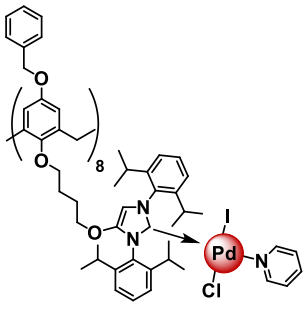
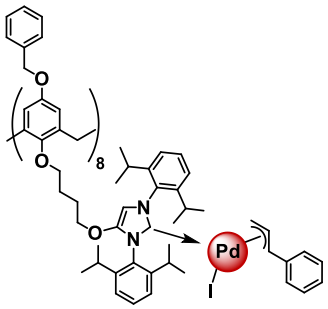
Supported catalysts for fine chemistry

Guidelines for the use of NOVECAT catalysts and ligands

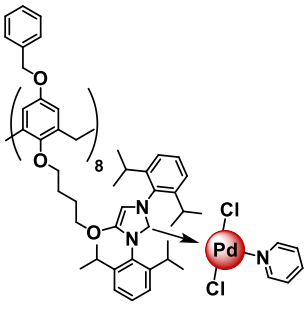
NOVECAT Supported Pd-NHC Catalysts



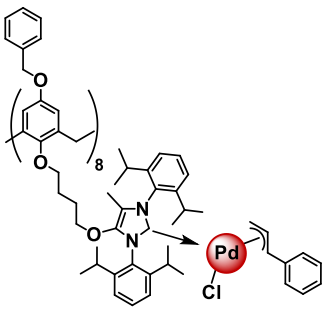
NOVECAT G2-01
MW = 8150.52 g.mol^{-1}



NOVECAT G2-02
MW = 8171.47 g.mol^{-1}



NOVECAT G2-03
MW = 7418.88 g.mol^{-1}



NOVECAT G3-01
MW = 7552.05 g.mol^{-1}

- **Handling and storage**: catalysts can be handled without specific precaution. They are stable for months when stored at room temperature without argon. However, for longer time storage (over a year) we recommend to keep it at low temperature (T < -10 °C).
- **General use**: The catalysts are not sensitive to water, therefore the use of anhydrous solvents is not necessary. They are soluble in dichloromethane, tetrahydrofuran, acetone and dimethyl sulfoxide. On the contrary, they are insoluble in alcohols, acyclic ethers, alkanes and water.

NOVECAT G2-01 and G2-03 for Suzuki-Miyaura couplings

- **Use**: Best performances of the catalysts **NOVECAT G2-01** and **G2-03** for the Suzuki-Miyaura reaction, in terms of both activity and leaching, are reached under inert atmosphere using alcoholic solvents such as ethanol in which they are insoluble. For optimal results, catalysis should be performed between 20 °C and 80 °C (temperatures higher than 80 °C may increase the leaching). Reactions are generally complete after 2 h at 80 °C, and no evolution occurs afterwards. To efficiently remove the catalyst, reaction mixtures are allowed to cool to room temperature before passing the solution through a pad of celite, or a filtrating device (in this case the porosity of the filter paper used should be 2.5 µm or thinner).[1,2,3]

- **Reaction settings**: Wide screening of the reaction parameters (solvent, concentration, temperature, amount of base and arylboronic acid) underlined two efficient sets of conditions for the Suzuki-Miyaura cross-coupling (see schemes below). For conditions B, water was used as a cosolvent with EtOH. We should add that arylboronic esters (ArBPin) can also be used efficiently as reagents. In addition, a deeper optimization should be performed for each new couple of reagents.

conditions A: $Ar_1–X$ (1 eq), **X = Br, Cl** + $Ar_2–B(OH)_2$ (1.1 to 1.5 eq) → **NOVECAT G2**, K_3PO_4 (1.2 to 2 eq), EtOH (C = 0.5-2 M), 20 °C < T < 80 °C, 2 h → $Ar_1–Ar_2$

conditions B: $Ar_1–X$ (1 eq), **X = Br, Cl** + $Ar_2–B(OH)_2$ (1.1 to 1.5 eq) → **NOVECAT G2**, K_3PO_4 (1.2 to 2 eq), $EtOH/H_2O$ (9:1, C = 0.5 M), 20 °C < T < 80 °C, 2 h → $Ar_1–Ar_2$

[1] I. Abdellah, P. Kasongo, A. Labattut, R. Guillot, E. Schulz, C. Martini, V. Huc. *Dalton Trans.* **2018**, *47*, 13843.

