Air Oxidation of Benzene to Biphenyl — A Dual Catalytic Approach

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Abstract: Facile oxidative homocoupling of benzenes to the respective biphenyls is effected under moderate conditions, using air or oxygen in the presence of catalytic $PdCl_2$ and AcOH/AcONa as solvent. The fast regeneration of the active Pd^{2+} species is accomplished by combining several oxygen-binding catalysts, such as Zr(IV), Mn(II), and Co(II) acetates. In this way, it is possible to increase the content of active oxygen in solution so that the rate of catalyst regeneration is faster than the rate of aggregation of the "spent catalyst", Pd(0), to palladium black. The effects of various process parameters are studied and some mechanistic implications are discussed.

Keywords: atom economy; C–C coupling; homogeneous catalysis; oxygen activation; oxidative coupling; palladium

For nature, the bonding of two carbon atoms together is a routine transformation. Conversely, *in vitro* synthesis of C–C bonds is a laborious process.[1] Most of the available pathways require the use of stoichiometric metallic reagents, or the presence of active leaving groups, or both. The coupling of aromatic rings is a worthy example in this case, since the desired products contain none of the reagents used in the coupling process — all of these reagents end up as chemical waste.[2]

Biphenyl compounds carry a strong industrial interest as key building blocks in various agrochemical and pharmaceutical processes.[3] They are commonly produced *via* the Ullmann[4] or Suzuki[5] protocols.[6] The use of iodoarenes in these reactions (Scheme 1, top) is lamentable, since chemicals react by their molarity, but are quantified by their mass. For example, one tonne of iodobenzene contains 620 kg of "iodo" and only 380 kg of "benzene". Chlorobenzene, as we have shown recently,[7] can be used to obtain a better waste to product ratio, but it is clearly worthwhile to search for a synthetic pathway to produce biphenyls without the use of massive leaving groups.

The "greenest" solution[8] would be to use "void" as a leaving group, as in the theoretical reaction between benzene and benzyne (Scheme 1, middle). In practice, however, the smallest leaving group which is easily available is a hydrogen atom, i.e., oxidative coupling of two benzene molecules to form biphenyl (Scheme 1, bottom). Ideally, such a reaction would be performed with air as the oxidant, so that water would be the only by-product.

The oxidative coupling of benzene to biphenyl using stoichiometric amounts of $PdCl_2$ was first described by VanHelden and Verberg.[9] Since then, several catalytic options for the coupling of thiophenes and substituted benzenes have been suggested, using high O_2 pressure (35–50 atm O_2) and homogeneous $Pd(OAc)_2$ together with Hg(II),[10] Tl(III),[11] Fe(III),[12] or Cu(II)[13] salts. The use of Pd(acac),[14] Pd(1,10-phenanthroline), and Pd(ETDA)[15] com-
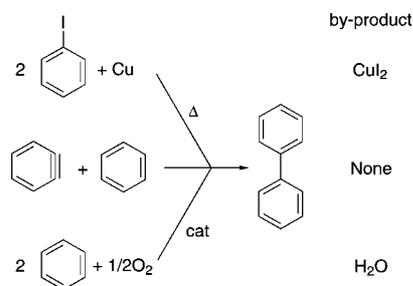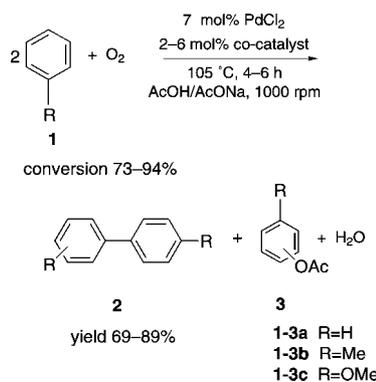

Scheme 1.

plexes has also been reported, as was the combination of Pd(II) and Zr(IV) salts, again at high O_2 pressures and temperatures.[16,17] Apparently, these extreme conditions are not dictated by the tardiness of the coupling process with Pd(II), but by the low availability of dioxygen in the reaction solution.

We recently studied the reductive coupling of haloarenes to biaryls under various conditions,[18] and also showed the feasibility of a tandem oxidative/reductive catalytic coupling process.[19] Here, we report that it is possible to combine two types of catalysts [PdCl$_2$ for the coupling reaction, and Co(II), Mn(II), and Zr(IV) salts to enhance the availability of molecular oxygen in the reaction medium] in a one-pot reaction to yield facile air oxidation of benzene to biphenyl under moderate conditions.

