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Protocol

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The use of methanol as a C1 building block

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Supplementary Methods

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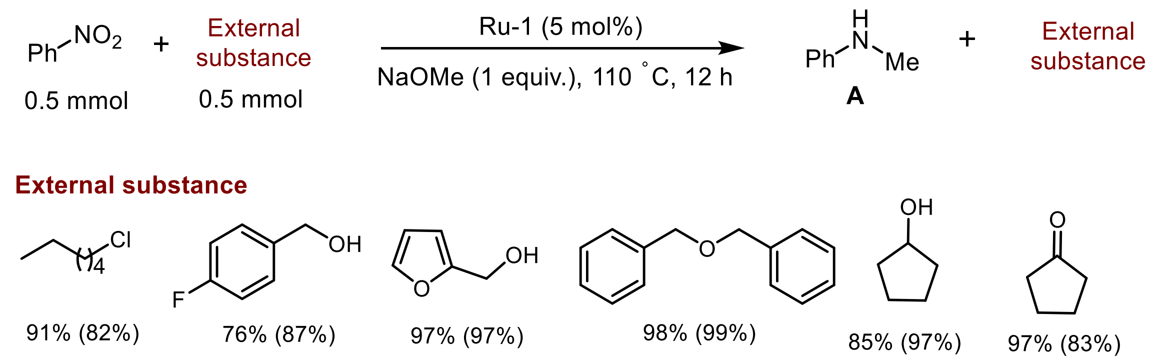
1. N-Methylation of nitrobenzene in the presence of external substances.[1]

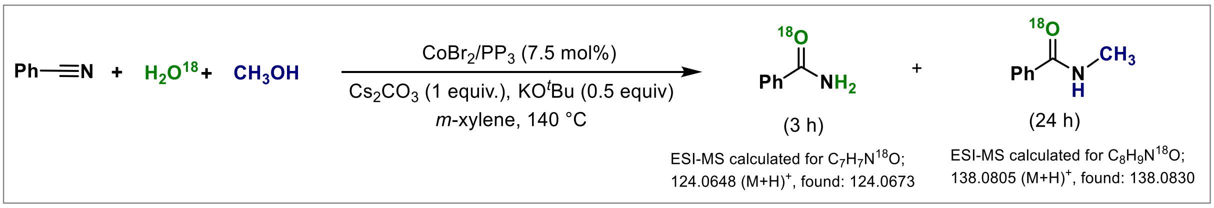
To an oven-dried pressure tube (9 mL), a magnetic stir-bar, nitro compound (0.5 mmol), external substance (0.5 mmol), NaOMe (0.5 mmol), Ru-1 (5 mol%), methanol (2.5 mL) and mesitylene (as internal standard) were added. Then, the pressure tube was sealed under an argon atmosphere and placed in a preheated oil bath at 110 °C (oil bath temperature) for 12 h. After that, the reaction mixture was cooled to room temperature, filtered through a small plug of silica, and analysed by GC to determine the conversion and selectivity.



Numbers outside and inside of parenthesis refer to GC yield of **A** and recovery of foreign substance, respectively

2. Labelling experiment with H_2O^{18} for the conversion of benzonitrile to N-methyl benzamide.[2]

Inside an argon-filled oven dried pressure tube (2.5 mL), benzonitrile (0.2 mmol), $CoBr_2$ (7.5 mol %), tris[2- (diphenylphosphino)ethyl]phosphine (PP_3) ligand (7.5 mol %), Cs_2CO_3 (0.2 mmol), KO^tBu (0.1 mmol), H_2O^{18} (2.0 mmol), and methanol/*m*-xylene (0.5 mL, 1:1 v/v) were added. Then, the pressure tube was sealed and placed in a preheated oil bath at 140 °C (oil bath temperature) for 3 h (nitrile hydration) and 24 h (nitrile hydration and methylation). The conversion and yield of the reactions were determined by GC analysis using mesitylene as an internal standard. The products were confirmed through the ESI-MS analysis.

