G3 and G4 Buchwald Precatalysts: Scale up, QC and application for the semi-automated parallel synthesis

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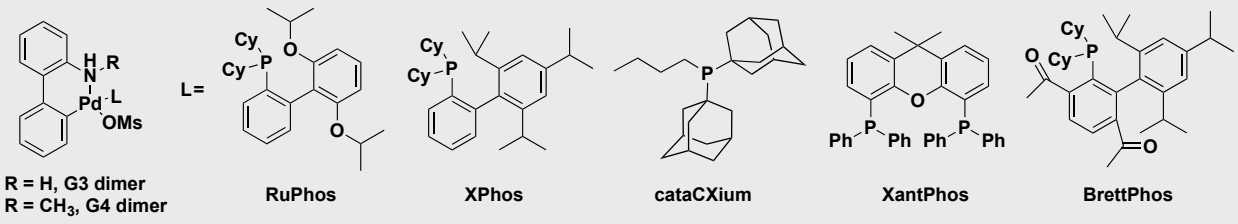
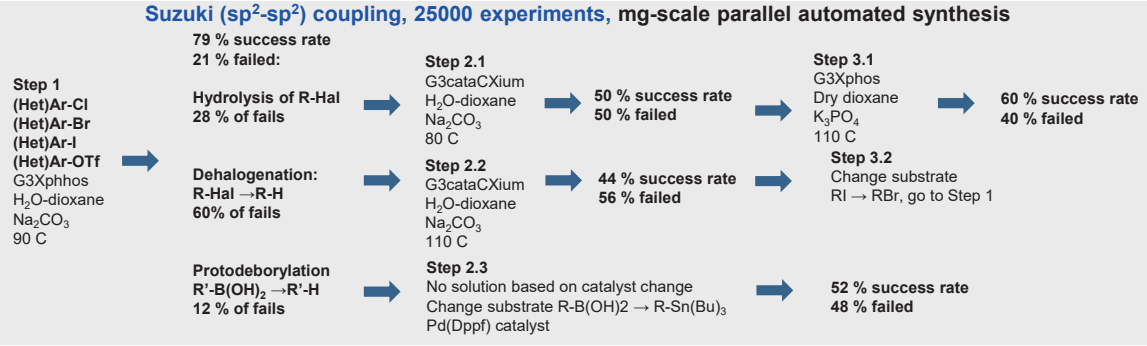
Introduction and Aim

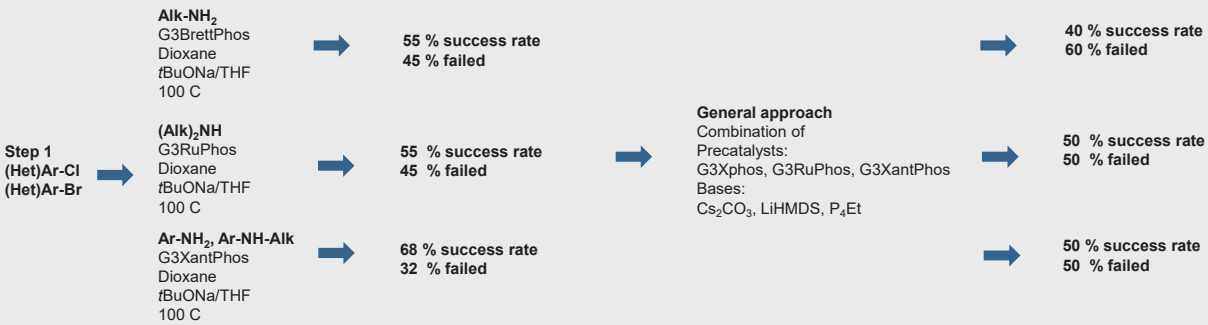
Suzuki (sp2-sp2) coupling and Buchwald coupling reactions are widely used in fine organic synthesis. It was found by us that Pd(dppf)-based catalysts were not applicable for automated synthesis because of difficult HT HPLC purification of products. Combinations of phosphine ligands with Pd2(dba)3 did not give predictable results due to uncontrolled degradation of Pd2(dba)3. Optimal results were achieved using G3 and G4 Buchwald precatalysts, but use of G4Xphos did not show statistically significant advantages on comparison of the product yield and precatalyst production cost. This finding was the reason for development of in-house laboratory scale up synthesis (up to 50 g from one synthetic run) and routine QC protocols of G3 and G4 Buchwald precatalysts.



Suzuki (sp^2-sp^2) coupling, 25000 experiments, mg-scale parallel automated synthesis



Buchwald coupling, 5000 experiments, mg-scale parallel automated synthesis

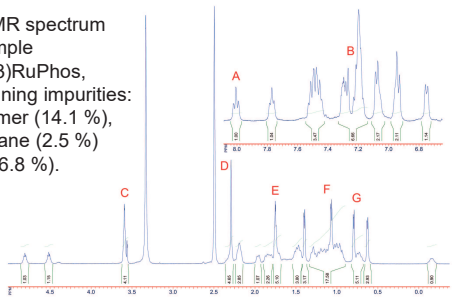


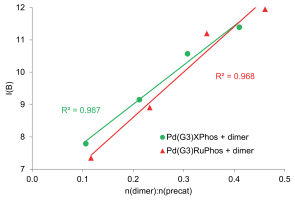
Catalysts QC by 1H NMR spectroscopy

It was found that synthesis of Buchwald precatalysts in CH_2Cl_2 was not desirable because solvate molecules of CH_2Cl_2 reduced product yields in further coupling reactions. By analysis of NMR spectra of in-house-made samples is was found that the main impurities were:

(i) unreacted dimer; (ii) THF; (iii) n-hexane. For example, in Pd(G3)XPhos, except O*CH*$_2$ signal of THF (C on the Fig.), the signals of impurities overlapped with the signals of the precatalyst: G3 dimer – B and D, hexane – F and G, THF – E.

^{1}H NMR spectrum of sample Pd(G3)RuPhos, containing impurities: G3 dimer (14.1 %), n-hexane (2.5 %) THF (6.8 %).





If we take the integral of weak-field signal **A** as 1 (I_A = 1), then:
n(dimer) = (I_B – 5) / 8,
n(hexane) = (I_F – a) / 8,
n(THF) = I_C / 4.
where a = 6 (XPhos) or 15 (RuPhos).
Weight fraction of impurity:
$w_i = n_i M_i / m_{total} \times 100$ %,
M – FW of the impurity,
M_{precat} – FW of the precatalyst,
$m_{total} = M_{precat} + \sum n_i M_i$

Conclusion

It was shown that G3, G4 Buchwald precatalysts could be used in automated milligram-scale synthesis by Suzuki and Buchwald reactions with HT HPLC purification, in contrast to the catalysts of earlier generations. Multi-gram protocol for synthesis of G3, G4 precatalysts was developed, QC method was proposed.

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