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Statistical experimental design-driven discovery of room-temperature conditions for palladium-catalyzed cyanation of aryl bromides

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Abstract—A combination of $Pd_2(dba)_3$ ·CHCl₃ (0.5 mol%) and commercially available, air-stable phosphonium salt [(*t*-Bu)₃PH]BF₄ (1.4 mol%) in a presence of Zn powder and Zn(CN)₂ as the cyanide source comprises an extremely efficient catalyst system for the cyanation of a diverse array of aryl bromides, at room temperature. This result emerged from an experimental strategy that combines the advantages of parallel, automated experimentation with the design of experiments (DOE) for the effective definition of an optimal set of reaction conditions.

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Mainly propelled by the quest for milder reaction conditions as compared to the classic Rosenmund-von Braun reaction,¹ transition metal-catalyzed cyanation of aryl halides is experiencing a remarkable renaissance.² Nevertheless, despite the discovery of new and more active catalytic systems, efficient halogen-cyanide exchange still necessitates temperatures substantially above the ambient temperature and/or high catalyst loadings. Presumably, this is required to compensate for catalyst deactivation by an excess of cyanide ions in the reaction mixture.^{2a} Obviously, the development of room-temperature reactions poses significant advantages with regard to selectivity/stability issues and becomes an especially attractive objective from an industrial standpoint.

In this paper we report a general procedure for roomtemperature palladium-catalyzed cyanation of a wide range of aromatic bromides.³ Initial attempts focussed around selecting pertinent ligands for moderate-temperature cyanation of 1-bromonaphthalene **1**. An evaluation of several ligands⁴ showed that a combination of Pd₂(dba)₃·CHCl₃ (1 mol%) and [(*t*-Bu)₃PH]BF₄ (2 mol%) in DMF (1 g/mL) generated a catalyst that

couples cyanide ions, from Zn(CN)2, with 1 at 50 °C to produce 1-cyanonaphthalene 2.5^{5} Although at this stage catalyst efficiency was still moderate, this crystalline solid and commercially available phosphonium salt, recently emerged as a user-friendly alternative to air-sensitive $P(t-Bu)_{3,6}^{6}$ furnished the cleanest reaction profile and was selected for further study. Ancillary experimentation showed that conversion could be improved by working at higher dilutions (0.3 g/mL) in wet N-methylpyrrolidone (NMP, 1 vol% water content⁷) and including Zn powder (25 mol%) in the reaction mixture.⁸ Under these conditions, however, considerable homocoupling of 1 was observed in addition to the usual hydridodebromination side reaction producing naphthalene. The large number of potential parameters influencing, often contradictorily, conversion and yield convinced us of the appropriateness of a multivariate approach in order to develop a reliable protocol within a reasonable number of independent experimental trials. In this light, the technique of design of experiments (DOE) stands as a precious tool for the effective investigation of an appropriate 'experimental space' as delimited by the low and high values of the experimental variables under study.9 By virtue of statistical experimental design approach, the influencing variables and, appealingly, their interactions are easily revealed and their effect quantified. Thus, generation of inferential models from aptly designed sets of experiments furnishes the experimentalist an optimum set of reaction

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conditions. A preliminary fractional factorial design¹⁰ unveiled robust reaction conditions and set the basis for the subsequent optimization design. Accordingly, a Box–Behnken design was implemented (Fig. 1) to allow a more precise quantification of the effect of significant factors on the cyanation yield with a minimum number of additional experimental runs.¹¹

Three factors, namely, amount of Zn(CN)₂ (variable A: from 1.0 to 1.2 equiv), $[(t-Bu)_3PH]BF_4/Pd(0)$ ratio (ligand to palladium ratio, L:Pd; variable B: from 0.8 to 2.0) and water content (variable C: from 0.1 to 2 vol%) were varied over three levels, while the amount of palladium pre-catalyst Pd₂ (dba)₃·CHCl₃ (0.5 mol%), of Zn $(5 \text{ mol}\%)^{12}$ and the temperature (25 °C) were kept at their best level as emerged from the previous factorial screening. Experiments were performed in parallel on an automated workstation (Anachem SK 233) and analyzed after 24 h.¹³ The plot, illustrated in Figure 2, was generated according to the quadratic model obtained from statistical analysis of the data and describes the dependence of in situ yield of 1-cyanonaphthalene 2 on the amounts of added water and the L:Pd ratio. On the contrary, the amount of $Zn(CN)_2$ was found not to have a significant influence on the reaction yield over the examined range.

