

Pd-Catalyzed Conversion of Aryl Chlorides, Triflates, and Nonaflates to Nitroaromatics

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Aromatic nitro compounds are of great importance to a variety of disciplines. They can be found in an array of pharmaceuticals,¹ dyes,² and materials.³ Moreover, they are important entities in synthesis and can participate in a range of useful transformations.⁴ Most commonly, nitrobenzenes are synthesized via electrophilic aromatic substitution using HNO₃ and a strong acid or with dinitrogen pentoxide.⁴ However, these methods suffer from issues of poor regioselectivity and imperfect functional group tolerance. Further, the application of these reactions is particularly problematic for the nitration of heteroaromatics. More recently, Prakash and Olah disclosed a method for the conversion of aryl boronic acids to aryl nitro compounds.⁵ This was followed by a report from Saito disclosing a copper catalyst for the transformation of aryl iodides to nitrobenzenes.⁶ These processes were important advances in this field and provided nitration protocols complementary to known chemistry; however, the substrate scope of these reactions is limited and does not include heterocycles.

Herein, we report a general Pd catalyst for the conversion of aryl chlorides, triflates, and nonaflates to nitroaromatics.⁷ This protocol circumvents issues of regioselectivity and proceeds efficiently under weakly basic conditions, allowing for excellent functional group compatibility. Moreover, it enables the formation of nitroarenes that cannot be accessed effectively by other means, most notably nitro-substituted heteroaryl compounds. Mechanistic insight into the “transmetalation” step of this catalytic process is also provided.

We began our studies by examining the reaction of 4-chloro-*n*-butylbenzene with commercially available nitrite sources. We hypothesized that a catalyst based on ligand **1** (Figure 1), which we have shown to be effective in amidation reactions of aryl chlorides,⁸ would be useful for this transformation, since we expected that N–Pd bond formation would be difficult, as in the latter transformation. Use of 0.5 mol % Pd₂(dba)₃, 1.2 mol % **1**, and sodium nitrite in *t*-BuOH afforded the desired 4-nitro-*n*-butylbenzene in 26% yield (Table 1). Since sodium nitrite is sparingly soluble in *t*-BuOH, we reasoned that use of a phase-transfer catalyst (PTC) might be beneficial. Adding 5 mol % tris(3,6-dioxahexyl)amine (TDA) improved the yield to 52%, whereas the use of other PTCs did not have a positive influence on the outcome of the reaction.

Catalysts based on other biarylphosphine ligands (**2**,⁸ **3**,⁹ **4**, and **5**)¹⁰ gave little to no desired product in these reactions. This demonstrates that in ligand **1**, both the di-*tert*-butylphosphino group

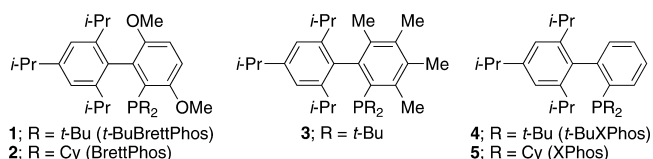


Figure 1. Biarylphosphine ligands.

Table 1. Pd-Catalyzed Formation of 4-Nitro-*n*-butylbenzene

entry	L	5% PTC	yield ^a	entry	L	5% PTC	yield ^a
1	1	—	26%	6	3	TDA	10%
2	1	TDA	52%	7	4	TDA	0%
3	1	TBACl	3%	8	5	TDA	0%
4	1	15-C-5	33%	9	1	—	2% ^b
5	2	TDA	0%	10	1	TDA	99% ^c

^a 4-Chloro-*n*-butylbenzene (1 mmol), NaNO₂ (2.0 mmol), Pd₂(dba)₃ (0.5 mol %), ligand (1.2 mol %), *t*-BuOH (2 mL), 110 °C, 24 h; GC yields. ^b (TBA)NO₂ was used. ^c Reaction temperature was 130 °C.

and the methoxy substituent ortho to the phosphine are critical to the reactivity of this catalyst system.

