Multicomponent Reactions

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Palladium-Catalyzed Aryl Iodide Carbonylation as a Route to Imidazoline Synthesis: Design of a Five-Component Coupling Reaction**

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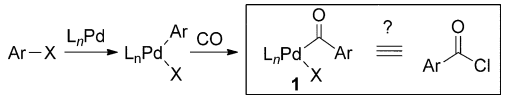
Since Heck's initial discovery in 1974,[1] the palladium-catalyzed carbonylation of aryl halides has emerged as an important approach to construct carbonyl-containing compounds.[2,3] In contrast to the traditional use of carboxylic acids to form nucleophile–acyl bonds, which often require the conversion of the acid into a more reactive unit with harsh substrates (e.g. acid chlorides, using thionyl or oxalyl chloride), or the use of stoichiometric coupling reagents (e.g. DCC, HOBt/HOAt),[4] aryl halide carbonylation generates these same products with catalytic palladium and a cheap and abundant carbon source, CO. In this regard, this palladium-catalyzed reaction can be considered an efficient and green alternative to generating electrophilic acyl analogues to acid chlorides in the form of palladium intermediate **1** (Scheme 1).

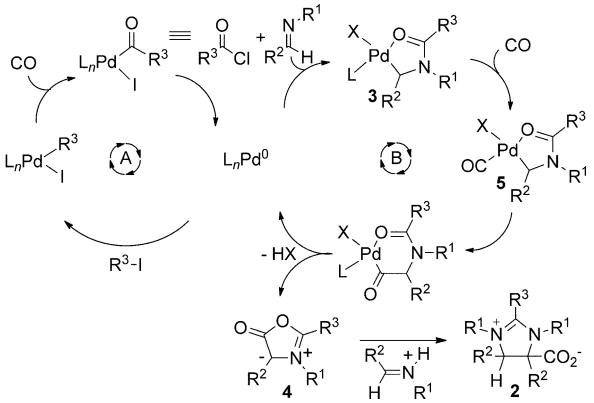


Scheme 1. Palladium-catalyzed aryl halide carbonylation.

Considering the analogy between intermediate **1** and acid chlorides, we have become interested in the potential of using palladium-catalyzed aryl halide carbonylation to access structures that are more advanced than nucleophile–acyl bonds. There exist a variety of synthetically useful reactions in which acid chlorides have been demonstrated to be key substrates, including, for example, initiating multicomponent reactions,[5] or the synthesis of biologically relevant heterocycles.[6] We postulated that intermediates of the form **1** might serve as replacements for acid chlorides in these reactions, thus providing a method to directly build-up useful molecular complexity from aryl halides and CO. In this regard, carbonylative cyclizations to form heterocycles are well established, and the cyclization of the ester and amide products of palladium-catalyzed carbonylation is also emerging as a useful synthetic approach.[7] We describe herein how aryl iodide carbonylation can initiate a multicomponent reaction for the generation of imidazolinium heterocycles. Imidazolines are an important class of pharmaceutically relevant heterocycles that are typically prepared by multistep approaches.[8–10] As an alternative, this palladium-catalyzed reaction provides these products directly from five available substrates.

Our approach to this reaction is outlined in Scheme 2. This involves coupling two mechanistically distinct processes: the reaction of aryl halides and carbon monoxide to form the palladium acyl intermediate **1** (Scheme 2; cycle A), and the established ability of acid chlorides to initiate a palladium-catalyzed reaction with imines and CO to form münchnones **4** (Scheme 2; cycle B).[11,12] The latter product can be spontaneously trapped by an iminium ion through a 1,3-dipolar cycloaddition to give **2**.[13] Notably, both of these processes are palladium-catalyzed carbonylation reactions: first of the aryl halide and then of intermediate **3**. Thus, while mechanistically complex, this suggests that there is the potential for a single palladium complex to mediate these two consecutive cycles, thus providing a synthesis of imidazolines with the inputs of just aryl iodide, two units of imine, and two units of CO.

