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Reductive Carbonylation − an Efficient and Practical Catalytic Route for the Conversion of Aryl Halides to Aldehydes

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Abstract:

Alternative routes for the introduction of aldehyde functionality are particularly desirable for fine chemical and pharmaceutical intermediates because of the wide range of further transformations that are possible. Catalytic processes are of particular interest for minimising waste, and therefore the reductive carbonylation of aryl halides has been explored. We have shown that high yields of aldehydes may be obtained for a wide selection of aryl iodides and bromides using mild conditions (3 bar of CO, temperatures 60−120 °C) and silanes as hydride source. A choice of conditions (catalyst, base, solvent) is required to cover the range of aryl substituents varying in electron donation and steric influence. This is related to the competing needs of the several steps of this reaction, including oxidative addition, CO substitution, CO insertion, hydride transfer, and reductive elimination.

Introduction

The formation of reactive functional groups in selective reactions from a choice of precursors is a matter of fundamental interest to chemists and, in particular, for the synthesis of fine and pharmaceutical chemicals. Aldehydes are particularly desirable as functional groups because of the wide range of further transformations that are possible. However, simple routes to aldehydes have proved difficult to develop. Stoichiometric reactions often involve harsh conditions and result in significant quantities of waste products. Therefore, catalytic processes to form aldehydes have been a focus of interest for some time. Early work by Heck[1] showed that aryl and vinyl halides (bromide and iodide) could be converted to aldehydes using a synthesis gas mixture (CO/H_2) and a palladium(0) catalyst, but only when using high pressure (>80 bar) and temperature (>80 °C). This severely restricts the applicability of this methodology for scale-up beyond the laboratory, and several groups have subsequently looked at this reaction with the aim of achieving the same conversion under milder conditions. Until very recently, the approach adopted was to use a hydrogen transfer agent in place of hydrogen to promote the elimination of the acyl species from the metal. Thus Stille and co-workers[2−4] found that Bu_3SnH was successful in converting aryl and vinyl iodides, bromides and triflates to aldehydes under 1 bar of CO at 50 °C. Similar conditions were applied by Smith et al.[5] However, contamination with Sn is highly undesirable for pharmaceutical products, and other groups found R_3SiH to be equally effective. Pri-Bar and Buchman[6] demonstrated that poly(methylhydrosiloxane) (PMHS) could be used at 50 psi of CO and 80 °C with Pd(0) or Pd(II). The reactivity of Et_3SiH was studied by Hidai et al.[7] for mixed metal Pd/Ru and Pd/Co systems, and they identified routes to some of the byproducts. The conversion of aryl/enol triflates to aldehydes was optimised by Kotsuki et al.[8] using Oct_3SiH and other silanes under 1 atm of CO in DMF at 70 °C with $Pd(OAc)_2$/1,3-*bis*(diphenylphosphino)-propane as catalyst. Pri-Bar and Buchman[6,9] also found that sodium formate could be used as a hydrogen donor in the absence of base in conjunction with 50 psi of CO. Cacchi et al.[10] recently developed the use of acetic formic anhydride as an in situ CO source in conjunction with R_3SiH for the conversion of aryl iodides.

In all these cases, the reactivity of the aryl halides follows the expected pattern of ease of oxidative addition to Pd(0), that is I > Br > Cl, with more extreme conditions being required to obtain high yields with the bromides than for the iodides, but with the chlorides being unreactive. Clearly, reactions with aryl chlorides would be desirable from an economic and practical point of view. Examples of this have been demonstrated by Basset et al.[11] using tricarbonyl(chloroarene)chromium with CO/H_2 and Milstein et al.[12] using formate as hydrogen donor. In the latter case, activity required the dippp ligand (1,3-*bis*(di-isopropylphosphino)-propane) that provides an electron-rich complex with a suitable chelate ring size for the best compromise between stability and activity. The oxidative addition step was shown to be significantly slower than the carbonylation reaction.