[2] A. Labattut, S. A. Fayssal, J. Buendia, I. Abdellah, V. Huc, C. Martini, E. Schulz, *React. Chem. Eng.* **2020**, *5*, 1509.

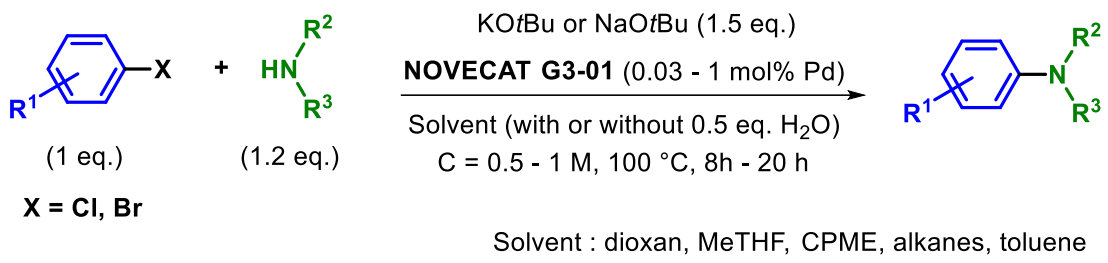
[3] S. Abi Fayssal, T. Naret, J. Buendia, A. Labattut, V. Huc, C. Martini, E. Schulz. *Adv. Synth. Catal.* **2022**, *364*, 1.

NOVECAT G2-02 and G3-01 for Buchwald-Hartwig couplings

- **Use**: Various solvents can be used for the Buchwald coupling, with excellent results. Among them, we can cite dioxan, THF or MeTHF, CPME (cyclopentylmethylether), toluene or methylcyclohexane. Ether type solvents (dioxan, THF and CPME) lead to the best yields at equal catalytic loading, therefore their use allows to perform the reactions with a lower catalytic amount than in toluene or alkanes. For some substrates, water (0.5 eq., associated with KO*t*Bu as base) has showed a positive effect on the outcome of the reaction (in alkanes and toluene in particular). Nevertheless, more than 1.5 eq. water should be avoided, since we then observed a strong decrease of the yield.[4]
- **Leaching considerations**: excellent values were obtained in all the above-mentioned solvents, with values between 5 and 60 ppm residual palladium. In general, alkanes might lead to the lowest values. For optimal results, catalysis should be performed between 80 °C and 100 °C (temperatures higher than 100 °C may increase the leaching). To efficiently remove the catalyst, reaction mixtures are allowed to cool to room temperature before passing the solution through a pad of celite (or silica), or a filtrating device (in this case the porosity of the filter paper used should be 2.5 µm or thinner) and washed with the appropriate solvent (ethyl acetate, ether, EtOH…). DCM, THF and all the solvents solubilizing our catalysts should be avoided to wash the pad or the filtrating device, since this may increase the palladium leaching considerably.
- **Reaction settings**: Wide screening of the reaction parameters (solvent, concentration, temperature, nature of the base) underlined the importance of some parameters:
  - KO*t*Bu gave the best results (with or without addition of 0.5 eq. H_2O), while NaO*t*Bu gives slightly lower yields. The use of carbonates or phosphates proved to be much less efficient. In some complex cases, LiHMDS can also be used to boost the reactivity of the amines.
  - A concentration between 0.5 and 1M appears to be optimal.
  - Reaction can be performed with either aryl chlorides or bromides, with almost no difference of reactivity.
  - Solvent, time and temperature should be adjusted depending on the couple of substrates, although general guidelines have been mentioned above. However, working in dioxan at 100 °C for 20 h generally gave the best yields.