A region of predicted maximum yield is observed at low levels of added water (0.1-0.3 vol%), where best performances are realized by adopting a L:Pd ratio equal to 1.2– 1.5. Higher L:Pd ratios (1.8-2.0) consistently hamper the catalyst system performances. This effect is particularly marked at high levels of added water, which lead to an almost complete inactivation of the catalyst, probably as a consequence of the increased concentration of dissolved cyanide ions. This well fits with the recent findings from Fu's and from Hartwig's group who



Figure 1. Box–Behnken optimization design. Spheres indicate the position of single experimental runs, that is, the setting of the experimental variables, within the experimental space. In turn, this is defined as the cubic region delimited by the coded value (actual values are reported in brackets) for the reaction variables under study. The grey dot positioned in the centre of the cubic region indicates four replicate experiments (factors setting: $Zn(CN)_2 = 1.1$ equiv, L:Pd = 1.4, water = 1 vol%), which allow experimental error to be estimated. Measured response values for in situ yield of 1-cyanonaph-thalene 2 for each experimental run are reported within the sphere area; the average value is reported for the replicate centre points.



Figure 2. Response surface plot, as produced by MODDE, describing the variation of the predicted in situ yield of 1-cyanonaphthalene **2** as a function of the two experimental variables which were found significant in the statistical analysis, namely B (L:Pd ratio) and C (amount of added water relative to the amount of solvent used).

independently observed the strong connection between cross-coupling reaction rates and L:Pd ratio with sterically congested ligands.¹⁴ While the resting state for palladium in the Pd₂(dba)₃/*t*-Bu₃P system has been identified as Pd[P(*t*-Bu)₃]₂ (L:Pd = 2) across a wide range of L:Pd ratios, oxidative addition has been shown to occur to a highly unsaturated monophosphine intermediate (L:Pd = 1) through a preequilibrium involving ligand dissociation.¹⁵ It was also noted that higher, up to 1.5, L:Pd ratio appears to stabilize the catalyst and decrease the precipitation of palladium metal.^{14b}

As a final confirmation, the cyanation of **1** was conducted in quadruplicate, on a 5 g scale, under the suggested optimal variables setting. An average in situ yield of **2** of 98.0% (isolated yield of 88%, Table 1, entry 1) was obtained when **1** was treated with $Zn(CN)_2$ (1.1 equiv) in the presence of $Pd_2(dba)_3$ ·CHCl₃ (0.5 mol%), [(*t*-Bu)_3PH]BF₄ (1.4 mol%) and Zn powder (5 mol%) in wet NMP (water content 0.1 vol%) at room temperature for 24 h.

Having established a proper set of conditions for the cyanation of 1-bromonaphthalene, the scope of the present findings was tested on a range of differently substituted aryl bromides. As illustrated in Table 1, Pd₂(dba)₃·CHCl₃/[(t-Bu)₃PH]BF₄ effectively promotes room-temperature cyanation of a sterically and electronically diverse array of aryl bromides. Particularly noteworthy are the reactions with sterically congested, electron-rich 2-bromoanisole 9 and with extremely electron-demanding 4-bromoaniline 12. This underlines the fundamental role of bulky, electron-rich phosphine ligands in facilitating oxidative addition to otherwise problematic substrates.¹⁶ However, these conditions were not completely general. Neither relatively acidic 3-bromophenol 13 nor potentially ligating¹⁷ 3- and 2bromopyridine 14 and 15 were effectively cross-coupled under these room-temperature conditions. Pleasingly

