Azidocarbonylation

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Palladium-Catalyzed Aromatic Azidocarbonylation**

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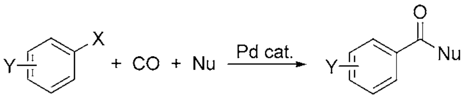
Aroyl azides, $ArCON_3$, are valuable intermediates and building blocks in the synthesis of various useful compounds, including isocyanates (the Curtius rearrangement), aromatic amides, iminophosphoranes,[1] and oxazoles.[2] Conventionally used general methods to synthesize aroyl azides are limited to diazotization of hydrazides and reactions of NaN_3 with acid chlorides, mixed anhydrides, and *N*-acyl benzotriazoles.[1,3] All of these procedures involve highly reactive chemicals which put significant limitations on functionalities that can be present on the aromatic ring of the substrate. The development of methodologically new, highly functional-group tolerant, catalytic routes to aroyl azides is particularly desirable and has been sought after.

Since its discovery by Heck and co-workers[4] in 1974, the palladium-catalyzed reaction of aryl halides ArX with CO and nucleophiles [Eq. (1); Tf = trifluoromethanesulfonyl] has been widely used for the synthesis of various carboxylic acids and their derivatives such as esters and amides.[5] Although it would be natural to consider this type of carbonylation for the synthesis of $ArCON_3$ [$Nu = N_3^-$ in Eq. (1)], this transformation has never been reported in spite of the substantial amount of work done in the area by numerous research groups exploring various nucleophiles in this process.[5]



(1)

X = I, Br, Cl, OTf, etc.; Nu = OH⁻, RO⁻, NHR₂, etc.

The total lack of reports on palladium-catalyzed azidocarbonylation, however, is not surprising considering the following:

- Migratory insertion of CO into the Pd–C bond of $[(R_3P)_2Pd(Ph)(X)]$ (X = I, Br, Cl), a key step in the catalytic loop governing the reaction [Eq. (1)], has long been known[6] to readily and cleanly occur at room temperature and atmospheric pressure. In sharp contrast, complexes of the type $[(R_3P)_2Pd(Ph)(N_3)]$ have been reported to not undergo CO insertion into the Pd–Ph bond under identical reaction conditions.[7] Moreover, upon treatment with CO (1 atm), the N_3 ligand in these complexes is converted into NCO (with concomitant release of N_2) at as low as room temperature [Eq. (2); THF = tetrahydrofuran].

$$[(R_3P)_2Pd(Ph)(N_3)] + CO \xrightarrow[\text{RT, 1 atm}]{\text{THF}} [(R_3P)_2Pd(Ph)(NCO)] + N_2 \qquad (2)$$

R = Me, Et

- Carboxylic acid salts, esters, amides, and all other products that are formed in the reaction shown in Equation (1) are thermally stable and hence easily survive the conditions that conventionally employ elevated temperatures and CO pressure. In contrast, aroyl azides are thermally unstable, undergoing the Curtius rearrangement at temperatures (80 °C and above) typically used for the carbonylation [Eq. (1)].
- The product, $ArCON_3$, is not only thermally unstable but also highly reactive toward tertiary phosphines that conventionally comprise palladium catalysts for the carbonylation and other coupling reactions. The exceedingly facile Staudinger reaction[8] of the aroyl azide product with the reversibly dissociated PR_3 ligand would lead irreversibly to the corresponding phosphinimine $ArC(O)N{=}PR_3$ and, as a result, to rapid catalyst deactivation.

As follows from the above, the azidocarbonylation differs principally, in a number of respects, from the already known palladium-catalyzed aromatic carbonylation reactions [Eq. (1)]. Each of the three aforementioned reactivity patterns alone seriously challenges the feasibility of the reaction [Eq. (1)] for $Nu = N_3^-$, if not buries altogether the very idea of palladium-catalyzed aromatic azidocarbonylation. Nevertheless, in this report we demonstrate that, against all expectations, this transformation is not only possible but can even be remarkably clean and high yielding for a carefully selected catalytic system.