Most recently,[13] the application of the proprietary ligand di-1-adamantyl-*n*-butylphosphine (Cata*CX*ium A) was found to be effective for the formylation of aryl and heteroaryl bromides using synthesis gas (1:1 CO/H_2) at much lower pressures than those previously possible. Typical reaction

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(1) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.
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(5) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971.
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(10) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Comb. Chem.* **2004**, *6*, 692.
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(12) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816.
(13) Klaus, S.; Neumann, H.; Zapf, A.; Strubing, D.; Huber, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W-R.; Rossen; K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154.

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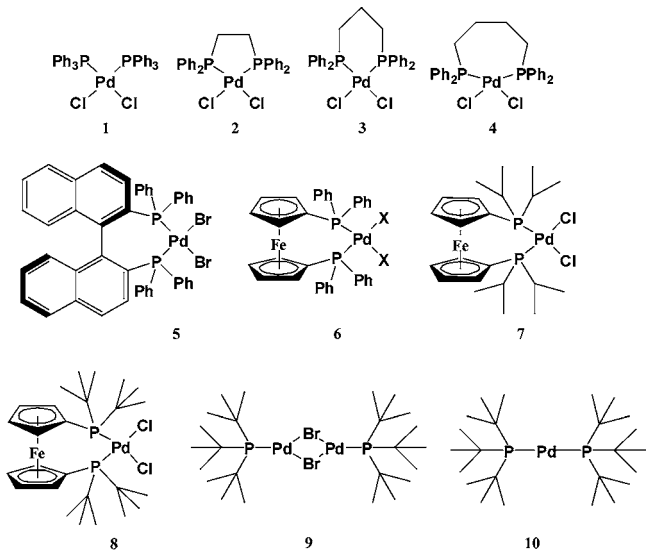


Ligand names/abbreviations

1 Triphenylphosphine (TPP)
2. 1,2-Bis(diphenylphosphino)ethane (dppe)
3. 1,3-Bis(diphenylphosphino)propane (dppp)
4. 1,4-Bis(diphenylphosphino)butane (dppb)
5. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)
6. Bis(diphenylphosphino)ferrocene (dppf)
7. Bis(di-iso-propylphosphino)ferrocene (d^ippf)
8. Bis(di-tert-butylphosphino)ferrocene (d^tbpf)
9 and 10. Tri-tertbutylphosphine

Figure 1. **Palladium catalysts.**

conditions were $Pd(OAc)_2$ (0.25 mol %), ligand (0.75 mol %), TMEDA (0.75 equiv), CO/H_2 (5 bar) for 16 h at 100 °C.

While these conditions are clearly advantageous in allowing formylation with a cheap reagent (CO/H_2) under relatively mild conditions, the reaction is shown to be very specific to the di-1-adamantyl-*n*-butylphosphine. We have therefore sought to exemplify the potential of the previously developed R_3SiH systems using a wider range of palladium catalysts containing nonproprietary ligands. The increased cost of the reducing agent may be offset by the lower ligand/catalyst cost.

Results

Experiments were carried out using a Baskerville Multi-Cell reactor, in which 10 simultaneous reactions could be run under identical temperatures and pressures. Initial investigations were carried out using 4-bromoacetanilide as a model substrate. Conditions were adapted from the work on triflates by Kotsuki et al.[8] The reaction was heated at 90 °C for 18 h under 6 bar of CO, and in contrast to their results, under these conditions satisfactory yields could be obtained with Et_3SiH as well as the more expensive Oct_3SiH. Other silanes, including Ph_3SiH, $(EtO)_3SiH$, $^iPr_3SiH$, and PMHS, were also tested but only gave minimal conversion of the starting material. The linear alkyl silanes are preferable for this reaction, although PMHS was used successfully with iodides by Pri-Bar and Buchman.[6]

A selection of palladium catalysts was tested under these conditions; the catalysts are shown in Figure 1, and results are given in Table 1 and illustrated in Figure 2. High yields of the aldehyde were achieved with catalysts containing bidentate phosphine ligands, such as $[PdCl_2(dppp)]$ **3**, $[PdBr_2$-(BINAP)] **5**, or $[PdCl_2(dppf)]$ **6**; the monodentate bis-(triphenylphosphine) catalyst **1** was less effective. Chelate ring size is an important factor in catalyst choice; $[PdCl_2$-(dppe)] **2** has a bidentate phosphine ligand with a small bite angle and is inactive in this reaction. It also appears that these preformed catalysts have an advantage over those generated in situ from $Pd(OAc)_2$ and the ligand.

