JOC Article

Productive Chloroarene C−Cl Bond Activation: Palladium/Phosphine-Catalyzed Methods for Oxidation of Alcohols and Hydrodechlorination of Chloroarenes

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The palladium/phosphine-catalyzed productive chloroarene C−Cl bond activation provides general, efficient, and functional group friendly methods for the selective oxidation of alcohols and the hydrodechlorination of chloroarenes.

Introduction

Chloroarenes are generally readily available and inexpensive and, therefore, the productive activation of C−Cl bonds in chloroarenes is of significant industrial interest. Traditionally, however, the C−Cl bond in chloroarenes has been found to be comparatively inert.[1] Recently, the productive activation of these C−Cl bonds has been the subject of intense investigations.[2] These pioneering studies have contributed enormously to the understanding of general principles for the activation and functionalization of chloroarenes. In particular, their cross-coupling reactions have been significantly advanced.[3,4] Herein, we describe the development of two related productive chloroarene C−Cl bond activation reactions which provide general, efficient, and functional group friendly methods for the selective oxidation of alcohols to carbonyl compounds and the reduction (hydrodechlorination) of chloroarenes.[4e] The oxygen-free oxidations and hydrogen/hydride-free reductions are comparable to the traditional oxygen and hydrogen/hydride based reactions, but preclude functional group tolerance, selectivity, and hazard issues associated with the traditional reactions. The reactions are of potential academic and industrial interest, particularly for the oxidation and reduction of substrates with oxygen- and hydrogen/hydride-sensitive functionalities.

High throughput methods at Symyx Technologies, Inc. have been previously employed for the development of efficient cross-coupling reactions of chloroarenes.[4,5] These reactions required precise combinations of catalyst and reaction conditions. Less than optimum conditions led to undesired side reactions. The hydrodechlorination of chloroarenes was a common side reaction observed in the C−N and C−O cross-coupling reactions of aliphatic amines and alcohols, respectively. Mechanistically, such side reactions most likely result from β-hydride elimination from a $L_nPd(Ar)(XR)$ ($R = CHR^1R^2$, $X = O$, NR^3) intermediate, followed by reductive elimination of Ar−H 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, respec-

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

(2) 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.* **1998**, *110*, 2154−2177; *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.

(3) For leading references to cross-coupling reactions of chloroarenes, see ref 4 and: (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9550−9561. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 4369−4378. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem*. **1999**, *111*, 2570−2573; *Angew. Chem., Int. Ed*. **1999**, *38*, 2413−2416. (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Angew. Chem*. **2000**, *112*, 4315−4317; *Angew. Chem., Int. Ed*. **2000**, *39*, 4153−4155. (e) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc*. **1999**, *121*, 3224−3225. (f) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc*. **1999**, *121*, 2123−2132. (g) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett*. **1998**, *39*, 617−620. (h) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett*. **1998**, *39*, 2367−2370. (i) Littke, A. F.; Fu, G. C. *Angew. Chem.* **1998**, *110*, 3586−3587; *Angew. Chem., Int. Ed*. **1998**, 37, 3387−3388. (j) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (k) Littke, A. F.; Fu, G. C. *Angew. Chem.* **1999**, *111*, 2568−2570; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411−2413. (*l*) Zhang, C.; Trudell, M. L. *Tetrahedron Lett*. **2000**, *41*, 595−598. (m) Bohn, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem*. **2000**, *595*, 186−190. (n) Zapf, A.; Beller, M. *Chem. Eur. J*. **2000**, *6*, 1830−1833. (o) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810. Selected related references of particular significance: (p) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742−8744. (q) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655−1664. (r) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem*. **1999**, *64*, 3804−3805. (s) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett*. **1999,** *1*, 1307−1309.

(4) Cross-coupling reactions of chloroarenes developed at Symyx Technologies: (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. The preliminary studies of Pd/ligand-catalyzed oxidation of alcohol with PhCl oxidant were recently communicated: (e) Guram, A. S.; Bei, X.; Turner, H. W. *Org. Lett.* **2003**, 5, 2485.

(5) Recent combinatorial catalysis reviews: (a) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem.* **1999**, *111*, 2648−2699; *Angew. Chem., Int. Ed.* **1999**, *38*, 2494−2532. (b) Dahmen, S.; Brase, S. *Synthesis* **2001**, 1431−1449.

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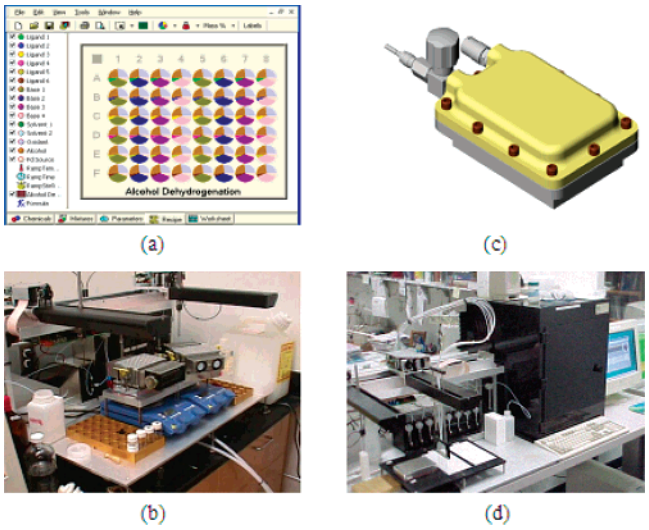
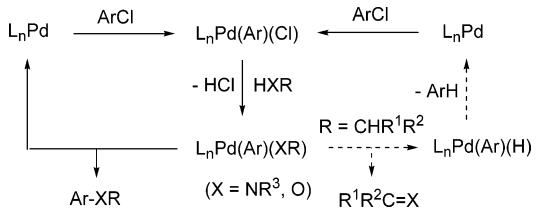


FIGURE 1. High throughput experimentation tools: (a) Library Studio design, (b) dispensing of reagents into reactor wells, (c) typical parallel reactor, and (d) parallel TLC station.

