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Palladium-free Suzuki–Miyaura cross-coupling at elevated pressures

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ABSTRACT

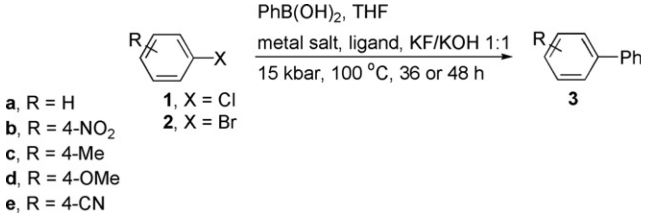
Elevated pressure (15 kbar) in the liquid phase improves yields and permits the use of cheaper Fe(III), Co(II), and Ni(II) metal salts as catalysts for the Suzuki-Miyaura cross-coupling of aryl halides and aryl boronic acids.

A number of papers have appeared recently analyzing the mechanism of palladium[1–5]- and nickel[6,7]-catalyzed cross-coupling reactions of aryl halides and aryl boronic acids or other nucleophiles.[8] Spectroscopic, kinetic, and modeling studies have provided strong evidence for most steps in this complex catalytic cycle (abbreviated in the figure), and it is likely that further elucidation of intermediates, transition states, and isomerization steps will emerge in the very near future. With this level of detail, it is possible to tune reaction conditions by choice of ligand, solvent, mode of activation, and reaction conditions. Rigorously excluding oxygen and adding a mild reducing agent, for example, predictably minimized aryl boronic acid homocoupling and allowed this reaction to be applied to large-scale synthesis of a pharmaceutical ingredient.[9]

Oxidative addition of an aryl halide to a low-valent metal (step B) is usually the turnover-limiting step for palladium-mediated reactions,[10] while there is evidence of rate-limiting transmetalation (step C) for nickel-mediated reactions[7] of particular substrates. Elevated pressures in the liquid phase are known to accelerate the oxidative addition of alkyl and aryl halides to square planar Ir(I),[11] Rh(I),[12] and Pt(II)[13] complexes which have relatively large, negative activation volumes ($\Delta V^{*} = -10$ to $-31\ \mathrm{cm^3\ mol^{-1}}$). The palladium-catalyzed cross-coupling of aryl halides and activated alkenes (Heck reaction) is accelerated by pressure (e.g., $\Delta V^{*} = -5$ to $-37\ \mathrm{cm^3\ mol^{-1}}$).[14–17] However, oxidative addition is not the rate-limiting step for this reaction.

The influence of pressure on the Suzuki–Miyaura reaction has not hitherto been investigated. Apart from promoting rate-limiting oxidative addition, it could also suppress undesirable ligand dissociation,[17] which is a common source of catalyst decomposition, particularly at higher temperatures. In this Letter, we report the promoting influence of high-pressure on transition metal-catalyzed cross-coupling of aryl halides and phenylboronic acid, and we highlight unique $FeCl_3$/dppy and $CoCl_2$/dppy catalyzed reactions.

The reagents were mixed in THF and subjected to atmospheric pressure of 15 kbar and a temperature of 100 °C for 36 or 48 h (Scheme 1).[18] The percent conversion was determined by GC/MS analysis. The mixed base KF/KOH proved optimal. We avoided DMF and alcohols as solvent which, while they assist Suzuki–Miyaura coupling, can react competitively with the aryl halide via high-pressure promoted S_NAr reaction of alkoxide or trace dimethylamine.[19] No pressure was required for the Pd-catalyzed coupling of electrophilic aryl chloride **1b** (Table 1, entry 1), although conversion improved at elevated pressure (entry 2) and was quantitative for this substrate (entry 3) and bromide **2e** (entry 14) with pressure and a change of ligand from monodentate triphenylphosphine to bidentate, potentially hemilabile 2-(diphenylphosphino)pyridine (dppy).[20] Good conversion could also be achieved using these conditions and the less reactive aryl bromide **2d** (entry 13). No product was observed for Ni(II), Co(II), or Fe(III)-catalyzed reaction at 1 bar (entries 4, 6, and 12), but cross-coupling was observed at 15 kbar (entries 5, 7–11, 13, and 14), together with small amounts of biphenyl from boronic acid homocoupling.



Scheme 1.

