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# Pd(0)-Catalyzed PMHS Reductions of Aromatic Acid Chlorides to Aldehydes

**Kyoungsoo Lee and Robert E. Maleczka, Jr.***

*Department of Chemistry, Michigan State University, East Lansing, Michigan 48824*

*maleczka@chemistry.msu.edu*

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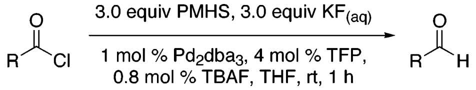
## ABSTRACT



**Contrary to previous reports, polymethylhydrosiloxane (PMHS) under Pd(0) catalysis can efficiently reduce aryl acid chlorides to their corresponding aldehydes without requiring an additional reductant, provided the reactions are run in the presence of fluoride.**

The reduction of acid chlorides to aldehydes is a basic functional group transformation. While reductions under Rosenmund conditions or by Li(*t*-BuO)$_3$AlH are classic means for effecting the reaction,[1] the quest for ever greater selectivity and efficiency has long prompted the search for alternative methods.[1] Among these, the palladium-mediated organotin hydride reductions invented by Guibé have proven particularly popular.[2]

Of course, organotin reagents carry the baggage of being relatively toxic, expensive, unstable, etc.[3] Thus, mindful of prior reactions made catalytic in tin through the use of polymethylhydrosiloxane (PMHS) as the stoichiometric reductant[4] and our recent report of a one-pot Pd-mediated hydrostannation/Stille coupling of acid chlorides,[5] we contemplated a tin-catalyzed version of Guibé's method for reducing acid chlorides to aldehydes.

As a prelude to that goal, we examined the Pd-catalyzed reduction of benzoyl chloride with a stoichiometric amount of Me$_3$SnH that was generated in situ by the reaction of Me$_3$SnCl with PMHS in the presence of aqueous KF[6] (Table 1, entry 1). Despite the potential for hydrolysis and unwanted reactions, this combination rapidly and quantitatively afforded benzaldehyde. We next looked to make the reaction catalytic in tin. Needless to say, we were pleased when reactions with 30 mol % and then 10 mol % tin worked nearly as well as the stoichiometric variant (entries 2−3). That satisfaction turned to surprise when, after 1 h, a tin-free control experiment (entry 4) also gave 100% benzaldehyde!

**Table 1.** Pd-Mediated Reduction of Benzoyl Chloride to Benzaldehyde with in Situ Generated Me$_3$SnH

$$\text{benzoyl chloride } (\mathbf{1}) \xrightarrow[\text{Pd}_2\text{dba}_3\text{/TFP (1:4), THF, rt}]{\text{Me}_3\text{SnCl, 1.5 equiv PMHS, aq KF}} \text{benzaldehyde } (\mathbf{2})$$

| entry | Pd(0) (mol %) | Me$_3$SnCl (equiv) | KF (equiv) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | 1 | 1.0 | 1.5 | 0.5 | 100 |
| 2 | 1 | 0.3 | 1.5 | 0.5 | 100 |
| 3 | 1 | 0.1 | 1.5 | 1.0 | 100 |
| 4 | 1 | | 1.5 | 1.0 | 100 |
| 5 | 1 | | | 24 | 12 |
| 6 | | | 1.5 | 24 | 0 |

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(1) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparation*, 2nd ed.; Wiley-VCH: New York, 1999; pp 1265−1266 and references therein.

(2) Four, P.; Guibe, F. *J. Org. Chem.* **1981**, *46*, 4439−4445.

(3) (a) Smith, P. J., Ed. *Chemistry of Tin*; Blackie Academic & Professional: New York, 1998. (b) Davies, A. G. *Organotin Chemistry*; VCH: New York, 1997.

(4) (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381−3391 and references therein. (b) Lavis, J. M.; Maleczka, R. E., Jr. Polymethylhydrosiloxane (PMHS). In *eEROS-Electronic Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Crich, D., Fuchs, P. L., Wipf, P., Eds.; Wiley: New York 2003; [Online] and references therein.

(5) Lee, K.; Gallagher, W. P.; Toskey, E. A.; Chong, W.; Maleczka, R. E., Jr. *J. Organomet. Chem.* **2006**, *691*, 1462−1465.

(6) Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342−343.

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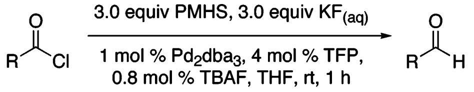
We were caught unawares by this result because, while organosilanes have long been used to convert acid chlorides to aldehydes,[1,7] it has been over 20 years since Keinan and Greenspoon reported that acid chlorides *"cannot be reduced just with PMHS/Pd(PPh$_3$)$_4$"*.[8,9] Their observation was later supported by Crabtree, who found that collidal Pd formed from Pd(hfacac)$_2$ and PMHS required the presence of $H_2$ gas to reduce benzoyl chloride to benzaldehyde.[10] In our system, it appeared that the presence of KF heightened the reactivity of the PMHS to where the acid chlorides can be converted to their aldehydes without the need for an additional reductant. This was supported by our own KF-free experiment (entry 5), which only gave 12% benzaldehyde after 24 h. That said, activation by KF is not sufficient to abolish the need for Pd catalysis (entry 6).