We observed that the yield of the reaction increased as the amount of TDA was increased from 0 to 5 mol %. However, the amount of product generated in these reactions dropped quickly when more than 5% TDA was used (Figure 2).¹¹ We reasoned that higher concentrations of nitrite in solution could oxidize Pd(0) or the ligand, which would explain the lower yields at higher loadings of TDA. To test this postulate, we ran the reaction with a soluble source of nitrite (tetrabutylammonium nitrite) and obtained only 2% 4-nitro-*n*-butylbenzene (Table 1, entry 9). These studies show that having the optimal amount of nitrite in solution is essential to the outcome of the reaction.

By increasing the reaction temperature, we were able to convert 4-chloro-*n*-butylbenzene to the desired nitro product in virtually quantitative yield (Table 1, entry 11). Using these conditions, we set out to explore the scope of the Pd-catalyzed transformation of aryl chlorides to nitroaromatics using a catalyst based on ligand **1** (Table 2). Ortho substituents as well as acid-sensitive functional groups such as an acetal, a pyrrole, and a free alcohol were all well-tolerated. Nitroarenes containing electron-withdrawing groups or amines in the para position and electron-donating substituents in the meta position were synthesized in high yields with this method; these compounds cannot be efficiently formed through traditional nitration protocols. Nitro heteroaromatics could also be

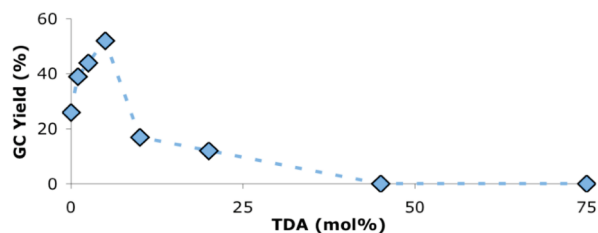
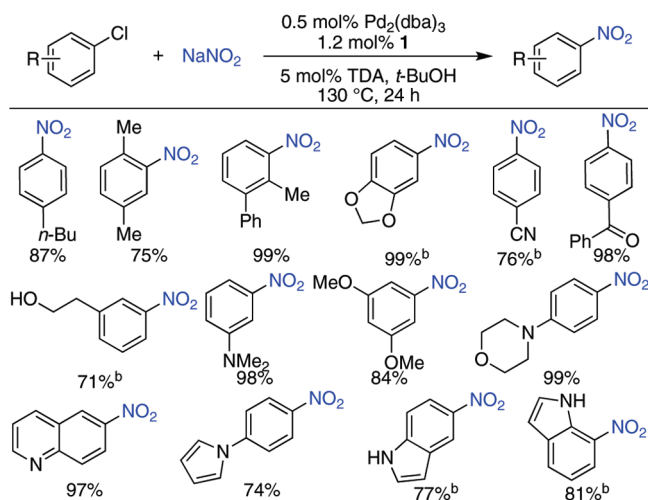
Figure 2. Effect of TDA on the yield of the Pd-catalyzed formation of 4-nitro-*n*-butylbenzene.