SCHEME 1. Mechanistic Pathways in Pd/L-Catalyzed C−X (X = N, O) Bond-Forming Reactions



tively, is also supported by this mechanistic hypothesis. High throughput methods were employed to exploit the hydrodechlorination inefficiency of C−O cross-coupling reactions to produce productive chloroarene C−Cl bond activation reactions.

Results

Selective Oxidation of Alcohols to Carbonyl Compounds. High throughput methods (Figure 1) were employed for the development of the palladium/phosphine-catalyzed oxidations of alcohols to carbonyl compounds. High throughput experiments were performed with computer-controlled automated manipulations. Symyx Library Studio software was used for the design of libraries. Symyx Impressionist software was used for the robotic mapping (aspirating and dispensing of reaction components) of libraries into suitable glass-lined multiwell reactors (8-, 12-, 48-, 96-well format). The experiments were performed at the desired temperatures, using a suitable heating mechanism and either magnetic or orbital mixing. The experiments were analyzed with automated parallel TLC and rapid serial GC methods.

Chlorobenzene was chosen as a suitable oxidant because of its low cost and industrial viability.[6,7] The oxidation reactions were found to be mostly influenced by the nature of the phosphine ligand, base, and the alcohol reactant. In one study, a library of 96 different phosphine ligands was screened for the oxidation of 1,5-dimethylbicyclo[3.2.1]octane-8-ol (**1a**) with chlorobenzene, using $Pd(dba)_2$ as the palladium catalyst source and NaO^tBu as the base (eq 1). The basic, sterically demanding ligands **A**−**D** were found to be most effective (Figure 2), affording the desired ketone product quantitatively in a short reaction time (1 h). The Buchwald ligands, **A** and **B**,[3a] in particular, were found to be more robust. The commonly available phosphine ligands including a variety of triaryls (e.g., PPh_3 and derivatives thereof) and trialkyls (e.g., PCy_3 and derivatives thereof) were found to be inefficient.

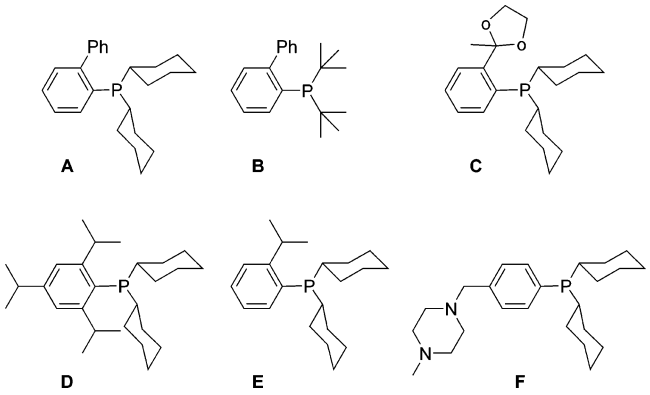
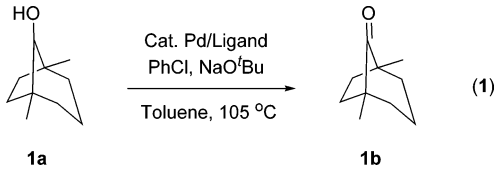
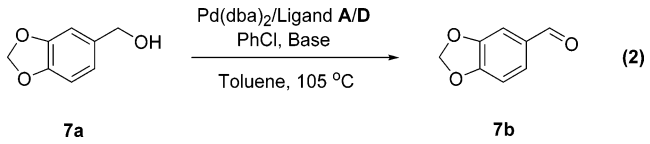


FIGURE 2. Structures of selected phosphines.



In another study, six different commonly employed bases in coupling reactions were screened for the oxidation of piperanol (**7a**) with chlorobenzene with $Pd(dba)_2$ as the palladium catalyst source and phosphines **A** and **D** as ligands (eq 2). NaO^tBu, K_3PO_4, K_2CO_3, and Cs_2CO_3 were found to be generally effective, while Na_2CO_3 and $NEt(^iPr)_2$ were not as effective.

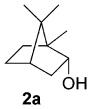
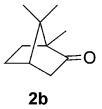
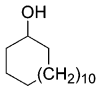
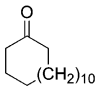
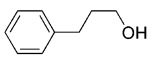
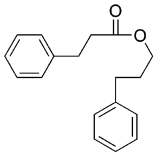


The utility of the $Pd(dba)_2$/ligand **A** catalyst in general oxidation of alcohols to carbonyl compounds was further investigated. The $Pd(dba)_2$/ligand **A** catalyst was efficient

(6) The related palladium/phosphine-catalyzed oxidations of alcohols with aryl bromides as oxidants have been described previously, see: (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. The simple extension of this methodology to chlorobenzene was not achievable with the common phosphine ligands such as triphenylphosphine, tricyclohexylphosphine, and related derivatives thereof.

