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Palladium-Catalyzed Coupling of Lactams with Bromobenzenes

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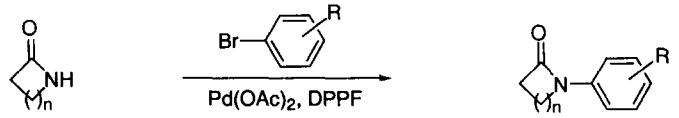
Abstract: An efficient method for the coupling of lactams with bromobenzenes mediated by palladium acetate and DPPF is presented. The reaction proceeds efficiently with a variety of lactams and both electron-rich and poor substituted bromobenzenes. © 1999 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed coupling of aryl and vinyl halides (or halide equivalents) to carbon nucleophiles is a well understood, and highly utilized process in organic chemistry.[1-7] To the contrary, the palladium-catalyzed formation of heteroatom-aryl bonds has only recently emerged as a means for effecting this type of transformation.[8-12] During the course of our investigation into the synthesis of novel kinase inhibitors, it was necessary to form a bond between an azole nitrogen and an aromatic ring. While there were several solutions to this problem,[13-15] a recent report by Mann and Hartwig[16] that palladium catalyzed the bond formation between indole and substituted bromobenzenes seemed attractive. While ultimately, in the case of our substrate, this reaction did not succeed, it prompted us to consider the coupling of other nitrogen-containing molecules whose reactivity might be similar to that of indole. Specifically, we wondered whether lactams, whose pK_as (and indirectly reactivity) are similar to that of indole, might be suitable substrates for this type of reaction (Scheme 1). The additional attraction of studying lactams is that, depending upon the ring size, their pK_as can vary by several log units,[17-19] providing more information regarding the scope of the reaction. Recently, Buchwald[20] has reported the successful intramolecular cyclization of amides and sulfonamides, however, the extension of this methodology to the intermolecular case was unsuccessful.

Scheme 1



n = 1-4 n = 1-4

The results of the investigation are summarized in Table 1. Reaction conditions identical to that described by Hartwig were employed.[16] Palladium(II) acetate, 1,1'-bis(diphenylphosphino)-ferrocene (DPPF), sodium *tert*-butoxide, a lactam, and a bromobenzene were heated in toluene at 120 °C for the indicated period of time. Depending upon the electronic nature of the bromobenzene (entry 2 vs. entry 1), reaction times varied

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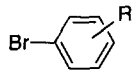
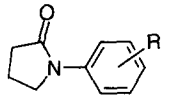
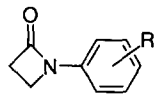
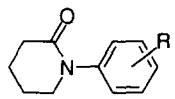
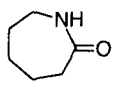
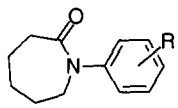
from 16-40 hr. To ensure that the process was catalyzed by palladium, the control experiments in which the reactions were run in the absence of catalyst were conducted and indeed there was no reaction.

Table 1. Palladium-Catalyzed Coupling of Lactams with Substituted Bromobenzenes

Entry	Lactam	 R =	Product	Time	Yield[a]	m.p.[b]
1		*p*-H		48 (hr)	82 (%)	66-67 °C[c]
2		*p*-CF_3		16	90	134-135
3		*p*-COPh		16	87	163-164
4		*p*-CN		16	70	115-116.5
5		*m*-OMe		48	83	55-56
6		*p*-H		48	20[f]	75-76[d]
7		*p*-CF_3		16	52	99-100.5
8		*p*-H		48	21[f]	94-95[e]
9		*p*-COPh		16	89	141-142
10		*p*-H		48	43[f]	69-70.5[e]
11		*p*-COPh		16	94	119-120

[a]Yields are based on isolated material after column chromatography and are the average of two runs. [b]Melting points are uncorrected. [c]m.p. 66-67 °C, ref. 21. [d]m.p. 79-81 °C, ref. 22. [e]ref. 23. [f]In entries 6, 8, and 10, 41, 62 and 38% of the starting lactam was recovered after chromatography.

