ORGANIC LETTERS
2008
Vol. 10, No. 21
5095−5097

Aromatic *ortho*-Benzylation Reveals an Unexpected Reductant

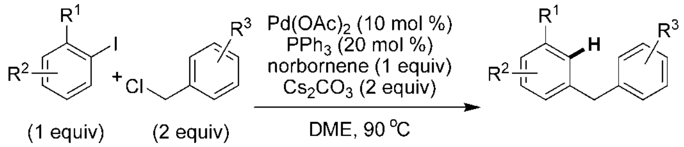
Andrew Martins and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto,
80 St. George Street, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

Received September 18, 2008

ABSTRACT

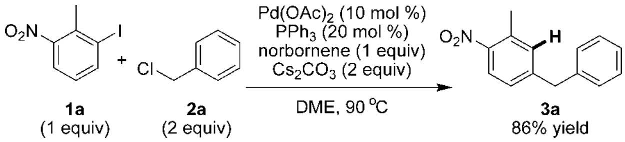


The discovery of a novel arylpalladium(II) reduction enables the synthesis of diarylmethanes via reductive benzylation. Benzyl chlorides were found to be the major source of hydride, acting as an alkylating agent and an aprotic surrogate for benzyl alcohol. This represents the first example of an arylpalladium(II) reduction mediated by a benzyl halide.

The palladium-catalyzed transfer hydrogenolysis of aryl halides generally employs stable, easily handled hydrogen transfer reagents (HCO_2Na, R_3SiH, ROH, etc.) as the hydride source, enabling the formation of hydridoarylpalladium(II) species via transmetalation or β-hydride elimination pathways.[1] When incorporated into domino processes,[2] hydrogenolysis reactions often suffer from the reduction of transient palladium(II) intermediates. Thus, selective domino hydrogenolysis reactions are highly desirable, especially when reagents can play multiple roles in the reaction sequence.[3] Herein, we report a reductive palladium-catalyzed, norbornene-mediated synthesis of diarylmethanes based upon the Catellani[4] method of *ortho*-C−H functionalization. Through our discovery and mechanistic study of this reaction, benzyl halides were found to act as both alkylating agents and reductants in a selective domino sequence.

While exploring Catellani-type reactions with benzyl chlorides as reaction partners, we isolated diarylmethane **3a** (Scheme 1), the product of *ortho*-benzylation and *ipso* reduction of aryl iodide **1a**, in low yield. Our previous observation of an *ortho*-alkylation/reduction sequence occurred in the presence of electrophiles containing β-hydrogens,[5] thus the isolation of **3a** was surprising to us, as benzyl chloride **2a** is not susceptible to traditional β-hydride elimination pathways. We believed that the reduction must be mechanistically distinct from our previous findings, so

Scheme 1. Optimized Reductive Benzylation Sequence



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(1) (a) Tsuji, J. In *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Tsuji, J., Ed.; Wiley-VCH: Weinheim, 2004. (b) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Eds.; Wiley-VCH: Weinheim, 2002.

(2) Tietze, L. F.; Brasche, G.; Gericke, K. In *Domino Reactions in Organic Synthesis*; Tietze, L. F., Ed.; Wiley-VCH: Weinheim, 2007.

(3) Excellent examples of this concept include the recent work of Krische and coworkers. See: (a) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220–5223. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338–6339.

(4) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122; *Angew. Chem.* **1997**, *109*, 142−145. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346. (c) Catellani, M. *Synlett* **2003**, 298–313. (d) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21–53.

(5) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053–4056. The reductants were found to be alkyl halide and isopropylboronic acid.

10.1021/ol802185x CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/08/2008

Scheme 2. Deuterium Labeling Studies

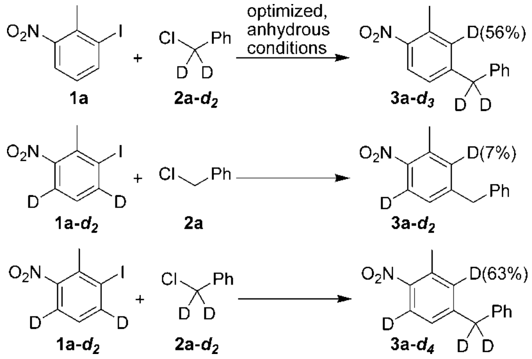
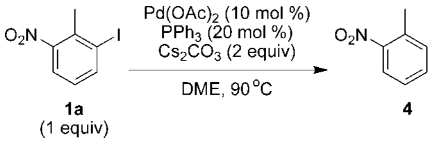


Table 1. Reductive Dehalogenation of **1a**



entry	additives	yield[a]
1	none	6
2	$PhCH_2OH$ (2 equiv)	70[b]
3	$PhCH_2Cl$ (2 equiv)	7
4	$PhCH_2Cl$ (2 equiv) + CsI (10 mol %)	50
5	$PhCH_2Cl$ (2 equiv) + CsI (1 equiv)	61

