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Cobalt Catalyzed N-Methylation of Amides using Methanol

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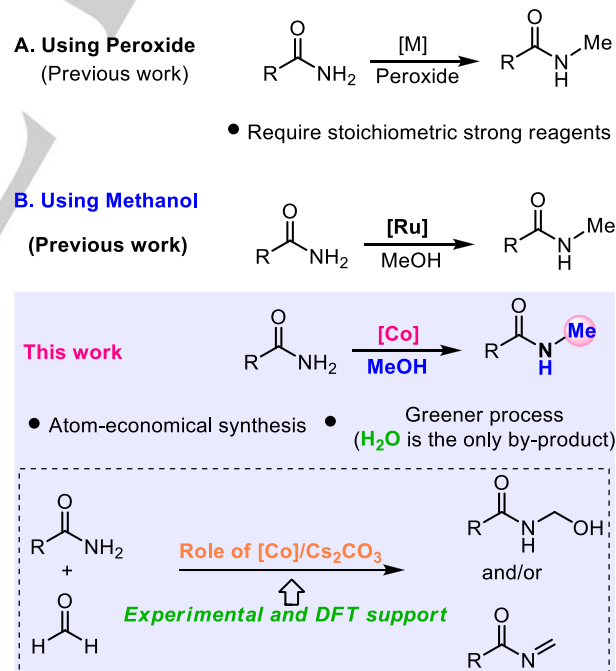
Abstract: N-Methylation of amide with methanol is reported in presence of an *in-situ* generated cobalt catalyst. With this simple protocol, various amides were methylated with up to 99% yields. Notably, the involvement of active cobalt (I) hydride in this methylation process was revealed by control experiment. Deuterium labelling studies were carried out using methanol- d_4 , taking benzamide and the possible intermediate N-(hydroxymethyl)benzamide to understand this transformation. Additionally, DFT calculations for the amide-formaldehyde coupling were performed to elucidate the influence of catalyst in this step.

Replacement of expensive noble metal based catalytic system with a more abundant and inexpensive 3d-metal catalyst is one of the emerging area of current research.^[1] Notably, 'Borrowing Hydrogen' (BH) principle has received significant momentum for the construction of new bonds using alcohol as greener and sustainable alkylating agent and extensively explored by using precious metal catalysts.^[2] In the recent year, most of the reports with 3d-metal based catalysts for such transformation were predominantly with benzyl alcohols and long chain alcohols.^[3] Among the 3d-metals, cobalt is very much attractive, for such transformation utilizing alcohols.^[3a] However, only few reports were known by using more challenging short chain alcohol methanol.^[4] In 2017, Liu and co-workers first reported, cobalt catalyzed C-methylation and N-methylation reactions using methanol by introducing a [Co]/PP₃ (PP₃ = *tris*[2-(diphenylphosphino)ethyl]phosphine) system.^[4a, 4b] Using [Co]/PP₃ catalytic system, we recently reported direct synthesis of N-methylated amides and quinazolinones by employing H₂O/ROH from nitriles and 2-aminobenzonitriles, respectively.^[4c, 5] Cobalt catalyzed numerous transformations using alcohol also explored in the recent years.^[3a] In 2018, Balaraman and co-workers developed an (NNN)-pincer cobalt complex for the efficient synthesis of N-alkylated imines and amines by using alcohol.^[6] In addition, Beller and co-workers explored cobalt catalyzed hydrogenation of carbonate to alcohols in the absence of any additive.^[7] Importantly, Jagadeesh and beller *et al.* employed a [Co]/triphos catalytic system for the reductive amination reaction to synthesize primary amines.^[8]

Amides are present in various natural products and pharmaceutically important molecules.^[9] Importantly, N-methylation of amides have a significant influence on their biological and physiological property.^[10] For example, to recognise the protein-protein interaction, methylation is an important tool.^[10b] Usually, N-methylated amides were synthesized from hazardous acid chlorides in presence of methylamine.^[11] Alternatively, in the recent years, few reports were immersed using peroxides for such N-methylation process.^[12] Therefore, a sustainable replacement of these reagents with methanol is exciting to explore. Methanol is highly

abundant and a biodegradable liquid which annually produced ~110 million metric tons (in 2018) from several natural resources (such as natural gas, biomass and coal).^[13] It is noteworthy to mention that, transition metal mediated utilization of methanol as C₁ building block has been explored in the recent years, for the α -methylation of nitriles/carbonyls, β -methylations of alcohols, and N-methylation/formylations of amines, etc. ^[14] However, significantly higher dehydrogenation energy of methanol ($\Delta H_{\text{MeOH}} = +84 \text{ kJ/mol}$)^[15] and poor nucleophilicity of amide,^[16] made the amide methylation process challenging. Thus, an efficient catalytic system is required to achieve the targeted amide methylation.

