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Letter

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Atom-Economical and Tandem Conversion of Nitriles to N-Methylated Amides using Methanol and Water

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ABSTRACT: A cobalt complex catalyzed tandem conversion of nitrile to N-methylated amide is described using methanol and water mixture. Using this protocol, several nitriles were directly converted to the desired N-methylated amides efficiently. Kinetic experiments using H_2O^{18} and CD_3OD suggested that water and methanol were the source of oxygen atom and methyl group respectively in the final N-methylated amides. Importantly, the participation of active Co(I)-H species in this transformation was realized from the control experiment. KIE study suggested that the activation of C-H bond of methanol was a kinetically important step. Hammett plot confirmed that the reaction was faster with the electron deficient nitriles. In addition, the plausible pathway for the formation of N-methylated amides from nitriles was supported by the computational study.

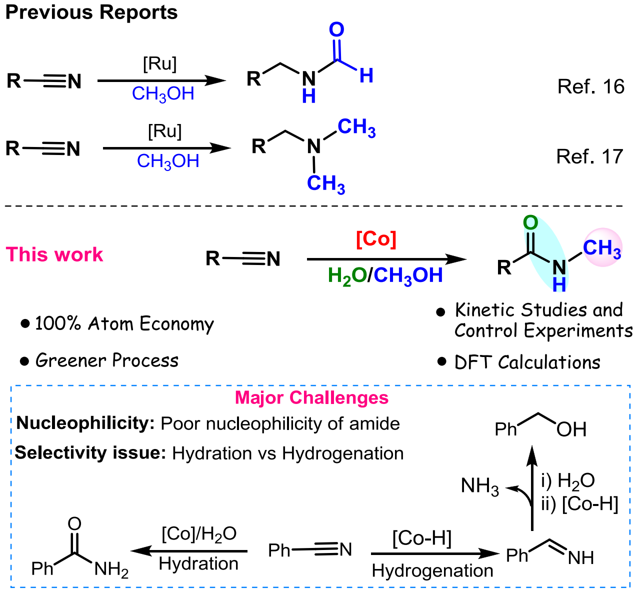
KEYWORDS: cobalt • methanol activation • nitrile hydration • N-methylated amide • mechanistic study • tandem process

Nitriles are the key building blocks in organic synthesis.[1] These molecules can be easily transformed to several valuable products through hydrolysis, hydration, reduction, etc.[1a, 2] Nitriles are found in the many natural resources such as fungi, bacteria, algae, sponges, cyan lipids, cyanogenic glycosides, cyanohydrine and also higher organism.[3] Notably, over 120 nitriles were isolated from terrestrial and marine sources.[4] Nitriles are easily accessible by different classical and industrial processes and for their synthesis; various protocols were established by employing several metallic and non-metallic cyanating reagents.[1b, 5]

N-Methylated amide is one of the essential motif present in numerous natural products and pharmaceutically important compounds.[6] Notably, N-methylation of amide has a significant impact on the biological activities and physical properties of the molecule.[7] These molecules are commonly synthesized from the hazardous acid chlorides in presence of volatile $MeNH_2$.[8] Therefore, a sustainable process to access the N-methylated amide molecules is essential.

In the last few decades, tandem catalysis has drawn much attention in the research and development.[9] In this process, new functional group can be incorporated in a molecule from the easily available starting materials.[10] In the tandem catalysis, multi-pot stepwise reactions is replaced with one-pot atom-economical processes.[11] However, to acquire success, compatibility in solvents, reagents, catalysts, etc. in the different sequential step is essential.[12] Moreover, absence of extensive work-up, isolation/purification of intermediates and functional group protection-deprotection technique reduces the time, efforts, cost and waste generation.[9, 13]

Although, transition metal mediated nitrile hydration to amide is well explored,[14] however greener methodology for the synthesis of N-methylated amides using methanol is not reported yet. There are few reports immersed in literature for the synthesis of N-alkylated amines or imines from nitriles and alcohols.[3c, 15] Notably, Hong *et al.* reported the Ru(II) mediated synthesis of amides and N-formylated amines from nitrile and long chain alcohol and methanol respectively.[10e, 16] Recently, we reported direct synthesis of N-methylated amines from nitrile and methanol.[17]