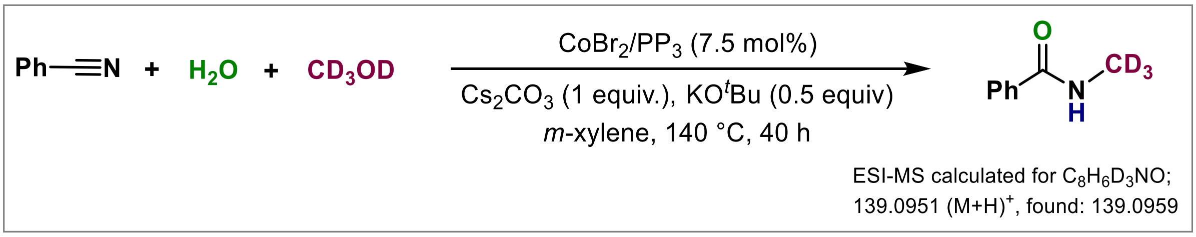


ESI-MS calculated for $C_7H_7N^{18}O$; 124.0648 $(M+H)^+$, found: 124.0673

ESI-MS calculated for $C_8H_9N^{18}O$; 138.0805 $(M+H)^+$, found: 138.0830

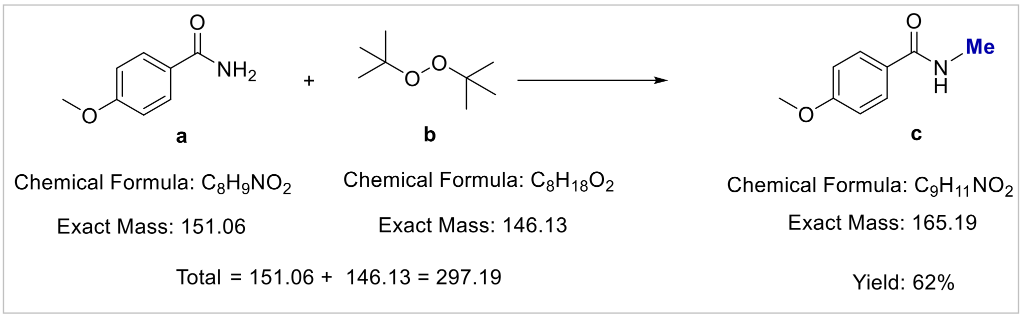
3. Labelling experiment with methanol-d_4 for the conversion of benzonitrile to N-methyl benzamide.[2]

Inside an argon-filled oven dried pressure tube (2.5 mL), benzonitrile (0.2 mmol), $CoBr_2$ (7.5 mol %), tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) ligand (7.5 mol %), Cs_2CO_3 (0.2 mmol), KO^tBu (0.1 mmol), H_2O (2.0 mmol), and methanol-d_4/*m*-xylene (0.5 mL, 1:1 v/v) were added. Then, the pressure tube was sealed and placed in a preheated oil bath at 140 °C (oil bath temperature) for 40 h. The conversion of the reactions was determined by GC analysis using mesitylene as an internal standard. The products were confirmed through ESI-MS analysis.



ESI-MS calculated for $C_8H_6D_3NO$; 139.0951 $(M+H)^+$, found: 139.0959

Supplementary Box 1| 'Green Chemistry Metrics' for N-methylation of 4-methoxybenzamide with di-*tert*-butyl peroxide.[3]



Reactant **a**	4-methoxybenzamide	75.5 mg	FW 151.06
Reactant **b**	Me_3CO-$OCMe_3$ (DTBP; 3 equiv.)	219.2 mg	FW 146.13
Solvent 1	H_2O	1000 mg	FW 18.01
Solvent 2	HOAc	1049 mg	FW 60.05
Product	4-methoxy-N-methylbenzamide	51.2 mg	FW 165.19

E factor = [{(75.5 mg + 219.2 mg + 1000 mg + 1049 mg) - (51.2 mg)}/51.2 mg] = [(2343.7 mg – 51.2 mg)/51.2 mg] = 2292.5 mg/51.2 mg = **44.77** kg waste/1 kg product