We recently reported a Ru(II)-complex catalyzed N-methylation of amide and tandem transformation of aldoxime to N-methylated amide using methanol as methylation reagent.^[17] Inspired by recent progress of methylation reactions using methanol as green methylating agent^[18] and the importance of methyl group in amide molecules^[10], herein we report a cobalt catalyzed N-methylation of amide using methanol (Scheme 1).



Scheme 1. Catalytic processes for the N-methylation of amide.

In our previous report, we disclosed CoBr₂/PP₃ (7.5 mol%) catalyzed tandem transformation of nitriles to N-methylated amides with H₂O/MeOH mixture.^[4c] However, in this transformation combination of two bases Cs₂CO₃ (1 equiv.) and KO^tBu (0.5 equiv.) was essential. Therefore, for the development

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of more sustainable synthesis of N-methylated amides by minimizing the amount catalyst and base, we were interested to explore cobalt catalyzed direct N-methylation of amides using methanol.

For the initial study, benzamide was selected as a model substrate for this N-methylation process (Table 1). In the first instance, we performed the reaction in a closed screw cap tube with the catalyst $\text{Co}(\text{acac})_2/\text{PP}_3$ ($\text{PP}_3 = \text{tris}[2\text{-}(\text{diphenylphosphino})\text{ethyl}] \text{phosphine}$) in presence of NaOMe, using methanol as sole solvent. However, selectivity of the N-methylbenzamide (**1**) was quite low (entry 1). A considerable amount of methylbenzoate was formed as side product (14%, entry 1). Selectivity for the desired product was improved significantly by substituting the strong base with a relatively weaker base like Cs_2CO_3 (entry 2). Next, we used a mixture of methanol and non-polar solvent toluene (to increase the reaction temperature of the closed vessel)^[19] at different ratio to identify its impact towards the yield of **1** (entries 4-7). Notably, an improved yield of N-methylbenzamide (74%) with higher selectivity was observed when 1:1 volumetric ratio of methanol/ toluene was used (entry 6). Then, we screened some other solvents (methanol/solvent; 1:1, v/v) and 82% yield of **1** was observed with *m*-xylene (entry 9).

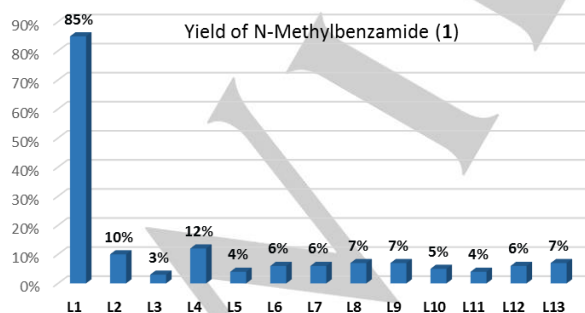
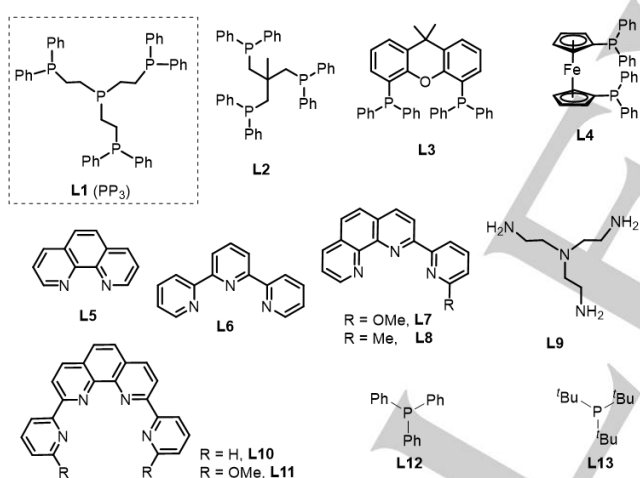
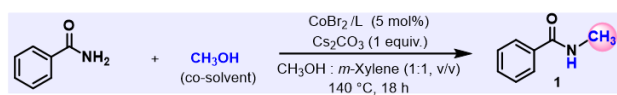


Figure 1. Effect of ligand in this transformation.