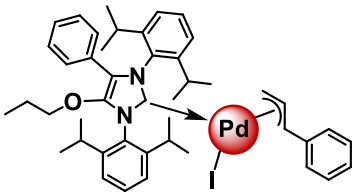
    N.B.: Reactions can be complete after 8 h at 100 °C, although we noticed that with low catalytic loading (0.1 mol% Pd), it is useful to warm for 20 h in order to reach full conversion.

The conditions described below briefly report all the aforementioned information:

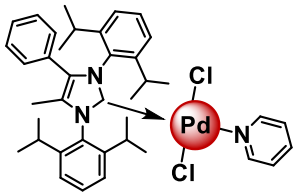


[4] S. Abi Fayssal, T. Naret, V. Huc, J. Buendia, C. Martini, E. Schulz. *Catalysis Science & Technology.* **2021**, *11*, 5223.

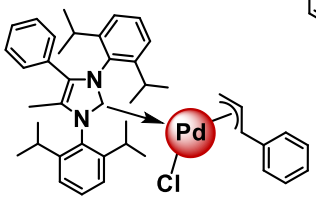
NOVECAT G4 and G5 - Homogeneous Pd-NHC Catalysts



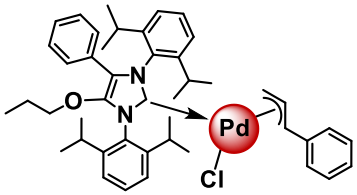
NOVECAT G4-01
MW = 873.27 g.mol^{-1}



NOVECAT G5-03
MW = 735.15 g.mol^{-1}



NOVECAT G5-04
MW = 737.77 g.mol^{-1}



NOVECAT G4-02
MW = 781.82 g.mol^{-1}

- **Handling and storage**: catalysts can be handled without specific precaution. They are stable for weeks when stored at room temperature without argon. However, for longer time storage (over a month) we recommend to keep it at low temperature (T < -10 °C).
- **General use**: These catalysts are not sensitive to water, therefore the use of anhydrous solvents is not necessary. They are soluble in most of the polar solvents, except alkanes and water.

NOVECAT G4 and G5 for Suzuki-Miyaura couplings

- **Use:** 2 sets of reaction conditions have been highlighted by our preliminary attempts. Conditions **A**, identical to the ones applied for supported catalysts, could include 10% v/v of water with EtOH. Water is particularly beneficial in the case of nitrogen containing heterocycles.

conditions A: $Ar_1–X$ (1 eq, **X = Br, Cl**) + $Ar_2–B(OH)_2$ (1.1 to 1.5 eq) → **NOVECAT G4-G5**, K_3PO_4 (1.2 to 2 eq), EtOH (or EtOH/H_2O 9:1), C = 0.5-1 M, 20 °C < T < 80 °C, 2 h → $Ar_1–Ar_2$

Conditions **B** imply the use of a strong base in dioxan (THF or Me-THF are also ok). These experimental conditions generally lead to similar yields compared to conditions **A**, except in the case of substrates bearing reactive functional groups (esters, nitriles…), for which conditions **A** prevail.

conditions B: $Ar_1–X$ (1 eq, **X = Br, Cl**) + $Ar_2–B(OH)_2$ (1.1 to 1.5 eq) → **NOVECAT G4-G5**, KO*t*Bu (1.2 to 1.5 eq), Dioxan (C = 0.5 - 1 M), 20 °C < T < 100 °C, 2 h → $Ar_1–Ar_2$