We have carried out a large number of experiments to explore the possibility of transforming PhX (X = I, Br) into $PhCON_3$ using CO and NaN_3 in the presence of various palladium catalysts. We were delighted to find, as a result of these exploratory runs, that Pd/Xantphos is an excellent catalyst for azidocarbonylation of iodobenzene. Herein we present only a very succinct summary of our scouting and optimization experiments that are described in full detail in the Supporting Information.

1. Pd/Xantphos was the only system that competently catalyzed the azidocarbonylation reaction. Other catalysts based on $Pd(OAc)_2$ or $[Pd_2dba_5]$[9] precursors and various ligands, including PPh_3, *o*-Tol_3P, Cy_3P, *t*Bu_3P, dppe, dppp,

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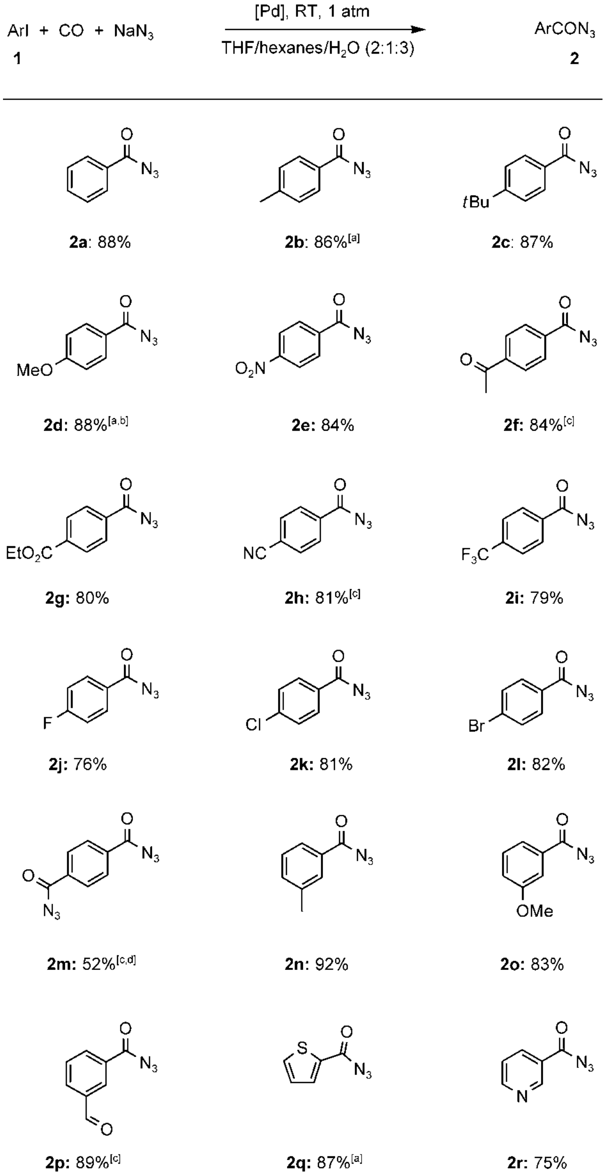
dppb, dppf, *rac*-BINAP, *i*Pr-Xantphos, *t*Bu-Xantphos, and DPEphos were inefficient. The yield of $PhCON_3$ from PhI using these ligands was only 0–6% under a variety of reaction conditions.

2. The highest catalytic activity was observed for a 1:1 Pd^0/Xantphos molar ratio, in accord with the literature data.[10] It is noteworthy that Xantphos[11] has been found[12] to be a superior ligand for a series of palladium-catalyzed carbonylation reactions.
3. In many instances, the product ($ArCON_3$) and the starting material (ArI) exhibited nearly identical R_f parameters and hence could not be separated by column chromatography. Therefore, to isolate the product in pure form the reaction should be driven to full conversion. Toward this goal, we found that nearly quantitative conversions of PhI could be obtained by running the reaction in the presence of water.[13] The promoting effect of water was particularly powerful when the reaction was performed under biphasic conditions[14] with THF/hexanes (2:1 *v*/*v*) as the organic phase of choice.[15] Although high conversions and yields of up to 87–88% could be obtained under such biphasic conditions with only 1% Pd, we settled on 2 mol% of the catalyst in order to reach full conversion that is critical for isolation of the product in pure form (see above).

