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Productive Utilization of Chlorobenzene: Palladium-Catalyzed Selective Oxidation of Alcohols

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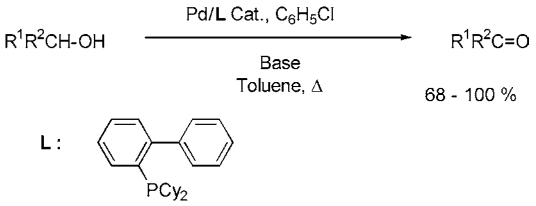
ABSTRACT



The palladium/ligand-catalyzed activation of chlorobenzene provides a general, efficient, and functional group friendly method for the selective oxidation of alcohols to carbonyl compounds.

The oxidation of alcohols to carbonyl compounds is one of the most significant and widely used methods in organic syntheses.[1] Consequently, many oxidation reaction methods have been developed. Oxidation methods based on [O]-containing oxidants, e.g., air, O_2, H_2O_2, metal oxides, NaOCl, and DMSO, are common and widely developed. But, oxidation methods based on non-[O]-containing oxidants are comparatively less common and underdeveloped. The development of economical and efficient oxidation methods based on non-[O]-containing oxidants are of potential academic and industrial significance, particularly for the oxidation of substrates with oxygen sensitive functionalities. Herein, we describe a general palladium/ligand-catalyzed chlorobenzene activation reaction that provides an economical, efficient, and functional group friendly method for the selective oxidation of alcohols to carbonyl compounds.

Chloroarenes are readily available and inexpensive and, therefore, represent attractive feedstock for commercial applications. Historically, chloroarenes have been found to be comparatively inert and hence of limited value.[2] Recently, the productive utilization of chloroarenes has been the subject of intense investigations.[3] These pioneering studies have contributed enormously to the understanding of general principles for the activation and functionalization of chloroarenes. In particular, the cross-coupling reactions of chloroarenes have been significantly advanced.[3]

High-throughput methods at Symyx Technologies were previously employed for the development of efficient cross-coupling reactions of chloroarenes.[4] These reactions required precise combinations of catalysts and reaction conditions. Dramatic inefficiencies resulted from less than optimum reaction conditions. Hydrodechlorination of the chloroarenes was one of the common inefficiencies observed particularly

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(1) (a) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, DC, 1990. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York, 2001; pp 1514−1517. (d) Sheldon, R. A.; Arends, I. W. C. E.; Dijksman, A. *Catal. Today* **2000**, *57*, 157−166.

(2) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(3) Reviews: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Beletskaya, I. P. *Chem. Rev.* **2000**, *100*, 3009−3066. (d) Grushin, V. V.; Alper, H. *Top. Organomet. Chem.* **1999**, *3*, 193−226. (e) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301−309.

(4) (a) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *Organometallics* **1999**, *18*, 1840−1853. (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803. (c) Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237−1240. (d) Bei; X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858.

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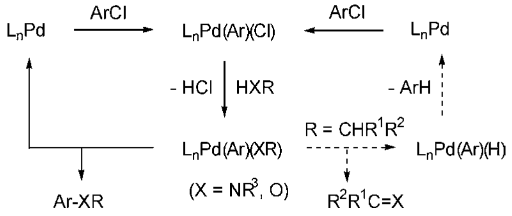
in the C−N and C−O cross-coupling reactions of chloroarenes with primary/secondary amines and alcohols, respectively. Mechanistically, this inefficiency most likely resulted from β-hydrogen elimination from a $L_nPd(Ar)(XR)$ (R = CHR^1R^2; X = NR^3, O) intermediate, followed by reductive elimination of ArH from a $L_nPd(Ar)(H)$ intermediate (Scheme 1). The formation of imine and aldehyde/ketone byproducts in C−N and C−O cross-coupling reactions, respectively, is also supported by this mechanistic hypothesis (Scheme 1).