Table 1. **Performance of catalysts for reductive carbonylation of 4-bromoacetanilide**

entry	catalyst	conv.[a] (%)	yield[a] (%) ArCHO	yield[a] (%) ArH	select.[a] (%)
1	$[Pd(OAc)_2]_3/2xPPh_3$	18	16	2	89
2	$[Pd(OAc)_2]_3$/dppf	32	1	31	3
3	$[Pd(OAc)_2]_3$/dppp	99	97	2	98
4	$[PdCl_2(PPh_3)_2]$	41	30	11	73
5	$[PdCl_2(dppf)]$	99	93	6	94
6	$[PdCl_2(dppp)]$[b]	99	98	1	99
7	$[PdBr_2(BINAP)]$	93	92	1	99
8	$[PdCl_2(d^tbpf)]$	100	0	100	0
9	$[PdCl_2(dppe)]$	2	0	2	0

[a] As determined by GC−MS peak area ratio. [b] Isolated yield 92.5%

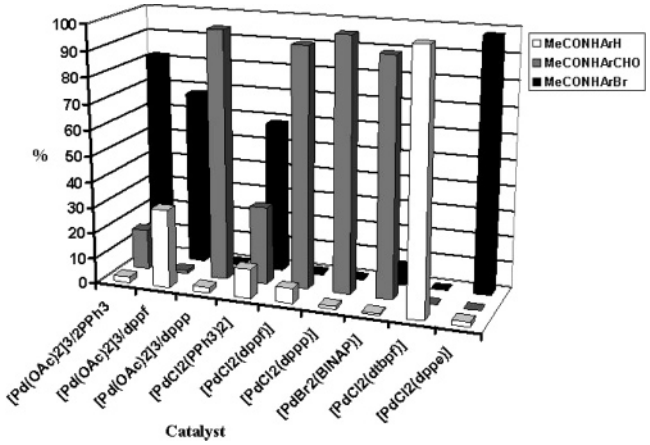


Figure 2. **Selection of catalysts for reductive carbonylation of 4-bromoacetanilide.**

Optimisation of Conditions. A selection of other aryl bromides with differing electronic properties were reacted under these conditions using **3** as catalyst. It was immediately clear that a general optimisation of conditions to produce the highest yield of aldehyde was not a suitable approach as each substrate posed different challenges. For example, 4-bromotoluene with **3** in DMF with Et_3N as base and Et_3-SiH gave almost complete conversion to an aryl species containing $-OSiEt_3$ as evidenced by IR, NMR, and mass spectroscopy. This was identified as the dimeric species $ArCH(OSiEt_3)CH(OSiEt_3)Ar$ (I, Ar = tolyl) by comparison with an authentic sample prepared by silylation of the alcohol. This may be formed via a benzoin condensation from the aldehyde or possibly arise from a double carbonylation reaction. The same product was also obtained with similar catalysts, such as **5** or **6**, but more electron-rich catalysts such as **7**, **8**, or, **9** gave poor conversion of the starting material to the required aldehyde only. The use of other solvents with **3** also gave poor conversion of the starting material, but by changing the base to an inorganic

salt, such as Na_2CO_3, the unwanted side reaction could be eliminated and high yields of the aldehyde were achieved.

