

Open air palladium catalyzed cyanation—the use of PMHS to protect from oxygen

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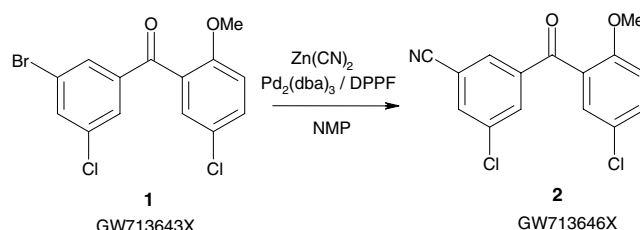
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Abstract—PMHS (polymethylhydrosiloxane) used in catalytic amounts has a remarkable ability to prevent catalyst poisoning by oxygen contamination during palladium catalyzed cyanation reactions. The procedure is applicable to a wide range of substrates and is so effective that it allows the reactions to be run fully open to the atmosphere.

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Conversion of aryl halides to aryl cyanides is a common and useful synthetic tool. Palladium catalyzed cyanation reactions are perhaps the most direct methods to produce this transformation. However, the palladium catalyzed cyanation of aryl halides is an often capricious reaction and lacks robustness due to catalyst poisoning resulting in stalled reactions.¹ One common cause of catalyst poisoning is contamination by oxygen which has given rise to many procedures that call for stringent degassing of solvents or even continuous sparging.² We have discovered that a simple and economical additive—polymethylhydrosiloxane (PMHS)—is capable of imparting the reaction with a remarkable protective effect from catalyst poisoning due to oxygen. Addition of as little as 1 wt % PMHS to these reactions allows them to progress even when fully exposed to the atmosphere and should therefore make the reaction robust while removing the need for a stringent degassing protocol when used in a process run under a normal inert atmosphere.

During the course of our development of a large-scale process for the palladium catalyzed cyanation of **1**, an intermediate in the synthesis of a potential non-nucleoside reverse transcriptase inhibitor, we were plagued by unexpected reaction failures. The reaction was unreliable and often required multiple charges of catalyst and ligand to afford complete conversion. Many of these stalled reactions could be directly attributed to contam-



ination from low-level amounts of oxygen either from the solvent or introduced during setup and monitoring. One solution we investigated was to rigorously sparge the reaction solvent with Argon before and during the process. While this achieved a more reliable reaction, it was cumbersome and expensive on pilot plant scale. To this end, we sought to identify a chemical method to minimize the deleterious effects of oxygen poisoning. There are various reports of adding chemical or even electrochemical reductants to palladium catalyzed cyanations in order to protect from catalyst oxidation, but none seemed to offer the level of success we were hoping to achieve.³ We felt the ultimate success would be to achieve complete conversion while running a reaction fully exposed to air. Upon screening a variety of additives as potential reductants (Ph_3P , Zinc, $(\text{EtO})_3\text{P}$, FeCl_2 , CuI and Et_3SiH), we found that indeed the addition of triethylsilane provided complete conversion while the reaction was open to the atmosphere. PMHS was found to be equally effective in this reaction and became the focus of this work based on the fact that it was inexpensive, non-toxic and safe to handle as compared

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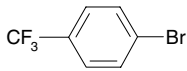
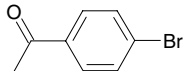
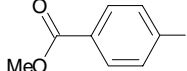
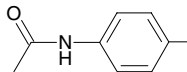
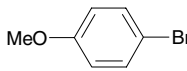
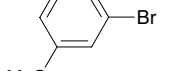
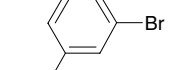
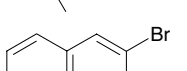
to triethylsilane.⁴ It was discovered that addition of only 1 wt % PMHS (0.06 equiv based on 60 g/mol hydride) was sufficient to fully progress the reaction to completion even when run fully exposed to the air.

This finding was confirmed on kilogram scale when the reaction was conducted without the use of nitrogen or solvent degassing. To further reduce the cost of this chemical stage on scale, we investigated the use of less expensive Pd(OAc)₂ as an alternative to the Pd₂(dba)₃ catalyst. With only 0.9 mol % Pd(OAc)₂ and 0.12 mol % DPPF, we found that the reaction reliably proceeded to completion in the presence of catalytic PMHS. By eliminating the need for subsequent charges of catalyst and ligand and utilizing the less expensive Pd(OAc)₂ system, we were able to significantly lower the cost of this reaction on pilot plant scale.

With these results in mind, we set out to test this protocol on a variety of representative aryl bromides to determine the scope of this process. Table 1 lists the aryl bromides that were subjected to cyanation reactions using this protocol. In all cases the reactions were run completely open to the atmosphere and without degassing the solvent. The reactions generally went to completion in 1–3 h. Some of the less reactive substrates (electron rich aryl halides for instance) required elevated temperatures to achieve complete conversion. The PMHS does not appear to accelerate the reaction or increase the reactivity of the catalyst system as compared to the non-PMHS reaction conditions. As with most palladium catalyzed processes, the catalyst/ligand combination has a finite lifetime under the reaction conditions and indeed this cyanation reaction can be viewed as a competition between catalyst lifetime and reaction progression. Given that these reactions were run open to the atmosphere, it is impressive to see that they were able to fully progress before the catalyst was sufficiently compromised to stall the reaction. Note that for these representative cases a higher loading of PMHS (10 wt %) was utilized in order to insure that both activated and deactivated substrates would progress to completion. A loading of 1 wt % is sufficient to allow open air reactions to go to completion in many cases and therefore should be completely effective against spurious air contamination in a typical reaction run under an inert atmosphere.