Scheme 1. Reactions of Nitriles with Methanol

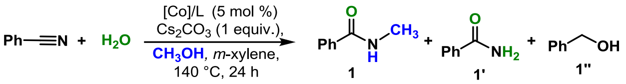
Earth abundant and inexpensive base metal mediated catalysis for the replacement of expensive noble metals based systems is an important challenge in homogeneous catalysis.[18] Inspired by the recent advancement in the methanol activation chemistry [17, 19] and the importance of the N-methylated amides,[6] herein we report an efficient cobalt mediated atom-economical and sustainable synthesis of N-methylated amides from nitriles. To the best of our knowledge, tandem conversion of nitrile to N-methylated amide using methanol/water is not reported yet (Scheme **1**).

Initially, we screened several bases for the N-methylation of benzamide using methanol in presence of $CoBr_2$/tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) (Table S6). Yields of the desired N-methylbenzamide was significantly higher with Cs_2CO_3 (1 equiv.) compare to other bases like NaOH, KO^{t}Bu, etc. (Table S6, entry 7). Afterward, we focused on the tandem transformation of benzonitrile to N-methylbenzamide by using methanol and water in presence of Cs_2CO_3 (1 equiv.). For this purpose, several cobalt precursors and ligands in presence of 10 equiv. of water were screened (Table **1**; entries 1-7). Among them, $CoBr_2$ and tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) displayed the superior result (entry 1). However, in this transformation significant amount of benzyl alcohol (**1"**) was formed as a side product. Formation of benzyl alcohol can be rationalized by the partial hydrogenation of nitrile to imine followed by hydrolysis which may produce benzaldehyde and subsequently was hydrogenated to yield the benzyl alcohol (Scheme **1**). Nevertheless, with strong bases such as NaOH, ^{t}BuOK, etc. formation of benzyl alcohol was relatively lower (Table **1**, entries 8-9; Table S7). Notably, for the nitrile hydration, strong bases exhibited better reactivity.[20] Therefore, to improve the yield of **1** and to minimize the formation of **1"**, rate of nitrile hydration to amide has to be faster than the rate of nitrile hydrogenation (Scheme **1**).

Thus, next we performed the experiments with Cs_2CO_3 in presence of the additional strong base (Table **1**, entries 10-12; Table S7). Screening of additional bases disclosed that 0.5 equiv. ^{t}BuOK was sufficient to minimize the formation of the side product (entry 12). Satisfactory yield of the desired N-methylbenzamide (96%) was observed by increasing the catalyst loading to 7.5 mol % (Table **1**; entry 13). Interestingly, in presence of only KO^{t}Bu or Cs_2CO_3 (1.5 equiv.), yields of the N-methylbenzamide was not adequate (Table **1**, entries 14 and 15). Hence, a mixture KO^{t}Bu (0.5 equiv.) and Cs_2CO_3 (1.0 equiv.) was used to maximize the yield of N-methylated amide. Amount of water also played a critical role in this transformation; 10 equiv. water was found to the optimum. Yield of **1** was dropped using 5 or 15 equiv. of H_2O (entries 16 and 17). Additionally, isolated Co(II) complex derived from 1:1 ratio of $CoBr_2$ and PP_3 in methanol also presented the similar result (Table **1**, entry 18; for complex structure see Figure S14).

Next, the scope of this protocol was explored for the direct synthesis of N-methylated amides from nitriles using methanol and water. In this study, it was observed that the nitriles bearing electron-withdrawing groups at *meta*- and *para*- position afforded the desired N-methylated amides more efficiently than the electron-rich nitriles (Table **2**, **2**-**11**). However, for the *ortho*-substituted nitrile, reactivity was lower probably due to the steric influence (**12**). *Di*- or *tri*-substituted nitriles smoothly delivered the corresponding N-methylated amides in 71-82% yields (**14**-**16**). For 4-formylbenzonitrile, the carbonyl group was reduced under the reaction conditions and furnished the corresponding N-methylated amide (**19**).