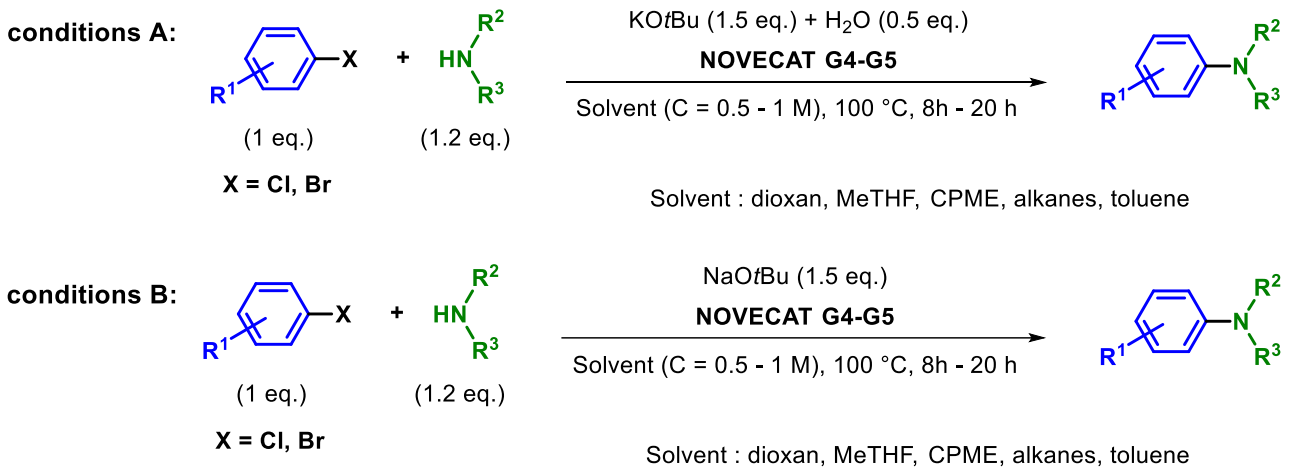
Finally, we recommend to start every new study with conditions **A**, using the following parameters: 1.5 eq $ArB(OH)_2$, 2 eq. K_3PO_4, in EtOH alone (C = 0.5 M), at 80 °C for 2 h.

NOVECAT G4 and G5 for Buchwald couplings

Use: Various solvents can be used for the Buchwald coupling, with excellent results. Among them, we can cite dioxan, THF or MeTHF, CPME (cyclopentylmethylether), *t*BuOH, toluene or methylcyclohexane. Ether type solvents and alcohols (dioxan, THF, CPME and *t*BuOH) lead to the best yields at equal catalytic loading, therefore their use allows to perform the reactions with a lower catalytic amount, although more tests should be performed with each couple of substrates to confirm that trend.

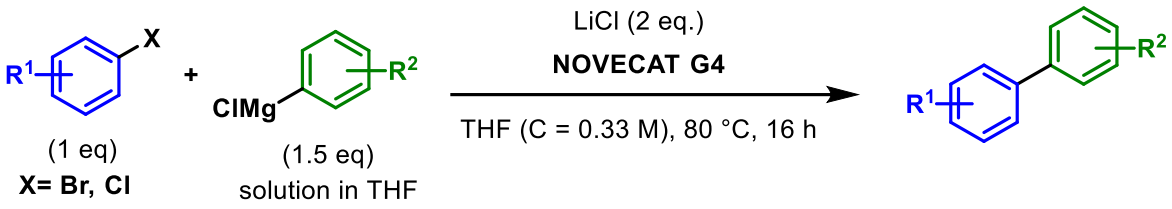
Choice of the base: KO*t*Bu and NaO*t*Bu gave the best results. In particular, KO*t*Bu associated with 0.5 eq. of water led to spectacular yields, while NaO*t*Bu should be used without water.

These considerations lead to 2 main sets of reaction conditions described below:



NOVECAT G4 for Kumada couplings

Use: Our optimization experiments revealed efficient conditions for the Kumada cross-coupling with G4 catalysts: addition of LiCl (anhydrous, 2 eq) in THF, at 80 C. Me-THF also gave good results, although slightly inferior. Other solvents led to much lower yields.
Grignard reagents are water sensitive, the use of anhydrous solvents is thus highly recommended.



NOVECAT G4 for Negishi couplings

Use: Our optimization experiments showed that the best conditions to use our homogeneous Pd-NHC catalyst are in a THF/DMI mixture, with the addition of LiCl (3 eq). We prepared the organozinc reagents by direct Zn insertion in DMI (dimethylimidazolidinone), and the reagents were then transferred in the reaction mixture containing all the reagents in THF. Concerning the temperature, similar results were obtained at room temperature or at 50 °C.
Room temperature was thus applied most of the time, due to its convenience. This might change for some couples of substrates.
Organozinc reagents are water sensitive, the use of anhydrous solvents is thus highly recommended.