With optimized reaction conditions in hand, a series of aryl iodides (**1**) were successfully converted to the corresponding aroyl azides (**2**; Scheme 1). All conversions were quantitative, thus allowing isolation of the pure products in high yield. The reaction exhibited high functional-group tolerance and smoothly and cleanly occurred with both electron-withdrawing (**2e–l**, **2p**) and electron-donating (**2b–d**, **2n**) substituents on the aromatic ring. The yields of the isolated products were usually in the range of 80–90% with a few exceptions, including the lower yield of the doubly azidocarbonylated benzene (**2m**, 52%) obtained from *p*-diiodobenzene and the higher, 92% yield of *m*-toluoyl azide **2n**.

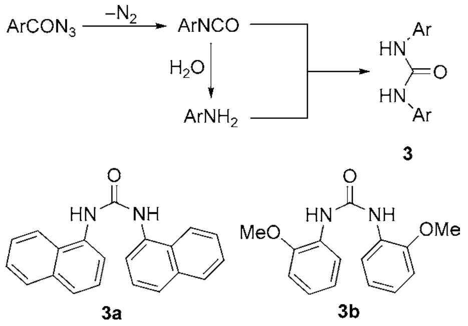
Both 2-iodothiophene and 3-iodopyridine were cleanly converted to the corresponding azidocarbonyl derivatives (**2q** and **2r**) in 87 and 75% isolated yield, respectively. In contrast, 2-iodopyridine produced a mixture of products under similar reaction conditions, including 2-PyNCO, 2-PyCONH_2, and 2-PyNH_2. This outcome is likely due to the lower thermal stability of 2-PyCON_3[16] and, possibly, to the well-known[17] dimerization of 2-pyridyl palladium derivatives through the N atoms of the pyridine ring.

Under the same reactions conditions, *ortho*-substituted iodoarenes gave mixtures of the corresponding amide, amine, and diarylurea, as was the case with 2-iodotoluene. The reaction was more selective toward the formation of ureas for 2-iodoanisole and 1-iodonaphthalene: *N*,*N'*-bis(1-naphthyl)urea (**3a**; see Scheme 2) was obtained pure in 76% yield and 2-iodoanisole gave *N*,*N'*-bis(2-methoxyphenyl)urea (**3b**) that was isolated in 74% yield (ca. 80% purity by ^{1}H NMR spectroscopy; see the Supporting Information). The different reaction outcome for 2-substituted iodoarene substrates is hardly surprising because $ArCON_3$ bearing an *ortho* substituent are 50–200 times more reactive toward the Curtius rearrangement than their *m* and *p* isomers.[16,18] As a result, an *ortho*-substituted aroyl azide originally produced in the reaction quickly rearranges to the corresponding isocyanate that may be partially converted into $ArNH_2$ under the reaction conditions. The aniline then adds to the as yet unreacted ArNCO to form the urea (Scheme 2).

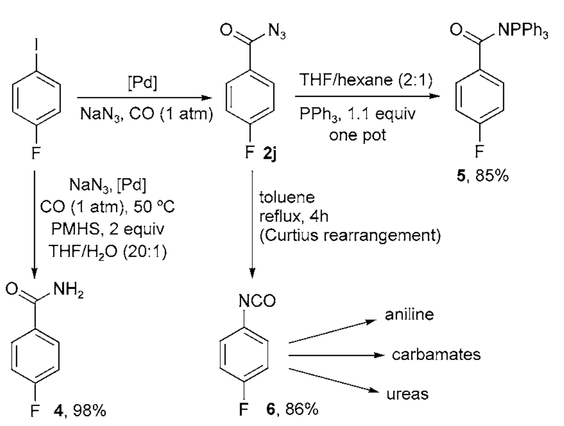


Scheme 1. Palladium-catalyzed azidocarbonylation of iodoarenes. Reaction conditions: ArI (1 mmol), NaN_3 (1.2 mmol), $[Pd_2dba_5]$[9] (0.01 mmol; 2 mol% Pd), Xantphos (2 mol%) in THF (2 mL), hexanes (1 mL), and water (3 mL) at 23 °C. All yields are isolated yields. [a] At 50 °C (oil bath). [b] Isolated product contained 2% of $PhCON_3$ as a result of P-Ar/Pd-Ar′ exchange. [c] Isolated product contained dba. [d] Obtained from 1,4-diiodobenzene (1 mmol) and double amounts of all reagents and solvents. dba = dibenzylideneacetone.