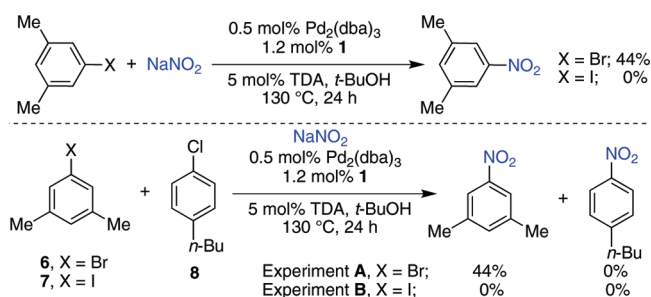
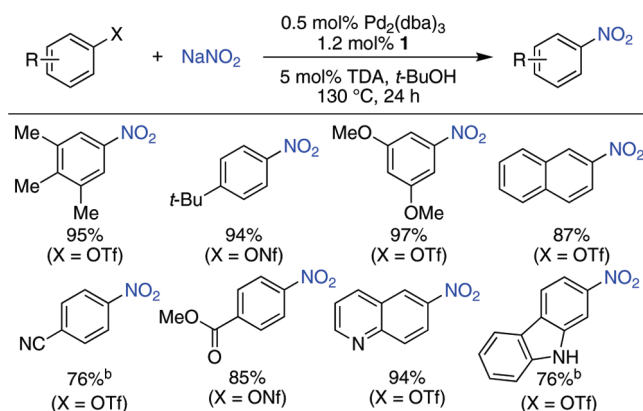
Table 2. Conversion of Aryl Chlorides to Nitroaromatics^a

^a ArCl (1 mmol), NaNO₂ (2.0 mmol), Pd₂(dba)₃ (0.5 mol %), **1** (1.2 mol %), *t*-BuOH (2 mL), 130 °C, 24 h; isolated yields, average of two runs. ^b Pd₂(dba)₃ (2.5 mol %), **1** (6 mol %).

prepared in good to excellent yields. For example, 5- and 7-chloroindole were transformed to the corresponding nitroindoles in good yields without the need of a protecting group. This catalyst system is complementary to current nitration protocols and allows for the synthesis of nitroaromatic compounds that are not readily accessible via other means.

On the basis of the broad scope this catalyst displayed for the nitration of aryl chlorides, we decided to explore nitrations of aryl bromides and iodides. Under the optimized reaction conditions, 3,5-dimethylbromobenzene (**6**) and 3,5-dimethyliodobenzene (**7**) gave the desired products in 44 and 0% yield, respectively (Figure 3). In order to aid our interpretation of this result, competition experiments involving the aryl bromide or iodide versus the aryl chloride were performed. In experiment A, where a 1:1 mixture of **6** and **8** was subjected to the reaction conditions, yields of 44 and 0% for the aryl bromide-derived and aryl chloride-derived coupling products, respectively, were observed. In experiment B, where a 1:1 mixture of **7** and **8** was used, no nitroaromatic products were formed. These results demonstrate that the catalyst undergoes oxidative addition with the aryl iodide or bromide faster than with the aryl chloride and that transmetalation is the slow (problematic) step for these processes.¹² Moreover, they establish that the rate of transmetalation follows the order Cl > Br > I in these reactions.

On the basis of these results and previous findings in our group,¹⁰ we postulated that aryl triflates and nonaflates would react with an accelerated rate of transmetalation and be suitable substrates for these reactions. With a catalyst consisting of **1** and Pd₂(dba)₃, an array of aryl nonaflates and triflates were converted to the

**Figure 3.** Reactions of aryl bromides and iodides.**Table 3.** Conversion of Aryl Triflates and Nonaflates to Nitroaromatics^a

^a ArX (1 mmol), NaNO₂ (2.0 mmol), Pd₂(dba)₃ (0.5 mol %), **1** (1.2 mol %), *t*-BuOH (2 mL), 130 °C, 24 h; isolated yields, average of two runs. ^b Pd₂(dba)₃ (2.5 mol %), **1** (6 mol %).

corresponding products in good to excellent yields (Table 3), including those containing esters and nitriles; heteroaryl triflates were also transformed with high efficiencies.

In summary, an effective catalyst for the conversion of aryl chlorides, triflates, and nonaflates to nitroaromatics has been developed. This method is complementary to previous nitration protocols and evades issues of regioselectivity and functional group compatibility. It has also been shown that the rate of transmetalation follows the order Cl > Br > I in these reactions. Further studies to better understand the mechanism of the reaction and extend its scope to aryl iodides, bromides, and tosylates are currently underway in our laboratory.

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Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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