Atom economy = (165.19/297.19) x 100 = **55.58%**

Atom efficiency = 62 x (55.58/100) = **34.46%**

Carbon efficiency = (9/16) x 100 = **56.25%**

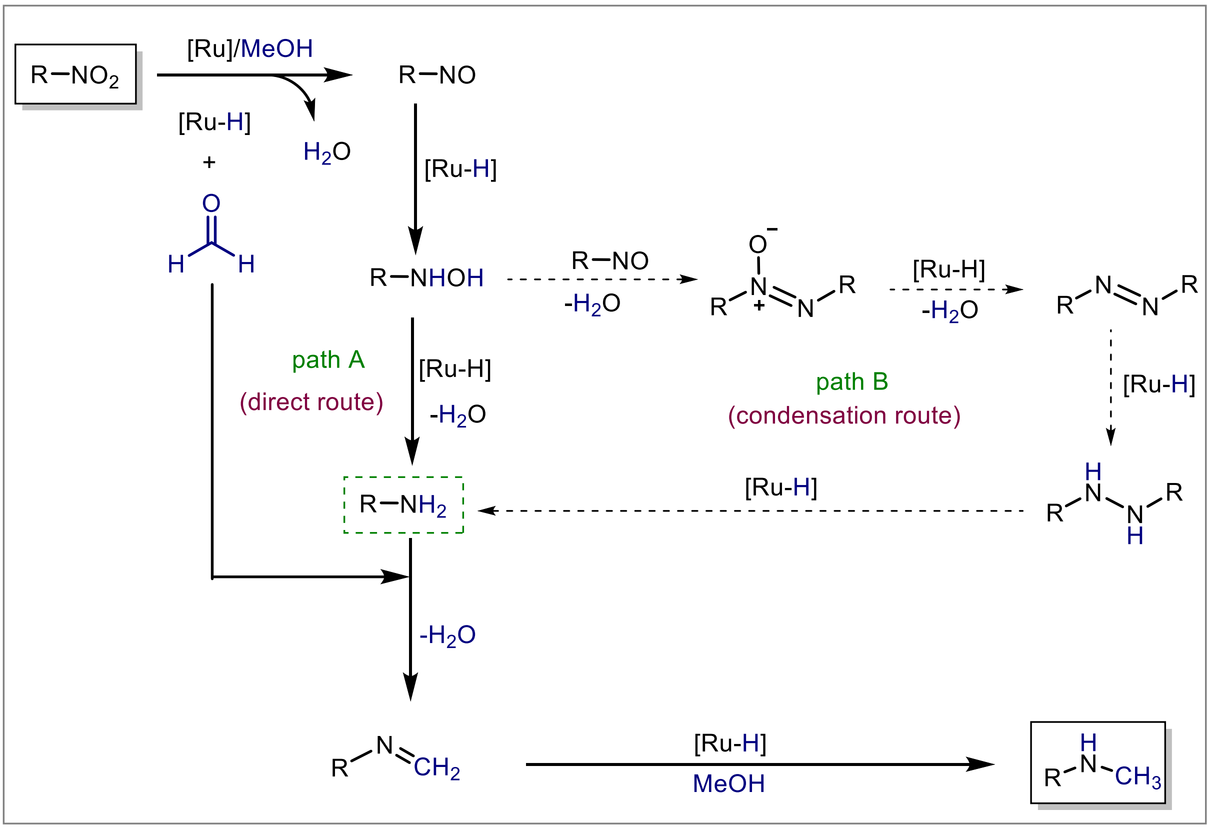
Reaction mass efficiency = [51.2 mg / (75.5 mg + 73.06 mg)] x 100 = **34.46%**

Supplementary References

1 Paul, B., Shee, S., Chakrabarti, K. & Kundu, S. Tandem Transformation of Nitro Compounds into N-Methylated Amines: Greener Strategy for the Utilization of Methanol as a Methylating Agent. *ChemSusChem* **10**, 2370-2374 (2017).