Importantly, aroyl azides produced in the reaction can be used for further transformations without isolation. This concept was successfully demonstrated with 4-fluoroiodobenzene, as shown in Scheme 3. Carrying out the azidocarbony-

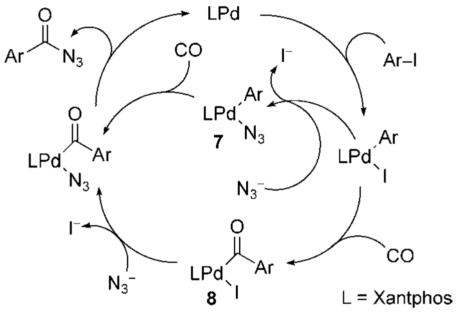


Scheme 2. In situ formation of ureas from the originally produced *ortho*-substituted ArCON$_3$.



[Pd] = [Pd$_2$dba$_5$] (1 mol %; 2 mol % Pd), Xantphos (2 mol %)

Scheme 3. Reaction scope experiments. Yields were determined by ^{19}F NMR spectroscopy. PMHS = polymethylhydrosiloxane.



Scheme 4. Azidocarbonylation mechanisms.

lation in the presence of PMHS (2 equiv) afforded 4-fluorobenzamide (**4**) in nearly quantitative yield. It is worth noting that one-step aminocarbonylation of aryl halides to primary benzamides is a challenging transformation.[19] In another experiment, after 4-fluorobenzoyl azide (**2j**) was produced (Scheme 1) the entire reaction mixture was treated with PPh$_3$ (1.1 equiv) to bring about the transformation of **2j** to iminophosphorane **5** that was formed in 85 % overall yield (Scheme 3). Running the azidocarbonylation in a toluene/water (1:1) solvent mixture allowed for conveniently carrying out the Curtius rearrangement by heating the toluene phase containing the ArCON$_3$ product. In this way 4-fluorophenylisocyanate (**6**) was obtained in 86 % yield, as calculated on the basis of the amount of 4-fluoroiodobenzene used. Aryl isocyanates are industrially important intermediates[20] that are widely used in the synthesis of various valuable chemicals, including carbamates, anilines, and ureas. Tkatchenko et al.[21] have patented the nickel-catalyzed reaction of haloarenes with NaOCN to produce aryl isocyanates and their derivatives in up to 50 % yield. Direct palladium-catalyzed transformation of aryl halides into aryl isocyanates is unknown. Attempts to azidocarbonylate bromoarenes were unsuccessful.[22]

A plausible mechanism for the azidocarbonylation reaction is presented in Scheme 4. After the Ar–I bond oxidatively adds to Pd^0, two reaction pathways could lead from the resultant σ-aryl Pd^{II} iodide to the key intermediate that reductively eliminates ArCON$_3$: 1) anionic ligand exchange to produce **7** with subsequent carbonylation and 2) migratory insertion of CO leading to **8**, followed by I$^-$/N$_3^-$ ligand exchange.