Next, we screened several cobalt precursors in presence of PP_3 ligand (entries 11-15). Among them, CoBr_2 presented the superior result in this transformation (85% yield, entry 15). Then,

we tested a set of *mono*-, *bi*- and *tri*- and *tetra*-dentate ligands (Figure 1). However, yields were very poor (3-12%) with these ligands (**L2-L13**). Therefore, we selected PP_3 as optimum ligand for this methylation process (Figure 1, **L1**). With the $\text{CoBr}_2/\text{PP}_3$ (5 mol%), next we screened different bases and where Cs_2CO_3 exhibited the best result (entry 15 and Table S5). Finally, a 96% yield of **1** was observed by increasing the reaction time to 24 h and we selected this as an optimum reaction condition for this transformation (entry 16). Importantly, the reaction could be performed successfully by using relatively lower catalyst loading (2.5 mol%) or shorter reaction time (12 h) at elevated oil bath temperature (150 °C, entries 17-18).

Table 1. Selected data for the screening of the optimal reaction conditions^[a]

Entry	PP ₃ / [Co] (5 mol%)	MeOH : Solvent (1:1)	Time (h)	Yield (%)
1 ^[b]	$\text{Co}(\text{acac})_2$	MeOH (1:0)	24	31 (14) ^[c]
2	$\text{Co}(\text{acac})_2$	MeOH (1:0)	24	27
3 ^[d]	$\text{Co}(\text{acac})_2$	MeOH (1:0)	24	51
4	$\text{Co}(\text{acac})_2$	MeOH : Toluene (0.25:1)	24	29
5	$\text{Co}(\text{acac})_2$	MeOH : Toluene (0.5:1)	24	48
6	$\text{Co}(\text{acac})_2$	MeOH : Toluene (1:1)	24	74
7	$\text{Co}(\text{acac})_2$	MeOH : Toluene (2:1)	24	58
8	$\text{Co}(\text{acac})_2$	MeOH : Benzene (1:1)	24	65
9	$\text{Co}(\text{acac})_2$	MeOH : <i>m</i> -Xylene (1:1)	24	82
10	$\text{Co}(\text{acac})_2$	MeOH : Dioxane (1:1)	24	26
11	$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	MeOH : <i>m</i> -Xylene (1:1)	18	73
12	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	MeOH : <i>m</i> -Xylene (1:1)	18	75
13	$\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$	MeOH : <i>m</i> -Xylene (1:1)	18	77
14	$\text{Co}(\text{OAc})_2$	MeOH : <i>m</i> -Xylene (1:1)	18	76
15	CoBr_2	MeOH : <i>m</i> -Xylene (1:1)	18	85
16	CoBr_2	MeOH : <i>m</i> -Xylene (1:1)	24	96
17 ^[e]	CoBr_2	MeOH : <i>m</i> -Xylene (1:1)	12	94
18 ^{[e],[f]}	CoBr_2	MeOH : <i>m</i> -Xylene (1:1)	24	92