The reaction proceeds efficiently with electron-neutral, electron-poor as well as electron-rich substituted bromobenzenes (entries 1-5), although with entries 1 and 5, longer reaction times were necessary to drive the reaction to completion. Interestingly, there appears to be a large dependence on the ring-size of the lactam to the overall efficiency of the reaction (entries 1, 6, 8, and 10). Formation of the five-membered N-aryl lactam is

highly efficient (entry 1) while the four, six and seven-membered ring analogs (entries 6, 8, and 10) are clearly less reactive. In the case of the latter three systems, this inefficiency can be overcome with the use of more electron-poor bromobenzenes (entries 7, 9 and 11) which are well known to increase the rate at which palladium complexes undergo reductive elimination.[11, 24]

One possible explanation for the difference in reactivities might be the difference in pK_a (or roughly nucleophilicity) between these four substrates. The pK_as for the four, five, six, and seven-membered ring lactams (determined in DMSO) are 24.5, 26.7, 27.2 and 27.2 respectively[17] (although Bordwell[18] calculated a 2.2 log difference between the five and six-membered ring systems). In the six and seven-membered ring cases then, under the current reaction conditions, if there is not a sufficient amount of the equilibrium anion present to undergo coordination with the catalyst, then this might in part explain the differences in reaction efficiency (relative to entry 1). There are two assumptions here. The first is that the anion and not the amide is the species which coordinates to palladium. The second is that coordination to the catalyst is involved in the rate determining step. Interestingly, in their studies on the effects of substrate acidity on conversion time, Hansen and Bordwell[19] reported a 10-fold rate difference, 2 vs. 21 hr, in the Boc protection of five and six-membered ring lactams respectively. A second possible explanation is that the different conformations of the five, six, and seven-membered lactams may affect their capacity to coordinate the catalyst efficiently. Finally, a third possibility is that the six and seven-membered ring lactams undergo competitive β-hydrogen elimination, however, this seems less plausible as the bulk of the starting lactams were recovered unchanged (see Table 1).

Similarly, in the case of the four-membered ring, one could argue that the increased acidity relative to the five-membered ring decreases reactivity, such that regardless of the increase in equilibrium anion present, the decrease in nucleophilicity reduces coordination to the catalyst, or more likely, diminishes the tendency of the formed complex to undergo reductive elimination to the product. In their work with amines, Driver and Hartwig[25] observed a direct correlation between the nucleophilicity of the amine and the rate at which the amido complex reductively eliminated to the product.

The present research demonstrates the first intermolecular palladium-catalyzed coupling of an amide to an arylbromide.[26] It represents a practical alternative to the construction of these systems, which often require high temperatures[21] or multiple synthetic transformations.[27] In conjunction with Buchwald's[20] observations that the reaction is applicable to intramolecular transformations but not to open chain amides in an intermolecular sense, it raises some very interesting mechanistic questions. It clearly calls into question the effects of amide bond conformation on catalyst coordination. This is particularly true if one considers the similar pK_as of the three systems. Additional work investigating certain mechanistic questions as well as those pertaining to the scope of this reaction are currently ongoing.

Representative Procedure

1-Phenyl-pyrrolidin-2-one (entry 1). 2-Pyrrolidinone (151 μL, 2.0 mmol), bromobenzene (316 μL, 3.0 mmol), 1,1'-bis(diphenylphosphino)-ferrocene (66 mg, 0.12 mmol), palladium(II) acetate (22 mg, 0.10 mmol) and sodium *tert*-butoxide (0.29 g, 3.0 mmol) in 10 mL of toluene under N_2 were heated in a sealed tube at 120 °C for 48 hr. The mixture was cooled to rt, filtered through Celite, and the filtrate concentrated onto silica gel. Flash chromatography (1:1 ethyl acetate/hexane) afforded the title compound as a white solid (0.27 g, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (q, J = 7.6 Hz, 2H), 2.67 (t, J = 8.1 Hz, 2H), 3.90 (t, J = 7.1 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 8.4 Hz, 2H), 7.66 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.4, 35.2, 120.4, 124.9, 129.2, 139.8, 174.6; m.p. 66-67 °C.

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