Table 1. Room temperature $Pd_2(dba)_3$ ·CHCl₃/[(*t*-Bu₃)PH]BF₄-catalyzed cyanation of aryl bromides^a

Entry	Aryl bromide		Conv. (%) ^b	Yield ^c (%)
1	Br	1	98	88
2	0 Br	3	>99	89
3	F Br	4	>99	79
4	OHC Br	5	>99	65
5	MeOOC Br	6	>99	75
6	OHC Br MeO	7	>99	98
7	MeO Br	8	>99	74
8	Br OMe	9	>99	85
9 ^d	Br	10	>99	86
10 ^e	Br N H	11	>99	49
11	H ₂ N Br	12	>99	88
12 ^f	HOBr	13	70	55
13 ^f	Br	3-Br 14 2-Br 15	47 0	40 NR

^a Conditions: Pd₂(dba)₃·CHCl₃ 0.5 mol%, [(*t*-Bu)₃PH]BF₄ 1.4 mol%, 5% Zn powder, 1.1 equiv Zn(CN)₂, wet NMP, 24 h, rt. Reaction scale: 23 mmol.

^b Measured by HPLC after 24 h reaction time.

^c Isolated yield by column chromatography or crystallization.

^d Pd₂(dba)₃ CHCl₃ 1.5 mol%, [(t-Bu)₃PH]BF₄ 4.2 mol%.

^fRxn run at 80 °C for 3 h.

enough, cyanation of these substrates, with the exception of 2-bromopyridine,¹⁸ does proceed rapidly at 80 °C (Table 1, entries 12 and 13), thus substantially expanding the scope of the present method to less reactive aryl halides.

In summary, a strategy based on parallel ligands screening succeeded by investigation of the experimental variables by means of statistical experimental design has unveiled a versatile catalyst system, which allows cyanation of a wide range of aryl bromides under mild conditions, typically at room temperature.¹⁹ This procedure fares well when compared with the recently reported room-temperature palladium-catalyzed cyanation of aryl bromides³ in terms of higher turnover number (100 vs 20), stability of the ligand (air-stable $[(t-Bu)_3PH]BF_4$ vs air-sensitive $P(t-Bu)_3$) and use of quasi-stoichiometric amounts of $Zn(CN)_2$ (1.1 vs 1.8 equiv) and provides an excellent complement to existing methods which operates under harsher conditions. Moreover, the present approach reveals the ability of statistical experimental design (DOE) in efficiently disclosing and understanding relationships between experimental variables in complex reaction environments and represents the first example of empirical multivariate modelling of the non-linear relationship between L:Pd ratio and reaction yields, in palladium catalyzed reactions. On-going efforts are directed at expanding the utility of this catalyst system with special focus on aryl chlorides and triflates.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.116. Results for the ligands screening experiment; design matrix, measured responses and ANOVA table for the screening design and for the Box–Behnken optimization design. Experimental procedures using the automated workstation Anachem SK 233. This material is available free of charge via the internet at http:// pubs.acs.org.

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^eIndole was also formed as the major side product (42%, HPLC).