In a typical reaction, benzene (**1a**), sodium acetate, and catalytic amounts of Zr(IV), Co(II), Mn(II) acetates, acetyl acetone, and PdCl$_2$ were stirred in acetic acid in an autoclave for 4–6 h at 105 °C under 1 MPa of air (Scheme 2).[20] Biphenyl (**2a**) was found to be the major product, together with minor amounts of acetylation products in some cases (depending on reaction conditions – see Table 1). In analogous reactions, PhMe gave 91% conversion and 69% selectivity to coupling (the remainder being acetylation and oxidation of the side chain) and PhOMe gave 73% conversion and 76% selectivity, the remainder being acetylation (these reactions were carried out only to demonstrate the feasibility of substrates other than benzene, and no attempt was made to separate the isomeric mixtures).

The rate of reaction was found to be a function of substrate concentration, PdCl$_2$ loading, and air or oxygen pressure, i.e., $-dC_1/dt = k[\mathbf{1}]W_{cat} P_{air}$. A first-order rate law was observed for fixed air pressure and Pd catalyst loading.

Increasing the air pressure enhanced the rate of reaction, but a decrease in the selectivity was observed above 1 MPa (Table 1, entries 1–4). Similar behavior was observed when pure O_2 gas was introduced instead of air (entries 5–7). Changes in temperature

strongly affected the product selectivity (entries 8–11), pointing to the difference in the activation energies between the coupling and the acylation reactions.[21] The energy of activation for the coupling process was calculated as 52.4 kJ mol^{-1} (12.53 kcal mol^{-1}, with r^2 = 0.989 for 4 observations at 85, 95, 105, and 115 °C). Addition of a phase transfer catalyst (tetrahexylammonium chloride) increased the rate and conversion but the selectivity remained unchanged. The addition of sodium acetate (entries 18–20) increased both the rate of reaction and the selectivity towards the coupling product. Homogeneous PdCl$_2$ afforded superior yields when compared with Pd(OAc)$_2$, indicating that the Cl$^-$ ligands do not undergo a rapid exchange reaction with the solvent.[22] Alternatively, it could be that the chloro complexes may be kinetically labile but thermodynamically fa-

Table 1. Oxidative coupling of PhH at various conditions.[a]

Entry	Parameter	Conversion (%)[b]	Selectivity (%) for 2a[b]
	Air pressure (MPa)		
1	0.4	54	61
2	0.6	78	79
3	1.0	94	89
4	1.2	94	83
	O_2 pressure (MPa)		
5	0.4	59	53
6	0.6	81	76
7	0.8	96	84
	Temperature (°C)		
8	85	68	73
9	95	82	83
10	105	94	89
11	115	94	81
	PdCl$_2$ (mol %)		
12	7.0	94	89[c]
13	6.1	72	81
14	5.2	58	69
15	4.4	27	41
	PTC		
16	None	95	82
17	THAC (1 mol %)[d]	94	89
	NaOAc (mol %)		
18	180	94	89
19	150	88	81
20	95	64	89
	Coupling catalyst		
21	PdCl$_2$	94	89
22	Pd(OAc)$_2$	79	72
	Water (mol %)		
23	0	96	78
24	250	94	89
25	450	86	91

[a] Standard reaction conditions: benzene, 64 mmol, AcONa, 71 mmol, PdCl$_2$, 4.5 mmol (7.0 mol % based on substrate), Zr(OAc)$_4$, 1.4 mmol, Co(OAc)$_2$, 1.2 mmol, Mn(OAc)$_2$, 1.2 mmol, acetylacetone, 2.0 mmol, water, 250 mmol, AcOH (total reaction volume 50 mL), 105 °C, 1.0 MPa air, 1000 rpm mechanical stirring for 6 h.
[b] Based on GC area, corrected by the presence of an internal standard.
[c] Yield of isolated product.
[d] Tetra(*n*-hexyl)ammonium chloride.

