Double Arylation of Diynes and Alkynylation of Functionalized Heteroaryl Halides by a Practical Heck Reaction in an Ionic Liquid

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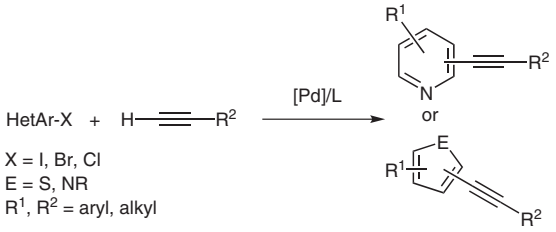
Abstract: The efficient palladium-catalyzed alkynylation of electron-rich bromoheteroarenes, incorporating deactivating electron-donating methyl and methoxy groups, and the (hetero)arylation of diynes, take place in the imidazolium ionic liquid [BMIM][BF_4], as a highly polar non-volatile solvent. This method may constitute a sustainable alternative to classical solvents such as dioxane, DMF, NMP, or DMAc. New enynes are formed in the presence of a system encompassing a copper-free palladium catalyst, triphenylphosphine as ligand, and various inexpensive bases. The enyne molecules reported are selectively synthesized in high yields and are mostly unprecedented.

Key words: arylation, diynes, heteroarenes, palladium, ionic liquid

The development of metal-catalyzed methods for incorporating alkynes into organic molecules has attracted growing interest in the recent years. Alkynes are recurring building blocks in a wide range of industrial intermediates and biologically active products.[1] In addition, the reactivity of the alkyne function opens the way to many valuable subsequent chemical transformations such as cyclization through hydroamination. Since significant numbers of current pharmaceutical and agrochemical compounds are based on heterocyclic scaffolds, the direct alkynylation of heteroaromatics can be a key synthetic step in the convergent and efficient construction of a range of complex molecules (Scheme 1).[2]



Scheme 1 Palladium-catalyzed alkynylation of heteroaryl halides

In the 1970s, Heck described the alkynylation of aryl-, vinyl-, and heterocyclic halides using either aromatic or aliphatic terminal alkynes.[3] The reactions were conducted in the presence of catalytic amounts of $[Pd(OAc)_2(PPh_3)_2]$, in an amine solvent at 100 °C. The major limitation of the system, underlined by the author, was that halides with strongly electron-donating substituents do not react well. Following this ground-breaking work, much progress has been accomplished in this aspect and others.[4–8] However, only a few catalytic systems, that are generally not easy to access have been reported for the coupling of a wide range of heteroaryl halides that include in their scope *N*-, *O*-, and *S*-heteroarenes,[2] especially when compared to systems focused on aryl halides. Reports that address the issue of extending arene alkynylation into more attractive solvents such as ambient-temperature ionic liquids (ILs) are mainly based on the coupling of expensive aryl iodides, thus precluding industrial applications.[9–11] Nevertheless, many palladium alkynylation reactions are conducted in potentially harmful polar organic solvents,[1] and more sustainable alternatives need to be investigated for further industrial progress. Due to their low vapor pressure, ease of handling, and potential for recycling, ILs have shown great promise.[12] As reaction media, their compatibility with transition metals and limited miscibility with classical organic solvents enable easy organic product separation, and possibly immobilization of the catalytic species. We herein report our efforts to develop efficient conditions for the Heck alkynylation of heteroaryl bromides functionalized with electron-donating groups in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]; Table 1). We additionally report an efficient double (hetero)arylation of terminal diynes using the same simple methodology. Until now, this type of simultaneous double cross-coupling reaction has only been rarely investigated in isolated examples, even though the products obtained have shown great potential in medicinal chemistry and materials science.[13]

Alkynylation of five- and six-membered electron-rich heteroaryl bromides incorporating one nitrogen or sulfur heteroatom proceeded satisfactorily. Good selectivity and excellent yields were obtained when phenylacetylene was coupled with 3-bromo-5-methoxypyridine (91% in 4 h; Table 1, entry 1), 3-bromo-6-methoxypyridine (90% in 4 h; entry 2), and with 3-bromo-6-methylpyridine (91% in 4 h; entry 3). Excellent yield was also obtained under the same conditions for the sterically deactivated substrate, 3-bromo-4-methylpyridine (92% in 4 h; entry 4). Only small amounts of side-product due to dimerization of the excess of phenylacetylene were detected, but this side re-