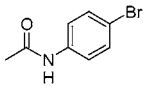
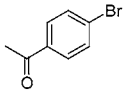
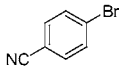
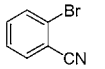
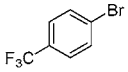
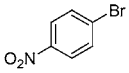
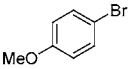
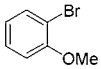
The electron-rich substrate, 4-bromoanisole, is deactivated towards oxidative addition of the aryl bromide to the catalyst. It was found that this lack of reactivity could be overcome by raising the reaction temperature to 120 °C. A screen of catalysts revealed similar behaviour to 4-bromotoluene; for example, **3** gave the triethylsilane derivative (I), and **8** gave poor yields of both the triethylsilane derivative (I) and the required aldehyde. The palladium(0) catalyst, $[Pd(P^tBu_3)_2]$ **10**, however gave high yields of the aldehyde without any side reactions. The results with this catalyst were reproducible in a variety of solvents including THF, DMA, toluene, and MeCN, but 1,4-dioxane proved to be preferable. It is necessary to use an organic base with this substrate {Et-(^{i}Pr)$_2$N gave better yields than Et_3N} as inorganic salts such as Na_2CO_3 resulted in incomplete reaction and formed significant quantities of anisole.

The activated electron-poor substrate, 4-bromobenzonitrile, gave almost complete conversion to the debrominated benzonitrile with **3** in DMF with Et_3N. The catalysts **5** and **6** also gave poor results with a mixture of that and the triethylsilane derivative (I). This problem could be overcome by the use of $[PdCl_2(d^ippf)]$ **7** or $[PdCl_2(d^tbpf)]$ **8** which gave good yields of the aldehyde and only a small amount of benzonitrile. A wide range of solvents could be used including DMF, NMP, 1,4-dioxane, and toluene, but THF gave the best results. Acetonitrile appeared to increase the proportion of benzonitrile formed, as did the use of inorganic bases with any of the solvents.

Although **3** was deemed to be the most appropriate catalyst for the reaction with 4-bromoacetanilide, the effect of solvent and base on the reaction was investigated in light of the results of work with the other substrates. Screens showed that Na_2CO_3 gave the highest yield of aldehyde followed by organic bases such as Et_3N. Other inorganic bases increased the formation of acetanilide. The best solvent was DMF.

Other conditions were also optimised to give the best results. Variation of the amount of catalyst in the range 1−5 mol % had little effect on the distribution of products, but at 1 mol% the reaction was noticeably slower, with significant amounts (up to 60%) of starting material remaining after 18 h. Under the original conditions 2 equiv of Et_3SiH and 2.1 equiv of base were used. It was found that by reducing either one of these components to 1 equiv higher yields of aldehyde were obtained, but reducing the quantity of both silane and base had a detrimental effect on results. As the reduction in amount of base appeared to have a stronger influence, all further experiments were carried out using 2 equiv of Et_3SiH and 1 equiv of the appropriate base. High yields of aldehyde could still be achieved when the CO pressure was lowered to 3 bar, but further decreases in pressure lead to the formation of a more debrominated side product from the more active substrates. Lowering the temperature to 60 °C did not result in a satisfactory reaction under the established conditions.

Table 2. **Reductive carbonylation of aryl bromides**

Entry	Substrate	Conv.(%)[a]	Yield.(%)[a] ArCHO	Yield.(%)[a] ArH	Select.(%)[a]
1[b]		100	79	21	79
2[b]		92	92	0	100
3[b]		0	0	0	0
4[b]		100	94	6	94
5[b]		1	0.5	0.5	50
6[b]		100	95	5	95
7[b]		100	82	18	82
8[c]		100	79	21	79
9[c]		94	14	80	15
10[c]		100	78	0[e]	78
11[c]		64	7	57	11
12[c]		100	4	96	4
13[d]		81	81	0	100
14[d]		60	43	17	72
15[b]		100	100	0	100
16[b]		100	100	0	100

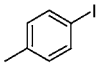
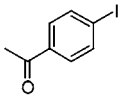
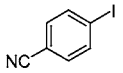
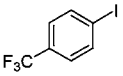
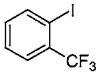
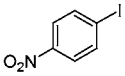
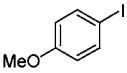
[a] As determined by GC−MS peak area ratio. [b] Method A (see Experimental Section). [c] Method B (see Experimental Section). [d] Method C (see Experimental Section). [e] In this case the only other product is $ArCH(OSiEt_3)CH(OSiEt_3)Ar$.