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Table 1
Suzuki–Miyaura cross-coupling at elevated pressure

Entry	Aryl halide[a]	Metal salt[b]	Ligand[c]	Pressure (bar)	Conv.[d] (%)
1	**1b**	$Pd(OAc)_2$	PPh_3	1	66
2	**1b**	$Pd(OAc)_2$	PPh_3	15,000	83
3	**1b**	$Pd(OAc)_2$	dppy	15,000	$\geqslant 99$
4	**1b**	$NiCl_2$(10%)	PPh_3	1	$\leqslant 1$
5	**1b**	$NiCl_2$	PPh_3	15,000	54
6	**1b**	$CoCl_2$	PPh_3	1	$\leqslant 1$
7	**2a**	$NiCl_2$	dppy	15,000	$\geqslant 99$
8	**2a**	$CoCl_2$	dppy	15,000	$\geqslant 99$
9	**2a**	$FeCl_3$	dppy	15,000	97
10	**2c**	$CoCl_2$	dppy	15,000	60
11	**2c**	$FeCl_3$	dppy	15,000	67
12	**2c**	$FeCl_3$	dppy	1	$\leqslant 1$
13	**2d**	$PdCl_2$	dppy	15,000	84
14	**2e**	$PdCl_2$	dppy	15,000	$\geqslant 99$

[a] Reactions with **1b** were performed for 36 h while reactions of other substrates were performed for 48 h.

[b] Catalyst loadings; 2% $Pd(OAc)_2$, 5% $CoCl_2$, 5% $FeCl_3$.

[c] Ligand/metal salt = 2:1.

[d] Conversion determined by GC. Most runs also contained some biphenyl and oxidized ligand.

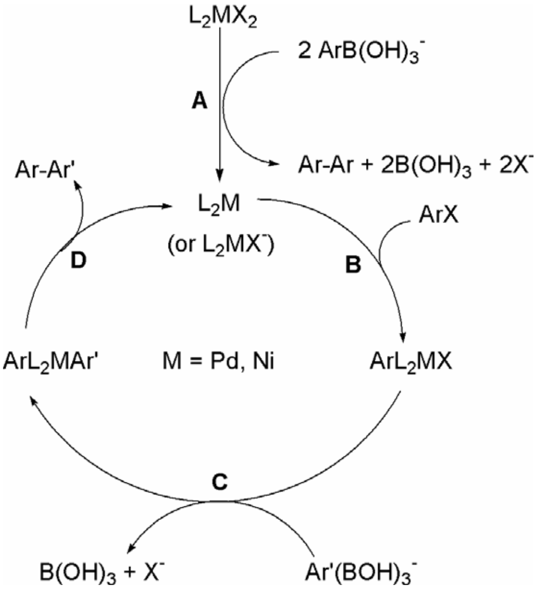

Figure 1. Abbreviated cross-coupling mechanism. Step A could also be achieved by a redox reaction involving ligand oxidation.

It is likely that the influence of pressure on the Pd-catalyzed Suzuki–Miyaura reaction is to accelerate turnover-limiting oxidative addition of the aryl halide (Fig. 1, step B). While it is also likely to inhibit reductive elimination (step D), this step appears not to be rate determining. We suggest that the primary influence of pressure on the corresponding nickel, cobalt, and iron catalyzed reactions may be accelerated reduction of the metal to a catalytically active oxidation state (step A). It is not easy to reduce cobalt[21] and iron[22] to their low-valent states, and a reducing agent such as a Grignard reagent is usually required. All of these pressure assisted reactions were accompanied by the formation of some biphenyl, which is consistent with homocoupling of phenyl boronic acid and concomitant reduction of the metal salt.[23] Biphenyl could also arise, however, from pressure assisted, oxidative homocoupling of phenylboronic acid in the presence of adventitious molecular oxygen.[5,9] Alternatively, reduction of the metal could be achieved by intramolecular oxidation of the ligand,[24] and some oxidized ligand was also observed in the GC/MS of each reaction. This redox reaction is reportedly accelerated by pressure.[14] Catalyst decomposition arising from ligand dissociation, which is especially serious under thermal conditions, is another common problem that could be suppressed at elevated pressure.[17]

In summary, we have demonstrated for the first time, the influence of high pressure on the Suzuki–Miyaura cross-coupling reaction. Improved yields are observed and expensive palladium salts can be replaced with cheaper nickel, cobalt, and iron salts. Some groups have reported Suzuki coupling with ligand free, 'homeopathic' concentrations of Pd(II) salts.[25] Our higher loading of 2 mol % Pd at 15 kbar highlights one disadvantage of current, commercial high-pressure reactors—the inability to stir reactions which presumably decreases the concentration of highly active Pd. Nevertheless, high-pressure does permit non-palladium catalyst systems and lower concentrations should be possible with a simple increment of the technology to include sonication.

Acknowledgments

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18. *Typical procedure:* To a Teflon reaction vessel was added a solution of 1.0 mmol 1-chloro-4-nitrobenzene **1b**, 1.2 mmol $PhB(OH)_2$, 2–10% catalyst/PPh_3 (1:2) in THF (7.0 mL) followed by 3.0 mmol of base (KF/KOH, 1:1). The vessel was then placed into a castor oil–ethanol mixture (85:15) and 15 kbar (1.5 GPa) pressure was applied. The reaction mixture was kept at 100 °C for 36 h. After this period, the sample was quenched with water, extracted with dichloromethane, purified by flash chromatography on silica gel, and subjected to analysis by GC/MS.
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