2 [benzene] + O_2 →(7 mol% PdCl$_2$, 2–6 mol% co-catalyst, 105 °C, 4–6 h, AcOH/AcONa, 1000 rpm) **1**

conversion 73–94%

2 + **3** + H_2O

yield 69–89%

1-3a R=H
1-3b R=Me
1-3c R=OMe

Scheme 2.

vored when compared with the acetato complexes. Indeed, if the mechanism of the catalytic coupling is analogous to that which was suggested for the stoichiometric reaction with $PdCl_2$, then it may be that Cl^- ligands are preferred (*vide infra*). Addition of water (entries 24–26) slowed down the reaction but at the same time increased the selectivity to biphenyl, perhaps by reducing the rate of the acetoxylation reaction.[25]

The catalytic pathway from benzene to biphenyl in the presence of Pd^{2+} may be better understood if we consider the *stoichiometric* reaction between $PdCl_2$ and benzene, which was studied in detail by VanHelden et al. There, a four-step mechanism was proposed: first, a reaction between C_6H_6 and $PdCl_2$, arising from π-σ interactions,[24] then a fast reaction of the $[C_6H_6]^+[PdCl_2]^-$ ion pair with an acetate ion, followed by dimerization to form the dimer complex **3** (shown in Scheme 3),[25] and disproportionation of **3** to obtain the coupling product, Pd(O), and $PdCl_2$. The first step was assumed to be rate-determining, and the requirement for stoichiometric amounts of $PdCl_2$ stemmed from the fact that the reduced palladium species [Pd(0)] precipitated as palladium black, and could not be recycled.

Thus, the major barrier in transforming this reaction into a catalytic process is the enabling of fast re-oxidation of Pd(0) back to Pd^{2+} so that it would be competitive with the aggregation reaction, nPd(0) $\Rightarrow$ $[Pd(0)]_n$. This regeneration reaction is slow because there is not enough "active oxygen" in solution ("active oxygen", in this context, describes an oxygen molecule that is dissolved in the solution and probably
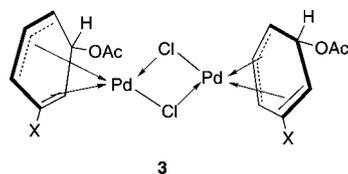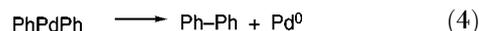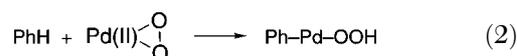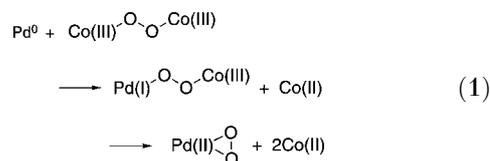

Scheme 3. Suggested dimer intermediate in the coupling of benzene with NaOAc and $PdCl_2$.

co-ordinated to a metal ion). Our solution was to employ a combination of Zr, Co, and Mn promoters as dioxygen fixators, together with acetylacetone.[26] Simple (but laborious) sequential screening afforded the desired combination (Table 2).

It must be said that the mechanisms of these reactions of non-functionalized hydrocarbons are very complex and still far from our understanding. We suggest, however, that dioxygen may react with Mn(II) to give Mn(III), which would then oxidize Co(II) to Co(III), in a manner similar to the terephthalic acid process.[27] Zr(IV), of course, could not have a similar role, as it cannot be oxidized further. Co(III) could then bind another molecule of dioxygen to form a superoxocobalt(III) species, $Co(III)-OO^\bullet$, which would probably dimerize to a μ-peroxocobalt(III) species, $Co(III)-OO-Co(III)$.[28] Reaction of Pd(0) with this species, followed by elimination of two Co(II) ions (Equation 1) could give a palladium(II)-peroxo complex that could release oxygen to give back Pd(II).

Alternatively, the palladium(II)-peroxo complex could insert into a Ph–H bond (Equation 2). A second insertion and elimination of HOOH, followed by reductive elimination of biphenyl (Equation 3 and Equation 4) would also complete the catalytic cycle.

$$Pd^0 + Co(III)\diagdown O\diagdown O\diagup Co(III)$$
$$\longrightarrow Pd(I)\diagdown O\diagdown O\diagup Co(III) + Co(II) \qquad (1)$$
$$\longrightarrow Pd(II)\langle {}^O_O + 2Co(II)$$

$$PhH + Pd(II)\langle {}^O_O \longrightarrow Ph-Pd-OOH \qquad (2)$$

$$Ph-Pd-OOH + PhH \longrightarrow PhPdPh + HOOH \qquad (3)$$

$$PhPdPh \longrightarrow Ph-Ph + Pd^0 \qquad (4)$$

By combining two catalytic systems, oxygen can be activated successfully for the regeneration of Pd^{2+}