Scope of Reaction. The preferred conditions (see Experimental Section, Method A) were applied to a wider range of aryl bromide substrates with differing electronic and steric properties. The results are shown in Table 2.

High yields were achieved for substrates with an electronically neutral substituent in the 4-position. These yields were not compromised if a single substituent was present in the 2-position, but the steric hindrance of 2,6 disubstitution prevented the reaction from taking place. Substrates with an electron-withdrawing group in the 4-position also gave good results, with the exception of 1-bromo-4-nitrobenzene. Nitro-substituted aromatics are known to sometimes show abnormal reactivity due to their coordinating ability and high electron deficiency.[13,14] An electron-withdrawing group in the 2-position, however, promoted reductive debromination

(14) Wang, B.; Bonin, M.; Micouln, L. *Org. Lett.* **2004**, *6*, 3481.

Table 3. **Reductive carbonylation of aryl iodides**

Entry	Substrate	Conv.(%)[a]	Yield(%)[a] ArCHO	Yield(%)[a] ArH	Select.(%)[a]
1		100	97	3	97
2		96	96	0	100
3		97	97	0	100
4		100	85	15	85
5		31	5	26	18
6		100	83	17	83
7		100	93	7	93
8		98	98	0	100
9		60	29	31	49
10		100	44	56	44
11		100	97	3	97
12		100	100	0	100

[a] As determined by GC−MS peak area ratio.

over reductive carbonylation. Substrates with an electron-donating group required a higher temperature for the reaction to take place, and again yields were reduced when the substituent is in the 2-position rather than the 4-position. The conditions used for neutral substrates also gave excellent results for the heteroaryl bromides, e.g., 3-bromopyridine.

Although aryl iodide substrates are less widely available than their aryl bromide counterparts, they show increased activity towards the oxidative addition step of the reductive carbonylation reaction. This could be used to carry out a selective carbonylation at the iodide of a mixed halide substrate. The conditions under which a range of aryl iodides undergoes reductive carbonylation was investigated with particular emphasis on their reactivity in comparison to the equivalent aryl bromides. Results are shown in Table 3.

For the aryl iodides it was found that a temperature of 60 °C was adequate to give high yields in most cases. This was even true of the deactivated, electron rich substrates and good results could be obtained using the **3**/DMF/Na_2CO_3 system as opposed to the palladium(0) catalyst that is required for the equivalent aryl bromide. The same system was also used for the activated substrates as **8**/THF/Et_3N resulted in reductive dehalogenation. These conditions did not prove to be suitable however, for the heteroaryl iodide.

Excellent selectivity between reaction at an aryl iodide and at an aryl bromide can be achieved using the **3**/DMF/Na_2CO_3 system at 60 °C, except in the case of activated substrates. Under these conditions near quantitative yields of aldehyde are observed with aryl iodides, but almost no reaction takes place with neutral or deactivated aryl bromides. This is illustrated by the reaction of 1-bromo-4-iodobenzene (Figure 3). For activated aryl bromides, e.g., 4-bromobenzonitrile, significant conversion to the aldehyde takes place at 60 °C; a lower temperature would be required to give similar selectivity.

An alternative method of achieving selectivity between aryl iodides and aryl bromides is to use PMHS as the silane instead of Et_3SiH. Pri-Bar and Buchman[6] were successful in using PMHS for the reductive carbonylation of aryl iodides, but with the conditions used in this study no reaction took place with PMHS and aryl bromides. When PMHS was used under the same conditions (**3**/DMF/Na_2CO_3 at 90 °C) with aryl iodides, however, near complete conversion took place.

Discussion

The range of results and conditions for this large variety of catalyst systems is illustrative of the complexity of this reaction in terms of the different reaction steps and the factors influencing them. An outline mechanism is shown in Scheme 1.