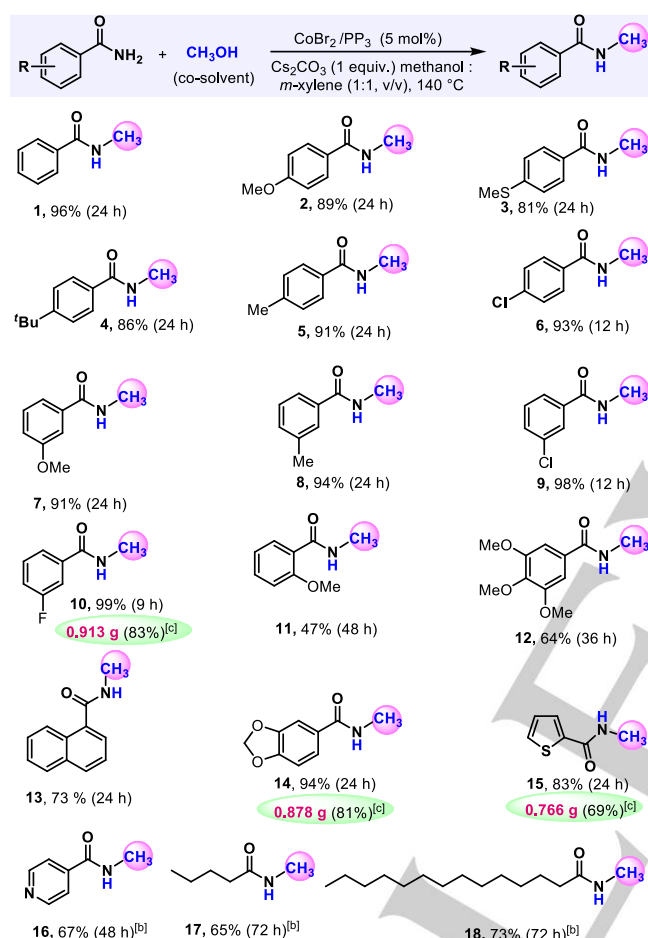
[a] Reaction conditions: benzamide (0.5 mmol), methanol/*m*-xylene (2.5 mL; 1:1, v/v), conversions and yields were determined by GC (using mesitylene as internal standard). [b] NaOMe (1 equiv.) instead of Cs_2CO_3 was used. [c] Yield of methyl benzoate in parenthesis. [d] 10 mol% catalyst. [e] 150 °C. [f] 2.5 mol% catalyst.

With this optimum conditions, next we moved to explore the scope of this transformation. Following this protocol, several substituted benzamides were converted to the desired N-methylated amides, efficiently (**2-10**, Table 2). Relatively lower

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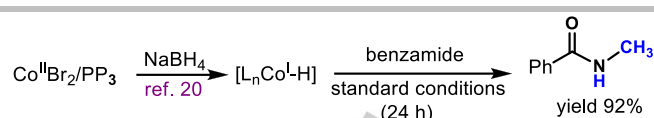
yield was observed with *ortho*-substituted benzamide (**11**). 3,4,5-Trimethoxybenzamide furnished the desired N-methylated product in 64% yield (**12**). For 1-naphthamide and benzo[d][1,3]dioxole-5-carboxamide, up to 94% yield was observed (**13** and **14**). Interestingly, *hetero*-nuclei containing amides and aliphatic amides were transformed to the desired N-methylated product in 65-83% yields (**15-18**). Notably, preparative scale synthesis of few N-methylated amides represents the practical applicability of this transformation (Table 2; For **10**, **14**, **15**).

Table 2. Substrate scope for the N-methylation of amides^[a]



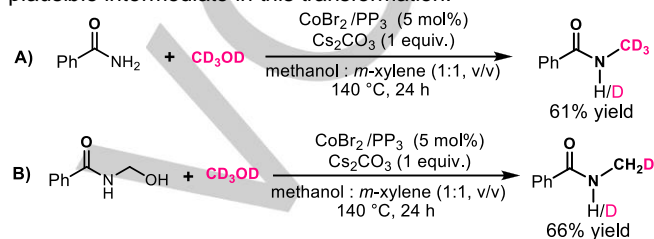
[a] Reaction conditions: amide (0.5 mmol), methanol/*m*-xylene (2.5 mL;1:1, v/v), isolated yield. [b] 7.5 mol% catalyst at 150 °C. [c] For preparative scale synthesis.

After exploring the scope of this process, next we performed several control experiments to understand the mechanism of this transformation. Initially, to identify the nature of active cobalt species, we synthesized cobalt(I) hydride *in situ* from $\text{CoBr}_2/\text{PP}_3$ by using NaBH_4 , as reported by Sacconi and co-workers.^[20] Under the optimized reaction conditions, this $[\text{Co}^{\text{I}}\text{-H}]$ species (5.0 mol%) furnished 92% yield of N-methylbenzamide (**1**). This experiment suggested the involvement of active $[\text{Co}^{\text{I}}\text{-H}]$ species, in this N-methylation process (Scheme 2).