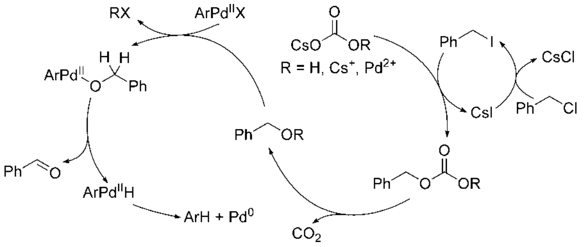
[a] Relative to mesitylene internal standard. [b] Isolated yield.

we were prompted to optimize the reaction and further investigate the reductive mechanism.

Through screening of reaction parameters, we identified the conditions outlined in Scheme 1 to be optimal, affording compound **3a** in 86% yield. The mechanism of *ortho*-benzylation is fairly well understood based upon the work of Catellani with stoichiometric palladium,[6,7] so we decided to perform deuterium labeling studies to help elucidate the mechanism of arylpalladium(II) reduction. We synthesized α,α-dideuterobenzyl chloride (**2a-*d*$_2$**) and 4,6-dideutero **1a** (**1a-*d*$_2$**) and set up the coupling reactions in Scheme 2in an anhydrous, inert atmosphere glovebox. When **2a-*d*$_2$** was used as a coupling partner, 56% deuterium incorporation at the *ipso* position was observed. When the reaction was set up under ambient conditions (i.e., traces of water may have been present), there was no change in deuterium incorporation. The use of **1a-*d*$_2$** led to 7% *ipso* deuterium incorporation; however, when set up under ambient conditions, no deuterium incorporation was observed. When we used both **1a-*d*$_2$** and **2a-*d*$_2$** in conjunction under anhydrous conditions, the algebraic sum of deuterium incorporation was observed as there was 63% deuterium at the *ipso* position.

From these labeling experiments, we conclude that there are several co-operative mechanistic pathways for arylpalladium(II) reduction. As the majority of deuterium incorporation came from the α-position of the benzyl halide, we sought to determine the fate of the benzyl donor. Analysis of the crude reaction by ^{1}H NMR revealed the production of an aldehyde, and we were able to isolate 4-chlorobenzaldehyde in 57% yield from the reaction of **1a** and 4-chlorobenzyl chloride (vide infra). We suspected that the in situ formation of a benzyl alcohol, a known reductant of arylpalladium(II) species,[8] was the culprit. Hydrolysis of the benzyl chloride may form benzyl alcohol; however, experiments conducted under ambient conditions, those under strictly anhydrous conditions, and those with added water all produced identical yields of product. The nucleophilicity of carbonate[9] and bicarbonate[10] anions toward alkyl halides and pseudohalides has been well documented, thus we proposed that the in situ formation of a benzyl carbonate or bicarbonate species could decarboxylate to form a benzyl alkoxide or alcohol species, which could then be used as a reductant for arylpalladium(II) species.

Scheme 3. Proposed Mechanism of Reduction



To further test this hypothesis, we performed a reductive dehalogenation of aryl iodide **1a** under our reaction conditions without norbornene (Table 1). In the absence of additives, only a small amount of dehalogenation product **4** was observed. In the presence of base, benzyl alcohol was an effective reductant, so we next examined a mixture of benzyl chloride (**2a**) and Cs_2CO_3 as a prereductant. This did not improve the yield, suggesting that benzyl chloride is unreactive toward carbonate under the reaction conditions. We noted that CsI, a byproduct of the *ortho*-benzylation reaction, could increase the reactivity of the benzyl halide through nucleophilic displacement. The addition of CsI in catalytic (entry 4) and stoichiometric (entry 5) amounts significantly increased the yield of **4** to levels comparable with benzyl alcohol. From these results, we propose the mechanism of reduction as depicted in Scheme 3, where the catalytic formation of benzyl iodide initiates the reductive mechanism. Moreover, the benzyl halide acts as an aprotic surrogate for benzyl alcohol in the hydrogenolysis reaction

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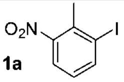
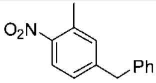
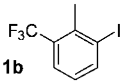
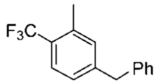
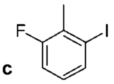
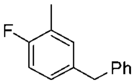
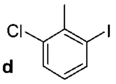
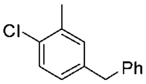
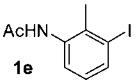
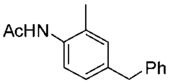
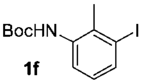
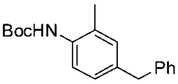
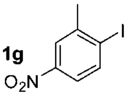
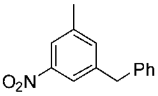
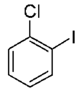
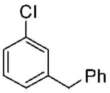
(6) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421–2422. This reaction was stoichiometric in palladium and involved the benzylation of the ortho C−H bonds, followed by hydrogenolysis with H_2 or $NaBH_4$ of the resultant arylpalladium(II) species.