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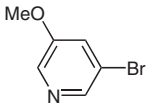
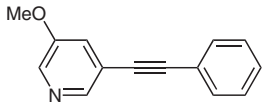
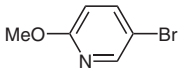
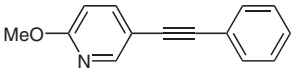
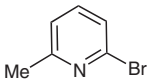
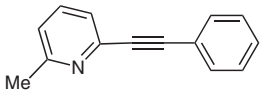
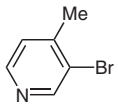
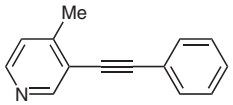
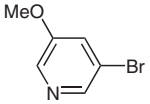
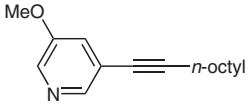
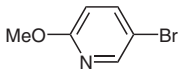
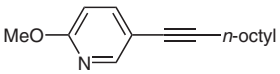
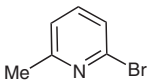
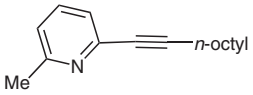
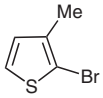
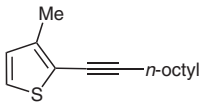
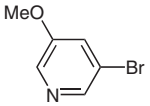
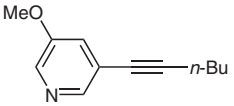
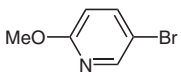
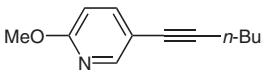
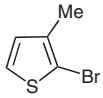
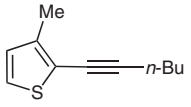
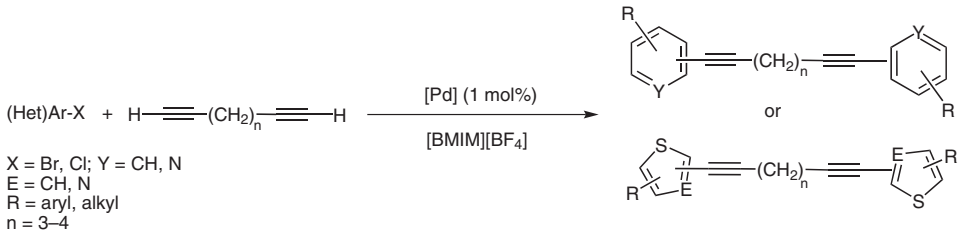
action did not hamper in any way the coupling of the heteroaryl bromides. Having demonstrated the efficient coupling of phenylacetylene with a variety of electron-rich pyridinyl bromides, we examined the alkynylation reaction with other terminal alkynes. A selection of electron-rich heterocycles was reacted with short or long chain aliphatic acetylenes (1-hexyne and 1-decyne). Yields above 90% were achieved in four hours for the coupling of methoxybromopyridines with 1-decyne (Table 1, entries 5–7). As observed with phenylacetylene, the position of the methoxy or methyl groups does not influence the course of the reaction. Additionally, bromides

Table 1 Copper-Free Palladium-Catalyzed Alkynylation of Functionalized Heteroarenes Bearing Electron-Donor Groups in an Ionic Liquid[a]

Entry	Heteroaryl bromide	Time (h)	Product	Yield (%)[b]
1		4	 **1**	91
2		4	 **2**	90
3		4	 **3**	91
4		4	 **4**	92
5		4	 **5**	91
6		4	 **6**	93
7		4	 **7**	91
8		4	 **8**	94
9		7	 **9**	95
10		7	 **10**	94
11		7	 **11**	70

[a] Reaction conditions: $[Pd(allyl)Cl]_2$ catalyst (0.5 mol%), Ph_3P (3 mol%), aryl bromide (1.0 equiv), alkyne (1.2 equiv, 3.42 mmol), base (1.2 equiv), $[BMIM][BF_4]$ (3 mL), 100 °C.

[b] Average yields of two runs, based on aryl bromide; isolated yields obtained after chromatography on silica column.



Scheme 2 Palladium-catalyzed double arylation of terminal diynes

substituted at positions 2- and 3- with respect to the heteroatom were equally efficiently coupled. The sterically deactivated 2-methyl-3-bromothiophene was also successfully coupled (94% in 4 h; entry 8). Longer reaction times were needed to couple the more volatile 1-hexyne, but good to excellent yields were obtained (70 to 95%; entries 9–11).