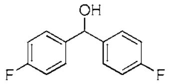
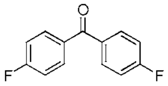
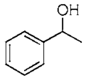
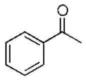
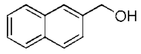
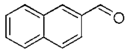
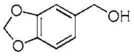
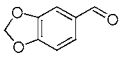
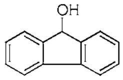
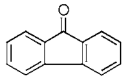
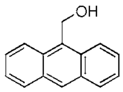
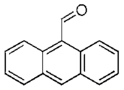
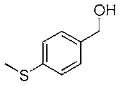
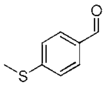
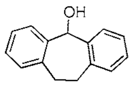
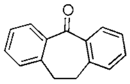
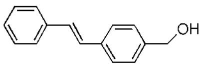
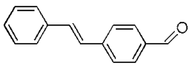
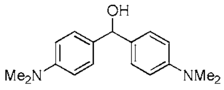
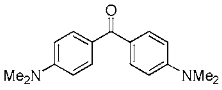
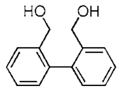
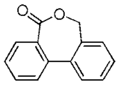
Scheme 1. Reductive and β-Hydrogen Elimination Pathways



High-throughput methods were now employed to exploit the hydrodechlorination inefficiency of C−O cross-coupling reactions for the development of an economical and efficient palladium/ligand-catalyzed method for the selective oxidation of alcohols to aldehydes and ketones.[5,6] Chlorobenzene was chosen as an inexpensive and industrially viable oxidant for this study. The palladium/ligand-catalyzed reactions of chlorobenzene with alcohols were investigated using our computer-controlled automated manipulations of reaction components.[7] It was observed that the reactions were particularly influenced by the nature of the phosphine ligands and bases. The recently described Buchwald ligand, 2-(dicyclohexylphosphino)biphenyl (**1**),[8] and bases such as K_3PO_4, K_2CO_3, and NaO^tBu were found to be the most efficient.

The $Pd(dba)_2$/ligand **1** catalyst efficiently catalyzed the chlorobenzene-based selective oxidation reaction of a wide variety of alcohols (Tables 1 and 2).[9] The bases, K_2CO_3 and K_3PO_4, were found to be most suitable for the oxidation of primary and secondary benzylic alcohols. Primary and secondary benzylic alcohols containing both electron-withdrawing and electron-donating substituents reacted efficiently to afford the desired carbonyl compounds in high isolated yields. Notably, oxygen-sensitive functionalities such as −C=C, −SR, and $-NR_2$ were compatible and not

Table 1. $Pd(dba)_2$/Ligand **1**-Catalyzed Selective Oxidations of Benzylic Alcohols[a]

entry	alcohol	base	product	yield(%)
1		K_2CO_3		98
2		K_2CO_3		68[b]
3		K_2CO_3		96
4		K_3PO_4		92
5		K_2CO_3		92
6		K_2CO_3		99
7		K_3PO_4		82[c]
8		K_2CO_3		95[d]
9		K_3PO_4		94[e]
10		K_3PO_4		95[e]
11		K_2CO_3		98

[a] Unless otherwise indicated, the reactions were performed in toluene at 105 °C. Molar equivalents of the reagents and catalyst were as follows: ROH (1.0 mmol), C_6H_5Cl (1.5 mmol), base (2.0 mmol), $Pd(dba)_2$ (1.0 mol %), and ligand **1** (3.0 mol %). Reaction times were not optimized and ranged from 4 to 48 h. Yields correspond to isolated product of >95% purity by GCMS and ^1H NMR. Additional general experimental details including reaction times are provided in the Supporting Information. [b] Reaction performed at 80 °C. [c] Reaction performed in xylene at 130 °C. [d] Reaction performed at 100 °C. [e] Reaction performed at 110 °C.

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(5) Palladium-catalyzed oxidations based on chlorohydrocarbons: (a) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, 1401−1404. (b) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286−1292. (c) Nagashima, H.; Tsuji, J. *Chem. Lett.* **1981**, 1171−1172. (d) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619−1620. (e) Poetsch, E.; Lannert, H. *Chem. Abstr.* **1996**, *124*, 145502d. (f) Bouquillon, S.; Henin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434−1437.

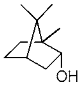
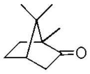
(6) Leading references for palladium-catalyzed oxidations based on O-containing oxidants: (a) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157−158. (b) Petersen, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189. (c) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755. (d) Nagashima, H.; Tsuji J. *Bull. Chem. Soc. Jpn.* **1981**, 1171−1172. (e) Tsuji, J.; Nagashima, H.; Sato, K. *Tetrahedron Lett.* **1982**, *23*, 3085−3088. (f) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620−6625.

