$], 229 (90), 228 (48), 226 (18), 215 (26), 114 (17), 101 (13).
[b] MS: (*Z*)- and (*E*)-4-(phenylethenyl)toluene: 12%, *m/z* (%) = 194 (84) [M$^+$], 193 (24), 179 (100), 178 (83), 165 (16), 115 (14); 8%, *m/z* (%) = 194 (98) [M$^+$], 193 (24), 179 (100), 178 (80), 165 (14), 115 (13).
[c] MS: (*Z*)- and (*E*)-1,2-diphenylethylene: 23%, *m/z* (%) = 180 (96) [M$^+$], 179 (100), 178 (65), 165 (48), 152 (13), 89 (18), 76 (14); 31%, *m/z* (%) = 180 (100) [M$^+$], 179 (100), 178 (62), 165 (50), 152 (13), 89 (24), 76 (16); 1,1′,2-tris(phenyl)ethylene: 14%, *m/z* (%) = 256 (100) [M$^+$], 255 (25), 241 (18), 239 (20), 179 (33), 178 (46), 165 (20).
[d] MS: *Z*- and *E*-aryl/alkyne hydrogenation isomers: 14%, *m/z* (%) = 205 (98) [M$^+$], 204 (100), 203 (34), 190 (43), 177 (15), 176 (16), 165 (14), 89 (13), 76 (13), 51 (14); 6%, *m/z* (%) = 205 (100) [M$^+$], 204 (94), 203 (33), 190 (42), 177 (15), 176 (16), 165 (15), 89 (15), 76 (14), 51 (15); pyrrolidinyl-4-benzonitrile: 10%, *m/z* (%) = 172 (68) [M$^+$], 171 (100), 129 (18), 116 (45), 102 (30).
[e] MS: Pyrrolidinyl-4-nitrobenzene: 17%, *m/z* (%) = 192 (100) [M$^+$], 191 (94), 145 (28), 136 (20), 106 (24), 77 (16); *Z*- or *E*-pyrrolidine addition product on the aryl/alkyne: 45%, *m/z* (%) = 294 (100) [M$^+$], 293 (86), 178 (25), 130 (98), 104 (28); unidentified product: 29%.
[f] Pyrrolidinyl-4-nitrobenzene: 34%; unidentified product: 8%.
[g] MS: *Z*- and *E*-aryl/alkyne hydrogenation isomers: 8%, *m/z* (%) = 316 (100) [M$^+$], 301 (20), 247 (22), 246 (26), 227 (20), 178 (41), 78 (19); 3%, *m/z* (%) = 316 (100) [M$^+$], 301 (19), 247 (21), 246 (24), 227 (19), 178 (38), 78 (17); *Z*- or *E*-pyrrolidine addition product on the aryl/alkyne: 14%, *m/z* (%) = 385 (53) [M$^+$], 384 (44), 366 (10), 246 (12), 158 (15), 130 (100), 104 (30), 70 (16); unidentified product: 6%.
[h] *Z*- or *E*-pyrrolidine addition product on the aryl/alkyne 2%; unidentified product: 6%.
[i] Enyne isomerisation. GC and GC-MS yields, external standard.

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4 hours: from bromobenzene (82%, entry 6, row 2), from 4-bromonitrobenzene (58%, entry 8) and from 3,5-bis(trifluoromethyl)bromobenzene (92%, entry 9). Therefore, and contrary to the case of deactivated substrates, an accurate control of the reaction time is required to increase the selectivity towards the desired enyne.

The coupling reaction of phenylacetylene to 4-bromonitrobenzene appeared as a particular case, for which a significant concurrent reaction was the arylation of the pyrrolidine base. Thus, substantial amounts of pyrrolidinyl-4-nitrobenzene (17–34%, entry 8) were formed whatever the reaction time (2–20 h). Eventually, this product spontaneously crystallised from the crude ethereal extraction mixture upon standing few hours at low temperature: the X-ray crystal structure determined is presented in Figure 2.[15]