A great deal of study has been given to the oxidative addition of aryl halides to palladium,[15,16] by the groups of Buchwald and Hartwig in particular, and strongly donating phosphines having bulky substituents (e.g., P^tBu_3) have been shown to be advantageous. This has been explained by the relative stability of the Pd(0) and Pd(II) complexes. However, less is known about the carbonyl insertion reaction, which consists of initial substitution of carbon monoxide into the coordination sphere and then insertion into the Pd−C bond. It might be presumed that initial opening of the phosphine chelate allows CO coordination and CO insertion will be favoured by return of this phosphorus donor into the vacant site created by ligand combination. The hydrogen transfer step and the relative ease of reductive elimination from the aryl and acyl intermediates are even less understood. However, the fact that it is possible by changing the conditions to increase reaction via the acyl complex relative to dehalogenation via the aryl complex indicates that there are significant differences between the factors controlling these rates.

The results in Table 2 illustrate some of these points. Substrates with electron-withdrawing groups in the 4-position give better yields with the bulky, electron-rich d^tbpf ligand (Method B, see Experimental Section) than with dppp (Method A). It is expected that these substrates would react more readily with the dppp catalyst than the alkyl substituted aryls, at least with regard to oxidative addition, so the change in catalyst performance must relate to later steps in the mechanism.

Conclusions

Efficient carbonylation of aryl iodides and bromides in the presence of the hydrogen donor Et_3SiH can be achieved provided that the conditions are modified to suit the substrate. In particular, the appropriate choice of catalyst, solvent, and

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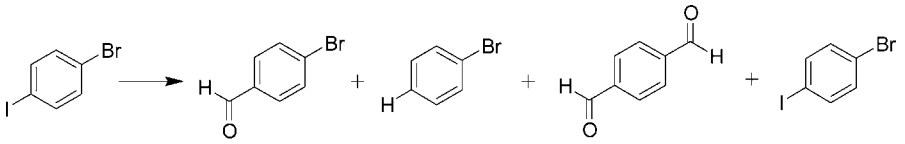
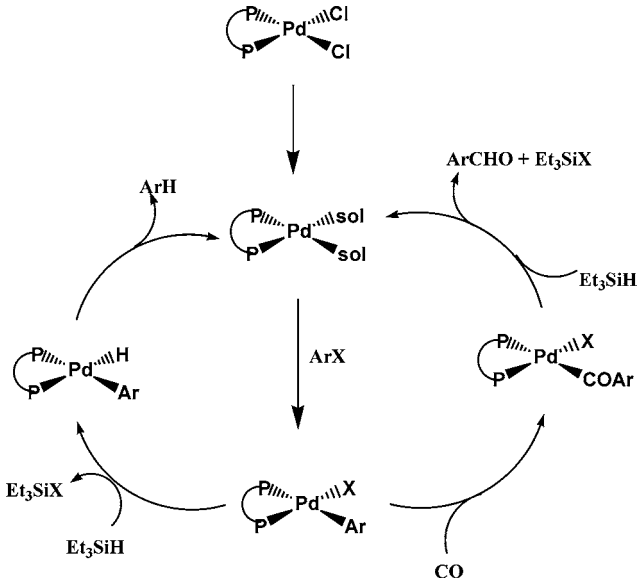


Figure 3. **Iodide vs bromide selectivity.**

Scheme 1. **Outline mechanism for reductive carbonylation**



base must be made. This methodology provides a suitable alternative to the use of proprietary ligands such as Cata*CX*ium A. Furthermore, this approach offers the prospect of adaptation to the conversion of aryl chlorides.

Much progress has been made in recent years by many groups studying C−C coupling reactions of aryl chlorides.[17] It has been shown that oxidative addition of aryl chlorides can be promoted, even at room temperature, using sterically demanding and electron-donating phosphines (cf. ref 12). Thus, the initial oxidative addition should no longer be a barrier to reactivity. However, a balance between the oxidative addition, carbonyl insertion, hydride transfer, and reductive elimination steps still needs to be found, so careful screening will be required to develop suitable catalysts. This is the focus of ongoing work.