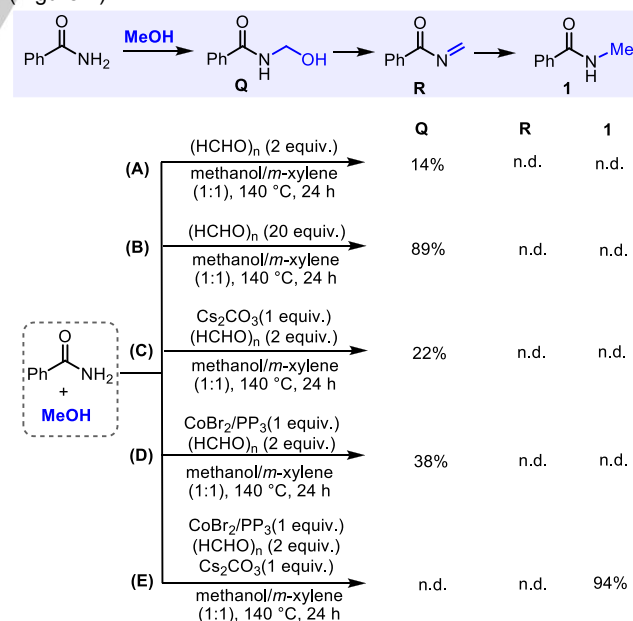
Scheme 2. Experiment with cobalt (I) hydride.

Then, we performed experiments using methanol- d_4 taking benzamide and the plausible intermediate N-hydroxymethylbenzamide; where fully and partially deuterated N-methylated amides were observed, respectively (Scheme 3). These experiments suggested methanol was the only source of methyl group and N-hydroxymethylbenzamide was one of the plausible intermediate in this transformation.



Scheme 3. Experiments with methanol- d_4 .

In our previous study on the cobalt catalysed tandem transformation of nitrile to N-methylated amide, we carried out a detailed DFT calculation for the methanol dehydrogenation as well as hydrogenation of N-methylenebenzamide (**R**) by $[\text{Co-H}]$.^[4c] In this process, the coupling of benzamide and formaldehyde and the dehydration step play an important role owing to the poor nucleophilicity of the amide as well as the lower concentration of aldehydes.^{[16] [21]} However, this step was not well investigated. In this work, we performed detailed DFT calculations and mechanistic experiments to understand this step more clearly (Figure 2).



Scheme 4. Controlled experiments.

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To investigate this process, when benzamide was reacted with 2 equiv. of paraformaldehyde in absence of catalyst and base, 14% of **Q** was obtained and an excess of paraformaldehyde (20 equiv.) produced 89% of **Q** (Scheme 4A and 4B). In addition, when similar reactions were performed in the presence of either catalyst or base, yield of **Q** was 22 and 38%, respectively (Scheme 4C and 4D). Notably, in none of the reactions **R** was obtained. Interestingly, under standard reaction conditions, in presence of paraformaldehyde (2 equiv.), a quantitative yield of **1** was obtained (Scheme 4E). These experiments suggested that the coupling of amide with formaldehyde is challenging with a lower concentration of formaldehyde. Furthermore, base and catalyst has significant role in both the coupling step as well as dehydration step.

Therefore, to check the feasibility of the coupling between amide and formaldehyde, we performed a DFT calculations for this amide-methanol coupling step without any catalyst/ base (Figure 2). The coupling of formaldehyde with benzamide *via* **I2**, generated the N-hydroxymethylbenzamide (**I3**) with an activation energy (E_a) barrier of 41.63 kcal/mol. To make the dehydration process favourable, the intermediate **I3** was transformed to **I4**, with a suitable orientation of $-CH_2OH$ fragment. The existence of the intermediate **I3/I4** was supported by the deuterium labelling experiment using methanol- d_4 and control experiments (Scheme 3 and 4). Then, intermediate **I5** was generated from **I4** through the dehydration process, with an activation energy barrier of 56.22 kcal/mol.^[22] These calculations suggested that the coupling between benzamide and formaldehyde followed by dehydration is energetically uphill in the absence of catalyst and the catalyst and base have a favourable influence on this transformation.

