# Communications to the Editor

## Dramatic Increase of Turnover Numbers in Palladium-Catalyzed Coupling Reactions Using High-Pressure Conditions

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Palladium-catalyzed coupling reactions of the Heck type have developed to become one of the most versatile carbon–carbon bond forming processes.[1] Numerous elegant transformations in natural and non-natural product synthesis based on palladium have been developed. However, the lack of reactivity in many of these reactions often requires high reaction temperatures, long reaction times, and large amounts of catalysts. While most palladium-catalyzed C–C-coupling reactions even in the case of optimized procedures have been reported to proceed with 2.5–5 mol % of catalyst, using Pd to phosphine ratios of 1:2–6,[2] quantities of 10–20 mol % often proved to be necessary to ensure a smooth conversion to the products.[3] There have been two successful approaches so far to extend the lifetime of palladium catalysts, i.e., the use of a large excess of metal-coordinating ligands such as PPh₃[4] and the use of specially designed ligands such as P(o-tolyl)₃[5] which form highly stable metal complexes.[6] We report here a third possibility for increasing the lifetime of palladium catalysts, making the use of excess or specially designed ligands unnecessary.

High pressure has been widely applied in order to activate addition reactions, cycloadditions in particular. This technique, however, has received only little attention in transition metal catalysis, mainly to influence the selectivity of a reaction.[7] Nevertheless, a rate enhancement through pressure in standard Heck reactions has also been qualitatively observed.[8] We report here that palladium-catalyzed cross-coupling reactions carried out under pressure (8 kbar) are slightly, but significantly, accelerated. *However, the decisive factor of high pressure is the increase of lifetime of the catalyst, reflected in its turnover numbers (TON).*

**Table 1.** Pd-Catalyzed Arylation of **1** at 60 °C[a]

| entry | Pd(OAc)₂ (mol%) | p (kbar) | t (h) | yield[b] (%) | TON | rate (TON/h) |
|---|---|---|---|---|---|---|
| 1 (**1a**) | 10⁻¹ | 10⁻³ | 2 | 19 | 190 | 95 |
| 2 (**1a**) | 10⁻¹ | 10⁻³ | 4 | 25 | 250 | 62 |
| 3 (**1a**) | 10⁻¹ | 10⁻³ | 12[c] | 27 | 270 | 22 |
| 4 (**1a**) | 10⁻² | 10⁻³ | 2 | 2.2 | 220 | 110 |
| 5 (**1a**) | 10⁻² | 10⁻³ | 4 | 2.8 | 280 | 70 |
| 6 (**1a**) | 10⁻² | 10⁻³ | 12[c] | 2.8 | 280 | 23 |
| 7 (**1a**) | 10⁻² | 8 | 12 | 13 | 1300 | 108 |
| 8 (**1a**) | 10⁻² | 8 | 24 | 61 | 6100 | 254 |
| 9 (**1a**) | 10⁻² | 8 | 36 | 100[d] | ≥10000 | ≥276 |
| 10 (**1a**) | 5 × 10⁻³ | 8 | 72 | 76 | 15200 | 211 |
| 11 (**1a**) | 5 × 10⁻³ | 8 | 120 | 99[e] | 19800 | 165 |
| 12 (**1a**) | 10⁻² | 2 | 96 | 98 | 9800 | 102 |
| 13[f] (**1a**) | 10⁻² | 8 | 36 | 100 | ≥10000 | ≥276 |
| 14[g] (**1a**) | 10⁻² | 8 | 36 | 64 | 6400 | 178 |
| 15[g] (**1a**) | 10⁻² | 8 | 72 | 75[c] | 7500 | 104 |
| 16 (**1b**) | 5 × 10⁻³ | 8 | 120 | 87 | 17400 | 145 |
| 17 (**1c**) | 10⁻³ | 8 | 120 | 100 | ≥100000 | ≥833 |

[a] PhI (1 equiv, 2.0 mmol), cycloalkene (3 equiv, 6.0 mmol), NEt₃ (3 equiv, 6 mmol), 1:2 Pd(OAc)₂/PPh₃, 3 mL of 1:1 THF/acetonitrile. [b] Combined GC yields of **2**, **3**, and **4** (**2a**:**3a** ≈ 9:1; **2b**:**3b** ≈ 15:1; **2c**:**3c**:**4c** ≈ 8:77:15), using pentamethylbenzene as internal standard. [c] Longer reactions times did not increase the yield. [d] Isolated yield of **2a**: 71%. [e] Isolated yield of **2a**: 69%. [f] 1:4 Pd(OAc)₂/PPh₃; **2a**:**3a** ≈ 6:1. [g] Without PPh₃; **2a**:**3a** ≈ 28:1.

As a first model system we have chosen the palladium-catalyzed arylation of 2,3-dihydrofuran (**1a**).[2c,d] This reaction has attracted considerable interest over the past few years since it offers the possibility of carrying out asymmetric coupling reactions,[9] as well as providing an indirect catalytic approach to acetate[10] and *anti*-aldol[11] products.