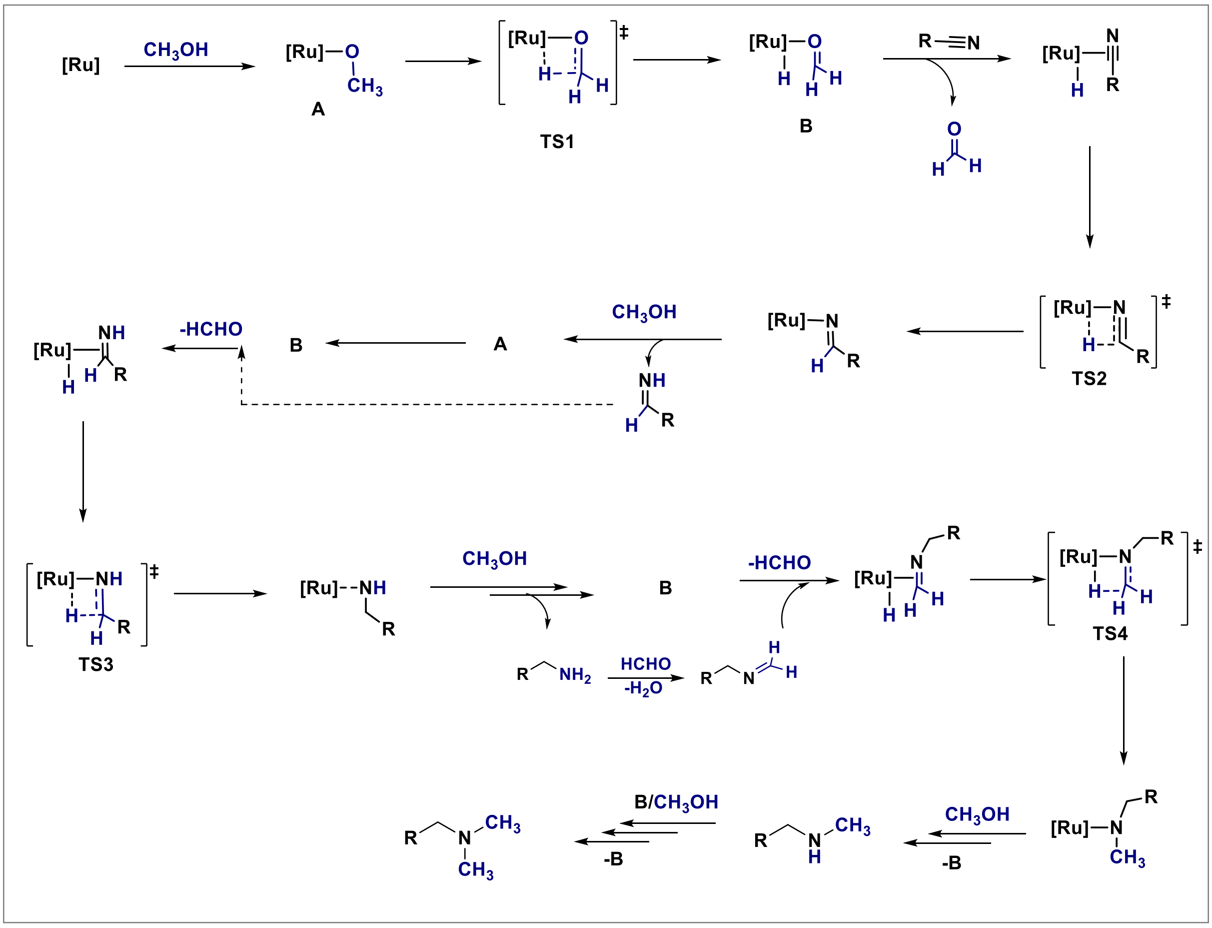
2 Paul, B., Maji, M. & Kundu, S. Atom-Economical and Tandem Conversion of Nitriles to N-Methylated Amides Using Methanol and Water. *ACS Catal.* **9**, 10469-10476 (2019).