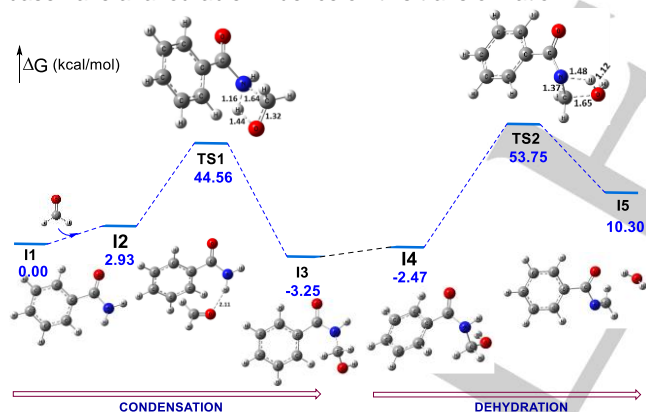
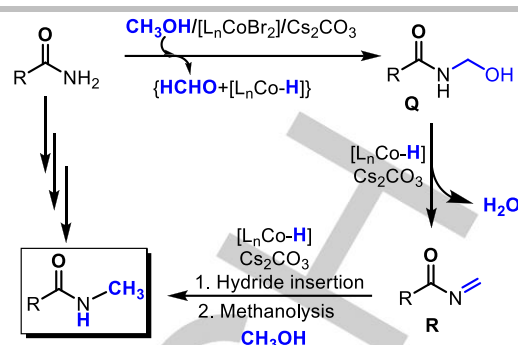


Figure 2. Calculated Gibbs free energies (kcal/mol) for the formation of N-methylenebenzamide from coupling of benzamide and formaldehyde (Hybrid functional, M06-2X was used with the 6-31G** basis set, bond length in Å).

Finally, we proposed a schematic pathway of this cobalt catalysed N-methylation process by using methanol (Scheme 5). At the start, dehydrogenation of methanol furnished formaldehyde and active $[Co^I-H]$ species in presence of Cs_2CO_3 . Then, the *in situ* generated formaldehyde reacted with amide and formed N-methyleneamide (**R**) by the influence of $[Co]/Cs_2CO_3$ at the reaction temperature. Finally, N-methylated amide was produced by the insertion of **R** into $[Co^I-H]$ followed by methanolysis.



Scheme 5. Schematic pathway.

In summary, we developed a cobalt catalyzed greener process for the N-methylation of amide using methanol. Various substituted aromatic, aliphatic and *hetero*-atom containing amides were transformed to the desired N-methylated amides, effectively. Preparative scale synthesis of several N-methyl amides revealed the scalability of this process. Importantly, control experiment suggested participation of active cobalt (I) hydride in this transformation. Experiments using methanol- d_4 supported that methanol was the source of methyl group and N-hydroxymethyl amide was the intermediate in this conversion.

Experimental Section

N-Methylation of Amide using Methanol. To an oven dried 9 mL screw cap tube a magnetic stir-bar, amide (0.5 mmol), $CoBr_2$ (5.0 mol%), *tris*[2-(diphenylphosphino)ethyl]phosphine (PP_3) ligand (5.0 mol%), Cs_2CO_3 (1.0 equiv.) were taken and then a mixture of methanol/*m*-xylene (2.5 mL, 1:1 v/v) was added. After that, the tube was sealed and placed in a preheated oil bath at 140 °C for specified time. After completion of the reaction, the tube was allowed to cool at room temperature. Then, a small portion of the reaction mixture was diluted with EtOAc, filtered through a small plug of silica and the sample was subjected for GC analysis to determine conversion as well as the product selectivity using mesitylene as internal standard. Finally, the desired N-methylated amide was purified through silica gel column chromatography using hexane-ethyl acetate as eluent. (**Caution:** All the reactions were performed inside the fume hood. After the reactions screw cap tubes were opened carefully under proper ventilation to release the produced hydrogen gas in the reactions.)

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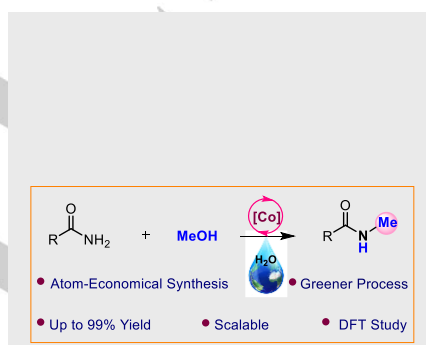
Keywords: amide • methanol activation • N-methylation • cobalt • control experiments and DFT calculations

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A cobalt catalyzed N-methylation of amide using methanol is reported. Control experiments and DFT calculations were performed to realize this catalytic process



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