(7) For related palladium-catalyzed oxidations of alcohols with aliphatic chlorohydrocarbons, see: (a) Nagashima, H.; Tsuji, J. *Chem. Lett.* **1981**, 1171−1172. (b) Tusji, J.; Nagashima, H.; Sato, K. *Tetrahedron Lett.* **1982**, *23*, 3085−3088. (c) Poetsch, E.; Lannert, H. *Chem. Abstr.* **1996**, *124*, 145502d. (d) Bouquillon, S.; Henin, F.; Muzart, J. *Organometallics* **2002**, *19*, 1434−1437. TEMPO-catalyzed: (e) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041−3043.

TABLE 1. Pd/Ligand A-Catalyzed Oxidation of Sterically Hindered Aliphatic Alcohols[a]

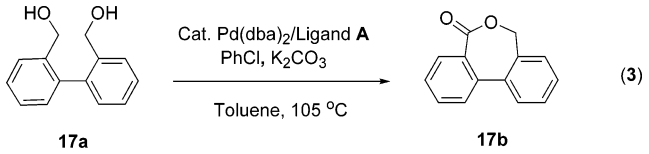
Alcohol	Base	Temp. (°C)	Product	Yield (%)
 **1a**	NaO^tBu	105	 **1b**	100 [b,c]
 **2a**	NaO^tBu	105	 **2b**	100 [b,c]
 **3a**	K_2CO_3	105	 **3b**	94[c,d]
 **4a**	K_2CO_3	105	 **4b**	98[c,d]
 **5a**	NaO^tBu	105	 **5b**	93
 **6a**	K_3PO_4	95	 **6b**	91[e]

[a] Unless indicated otherwise, all reactions were performed in toluene with molar equivalents of reagents and catalyst as follows: ROH (1.0 mmol), C_6H_5Cl (1.1−1.5 mmol), base (2.0 mmol), $Pd(dba)_2$ (1.0 mol %), and ligand **A** (2.0 mol %). Reaction times are indicated in the Experimental Section, but are not exhaustively optimized. Yields correspond to isolated products of >95% purity as determined by NMR. [b] $Pd(dba)_2$ (0.2 mol %) and ligand **A** (0.6 mol %). [c] Yields correspond to GC yields. [d] 2-Chlorotoluene was used as the oxidant. [e] 2-Chloro-*m*-xylene was used as the oxidant.

in catalyzing the chlorobenzene-based oxidation of cyclic aliphatic alcohols. NaO^tBu was found to be a suitable base for sterically hindered bicyclic alcohols, while K_2CO_3 was found to be a suitable base for less hindered monocyclic alcohols. Thus, the sterically hindered bicyclic alcohols reacted efficiently to afford the desired industrially significant ketones[8] in high yields (Table 1).[9] High catalyst turnover frequency and number were observed in these oxidations. However, the $Pd(dba)_2$/ligand **A** catalyst was less efficient in catalyzing the oxidation of aliphatic acyclic alcohols. The $Pd(dba)_2$/ligand **A**-catalyzed reactions of certain aliphatic alcohols in the presence of 2-chloro-*m*-xylene oxidant and K_3PO_4 formed ester products (Table 1).

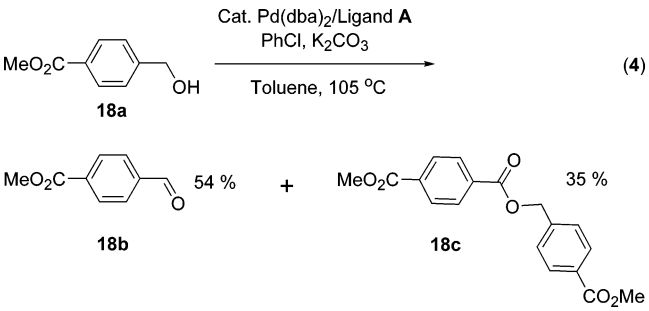
The $Pd(dba)_2$/ligand **A** catalyst also efficiently catalyzed the chlorobenzene-based selective oxidation of a wide variety of primary and secondary benzylic alcohols. K_2CO_3 and K_3PO_4 were suitable bases for these reactions. Primary and secondary benzylic alcohols containing both electron-withdrawing and electron-donating substituents reacted efficiently to afford the desired carbonyl compounds in high isolated yields (Table 2). Remarkably, functionalities such as C=C, −SR, and $-NR_2$ were found to be compatible and unaffected under these oxidation reaction conditions.

The oxidation of 2,2′-hydroxymethylbiphenyl (**17a**) resulted in the formation of the lactone product **17b** with an isolated yield of 98% (eq 3).



(3)

Similarly, the oxidation of the ester group containing benzyl alcohol **18a** afforded the mixture of the expected aldehyde product **18b** along with ester **18c** in a 1.5:1 ratio and a 89% combined isolated yield (eq 4).