Experimental Section

All solvents and reagents were obtained from commercial suppliers and used without further purification. All catalysts and ligands may be obtained from Johnson Matthey Catalysts or Alfa Aesar. Reactions were performed in a Baskerville 10 × 30 mL Multi-Cell Pressure Reactor rated to 50 bar and 200 °C. Analysis of the reaction mixture was carried out by GC−MS using a Perkin-Elmer AutoSystem XL gas chromatograph with a TurboMass mass spectrometer. Conditions used: 1.0 μL sample injection; column, 30 m × 0.25 mm and DF 0.25 μm Elite Series PE-5MS; injection port 320 °C; initial temperature 130 °C, hold 4 min, ramp at 30 °C/min to 300 °C, hold 5 min; split ratio 100/1; MS scan 40.0 to 400.0 EI+ (centroid).

General Procedure for the Reductive Carbonylation of 4-Bromotoluene (Method A). To 4-bromotoluene (0.616 g, 3.6×10^{-3} mol), [$PdCl_2$(dppp)] (0.053 g, 9×10^{-5} mol), and Na_2CO_3 (0.381 g, 3.6×10^{-3} mol) were added DMF (5 mL), mesitylene (0.25 mL, 1.8×10^{-3} mol) as reference, and Et_3SiH (1.166 mL, 7.2×10^{-3} mol). Once sealed inside the reactor the system was purged with CO several times. The temperature was raised to 90 °C, and the reactor was charged with 3 bar of CO. The reaction was stirred under these conditions for 18 h after which the reactor was allowed to cool. The reaction was filtered, and the filtrate was analysed by GC−MS to determine the conversion and yield of aldehyde.

General Procedure for the Reductive Carbonylation of 4-Bromobenzonitrile (Method B). To 4-bromobenzonitrile (0.655 g, 3.6×10^{-3} mol) and [$PdCl_2$(d^tbpf)] (0.065 g, 9×10^{-5} mol) were added THF (5 mL), mesitylene (0.25 mL, 1.8×10^{-3} mol) as reference, Et_3N (0.504 mL, 3.6×10^{-3} mol), and Et_3SiH (1.166 mL, 7.2×10^{-3} mol). Once sealed inside the reactor the system was purged with CO several times. The temperature was raised to 90 °C, and the reactor was charged with 3 bar of CO. The reaction was stirred under these conditions for 18 h after which the reactor was allowed to cool. The reaction was filtered, and the filtrate was analysed by GC−MS to determine the conversion and yield of aldehyde.

General Procedure for the Reductive Carbonylation of 4-Bromoanisole (Method C). To [$Pd(P^tBu_3)_2$] (0.046 g, 9×10^{-5} mol) were added dioxane (5 mL), mesitylene (0.25 mL, 1.8×10^{-3} mol) as reference, 4-bromoanisole (0.451 mL, 3.6×10^{-3} mol), $Et(^i Pr)_2N$ (0.658 mL, 3.6×10^{-3} mol), and Et_3SiH (1.166 mL, 7.2×10^{-3} mol). Once sealed inside the reactor the system was purged with CO several times. The temperature was raised to 120 °C, and the reactor was charged with 3 bar of CO. The reaction was stirred under these conditions for 18 h, after which the reactor was allowed to cool. The reaction was filtered, and the filtrate was analysed by GC−MS to determine the conversion and yield of aldehyde.

Product Isolation. 4-Acetamidobenzaldehyde prepared from 4-bromoacetanilide according to method A (2.16mmol substrate) was isolated by filtration of the reaction solution and evaporation of the solution to low volume. The slurry was taken up in acetone and chromatographed on silica using hexane/acetone eluant. The product was isolated by evaporation under reduced pressure and washed with hexane. The product was collected by filtration and dried in air. Yield: 3.25 g (1.99 mmol, 92.5%).

Note Added after ASAP Publication: Errors in Figure 1 in the version published on the Internet December 14, 2006, have been corrected in the version published ASAP December 15, 2006, and in the print version.

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