(7) Catellani, M.; Cugini, F.; Tiefenthaler, D. *Can. J. Chem.* **2001**, *79*, 742–751.

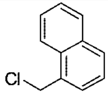
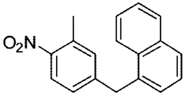
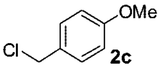
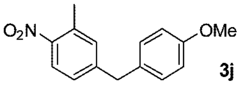
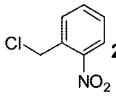
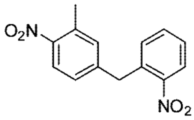
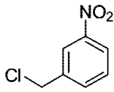
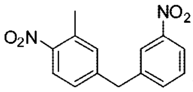
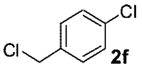
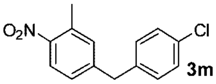
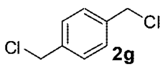
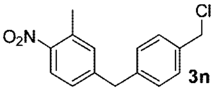
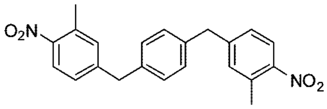
(8) Deledda, S.; Motti, E.; Catellani, M. *Can. J. Chem.* **2005**, *83*, 741–747.

Table 2. Scope of Aryl Iodides[a]

entry	1	2	3	yield[b]
1	 **1a**	**2a**	 **3a**	86
2	 **1b**	**2a**	 **3b**	56
3	 **1c**	**2a**	 **3c**	77
4	 **1d**	**2a**	 **3d**	67
5	 **1e**	**2a**	 **3e**	75
6	 **1f**	**2a**	 **3f**	71
7	 **1g**	**2a**	 **3g**	73
8	 **1h**	**2a**	 **3h**	34

[a] See Scheme 1 for reaction conditions. [b] Isolated yield (%).

Table 3. Scope of Benzyl Chlorides[a]

entry	1	2	3	yield[b]
1	**1a**	 **2b**	 **3i**	60
2	**1a**	 **2c**	 **3j**	80
3	**1a**	 **2d**	 **3k**	53
4	**1a**	 **2e**	 **3l**	75
5	**1a**	 **2f**	 **3m**	69
6	**1a**	 **2g**	 **3n**	36 16[c]
7			 **3o**	34[c]

[a] See Scheme 1 for reaction conditions. [b] Isolated yield (%). [c] 1 equiv of **2g** used.

and, to the best of our knowledge, represents the first example of an arylpalladium(II) reduction mediated by a benzyl halide.

We explored the scope of the domino reaction by screening *ortho*-substituted aryl iodides with a variety of functional groups (Table 2). Overall, electron-deficient aryl iodides containing an *ortho*-methyl group performed best, while electron-rich aryl iodides or those without an *ortho*-methyl group (such as **1h**) afforded little to no desired product. Electron-deficient aryl iodides with Lewis basic *ortho* functional groups solely afforded the unsymmetrical biaryl dimer.[8] Chemoselective aromatic benzylation was observed for aromatic amide **1e** and carbamate **1f**, affording solely desired products **3e** and **3f** in good yields with no products of *N*-benzylation detected.

We also screened several benzyl chlorides as coupling partners (Table 3). Both electron-rich and electron-deficient benzyl chlorides worked quite well. However, when a coordinating functional group was *ortho* to the benzylic carbon (as in **2d**), yields were slightly reduced. Bifunctional benzyl halide **2g** gave a poor yield of product; however, when the amount of **2g** was reduced to 1 equiv, a considerable amount of the (bis)diarylmethane product **3o** was obtained.

In summary, we have identified a novel and interesting mechanism for the hydrogenolysis of arylpalladium(II) species which was further applied to the synthesis of diarylmethanes. Although we have significant insight into part of the mechanistic puzzle, we are currently working toward determining the source of the remaining reducing equivalents, which will be reported in due course.

Acknowledgment. We thank the National Science and Engineering Council of Canada and Merck Frosst Canada & Co. for financial support in the form of an Industrial Research Chair. We also thank Prof. D. B. Collum (Cornell University) for helpful suggestions.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Shi, M.; Shen, Y.-M. *Molecules* **2002**, *7*, 386–393. (b) Verdecchia, M.; Feroci, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* **2002**, *67*, 8287–8289.

(10) Bosworth, N.; Magnus, P.; Moore, R. *J.C.S. Perkin 1* **1973**, 2694–2697.