With regard to the results obtained in the arylation of terminal alkynes, we investigated the double arylation of terminal diynes using the same methodology (Scheme 2). One objective was to examine whether the first alkynylation would modify the course of the second alkynylation. In this case, interesting unsymmetrical double alkynylation products might be envisaged. Additionally, the resulting heteroarylated diynes may be interesting precursors for further annulation leading to indoles and carbazoles, for instance by catalyzed hydroamination.[14] Table 2 summarizes the successful results obtained under conditions similar to those optimized for the simple arylation of monoalkynes.

Table 2 Copper-Free Palladium-Catalyzed Double Arylation of Diynes in an Ionic Liquid[a]

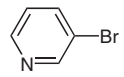
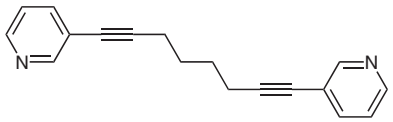
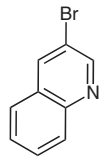
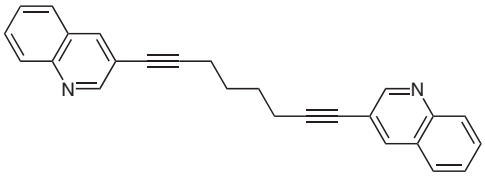
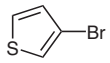
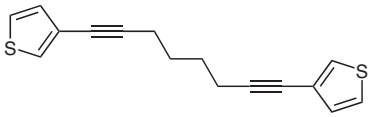
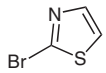
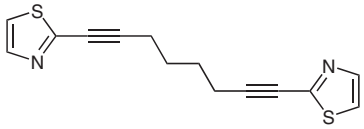
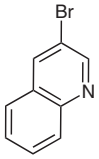
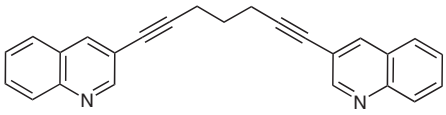
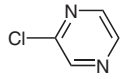
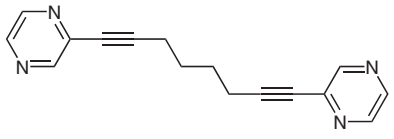
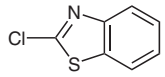
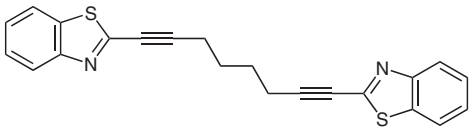
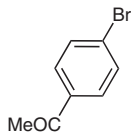
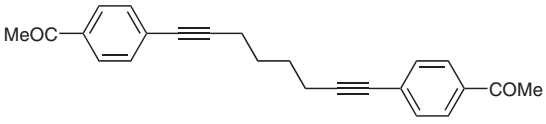
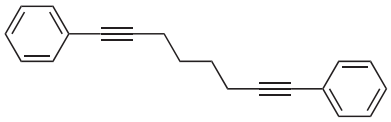
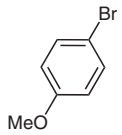
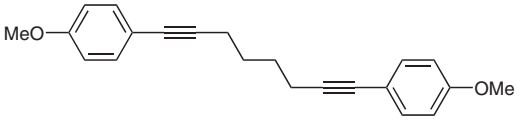
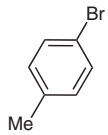
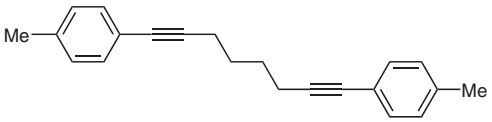
Entry	Haloarene	Base	Time (h)	Product	Yield (%)[d]
1		pyrrolidine	5	 **12**	98
2		pyrrolidine	5	 **13**	91
3		pyrrolidine	5	 **14**	93
4		Et_3N	5	 **15**	54
5[b]		pyrrolidine	5	 **16**	92

Table 2 Copper-Free Palladium-Catalyzed Double Arylation of Diynes in an Ionic Liquid[a] (continued)

Entry	Haloarene	Base	Time (h)	Product	Yield (%)[d]
6		Et_3N	5	 **17**	80
7		Et_3N	5	 **18**	69
8[c]		pyrrolidine	40	 **19**	30
9[c]		pyrrolidine	40	 **20**	64
10[c]		pyrrolidine	40	 **21**	51
11[c]		pyrrolidine	40	 **22**	50

[a] Reaction conditions: $[Pd(allyl)Cl]_2$ (0.5 mol%), Ph_3P (3 mol%), aryl bromide (or chloride) (1.0 mmol), 1,7-octadiyne (0.55 mmol), base (1.2 mmol), [BMIM][BF_4] (3 mL), 100 °C.
[b] 1,6-Heptadiyne.
[c] 130 °C.
[d] Isolated yields obtained after chromatography on silica column.