(4)

The formation of ester products **6b**, **17b**, and **18c** most likely results from sequential steps, which presumably include (i) palladium/phosphine-catalyzed oxidation of the alcohol functionality to an aldehyde functionality, (ii) reaction of the newly formed aldehyde functionality with an unreacted alcohol functionality to form a hemiacetal intermediate, and (iii) palladium/phoshine-catalyzed dehydrogenation of the hemiacetal intermediate to the ester product.[10]

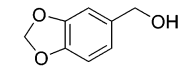
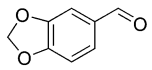
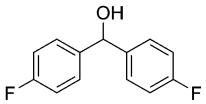
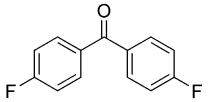
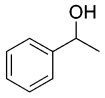
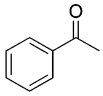
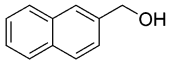
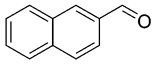
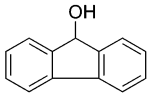
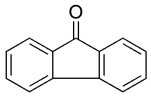
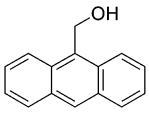
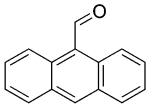
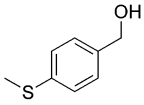
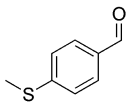
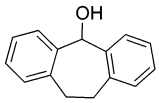
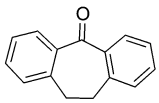
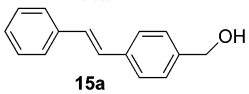
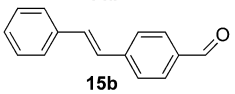
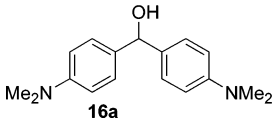
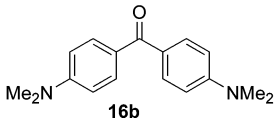
Hydrodechlorination of Chloroarenes. Similarly, high throughput methods were also employed for the development of the related palladium/phosphine-catalyzed hydrodechlorination of chloroarenes. 2-Propanol (IPA) was chosen as a suitable H-atom donor solvent and K_2CO_3 was chosen as the base because of their low cost

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

(9) The palladium/phosphine-catalyzed oxidations of sterically less hindered aliphatic alcohols were not rigorously investigated or optimized. Inefficiencies resulting in undesired products were observed in preliminary studies involving oxidations of unhindered primary alcohols under the reaction conditions described for hindered secondary alcohols. Although steric factors are known to favor the reductive elimination process, see ref 2 and. (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

(10) The proposed mechanism of ester formation is similar to the mechanism proposed by Buchwald for the formation of amide side products in the Ni-catalyzed amination of 4-chlorobenzaldehyde with pyrolidine, see: Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058.

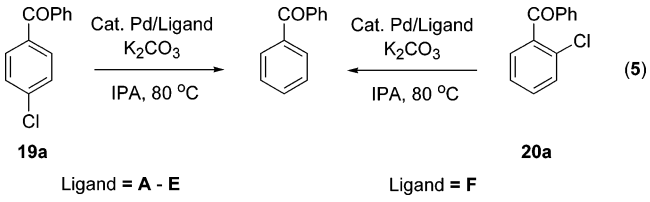
TABLE 2. Pd(dba)$_2$/Ligand A-Catalyzed Selective Oxidation of Benzylic Alcohols[a]

Alcohol	Base	Temp. (°C)	Product	Yield (%)
 **7a**	K_3PO_4	105	 **7b**	92
 **8a**	K_2CO_3	105	 **8b**	98
 **9a**	K_2CO_3	80	 **9b**	68
 **10a**	K_2CO_3	105	 **10b**	96
 **11a**	K_2CO_3	105	 **11b**	92
 **12a**	K_2CO_3	105	 **12b**	99
 **13a**	K_3PO_4	130	 **13b**	82[b]
 **14a**	K_2CO_3	100	 **14b**	95
 **15a**	K_3PO_4	110	 **15b**	94
 **16a**	K_3PO_4	110	 **16b**	95

[a] Unless indicated otherwise, 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 (1.1−1.5 mmol), base (2.0 mmol), $Pd(dba)_2$ (1.0 mol %), and ligand **A** (3.0 mol %). Reaction times were not exhaustively optimized and ranged from 4 to 48 h (for details, see the Experimental Section). Yields correspond to isolated product of >95% purity by GCMS and ^{1}H NMR. [b] Reaction performed in xylene.

and industrial viability.[11] The hydrodechlorination reactions were found to be most influenced by the nature of the phosphine ligand and the chloroarene reactant.

A focused library of 12 different phosphine ligands (ligand choice was narrowed based on its potential demonstrated in oxidation studies) was screened for the hydrodechlorination of the regioisomeric chlorobenzophenones **19a** and **20a** with IPA as solvent, $Pd(dba)_2$ as the palladium catalyst source, and K_2CO_3 as the base. For the hydrodechlorination of 4-chlorobenzophenone **19a**, the electron-rich and sterically crowded phosphine ligands **A**−**E** were found to be generally effective (eq 5). The

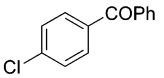
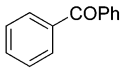
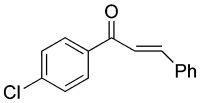
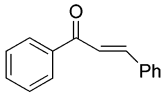
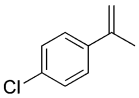
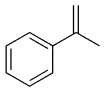
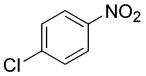
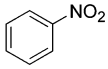
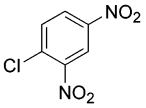
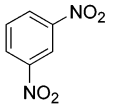
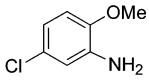
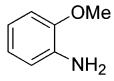
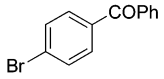
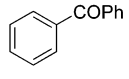
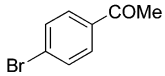
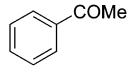


(5)

ligand **D**, in particular, was most efficient, affording complete hydrodechlorination of **19a** in 3 h. In contrast,

(11) (a) Dovganyuk, V. F.; Antokol'skaya, I. I.; Sharf, V. Z.; Bol'shakov, L. I. *Izv. Akad. Nauk SSR, Ser. Khim.* **1988**, *2*, 492−493. (b) Ukisu, Y.; Miyadera, T. *J. Mol. Catal. A: Chem.* **1997**, *125*, 135−142. (c) Ukisu, Y.; Miyadera, T. *Nippon Kagaku Kaishi* **1998**, *5*, 369−371.