**1a**: X = O
**1b**: X = NCO₂Et
**1c**: X = CH₂

**2a-c**    **3a-c**    **4c**
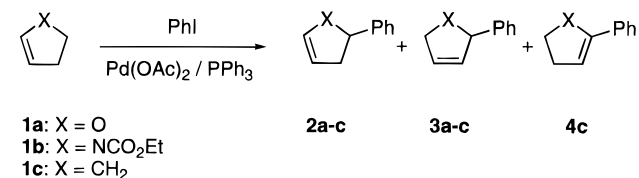
Kinetic studies of the phenylation of **1a** at 1 bar and 60 °C indicated that the catalyst, formed *in situ* from 1:2 palladium-(II) acetate/triphenylphosphine, displays an initial activity of about 100 cycles/h, which subsequently decreases constantly (e. g., after 6 h the activity had dropped to about 5 cycles/h). Experiments with 0.1 and 0.01 mol % palladium under normal pressure (Table 1, entries 1–6) reveal that the maximum TON for the palladium catalyst are about 250–280. However, experiments carried out under high pressure clearly show that the lifetime of the catalyst is dramatically prolonged. While the maximum catalyst activity is only up to 3 times higher at 8 kbar (entries 7 and 8), catalyst decomposition with time seems to be very slow, in sharp contrast to the normal pressure reactions. Thus, reactions carried out at 60 °C on a 2 mmol scale at 8 kbar reproducibly[12] gave TON between 10 000 and

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(12) All runs at high pressure were performed several times and were reproducible within 5%. In Table 1, the lowest yield obtained is always given.

**Table 2.**   Pd-Catalyzed Arylation of **1** at 100 °C[a]

| entry | Pd(OAc)$_2$ (mol %) | $p$ (kbar) | $t$ (h) | yield[b] (%) | TON | rate (TON/h) |
|---|---|---|---|---|---|---|
| 1 (**1a**) | $5 \times 10^{-4}$ | 8 | 72 | 73 | 146000 | 2030 |
| 2 (**1b**) | $5 \times 10^{-4}$ | 8 | 72 | 67 | 134000 | 1860 |
| 3 (**1c**) | $10^{-4}$ | 8 | 168 | 77 | 770000 | 4580 |
| 4[c] (**1c**) | $10^{-4}$ | 8 | 168 | 47 | 470000 | 2800 |

[a] For conditions, see footnote *a* in Table 1. [b] Combined GC yields of **2**, **3**, and **4** (**2a:3a** ≈ 19:1; **2b:3b** ≈ 18:1; **2c:3c:4c** ≈ 11:85:4), using pentamethylbenzene as internal standard. [c] 1:12 Pd(OAc)$_2$/PPh$_3$; **2c:3c:4c** ≈ 10:85:5.

20 000 (entries 9–11).[13] Moreover, high turnover numbers can be reached already at a pressure of 2 kbar (entry 12). The reaction proceeded also in the presence of larger amounts (entry 13) and in the absence of any PPh$_3$ (entries 14 and 15), although slightly lower TON were observed in the latter case. The 2,3-dihydropyrrole **1b** gave equally good results as **1a** (entry 16), while cyclopentene (**1c**) proved to be even more reactive than **1a** or **1b** (entry 17).
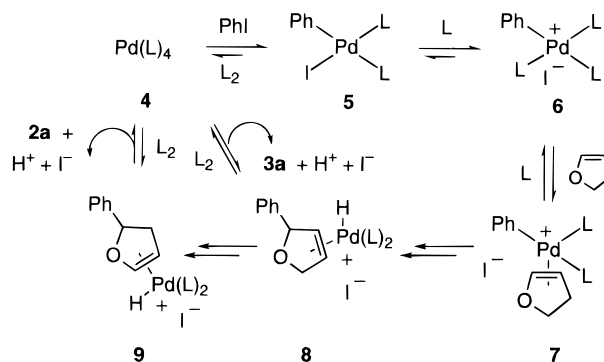
Increasing the reaction temperature to 100 °C resulted in considerably higher TON and rates for all substrates, demonstrating that pressure also stabilizes the catalyst at elevated temperatures (Table 2). Again, best results were obtained with a catalyst preformed from 1:2 Pd(OAc)$_2$/PPh$_3$, while larger phosphine concentrations decreased the reaction rate (*cf.* entries 3 and 4). A pleasant side effect is that the main products **2a**, **2b**, and **3c** are formed with better regioselectivity than at the reaction temperature of 60 °C.

One mode of deactivation of a homogenous palladium–phosphine catalyst is the dissociation of the stabilizing ligand from the metal during the reaction followed by precipitation of palladium from the reaction mixture. This effect is usually countered by the use of an excess ligand; however, a decrease of the reaction rate might result in parallel.[14] High pressure is apparently capable of stabilizing the catalyst by strongly enforcing coordination of even weak ligands such as solvent molecules to the metal. Ligand/substrate exchange is nevertheless still facile, and consequently the catalyst activity is maintained.

The prediction of the net effect of pressure on a metal-catalyzed reaction is not easy in light of the multiple reaction

**Scheme 1**



steps occurring. A preliminary analysis for the arylation of **1a** is nevertheless given (Scheme 1). Generally, all addition steps of neutral compounds as well as all dissociation steps in which ions are formed (electrostriction)[15] might be favored. Moreover, even decomplexation reactions, e.g., elimination of a palladium hydride species in **9**, should proceed by an associative substitution mechanism and therefore be favored by pressure.[16] Following these principles, pressure should have an activating effect on all but the intramolecular insertion and migration steps, e.g., **7** to **9**, which are regarded as neutral toward pressure.

This analysis is supported by our finding that the regioisomeric ratio **2a:3a** is not influenced by pressure at low PPh$_3$ concentrations. Using an excess of PPh$_3$, which acts as a good nucleophile, substitution of the dihydrofuran ligand in **8** can successfully compete with the migration pathway. Consequently, under such conditions **3a** is found as the main product.[7a]

In conclusion, we have demonstrated that high pressure might be used in palladium catalysis as a tool to greatly increase the lifetime of the catalyst. Further investigations to explore the effects of high pressure in transition metal catalysis are currently under way.

(13) Addition of the catalyst: 0.05 mmol of Pd(OAc)$_2$ and 0.1 mmol of PPh$_3$ were dissolved in 25 mL of 1:1 THF/acetonitrile, and the appropriate volume of this catalyst solution was added to the reaction mixture.
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