3-Bromopyridine was quantitatively coupled to 1,7-octadiyne to give 1,8-di(pyridin-3-yl)octa-1,7-diyne (98% in 5 h; Table 2, entry 1).[15,16] 3-Bromoquinoline and 3-bromothiophene were also efficiently coupled to 1,7-octadiyne, with yields around 90%, under the same conditions (Table 2, entries 2 and 3). A limitation appeared for the coupling of diheteroaromatic 2-bromothiazole since, in the presence of pyrrolidine, coupling of this base to bromothiazole was mainly observed. Conversely, 1,8-di(thiazol-2-yl)octa-1,7-diyne was obtained in 54% isolated yield using a tertiary base (Et_3N; Table 2, entry 4). Excellent yield was also obtained when 3-bromoquinoline was reacted with the slightly shorter chain substrate 1,6-heptadiyne under the same conditions (Table 2, entry 5). We also tested the reaction using heteroaryl chlorides, which are substrates that are more challenging but clearly more valuable from a sustainability and economic point of view. Good yields were obtained with 2-chloropyrazine and 2-chlorobenzothiazole coupled to 1,7-octadiyne (Table 2, entries 6 and 7). These interesting results prompted us to extend the study of the double arylation reaction by using functionalized aryl bromides (electron-rich activated and electron-poor deactivated substrates). Moderate to good conversions were obtained for the arylation of 1,7-octadiyne with the electronically activated 4-bromoacetophenone (30%; Table 2, entry 8) and the unactivated bromobenzene (64%; Table 2, entry 9), although increased temperature and time was required (130 °C for 40 h). Fairly good results were obtained with electronically deactivated substrates, with 4-bromanisole being converted in 51% yield (Table 2, entry 10) and 4-bromotoluene in 50% yield (Table 2, entry 11), albeit in much longer reaction times (40 h). In these latter cases, we detected a competitive oligomerization of the diynes (present in excess), which diminished the final yield relative to enyne. Attempts to make unsymmetrical arylated

diynes either in one pot or stepwise, remained unsuccessful, giving mixtures of products. This suggests that, contrary to our initial expectations, the first alkynylation has little influence on the remaining terminal alkyne.

In summary, we have reported the efficiency of a simple system [Pd/3PPh$_3$] (1 mol%) in the ionic liquid [BMIM][BF$_4$] for the coupling of a variety of electron-rich functionalized heteroaryl bromides with phenylacetylene and the aliphatic 1-hexyne and 1-decyne terminal alkynes.[15] A double arylation of bifunctional terminal diynes can be efficiently performed using the same catalytic system. Depending on the heterocycle, a primary or tertiary amine can be used as soluble base. Both aryl and heteroaryl bromides are suitable substrates, as well as 2-chloroheteroarenes. The accessibility of the system, which features inexpensive ligands, organic base, and IL solvent, make these results of interest for further development of Heck and Sonogashira type coupling reactions in ionic liquids. Importantly, we have shown that, as well as iodoarenes, aryl and heteroaryl bromides and some chlorides are suitable substrates for copper-free palladium alkynylation in ionic liquid.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **Typical procedure**: The catalyst was prepared as a solid mixture of [Pd(allyl)Cl]$_2$ (6.3 mg, 0.034 mmol of Pd) and Ph$_3$P (26.9 mg, 0.102 mmol), and 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 heteroaryl halide (either solid or liquid, 3.42 mmol) and [BMIM][BF$_4$] (3 mL). The mixture was further degassed under reduced pressure for 10 min. The Schlenk tube was heated in an oil bath at 60 °C to give a red solution. The vessel was removed from the heating bath and, to the ionic liquid solution, was then added pyrrolidine (0.35 mL, 292 mg, 4.1 mmol) and the terminal alkyne (4.1 mmol). The resulting mixture was heated at 100 °C for 4 h under argon and, after extraction with diethyl ether (4 × 5 mL), the product was purified by silica gel chromatography (ethyl acetate–heptane, 1:9) to give the enyne compound. The recovered ionic liquid can be reused without treatment for further catalytic couplings, after removal of ether traces by simple evaporation under vacuum. Reloading of triphenylphosphine may be necessary after three runs due to a partial organic extraction, no amine salt removal was done during this recycling.

(16) Copies of ^{1}H and ^{13}C NMR spectra of products **1**–**22** and detailed assignment are reported as Supporting Information.