TABLE 3. Pd/Ligand D-Catalyzed Hydrodechlorination of Chloroarenes[a]

Aryl halide	Product	Reaction Time (h)
 **21 a**	 **21b**	5[b]
 **22a**	 **22b**	7[c]
 **23a**	 **23b**	22[d]
 **24a**	 **24b**	1
 **25a**	 **25b**	1
 **26a**	 **26b**	25
 **27a**	 **27b**	2[c]
 **28a**	 **28b**	4[d]

[a] All reactions were performed in IPA at 80 °C until all starting chloroarene was consumed. Unless indicated otherwise, the molar equivalents of the reagents and catalyst were as follows: ArCl (1.0 mmol), $Pd(dba)_2$ (1.0 mol %), ligand **D** (3.0 mol %), and K_2CO_3 (2.0 mmol). [b] TON = 551. [c] TON = 2000, K_2CO_3/ArBr = 1.1. [d] TON = 1019.

for the hydrodechlorination of 2-chlorobenzophenone **20a**, the sterically less crowded ligand **F** was found to be most effective.[12] As with oxidation reactions, the commonly available phosphine ligands including a variety of triaryls (e.g., PPh_3 and derivatives thereof) and trialkyls (e.g., PCy_3 and derivatives thereof) were found to be inefficient.

The utility of the $Pd(dba)_2$/ligand **D** catalyst for general hydrodechlorination of chloroarenes was further investigated. The $Pd(dba)_2$/ligand **D** catalyst efficiently catalyzed the selective hydrodechlorination of a variety of chloroarenes in the presence of K_2CO_3 base and IPA solvent (Table 3). Notably, hydrogen/hydride-sensitive functionalities such as −C═C, −C═O, and $-NO_2$ were compatible, and not affected under these reduction conditions. However, the hydrodechlorination reactions of ester and aldehyde group containing chloroarenes exhibited side products resulting from the reaction of the functionalities. The catalyst was also found to be suitable for the hydrodebromination of bromoarenes with high turnover numbers and turnover frequencies.

(12) $PhPCy_2$ was also found to be a reasonably suitable ligand for the palladium/phosphine-catalyzed hydrodechlorination of 2-chlorobenzophenone affording the desired benzophenone product in 91% yield under similar reaction conditions.

Discussion

Productive palladium/phosphine-catalyzed chloroarene C−Cl bond activation reactions for the selective oxidation of alcohols to carbonyl compounds and the reduction (hydrodechlorination) of chloroarenes are achieved from precise combinations of catalyst and reaction conditions. The reactions are influenced by the nature of phosphine ligands, bases, and the chloroarene and alcohol reactants.

For the PhCl oxidant based selective oxidation of alcohols to carbonyl compounds, the electron-rich, sterically crowded phosphine ligands **A**−**D** in the presence of suitable bases (e.g., NaO^tBu, K_2CO_3, K_3PO_4, and Cs_2CO_3) provide efficient Pd/ligand catalysts. The $Pd(dba)_2$/ligand **A** catalyst, in particular, efficiently catalyzes the oxidation of a variety of benzylic and sterically crowded secondary aliphatic alcohols with various electronic and steric substitution patterns. The reactions exhibit good functional group tolerance. Notably, functional groups such as −C═C, −SR, and $-NR_2$ are compatible and unaffected under these oxygen-free oxidation conditions. Ester and lactone products are observed in reactions of aliphatic acyclic primary alcohols. Overall, the palladium/phosphine-catalyzed oxidation provides a general and efficient method for the oxidation of alcohols to carbonyl compounds. The method is similar to the previously described alcohol oxidation methods based on aryl bromides[6] and aliphatic chlorohydrocarbons,[7] but exhibits broader scope and viability. The method compares favorably to the traditional alcohol oxidation methods based on [O]-containing oxidants (e.g., air, O_2, H_2O_2, DMSO, transition metal oxides, and NaOCl),[13,14] but precludes functional group tolerance, selectivity, and hazard issues of the traditional methods.

For the IPA-based hydrodechlorination of chloroarenes, the electron-rich sterically crowded phosphine ligands **A**−**D** in the presence of K_2CO_3 base provide efficient Pd/ligand catalysts. The $Pd(dba)_2$/ligand **D** catalyst, in particular, efficiently catalyzes the hydrodechlorination of chloroarenes with various functional groups. Notably,

(13) Leading references to traditional alcohol oxidations: (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.