Table 2. Oxidative coupling of PhH at using different catalyst combinations.[a]

Entry	PdCl$_2$ (mol %)	Zr(OAc)$_4$ (mol %)	Co(OAc)$_2$ (mol %)	Mn(OAc)$_2$ (mol %)	acac (mol %)	Conversion of 1a (%)[b]	Selectivity for 2a (%)[c]
1	0	2.0	1.8	1.8	3.1	0	–
2	7.0	0	1.8	1.8	3.1	86	83
3	7.0	2.0	0	1.8	3.1	82	76
4	7.0	2.0	1.8	0	3.1	93	79
5	7.0	2.0	1.8	1.8	0	73	82
6	7.0	2.0	1.8	1.8	3.1	94	89^c

[a] Standard reaction conditions: benzene, 64 mmol, AcONa, 71 mmol, PdCl$_2$, 4.5 mmol (7.0 mol % based on substrate), Zr(OAc)$_4$, 1.4 mmol, Co(OAc)$_2$, 1.2 mmol, Mn(OAc)$_2$, 1.2 mmol, acetylacetone, 2.0 mmol, water, 250 mmol, AcOH (total reaction volume 50 mL), 105 °C, 1.0 MPa air, 1000 rpm mechanical stirring for 6 h.
[b] Based on GC area, corrected by the presence of an internal standard.
[c] Yield of isolated product.

from Pd(0). The re-oxidation is faster than the aggregation of Pd(0) to palladium black, and this enables the catalytic oxidative coupling of benzene to biphenyl under moderate conditions. This utilization of metal salts as "oxygen transfer" catalysts enables the reaction to run at lower oxygen (and/or air) pressures. The disadvantages of this process are that the coupling is not regioselective, and the absence of a "functional leaving group" precludes cross-coupling applications. Also, the transfer of oxygen from the gas phase into the solvent and its activation are very complex processes, sensitive to the type and the concentration of the catalyst and to the reaction conditions. In such a case, combinatorial screening may prove to be beneficial in finding the optimal catalysts and conditions.

Experimental Section

General Remarks

GC and GCMS analyses were performed using an HP-5890 gas chromatograph with a 50% diphenyl-50% dimethyl-polysiloxane packed column (25 m × 0.53 mm). Unless stated otherwise, chemicals were purchased from commercial firms (>98% pure) and used without further purification. Products were either isolated and identified by comparison of their ^{1}H NMR spectra to standard samples, or identified by MS data and comparison of their GC retention times with standard samples (the preparation and analysis of reference materials was described previously, cf. refs.[7,18]). All reactions were performed in a 300 mL stainless steel Parr autoclave, equipped with a six-bladed impeller, an external heating mantle and a gas cooling system.

General Procedure for Oxidative Coupling of Arenes

Example: Biphenyl (2) from benzene (1): Benzene (5.0 g, 64 mmol), AcONa (9.7 g, 71 mmol), PdCl$_2$ (0.8 g, 4.5 mmol, 7.0 mol % based on substrate), Zr(OAc)$_4$ (0.3 g, 1.4 mmol), Co(OAc)$_2$ (0.3 g, 1.2 mmol), Mn(OAc)$_2$ (0.3 g, 1.2 mmol), and acetylacetone (0.2 g, 2.0 mmol) were charged to an autoclave as described above. AcOH was used to make up the reaction volume to 50 mL. The autoclave was heated to 105 °C, and then pressurized with 1 MPa air and stirred at 105 °C for 6 h. Reaction progress was monitored by GC. The mixture was then cooled and a large excess of water (*ca.* 100 mL) was added. Extraction of the organic layer with CH$_2$Cl$_2$ (3 × 40 mL), solvent evaporation and recrystallizing (cold EtOH) afforded biphenyl; yield: 4.3 g (89 mol % based on benzene). The product gave satisfactory analytical data.

   Supporting information available: Detailed description of kinetic and process parameter studies (15 experiments; 5 graphs).

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