Table 1. Data for the Screening of Optimal Conditions for Nitrile Conversion[a]

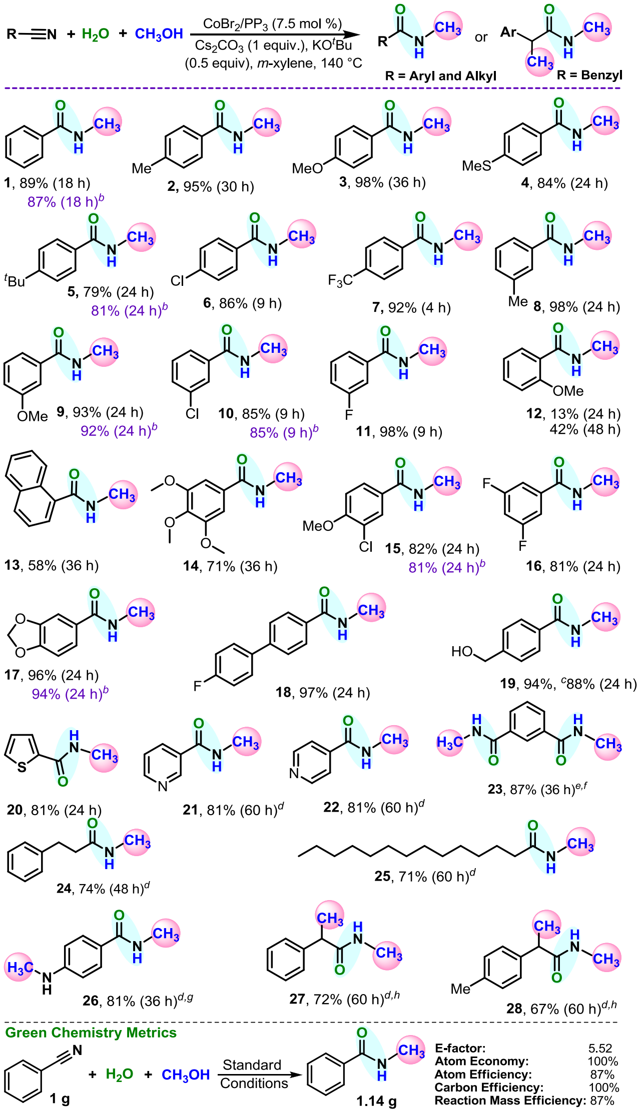


Entry	[Co]/Ligand (mol %)	Additional Base (equiv.)	Yield (**1**) (%)	Yield (**1'**) (%)	Yield (**1"**) (%)
1	$CoBr_2$/ PP_3 (5)	-	43	30	27
2	$CoBr_2$/ DPPF (5)	-	7	81	10
3	$CoBr_2$/ Xantphos (5)	-	2	84	14
4	$CoBr_2$/ Triphos (5)	-	7	78	12
5	$Co(BF_4)_2.6H_2O$/ PP_3 (5)	-	39	37	21
6	$Co(OAc)_2$/ PP_3 (5)	-	37	36	23
7	$Co(acac)_2$/ PP_3 (5)	-	41	31	24
8[b]	$CoBr_2$/ PP_3 (5)	-	25	56	16
9[c]	$CoBr_2$ / PP_3 (5)	-	21	66	11
10	$CoBr_2$/ PP_3 (5)	KOH (0.2)	53	28	19
11	$CoBr_2$/ PP_3 (5)	KO^{t}Bu (0.2)	68	22	7
12	$CoBr_2$/ PP_3 (5)	KO^{t}Bu (0.5)	69	30	0
13	$CoBr_2$/ PP_3 (7.5)	KO^{t}Bu (0.5)	96	2	0
14[d]	$CoBr_2$/ PP_3 (7.5)	KO^{t}Bu (1.5)	54	43	0
15	$CoBr_2$ / PP_3 (7.5)	Cs_2CO_3 (1.5)	66	5	24
16[e]	$CoBr_2$/ PP_3 (7.5)	KO^{t}Bu (0.5)	67	5	26
17[f]	$CoBr_2$/ PP_3 (7.5)	KO^{t}Bu (0.5)	85	14	0
18	isolated complex (7.5)	KO^{t}Bu (0.5)	97	2	0
19[d]	$CoBr_2$/ PP_3 (7.5)	-	2	3	2
20	-	KO^{t}Bu (0.5)	6	87	5
21[g]	-	KO^{t}Bu (0.5)	N. D.	12	N. D.