Initial attempts at this coupling reaction employing standard aryl halide carbonylation catalysts such as [Pd(OAc)$_2$/PPh$_3$] yielded only starting materials (Table 1,



Scheme 2. Mechanistic postulate for imidazoline formation.

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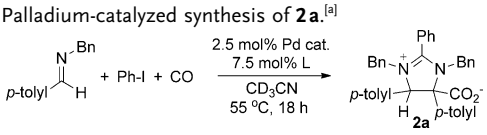
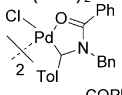
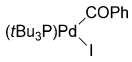
Table 1: Palladium-catalyzed synthesis of **2a**.[a]



Entry	Pd cat.		PR_3	Yield [%][b]
1[c]	$Pd(OAc)_2$		PPh_3	–
2[c]		**7**	–	12
3[c]		**6**	–	47
4[c]	**7**		$PtBu_3$	46
5	**7**		$PtBu_3$	83
6	**7**		$P(o\text{-tolyl})_3$	63
7	**7**		tBu_2P(2-biphenyl)	76
8	**7**		$tBu_2P(2,4,6\text{-}iPr_3C_6H_2)$	63
9	**7**		PPh_3	–
10	**7**		dppe	–
11	**7**		PCy_3	–
12[d]	$[\{Pd(allyl)Cl\}_2]$		$PtBu_3$	75

[a] Reaction conditions: iodobenzene (102 mg, 0.50 mmol), imine (21 mg, 0.10 mmol), Pd cat. (2.5 μmol), PR_3 (7.5 μmol), and 5 atm CO in 0.8 mL CD_3CN. [b] Yields determined by ^1H NMR spectroscopy using benzyl benzoate as an internal standard. [c] 10.2 mg, 0.050 mmol iodobenzene. [d] 12.5 μmol PR_3. Bn = benzyl, dppe = 1,2-bis(diphenylphosphino)ethane.

entry 1). In considering the mechanism shown in Scheme 2, the presence of the strongly coordinating PPh_3 and acetate ligands likely inhibit the formation of the four-coordinate, CO-bound intermediate **5** for the second carbonylation step. Similarly, catalysis under the ligandless conditions that favor the formation of intermediate **5** and carbonylation of N-acyl iminium salts also yielded only trace amounts of product (entry 2).[11a] In this case, the lack of stabilizing ligands results in palladium black precipitation before the phenyl iodide can undergo oxidative addition to the ligandless palladium(0).

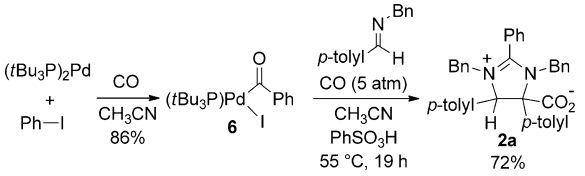
Stoichiometric experiments provide some insight into how these carbonylation reactions might be coupled. Bulky phosphines such as $PtBu_3$ have recently been shown to stabilize both three-coordinate aryl and aroyl palladium complexes.[14] Similarly, the reaction of $[Pd(PtBu_3)_2]$ and PhI with CO allows the generation of the complex **6** [Eq. (1)]. In addition, subjecting **6** to reaction with imine and CO leads to the formation of the heterocycle **2a** in 72 % yield (19 h, 55 °C).