(7) Details of high-throughput methods and additional experimental results will be reported separately in a full article.

(8) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

(9) **Typical Experimental Procedure.** A mixture of 4,4′-diflourobenzhydrole (220 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **1** (10 mg, 30 μmol) was loaded into a Schlenk reaction tube. The mixture was thoroughly degassed using vacuum and argon purge cycles. Chlorobenzene (0.15 mL, 1.33 mmol) and toluene (4 mL) were added, and the mixture was heated at 105 °C for 12 h. The reaction mixture was taken up in ether (100 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to afford 4,4′-diflourobenzophenone as an off-white solid (215 mg, 98%) after drying under vacuum.

Table 2. Pd(dba)$_2$/Ligand **1**-Catalyzed Oxidations of Sterically Hindered Aliphatic Alcohols[a]

entry	alcohol	base	product	yield(%)
1		NaO^{t}Bu		100
2		NaO^{t}Bu		100

[a] The reactions were performed in toluene at 105 °C using molar equivalents of reagents and catalyst as follows: ROH (1.0 mmol), C_6H_5Cl (1.5 mmol), base (2.0 mmol), Pd(dba)$_2$ (0.2 mol %), and ligand **1** (0.6 mol %). Yields correspond to GC yields at a reaction time of 2 h.

affected under these oxygen-free oxidation reaction conditions (entries 7, 9, and 10; Table 1). The oxidation of 2,2′-hydroxymethylbiphenyl resulted in the formation of the lactone product in high isolated yield (entry 11; Table 1). The formation of the lactone product most likely proceeded in sequential steps, which presumably included palladium/ligand-catalyzed oxidation of one of the alcohol functionality to an aldehyde functionality, intramolecular reaction of the newly formed aldehyde functionality with the remaining alcohol functionality to form a hemiacetal intermediate, and palladium/ligand-catalyzed oxidation of the hemiacetal intermediate to the lactone product.

The Pd(dba)$_2$/ligand **1** catalyst was also found to be efficient in catalyzing the oxidation of sterically hindered aliphatic alcohols. The base, NaO^{t}Bu, was found to be most suitable for these reactions. Thus, the sterically hindered bicyclic alcohols reacted efficiently to afford the desired industrially significant ketones[10] in high yields (Table 2).[11] High catalyst turnover frequencies were observed in these reactions. It is remarkable that these sterically crowded substrates favor the β-hydrogen elimination process over the C−O reductive elimination process.[12]

In summary, we have developed a general palladium/ligand-catalyzed chlorobenzene activation reaction that provides an economical, efficient, and functional group friendly method for the selective oxidation of primary and secondary alcohols. The chlorobenzene-based oxidation is economically comparable to the popular DMSO, NaOCl, H_2O_2, and CrO_3 oxidant based oxidations, but precludes functional group tolerance, selectivity, and hazard issues related to the DMSO, H_2O_2, O_2, NaOCl, and CrO_3 based oxidations.[1] The utility of this reaction in the oxidation of other commercially significant alcohols, general oxidation of aliphatic alcohols, kinetic resolution of racemic alcohols, and the desymmetrization of *meso*-diols is currently being investigated.

Acknowledgment. We thank Dr. Alfred Hagemeyer, Dr. Tetsuo Uno and Dr. Damodara Poojary for insightful discussions and suggestions.

Supporting Information Available: Details of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) These intermediates are of significance as perfume additives in the fragrance industry; see: (a) Naarden & Shell Aroma Chemicals. German Patent Application DE 2,945,812, 1980. (b) Kao Corp. Japanese Patent Application JP 92-77446, 1992.

(11) The Pd/L-catalyzed oxidation of sterically less hindered aliphatic alcohols was not rigorously investigated or optimized. Aldol reaction induced inefficiencies were observed in preliminary studies. However, it is anticipated that such inefficiencies could be alleviated under optimized reaction conditions.

(12) Steric factors are known to favor the reductive elimination process; see: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (b) Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615−2622. For pioneering studies of C−O bond forming reductive elimination from nickel complexes, see: (c) Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135−8136.