- 3. While this work was well in progress, room-temperature cyanation of aryl bromides/iodides using P(t-Bu)₃ as ligand was reported. Under the described conditions, the catalyst system performances were highly dependent on catalyst loading and no reaction was observed on 4-bromoacetophenone using 1.25 mol% of Pd catalyst. Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S. P. Synlett 2003, 2237–2239.
- 4. Eighteen commercially available ligands were screened in parallel. Besides [(*t*-Bu)₃PH]BF₄, the following bulky phosphines-catalyzed cyanation of 1-bromonaphthalene at 50 °C in comparable yield albeit at the expense of more consistent dehalogenation to generate naphthalene, which is the major side product under the conditions tested: P(*o*-Tol)₃, 2-(di-*t*-butylphosphino)biphenyl; 2-(di-*t*-butylphosphino)-1,1'-binaphthyl; 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl and P(*t*-Bu)₃. See the supplementary data.
- 5. Such a cyanation reaction proceeds without any added base, which is regarded as necessary in order to deprotonate [(*t*-Bu)₃PH]BF₄ and promote formation of the active catalyst, see Ref. 6. While cyanide ion can be considered a competent Brønsted base, we observed in the ³¹P NMR spectrum partial formation of Pd[P(*t*-Bu)₃]₂ (δ = 86 ppm) upon mixing Pd₂(dba)₃ and [(*t*-Bu)₃PH]BF₄ (δ = 52 ppm) in DMF in the absence of any base.
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- 10. This two-level factorial design (2⁵⁻¹, 16 randomized experiments plus three center points) was performed on an automated workstation (Anachem SK 233). Five factors were screened at two levels, namely amount of Pd (range: 1–5 mol%), L:Pd ratio (range: 0.8–2), amount of Zn powder (range: 5–50 mol%), amount of water (range: 0.1–1 vol%) and temperature (range: 25–75 °C). See the supplementary data. Based on results from this screening, two-variable interactions could be revealed and uniformly high yields were observed by setting the reaction variables Pd, Zn and temperature at their low level. As for the amount of water and L:Pd ratio, the situation was less clear cut and warranted further investigation. Both Design Expert, version 6.0.4, by Stat-Ease (www.statease.com)

and MODDE, version 7.0.0, by Umetrics (http:// www.umetrics.com) were used for generation and analysis of experimental designs.

- 11. With three factors, Box–Behnken designs represent an attractive alternative to the more commonly utilized central composite designs since they still allow to model quadratic response surfaces with a reduced number of experimental runs (12 vs 14 non-center points).
- 12. In the absence of Zn powder under otherwise identical conditions, we observe cyanation of 1-bromonaphthalene to occur in comparable yields and purity. However, inconsistent results were often obtained. We believe this may indicate an easier inactivation of the catalyst system by adventitious oxygen in the reaction mixture.
- 13. Reactions were run in a random order under nitrogen on 1.0 g scale, in 3 mL of NMP and quantified by HPLC gauging the in situ yield of 2 and the amount of residual starting material 1. See the supplementary data for details. The final equation (scaled experimental variables) for the in situ yield of **2** is given by yield = $84.2 - 25.5 \times B - 12.2 \times C - 17.1 \times B^2 + 8.0 \times$ $\dot{C}^2 - 13.6 \times B \times C$. The model parameters were estimated by means of the partial least squares regression method (PLS) including the result of one run from the 2^{5-1} factorial design which falls in the actual design space (i.e., run 3, factors setting: $Zn(CN)_2 = 1.2$ equiv, L:Pd = 1.2, water = 0.1% with Pd amount = 1%, Zn amount = 5% and temperature = 25 °C. The measured in situ yield of 1cyanonaphthalene 2 for this run was 83.5%). The product statistics indicate a significant model with fairly good predictability ($\mathbf{R}^2 = 0.840$, $\mathbf{R}_{adj}^2 = 0.767$ and $\mathbf{Q}^2 = 0.584$). See the supplementary data.
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- 19. General procedure. A two-necked reaction flask was charged with $Pd_2(dba)_3$:CHCl₃ (120 mg, 0.116 mmol, 0.5 mol%), [(*t*-Bu)₃PH]BF₄ (94 mg, 0.324 mmol, 1.4 mol%), Zn powder (76 mg, 1.16 mmol, 5 mol%) and Zn(CN)₂ (1.50 g, 12.77 mmol, 1.1 equiv) and purged with nitrogen. A solution of the aryl bromide (23.30 mmol) in wet NMP (0.1% water content, 15 mL) was added and the mixture was stirred at rt. After 24 h, the reaction was diluted with EtOAc and then washed with a 2 N NH₄OH solution and brine. The organic phase was concentrated and the residue purified on silica gel or by crystallization.