These stoichiometric results suggest that catalysis should be viable provided that the palladium acyl intermediate such as **6** can be generated with labile ligands. This can be achieved by employing the palladium complex **6** itself as the catalyst (Table 1, entry 3). Alternatively, the palladacycle **7** is also a viable catalyst with $PtBu_3$ (entry 4). Under these reaction conditions, palladium black is still generated, thus limiting the overall product yield. The latter can be inhibited by the use of an excess of phenyl iodide (entry 5). In addition to $PtBu_3$, several bulky phosphine ligands provide the correct balance of the ability to mediate aryl iodide oxidative addition and lability to favor the carbonylation via **5** (entries 6–8), whereas smaller ligands inhibit catalysis (entries 9–11). In addition to the use of the palladacycle **7**, commercial $[\{Pd(allyl)Cl\}_2]$ is also a viable catalyst precursor for this reaction, and avoids the need to pre-synthesize the catalyst (entry 12).

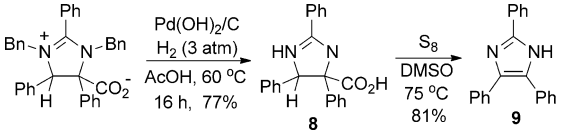
Interestingly, the reactions that employ bulky phosphine ligands are found to proceed at comparable rates (Table 1, entries 5–8). Insight into this effect can be obtained by monitoring the catalytic reaction of entry 12, in Table 1 by ^{31}P NMR spectroscopy. This data shows the immediate formation of the palladium benzoyl complex **6** (δ = 72.3 ppm), thus confirming the generation of this intermediate in the catalysis (Scheme 2; cycle A). However, this complex rapidly disappears, and the phosphine is quantitatively converted into its protonated form after one catalytic cycle (δ = 54 ppm).[15,16] Thus, phosphine plays a critical role in the initial stage of catalysis to presumably inhibit the immediate generation of inactive palladium black, but once the catalysis is underway it is a nonphosphine-bound palladium that mediates this reaction. Consistent with this observation, is the monitoring of the stoichiometric reaction of the palladium benzoyl complex **6** and imine [Eq. (1)] that shows **6** cleanly converting into this same protonated phosphine and imidazoline **2a.** No palladium intermediates are observed in this stoichiometric reaction. This observation is consistent with the coupling of the palladium benzoyl complex with the imine as a slow step in imidazoline formation, and once **3** (Scheme 2) is formed it rapidly converts into product.

Overall, this reaction provides a straightforward approach to assemble 2-aryl-substituted imidazolines from five separate components.[17] As shown in Table 2, a number of N-alkyl-, N-benzyl-, or N-PMP-substituted (PMP = *para*-methoxyphenyl) imines are viable in this reaction, as are variously functionalized C-aryl and even C-heteroaryl imines (e.g., **2l**; entry 12). More sterically encumbered N-substituted imines react slowly in this reaction (entries 4 and 11), which is consistent with the imine coupling with **6** as a slow step in catalysis. Both electron-rich and electron-poor aryl iodides are compatible with the reaction, although the latter leads to lower yields (entry 5 versus entry 8).

As an illustration of the potential utility of this reaction, triaryl-substituted imidazoline derivatives of the general form **8** [Eq. (2)] have recently been identified as potent cancer cell sensitizers as well as potential therapeutics for rheumatoid arthritis.[18] As an alternative to their typical synthesis by cycloaddition to give preformed münchnones, these core structures can be generated through this palladium-catalyzed multicomponent coupling and subsequent hydrogenolysis to

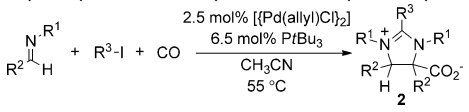


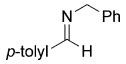
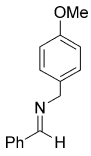
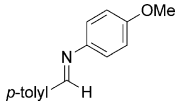
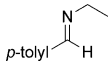
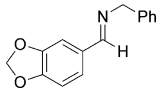
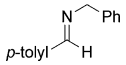
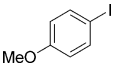
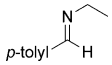
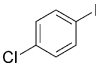
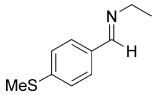
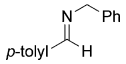
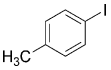
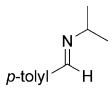
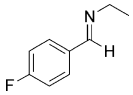
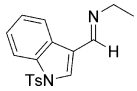
(1)