In order to more fully demonstrate the effectiveness of PMHS in this process, we utilized ReactIR⁵ to monitor the cyanation of bromobenzotrifluoride run under both inert conditions and fully exposed to air. We chose Pd₂(dba)₃ as the catalyst source for these comparisons as it is already in the correct oxidation state to initiate the catalytic cycle. Figure 1 shows that the reaction performed under inert conditions was complete within 1 h whereas, the reaction exposed to air stalled after only 30 min. When the same reaction was performed exposed to air but in the presence of 10 wt % PMHS, the reaction progressed at essentially the same rate as the inert atmosphere reaction. Note that the absorption of the PMHS at 1073 cm⁻¹ overlaps that of the aryl C–Br bond stretch and therefore the relative concentration curves for the

Table 1. Open air cyanation of aryl bromides in the presence of PMHS

| Starting material ^a | Time (h) | Temperature (°C) | Isolated yield |
|---|----------|------------------|-----------------|
|  | 1.5 | 80 | 61 ^b |
|  | 1.5 | 80 | 94 |
|  | 3 | 80 | 91 |
|  | 1 | 120 | 97 |
|  | 3 | 120 | 89 |
|  | 3 | 120 | 63 |
|  | 2 | 80 | 78 |
|  | 3 | 80 | 95 |

^a All reactions were carried out on 1-g scale in round bottom flasks fully open to air. The reactions were followed by HPLC and products characterized by ¹H NMR and ¹³C NMR.

^b Product is volatile.

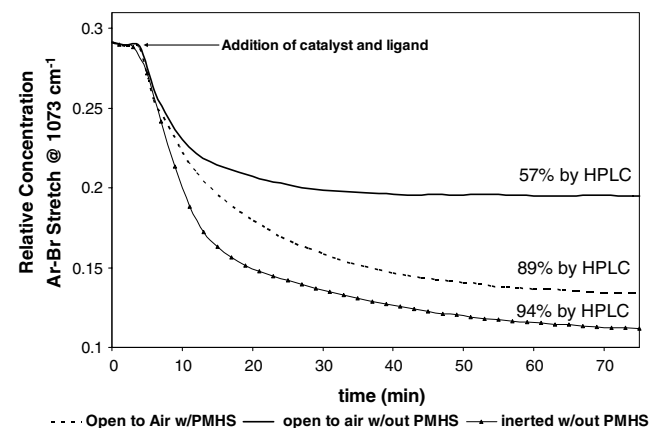


Figure 1.

inerted reaction and PMHS treated reactions do not overlay precisely.

The extent of reaction completion was verified by HPLC. A possible explanation could involve a silyl hydride reduction of the oxidized palladium back to palladium(0). However, in reactions that were purpo-

sefully stalled by exposure to air prior to addition of the PMHS, the addition of PMHS failed to restart the catalytic cycle. In these stalled reactions the addition of either fresh Pd₂(dba)₃ or DPPF alone also failed to restart the reactions, suggesting that both the catalyst and ligand were irreversibly inactivated. The addition of both fresh catalyst and ligand did restart the reaction as expected. These observations demonstrate that the PMHS is capable of maintaining the palladium in its correct oxidation state and thus protecting the catalyst from oxidative inactivation yet it is not capable of actually reactivating catalyst that has been deactivated.

In a typical procedure, 3-bromoacetophenone (1.0 g, 5.3 mmol), zinc cyanide (0.32 g, 2.7 mmol), NMP (5 ml) and water (0.5 ml) are stirred in a one neck round bottom flask open to the atmosphere. The contents are heated to 80 °C and treated with PMHS (0.10 g) followed by a slurry of Pd(OAc)₂ (11.3 mg, 0.05 mmol) and DPPF (36.2 mg, 0.0065 mmol) in NMP (0.5 ml). The contents are heated at 80 °C for approximately 2 h and monitored for completion by HPLC. The reaction is cooled and the contents placed on a silica gel column and eluted with 50% heptane/ethyl acetate. The purified product is isolated as an off white solid, (596 mg, 78%) by evaporation of volatiles. All products were fully characterized by H NMR, ¹³C NMR and HPLC.

This discovery of using PMHS as a protectant in palladium catalyzed cyanation reactions represents a signifi-

cant advancement in achieving a higher level of robustness for these reactions. The use of PMHS in conjunction with other palladium catalyzed reactions known to be highly air sensitive is currently under investigation in our labs.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2007.02.018](https://doi.org/10.1016/j.tetlet.2007.02.018).

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