3 Li, Z.-l. & Cai, C. Pd/Ni catalyzed selective N–H/C–H methylation of amides by using peroxides as the methylating reagents via a radical process. *Org. Chem. Front.* **4**, 2207-2210 (2017).



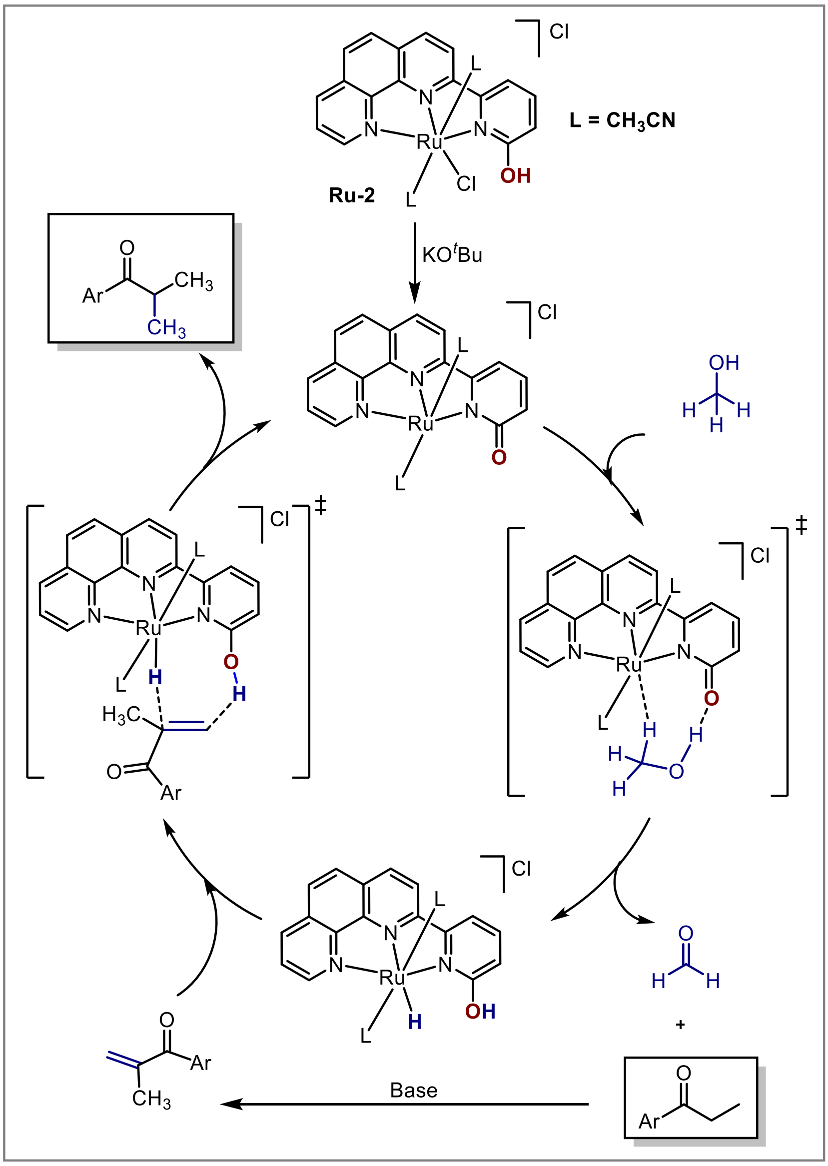
Supplementary Figure 1

Proposed mechanism of the ruthenium catalysed formation of N-methylated amine from nitrocompound using methanol.