(2)

Table 2: Scope of palladium-catalyzed multicomponent synthesis.[a]



Entry	Imine	Aryl iodide	2	Yield [%][b]
1			**2a**	84
2			**2b**	62
3			**2c**	76[c]
4			**2d**	64
5			**2e**	94
6			**2f**	76
7			**2g**	82
8			**2h**	72
9			**2i**	86
10			**2j**	89
11[d]			**2k**	46
12			**2l**	65
13			**2m**	43

[a] Reaction conditions: aryl iodide (2.5 mmol), imine (0.5 mmol), [{Pd(allyl)Cl}$_2$] (5 mg, 12.5 μmol), P*t*Bu$_3$ (14 mg, 32.5 μmol), 4 atm CO, 3 mL CH_3CN, 55 °C, 24–48 h. [b] Yield of isolated product. [c] Run for 8 days; yield is that determined by ^{1}H NMR spectroscopic methods; product was isolated in 25% yield. [d] Run for 6 days.

yield **8**. This both provides a one-pot approach to **8**, and does so from available substrates (phenyl iodide, imines, CO). Similarly, the subsequent decarboxylation of **8** provides a route to prepare polysubstituted imidazoles (e.g., **9**) from the same building blocks.

In conclusion, aryl iodide carbonylation can initiate a cascade of palladium-catalyzed operations in the presence of imines, thereby providing an overall route to prepare imidazolines directly from available substrates. More generally, this reactivity relies upon the ability of the palladium intermediate **1** to behave as an accessible analogue to acid chlorides, thereby initiating a sequence of operations to build-up molecular complexity. Studies directed towards the application of this approach to the synthesis of other products typically derived from acid chlorides, including the generation of alternative classes of heterocycles, are currently in progress.

Experimental Section

Representative procedure for synthesis of **2a**: Imine (104.6 mg, 0.50 mmol), aryl iodide (510.0 mg, 2.5 mmol), [Pd(allyl)Cl]$_2$ (5 mg, 12.5 μmol), and P*t*Bu$_3$ (14 mg, 32.5 μmol) were dissolved in acetonitrile (3 mL) and placed in a sealable glass reaction tube. One freeze/pump/thaw cycle was conducted then the vessel was pressurized with 4 atm of CO and stirred at 55 °C for 48 h. The solvent was removed in vacuo, the residue dissolved in dichloromethane, and washed sequentially with brine, 1M HCl, saturated Na_2CO_3, and then dried over $MgSO_4$. The solvent was removed, and the crude residue was purified by column chromatography on silica gel (eluent: dichloromethane/acetonitrile 1:1 then dichloromethane/methanol 9:1) to provide **2a** in 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.71$–7.68 (m, 3H), 7.59–7.53 (m, 2H), 7.42–7.36 (m, 7H), 7.31–7.28 (m, 4H), 7.02 (t, $J = 7.4$ Hz, 1H), 6.93–6.88 (m, 5H), 6.35 (d, $J = 7.5$ Hz, 2H), 5.54 (s, 1H), 4.99 (d, $J = 15.8$ Hz, 1H), 4.57 (d, $J = 15.8$ Hz, 1H), 4.33 (d, $J = 14.9$ Hz, 1H), 3.98 ppm (d, $J = 14.9$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.4$, 165.2, 139.6, 135.7, 133.5, 132.25, 132.08, 130.0, 129.6, 129.26, 129.22, 129.07, 128.86, 128.78, 128.76, 128.73, 128.48, 128.30, 128.1, 127.34, 127.23, 123.8, 84.6, 73.5, 51.5, 49.1 ppm; FT-IR (cm^{-1}): 1636.1; HRMS ($C_{36}H_{31}N_2O_2$): calcd ($M+1$) 523.2380, observed 523.2371.

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