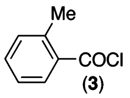
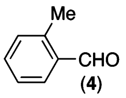
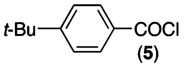
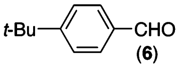
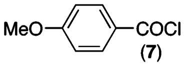
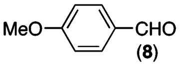
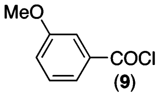
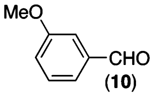
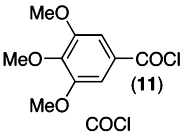
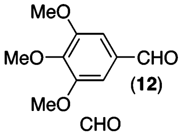
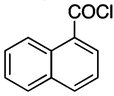
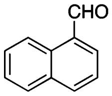
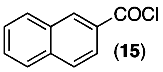
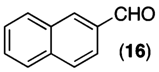
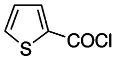
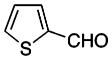
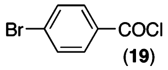
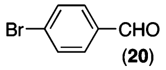
We presume the fluoride activates PMHS by making it hypercoordinate.[11] Nonetheless, unlike acid chlorides, acid fluorides can be reduced by just PMHS/Pd(0).[12] Therefore, we had to consider if benzoyl chloride was first converted to benzoyl fluoride[13] and then reduced to benzaldehyde. However, GC monitoring never indicated the presence of benzoyl fluoride. Furthermore subjecting benzoyl fluoride to our reaction conditions failed to afford any benzaldehyde.

With an acid fluoride intermediate ruled highly unlikely,[14] this reduction represents a noteworthy refinement of the literature. Moreover, given that PMHS is mild, safe, and cheap,[4] these conditions may be attractive as a general way to convert acid chlorides to aldehydes.

To assess this prospect, we tested a series of acid chlorides against the PMHS/KF/Pd(0) conditions (Table 2). We soon saw that not all substrates underwent complete reaction with 1.5 equiv of PMHS (e.g., **7**). In contrast, 3.0 equiv of PMHS and aqueous KF in the company of substoichiometric amounts of Pd(0), trifurylphosphine (TFP), and TBAF[15] uniformly reduced a variety of electron-rich and neutral aryl acid chlorides (entries 1−8), including heterocyclic 2-thiophenoyl chloride (entry 9), to their aldehydes within 1 h at room temperature.[16] Despite the ability of PMHS/Pd(0) to reduce aryl halides,[17] 4-bromobenzoyl chloride was selectively reduced to 4-bromobenzaldehyde (entry 10).[18]

**Table 2**



| entry | acid chloride | aldehyde | yield[a] |
|---|---|---|---|
| 1 | benzoyl chloride (**1**) | benzaldehyde (**2**) | 99% |
| 2 |  **(3)** |  **(4)** | 83% |
| 3 |  **(5)** |  **(6)** | 99% |
| 4 |  **(7)** |  **(8)** | 91% |
| 5 |  **(9)** |  **(10)** | 98% |
| 6 |  **(11)** |  **(12)** | 82% |
| 7 |  **(13)** |  **(14)** | 86% |
| 8 |  **(15)** |  **(16)** | 81% |
| 9 |  **(17)** |  **(18)** | 92% |
| 10 |  **(19)** |  **(20)** | 68% |

[a] Average isolated yields over two runs.

Unfortunately, the reductions were not universally applicable. Water in the reaction hydrolyzed electron-poor benzoyl chloride derivatives and aliphatic acid chlorides too fast to allow for their reductions.[19]

In summary, the presence of fluoride allows Pd(0)-catalyzed PMHS reductions of electron-rich and neutral aryl acid chlorides. Yields are generally high and reaction times short. *Perhaps most importantly, these results amend the existing literature.*

**Acknowledgment.** We thank the NIH, NSF, and the Astellas USA Foundation for generous support.

**Supporting Information Available:** Experimental details and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060463V

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(7) Corriu, R. J. P.; Lanneau, G. F. Perrot, M. *Tetrahedron Lett.* **1988**, *29*, 1271−1274 and references therein.

(8) Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545−3548.

(9) Rh-catalyzed PMHS reductions have been modestly successful. See: Blum, J.; Pri-bar, I.; Alper, H. *J. Mol. Catal.* **1986**, *37*, 359−367.

(10) Fowley, L. A.; Michos, D.; Luo, X.-L.; Crabtree, R. H. *Tetrahedron Lett.* **1993**, *34*, 3075−3078.

(11) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448.

(12) Braden, R.; Himmler, T. *J. Organomet. Chem.* **1989**, *367*, C12−C14.

(13) Cuomo, J.; Olofson, R. A. *J. Org. Chem.* **1979**, *44*, 1016−1017.

(14) We cannot rule out fluoride converting a RCO-Pd(II)-Cl species to RCO-Pd(II)-F.

(15) TBAF presumably facilitates phase transfer.

(16) Typical procedure: Pd$_2$dba$_3$ (0.01 mmol, 9.2 mg) and trifurylphosphine (TFP) (0.04 mmol, 9.3 mg) were added to THF (5 mL), and the resulting mixture was stirred at rt for 15 min. The acid chloride (1 mmol), PMHS (3.0 mmol, 0.18 mL), aq KF (3.0 mmol, 174.5 mg in 1 mL of $H_2O$), and TBAF (1 drop of a 1 M solution in THF (∼0.008 mmol)) were then added successively. The reaction was then stirred at rt until judged complete by GC (∼1 h). At that time, the reaction was extracted with $Et_2O$ and the aqueous phase back extracted with $Et_2O$. The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification of the resulting residue by silica gel chromatography afforded the aldehyde.

(17) Maleczka, R. E., Jr.; Rahaim, R. J., Jr.; Teixeira, R. R. *Tetrahedron Lett.* **2002**, *43*, 7087−7090.

(18) No benzaldehyde was detected by GC.

(19) Reactions run under anhydrous conditions have met with mixed results. We will disclose the details of these experiments once they are suitably understood.