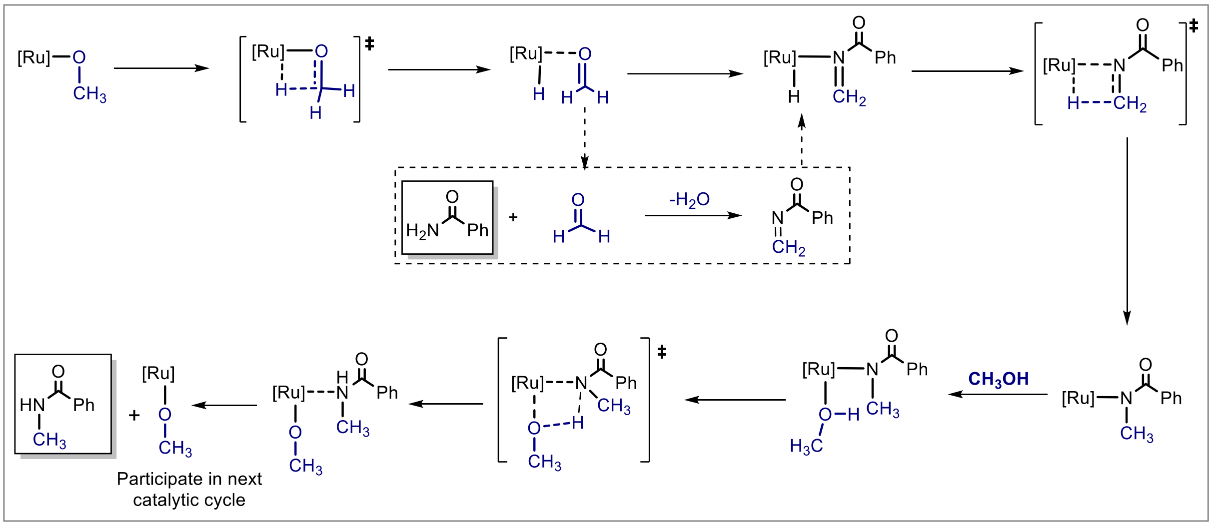
Supplementary Figure 2

Plausible pathway of the ruthenium catalysed conversion of nitrile to N-methylated amine with methanol.



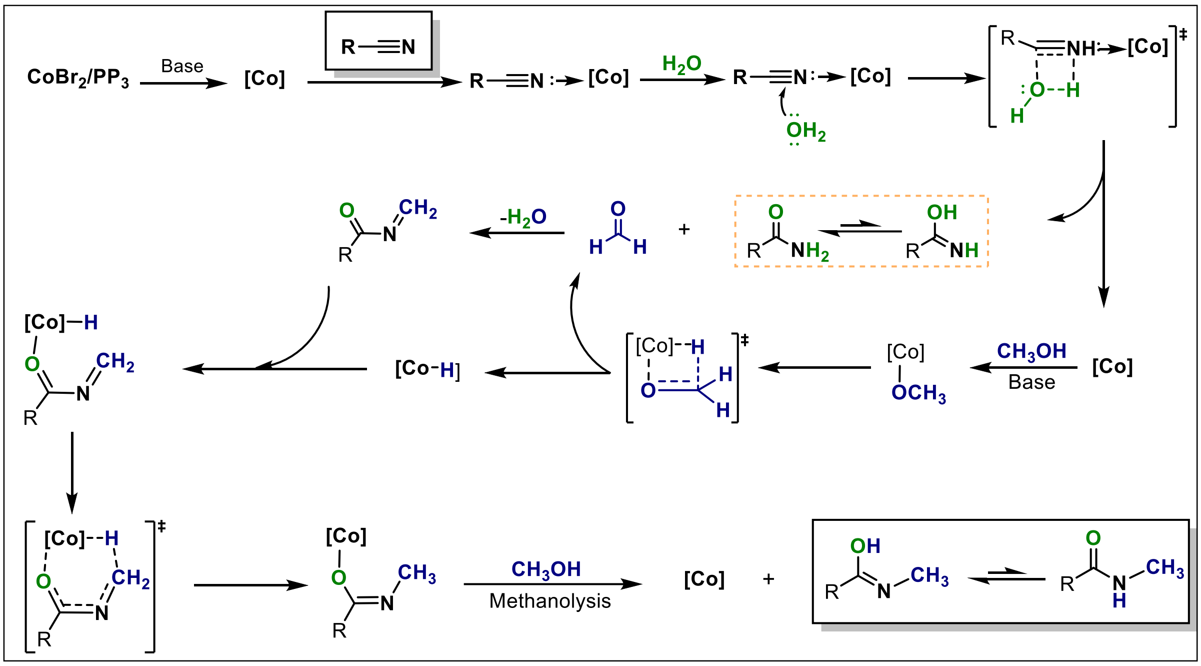
Supplementary Figure 3

Proposed mechanism of the α-methylation of ketone with methanol in presence of a bifunctional ruthenium catalyst.