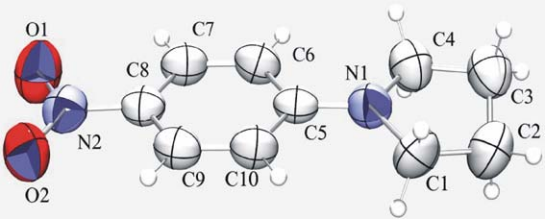
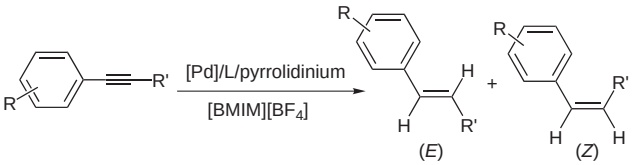


Figure 2 POV-Ray representation (ORTEP) of the molecular structure of the amine arylation product pyrrolidinyl-4-nitrobenzene.

We checked the possibility, using our catalytic system, to employ aliphatic acetylenes for Heck alkynylation in [BMIM][BF_4]. For this purpose, we chose the long-chain aliphatic terminal alkyne 1-decyne. Without optimisation, good to excellent conversions were obtained using either activated or deactivated bromides (Table 1, entries 10–13); the side products obtained were mostly the result of triple-bond isomerisation, with some hydrogenation products also detected.

The enyne hydrogenation observed (Scheme 2) suggests that after completion of the coupling reaction, the palladium catalyst then acts as a hydrogen-transfer catalyst. Although at this point the formation of a palladium-hydride species through insertion of the metal into the imidazolium C_2–H bond cannot be totally ruled out,[16] it seems more reasonable to propose a protonation of a Pd(0) centre by the acidic hydrogenopyrrolidinium salt resulting from the terminal acetylene deprotonation step of the C–C coupling.[17] The origin of the side reactions detected, namely (i) the addition reactions onto the enyne triple bond (mainly hydrogenation), and (ii) the amine arylation, would then be rather different. While the triple-bond activation probably originates from a palladium-catalysed process, blank experiments performed in [BMIM][BF_4] and in the absence of any metal and ligand have shown that pyrrolidine can be coupled in non-negligible yields to electronically activated substrates such as 4-bromobenzonitrile (33% in 6 h) or 4-bromoacetophenone (20% in 2 h).[18]



Scheme 2 Hydrogenation side products obtained from enynes.

In summary, we have disclosed the first methodology allowing the alkynylation of a variety of functionalised aryle bromides in an ionic liquid medium. The copper-free system combining 0.5 mol% of [Pd(allyl)Cl]$_2$, 3 mol% PPh_3 and 1.2 equiv pyrrolidine is economic, simple and readily accessible. In [BMIM][BF_4] the coupling of demanding bromides is more selective comparatively to the coupling of activated aryl bromides. This fact is probably due to the inertness of demanding substrates (electronic or steric in origin) as supported by the various side reactions obtained from activated bromides. Finally, the presumed palladium-catalysed hydrogenation of aryl/alkyne subsequent to Heck or Sonogashira reaction has never been documented before, and could lead, after development and optimisation, to very elegant cascade-type catalysis.

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(13) Extensive studies with optimised results will be reported in due course.

(14) **Typical Procedure.**
The catalyst was prepared as a solid mixture of $[Pd(allyl)Cl]_2$ (6.3 mg, 0.03416 mmol of Pd), PPh_3 (26.9 mg, 0.10256 mmol) degassed for 15 min in a 20-mL Schlenk tube equipped with a magnetic stirrer bar and a reflux condenser. Under argon were added the aryl halide (either solid or liquid, 3.416 mmol) and 3 mL of $[BMIM][BF_4]$. 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 a coloured solution. To the ionic liquid solution was added, out of the oil bath, 0.35 mL pyrrolidine (292 mg, 4.099 mmol, d = 0.87) and then the terminal alkyne (4.099 mmol). The resulting mixture was heated at 130 °C for 2–48 h under argon. The product was extracted from the ionic liquid phase by the addition of Et_2O (six portions of 5–10 mL) and decanting off the Et_2O from the IL phase. After evaporation the residue was purified by silica gel chromatography (Et_2O–hexane, 1:9) to give the enyne compound. $[BMIM][BF_4]$ is commercially available (see for instance SOLVIONIC.com).

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