The proposed reaction pathways (Scheme 4) were confirmed by independent mechanistic studies. Both intermediates, [(Xantphos)Pd(Ph)(N$_3$)] (**7**) and [(Xantphos)Pd(COPh)(I)] (**8**), were synthesized and fully characterized, including by single-crystal X-ray diffraction (Figure 1).[23] Bubbling CO through a [D$_6$]benzene solution of **7** or adding Bu$_4$N$^+$ N$_3^-$ to a solution of **8** in [D$_6$]benzene under CO at room temperature resulted in immediate reductive elimination leading to a single ^{31}P NMR-observable compound (s, δ = 10.5 ppm). The same species was formed, as detected by ^{31}P NMR spectroscopy, upon treatment of [Pd$_2$dba$_5$] with Xantphos and CO in benzene or toluene, thus indicating that the signal at δ = 10.5 ppm was likely from a zero-valent palladium carbonyl phosphine complex. Layering the benzene solution with ether produced X-ray quality crystals of [(Xantphos)Pd(CO)$_2$] co-crystallized with [(Xantphos)Pd(dba)] and benzene in a 1:1:1.5 molar ratio. The X-ray determination of the structure of [(Xantphos)Pd(CO)$_2$][23] resonating at δ = 10.5 ppm in the ^{31}P NMR spectra (see above) provided unambiguous evidence for the existence of the two reaction pathways, via **7** and via **8**, leading to the final product that is apparently produced from [(Xantphos)Pd(COPh)(N$_3$)] (Scheme 4). The competition between the two pathways involving **7** and **8** is expected to strongly depend on

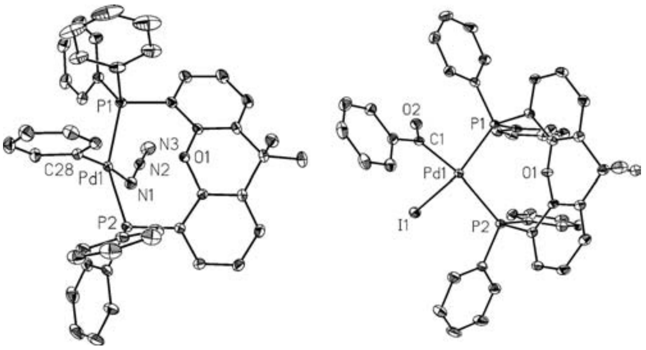


Figure 1. ORTEP drawings of **7** (left) and **8** (right) with H atoms omitted and thermal ellipsoids drawn to the 50% probability level.

the CO pressure, N_3^- concentration, and the nature of the medium, among numerous other factors. Regardless of which of the two internal pathways prevails, the process invariably leads to the aroyl azide product. What is crucial to the overall catalytic process, however, is that unlike the $[(R_3P)_2Pd(Ph)(N_3)]$ [Eq. (2)], **7** does not form a Pd−NCO species by N_2 loss upon treatment with CO.

The uniqueness of the catalytic system based on Xantphos is not fully understood. The remarkable ability of Xantphos to promote various transformations at the metal center is well-documented,[11] including particularly challenging ones, such as Ar−CF$_3$ reductive elimination from Pd^{II}.[24] Although this behavior of Xantphos has often been linked to its wide bite angle,[11] the latter might not always be the key contributing factor.[25] Studies of the critical role of Xantphos in the azidocarbonylation reaction are currently underway in our laboratories.

In conclusion, we have demonstrated, for the first time, the possibility of palladium-catalyzed aromatic azidocarbonylation. Careful catalyst selection and mechanistic insights have led to the identification of reaction conditions that are sufficiently mild to circumvent the multiple dangers of failure stemming from the Curtius rearrangement of the aroyl azide product, its Staudinger reaction with the phosphine ligand, and, as a result, immediate catalyst degradation. The catalytic reaction smoothly occurs at temperatures as low as 25–50 °C and 1 atm to cleanly give aroyl azides from the corresponding aryl iodides, CO, and NaN$_3$. Unlike the traditional routes to ArCON$_3$, our method does not require stoichiometric quantities of acid activators (Cl-containing reagents or oxidants), and therefore can be used to prepare otherwise hardly accessible aroyl azides such as **2p** that bears a formyl group on the ring. The reaction exhibits high functional-group tolerance and can also be conveniently used for one-pot, two-step procedures furnishing primary benzamides, iminophosphoranes, isocyanates, and ureas in high yield without isolation of the primary benzoyl azide product.

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[23] CCDC 860745 (**7**), 860746 (**8**), and 860747 ($[(Xantphos)Pd(CO)_2]\cdot[(Xantphos)Pd(dba)]\cdot 1.5\,C_6H_6$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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