(14) Leading references to palladium-catalyzed oxidations based on [O]-containing oxidants: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726. (c) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157. (d) Petersen, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (e) Noronha, G.; Henry, P. M. *J. Mol. Catal. A* **1997**, *120*, 75. (f) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755. (g) Nagashima, H.; Tsuji J. *Bull. Chem. Soc. Jpn.* **1981**, 1171−1172. (h) Tsuji, J.; Nagashima, H.; Sato, K. *Tetrahedron Lett.* **1982**, *23*, 3085−3088. (i) Bouquillon, S.; Henin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434−1437. (j) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476. (k) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766−767.

functional groups such as NO_2, C=C, and C=O (ketone) are compatible and unaffected under these hydrogen-free reduction conditions. However, side reactions are observed with functional groups such as esters and aldehydes. The hydrodebromination of bromoarenes can also be efficiently accomplished with high TON. While Pd/ligand **D** catalyst is not efficient for the hydrodechlorination of certain sterically crowded chloroarenes, the electron-rich, but sterically uncrowded phosphine ligand **F**, in the presence of K_2CO_3 base, appears to provide efficient Pd/ligand catalyst for such chloroarene reactants. Overall, the palladium/phosphine-catalyzed hydrodechlorination with IPA reductant provides a general and efficient method for the hydrodechlorination of chloroarenes.[15−19] The method is similar to the previously reported IPA based hydrodechlorination methods;[15f−k] however, it utilizes a milder K_2CO_3 base instead of the high concentrations of strong bases such KOH and NaOH typically utilized in the previous methods. The method also exhibits high catalyst turnover frequency, which is superior to that reported previously for the heterogeneous Rh/C, Pd/C, and polymer supported $RhCl_3$ and Na_2PdCl_4 catalyst systems, and comparable to the homogeneous Ru/ligand system reported recently.[15f] The method offers milder reaction conditions compared to the previous IPA/metal hydroxide, H_2,[16] HCOOH,[17] HCOONa,[17] and hydrazine hydrochloride[18] reductant based hydrodechlorination systems, and therefore it offers a complementary method, particularly for the hydrodechlorination of chloroarenes with sensitive functionalities.[19]

The palladium/phosphine-catalyzed chloroarene activation reactions for the oxidation of alcohols and hydrodechlorination of chloroarenes most likely proceed by the mechanism described in Scheme 1. The reactions are mostly influenced by the nature of the phosphine ligand, base, and the chloroarene and alcohol reactants. Particularly, the interaction of electronic and steric properties of the phosphine ligand and the chloroarene and alcohol reactants play a critical role. The oxidative addition of the ArCl to the Pd center is favored by electron-rich phosphine ligands, and the β-hydrogen elimination from Pd−O−CHR^1R^2 and subsequent reductive elimination of ArH are influenced by combined steric properties of the phosphine ligand, and the chloroarene and alcohol reactants. Generally, sterically bulky electron-rich phosphine ligands are required, but the optimum extent of the phosphine ligand steric bulk depends on the sterics of the chloroarene and alcohol reactants. When alcohol reactants such as benzyl alcohols or sterically crowded secondary aliphatic alcohols are involved, the ortho-substituted phosphine ligands (e.g., ligands **A**, **B**, and **C**) are suitable for the effective oxidation of such reactants with the PhCl oxidant. For smaller alcohol reactants such as IPA, more bulky ortho-disubstituted phosphine ligands (e.g., ligand **D**) are more suitable for the effective hydrodechlorination of typical chloroarenes. However, for the IPA-based hydrodechlorinations, an increase in sterics of the chloroarene requires a decrease in sterics of the phosphine ligand. Thus, sterically uncrowded electron-rich phosphine ligand **F** (no ortho substituents) is suitable for the hydrodechlorination of crowded chloroarenes.

Conclusion

The palladium/phosphine-catalyzed chloroarene C−Cl bond activation reactions provide general, efficient, and functional group friendly methods for the oxidation of alcohols to carbonyl compounds and for the hydrodechlorination of chloroarenes. The reactions are most influenced by the nature of the phosphine ligand, base, and the chloroarene and alcohol reactants. Optimum conditions for productive reactions are produced by the subtle interplay of steric and electronic properties of the phosphine ligand and the chloroarene and alcohol reactants. The Pd/ligand **A** catalyst is suitable for the PhCl-based oxidation of a variety of benzylic primary and secondary alcohols, and crowded secondary aliphatic alcohols. While, the Pd/ligand **D** catalyst is most suitable for the IPA based hydrodechlorination of typical chloroarenes, the Pd/ligand **F** catalyst is suitable for the IPA-based hydrodechlorination of crowded chloroarenes.

The oxygen- and hydrogen/hydride-free palladium/phosphine-catalyzed C−Cl bond activation reactions for alcohol oxidations and chloroarene hydrodechlorinations, respectively, are comparable to the traditional oxygen and hydrogen/hydride based methods, but preclude functional group tolerance, selectivity, and hazard issues related to the traditional methods. The reactions offer complementary, tunable, and attractive methodologies for the productive utilization of the industrially significant chloroarenes.