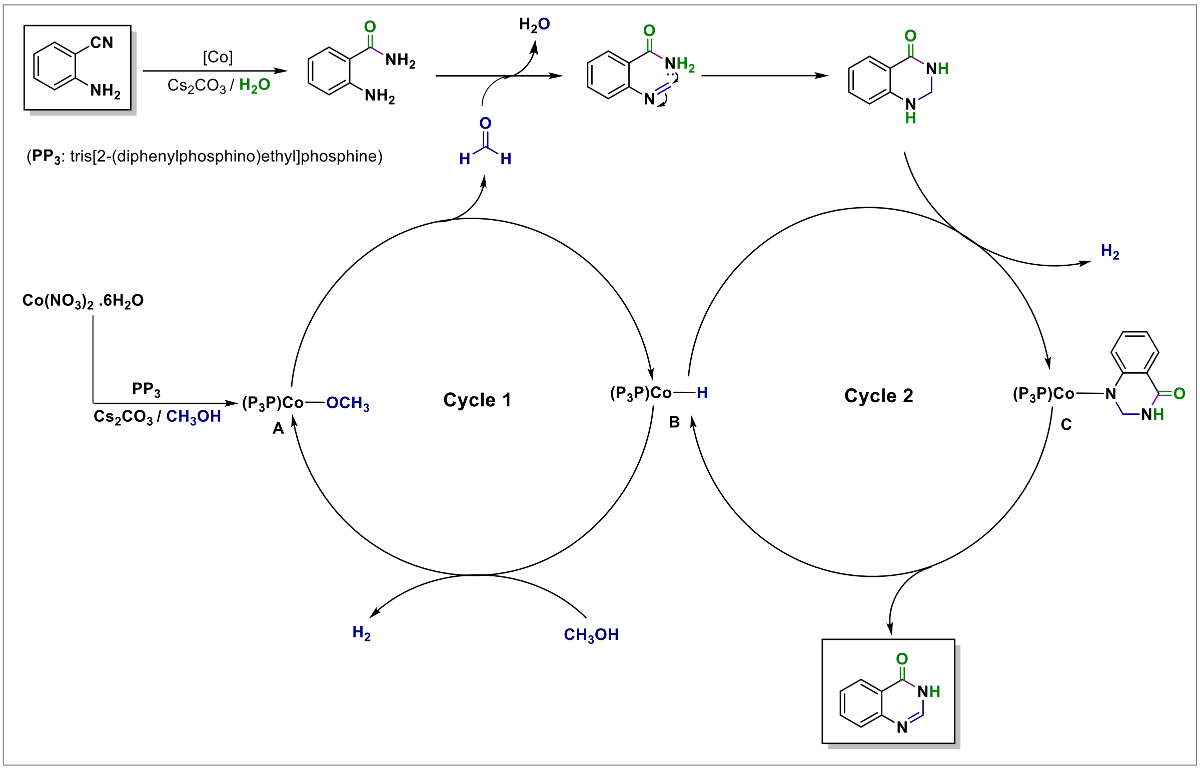
Supplementary Figure 4

Plausible pathway of the ruthenium catalysed N-methylation of the amide with methanol.



Supplementary Figure 5

Proposed mechanism of the cobalt catalysed direct synthesis of N-methylated amide from nitrile using CH_3OH/H_2O.



Supplementary Figure 6

Proposed mechanism of the cobalt catalysed synthesis of quinazolinone from 2-aminobenzonitrile using CH_3OH/H_2O.