Experimental Section

General Comments. High throughput screening experiments were performed by using computer controlled robotic manipulations with Symyx proprietary software and hardware tools. Subsequent scale-up reactions were performed under argon atmosphere with standard oven-dried glassware and Schlenk techniques. Bis(dibenzylideneacetone)palladium, alcohols, chloroarenes, and bases were purchased from commercial sources and used as such. Anhydrous, sure-seal grade solvents were used as purchased for all the reactions. The phosphine ligands were synthesized as described previously.[3,4] All reactions were performed until complete consumption of the starting alcohols or chloroarenes, but the reaction times

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and conditions were not optimized. Stock solutions of the metal precursor and ligand were used for high TON experiments in which desired aliquots of stock solutions were added after the addition of the alcohol and chloroarene. Column chromatography was performed with commercially available Silica Gel 60 (particle size: 0.063−0.100 mm), hexanes, and ethyl acetate. The oxidation and hydrodechlorination products are known compounds and are commercially available from Aldrich (**5b**, **7b**−**16b**, **19b**−**28b**) and TCI, Japan (**3b**, **4b**). Isolated yields correspond to products of >95% purity as determined by GC and NMR. GC yields correspond to calibrated GC yields with a suitable standard.

General Procedure for PhCl-Based Oxidation Experiments. A mixture of an alcohol, a base, $Pd(dba)_2$, and ligand **A** was loaded into a Schlenk reaction tube. The mixture was thoroughly degassed with vacuum and argon purge cycles. Chlorobenzene and toluene were added and the mixture was heated at reaction temperature until the reaction was completed (all starting alcohol was consumed as determined by GC-MS). The reaction mixture was taken up in ether and washed with H_2O and brine. 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 the desired product.

1,5-Dimethylbicyclo[3.2.1]octane-8-on (1b): This compound was formed (quantitative calibrated GC yield, 86% isolated yield) from the reaction of 1,5-dimethylbicyclo[3.2.1]-octane-8-ol (154 mg, 1.0 mmol), chlorobenzene (0.14 mL, 1.4 mmol), NaO^{t}Bu (192 mg, 2.0 mmol), $Pd(dba)_2$ (0.29 mg, 2.0 μmol), and ligand **A** (2 mg, 6.0 μmol) in toluene at 105 °C for 2 h.

(1*S*)-(−)-Camphor (2b): This compound was formed (quantitative GC yield) from the reaction of [(1*S*)-*endo*]-(−)-borneol (171 mg, 1.1 mmol), chlorobenzene (0.14 mL, 1.4 mmol), NaO^{t}Bu (192 mg, 2.0 mmol), $Pd(dba)_2$ (0.29 mg, 2.0 μmol), and ligand **A** (2 mg, 6.0 μmol) in toluene at 105 °C for 2 h.

Cyclododecanone (3b): This compound was formed (94% GC yield) from the reaction of cyclododecanol (185 mg, 1.0 mmol), 2-chlorotoluene (0.17 mL, 1.4 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 24 h. Chlorobenzene or 2-chloro-*m*-xylene were also found to be effective oxidants.

Cyclopentadecanone (4b): This compound was formed (98% GC yield) from the reaction of cyclopentadecanol (226 mg, 1.0 mmol), 2-chlorotoluene (0.17 mL, 1.4 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 24 h. Chlorobenzene or 2-chloro-*m*-xylene were also found to be effective oxidants.

Tropinone (5b): This compound was obtained as a white solid (129 mg, 93%) from the reaction of tropine hydrate (156 mg, 1.0 mmol), chlorobenzene (0.14 mL, 1.4 mmol), NaO^{t}Bu (192 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 6 h.

Ester 6b: This compound was obtained as a yellow oil (124 mg, 91%) from the reaction of 1-phenyl-3-propanol (137 mg, 1.0 mmol), 2-chloro-*m*-xylene (0.18 mL, 1.4 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 95 °C for 12 h. ^{13}C NMR ($CDCl_3$) δ 172.8 (C(=O)−O), 141.1, 140.4, 128.4, 128.3, 128.3, 128.2, 126.2, 125.9, 63.7, 35.8, 32.1, 30.9, 30.1.

Piperonal (7b): This compound was obtained as a pale yellow solid (138 mg, 92%) from the reaction of piperonyl alcohol (152 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 14 h.

4,4′-Diflourobenzophenone (8b): This compound was obtained as an off-white solid (215 mg, 98%) from the reaction of 4,4′-diflourobenzhydrol (220 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 12 h.

Acetophenone (9b): This compound was obtained as an oil (82 mg, 68%) from the reaction of *sec*-phenethyl alcohol (0.12 mL, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 80 °C for 24 h.

2-Naphthaldehyde (10b): This compound was obtained as a yellowish solid (149 mg, 96%) from the reaction of 2-naphthalenemethanol (158 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 6 h.

9-Fluorenone (11b): This compound was obtained as a yellow solid (179 mg, 100%) from the reaction of 9-hydroxyfluorene (182 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (284 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (11 mg, 33 μmol) in toluene at 105 °C for 12 h.

9-Anthraldehyde (12b): This compound was formed (99% yield) from the reaction of 9-anthracenemethanol (208 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 24 h.

***p*-Methylthiobenzyaldehyde (13b):** This compound was obtained as a yellow oil (125 mg, 82%) from the reaction of *p*-methylthiobenzyl alcohol (154 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in *o*-xylene at 130 °C for 4 h.

Dibenzosuberone (14b): This compound was obtained as a yellow oil (197 mg, 95%) from the reaction of dibenzosuberol (210 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 48 h.

***trans*-4-Stilbenecarboxaldehyde (15b):** This compound was obtained as an off-white solid (196 mg, 94%) from the reaction of *trans*-stilbenemethanol (210 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 110 °C for 14 h.

4,4′-Bis(dimethylamino)benzophenone (16b): This compound was obtained as an off-white solid (255 mg, 95%) from the reaction of 4,4′-bis(dimethylamino)benzhydrol (270 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 110 °C for 18 h.

3,4-Benzocoumarin (17b):[20] This compound was obtained as an off-white solid (202 mg, 96%) from the reaction of 2,2′-biphenyldimethanol (214 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 105 °C for 11.5 h.

Methyl 4-formylbenzoate (18b) and Ester 18c: Compounds **18b** and **18c** were isolated as white solids (89 mg for **18b** and 57 mg for **18c**) from the reaction of methyl (4-hydroxymethyl)benzoate (166 mg, 1.0 mmol), chlorobenzene (0.15 mL, 1.5 mmol), K_2CO_3 (276 mg, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **A** (10 mg, 30 μmol) in toluene at 100 °C for 12 h. **18b**: ^{1}H NMR ($CDCl_3$) δ 10.07 (1H, C(O)*H*), 8.16 (d, 2H, ArH), 7.92 (d, 2H, ArH), 3.93 (s, 3H, O*Me*). **18c**: ^{1}H NMR ($CDCl_3$) δ 8.15−8.0 ppm (m, 6H, ArH), 7.48 (d, 2H, ArH), 5.40 (s, 2H, C(O)O*CH*$_2$), 3.91 (s, 3H, O*Me*), 3.89 (s, 3H, O*Me*). ^{13}C NMR ($CDCl_3$) δ 166.6, 166.1, 165.4, 140.6, 134.1, 133.5, 130.1, 129.9, 129.6, 129.6, 127.7, 66.3, 52.4, 52.1.

General Procedure for Hydrodechlorination Experiments. A reaction mixture of a chloroarene, base, $Pd(dba)_2$, and ligand was loaded into a Schlenk reaction tube. The mixture was thoroughly degassed with vacuum and argon purge cycles. Isopropanol was added and the mixture was heated at 80 °C until the reaction was completed (all starting chloroarene was consumed as determined by GC-MS). All

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reactions were quantitative by GC-MS analysis. The mixture was taken up in ether and washed with H_2O and brine. 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 the desired product.

Hydrodechlorination of 4-chlorobenzophenone (21a): The reaction mixture of 4-chlorobenzophenone (418 mg, 1.9 mmol), 2-propanol (7.0 mL), K_2CO_3 (481 mg, 3.5 mmol), $Pd(dba)_2$ (2 mg, 3.5 μmol), and ligand **D** (4 mg, 10 μmol) was heated at 80 °C. The dechlorination reaction was completed within 5 h as determined by GC-MS. The dechlorination product was isolated as a white solid (335 mg, 95.4%) and confirmed by NMR.

Hydrodechlorination of 4′-chlorochalcone (22a): The reaction mixture of 4′-chlorochalcone (243 mg, 1.0 mmol), 2-propanol (4.0 mL), K_2CO_3 (276 m, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **D** (13 mg, 30 μmol) was heated at 80 °C. The reaction was completed within 7 h as determined by GC-MS.

Hydrodechlorination of 4-chloro-α-methylstyrene 23a: The reaction mixture of 4-chloro-α-methylstyrene (0.14 mL, 1.0 mmol), 2-propanol (4.0 mL), K_2CO_3 (276 m, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **D** (13 mg, 30 μmol) was heated at 80 °C. The reaction was completed within 21.5 h as determined by GC-MS.

Hydrodechlorination of 4-nitrochlorobenzene (24a): The reaction mixture of 4-nitrochlorobenzene (168 mg, 1.1 mmol), 2-propanol (4.0 mL), K_2CO_3 (276 m, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **D** (13 mg, 30 μmol) was heated at 80 °C. The reaction was completed within 1 h as determined by GC-MS.

Hydrodechlorination of 2,4-dinitrochlorobenzene (25a): The reaction mixture of 2,4-dinitrochlorobenzene (202 mg, 1.0 mmol), 2-propanol (4.0 mL), K_2CO_3 (276 m, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **D** (13 mg, 30 μmol) was heated at 80 °C. The reaction was completed within 1 h as determined by GC-MS.

Hydrodechlorination of 5-chloro-*o*-anisidine (26a): The reaction mixture of 5-chloro-*o*-anisidine (158 mg, 1.0 mmol), 2-propanol (4.0 mL), K_2CO_3 (276 m, 2.0 mmol), $Pd(dba)_2$ (6 mg, 10 μmol), and ligand **D** (13 mg, 30 μmol) was heated at 80 °C. The reaction was completed within 25 h as determined by GC-MS.

Hydrodebromination of 4-bromobenzophenone (27a): The reaction mixture of 4-bromobenzophenone (1826 mg, 7.0 mmol), 2-propanol (10.0 mL), K_2CO_3 (1063 mg, 7.7 mmol), $Pd(dba)_2$ (2 mg, 3.5 μmol), and ligand **D** (4 mg, 10 μmol) was heated at 80 °C. Reaction was completed within 4 h as determined by GC-MS. The debromination product was isolated as a white solid (1203 mg, 94.6%) and confirmed by NMR.

Hydrodebromination of 4-bromoacetophenone (28a): The reaction mixture of 4-bromoacetophenone (710 mg, 3.6 mmol), 2-propanol (4.0 mL), K_2CO_3 (481 mg, 3.5 mmol), $Pd(dba)_2$ (2 mg, 3.5 μmol), and ligand **D** (4 mg, 10 μmol) was heated at 80 °C. The reaction was completed within 2 h as determined by GC-MS.

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