[a]Reaction conditions: benzonitrile (0.5 mmol), methanol/*m*-xylene (2.5 mL, 1:1 v/v), water (10 equiv.), GC yield (using mesitylene as internal standard); [b]1.0 equiv. KO^{t}Bu; [c]1.0 equiv. NaOH; [d]absence of Cs_2CO_3; [e]5 equiv. H_2O; [f]15 equiv. H_2O; [g]3 h (N.D. = not detected).

Challenging substrates like hetero nuclei containing aromatic nitriles, *di*-nitrile and aliphatic nitriles also furnished the desired N-methylated amides although, longer reaction time and slightly higher temperature was essential (**20**-**25**). Remarkably, employing this protocol tandem C-methylation as well as N-methylation was observed for the benzyl nitriles (**27** and **28**). However, N-methylation of secondary amides did not work under this catalytic condition. Additionally, instead of anhydrous cobalt (II) bromide, with readily available and inexpensive $CoBr_2.6H_2O$, similar result was observed (Table **2**). For the preparative scale synthesis of N-methylbenzamide, the green chemistry metrics[21] with an E-factor of 5.52, 100% atom economy, 87% atom efficiency, 100% carbon efficiency and 87% reaction mass efficiency, clearly exposed the technical and environmental benefits of this methodology (Table **2**).

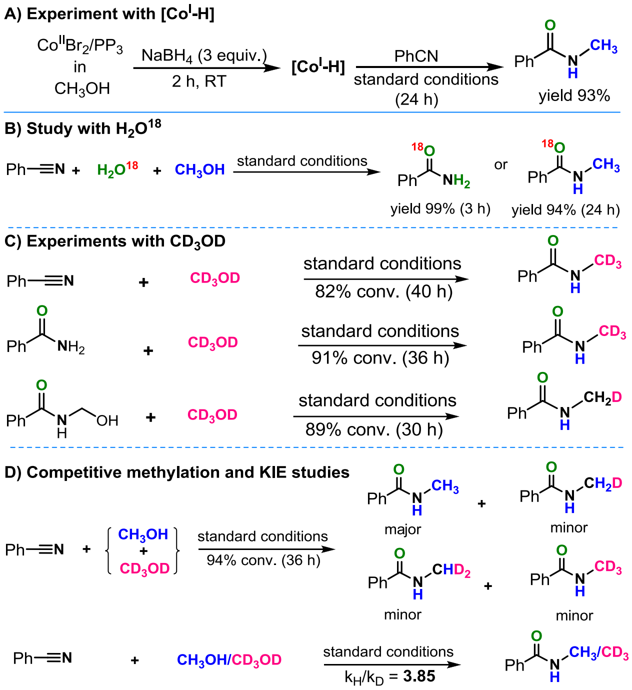
Table 2. N-Methylated Amide Synthesis from Nitrile using Methanol-Water/Cobalt System[a]



[a]Reaction conditions: nitrile (0.5 mmol), methanol/*m*-xylene (2.5 mL, 1:1 v/v), water (10 equiv.); isolated yield; [b]$CoBr_2.6H_2O$ was used; [c]from 4-formylbenzonitrile; [d]$CoBr_2/PP_3$ (10 mol %) at 150 ˚C; [e]$CoBr_2/PP_3$ (15 mol %); [f]From 1,3-dicyanobenzene; [g]from 4-amino benzonitrile. [h]from corresponding phenylacetonitriles.

After successfully synthesized various N-methylated amides from nitriles, we focused at investigating the mechanism of this tandem transformation. For that purpose several control experiments and kinetic studies were performed. Initially, to know the nature of active cobalt catalyst, cobalt (I) hydride was synthesized *in situ* by treating the $CoBr_2/PP_3$ system with 3 equiv. of $NaBH_4$.[22] This Co-H species (7.5 mol %), under the optimized reaction conditions delivered the desired N-methylbenzamide in 93% yield from benzonitrile which advocated the involvement of cobalt (I) hydride species in this transformation (Scheme **2A**).

Notably, when the reaction was carried out in H_2O^{18}/MeOH, O^{18} incorporated benzamide and N-methylbenzamide were formed within 3 h and 24 h respectively (Scheme **2B**). This result undoubtedly established that the water was the source of the oxygen atom in the amide products. Using CD_3OD as a solvent under the optimized reaction conditions, deuterium incorporated N-methylated amide products were observed from nitrile as well as from the plausible intermediates, which confirmed that methanol acted as the hydrogen and C1 source (Scheme **2C**).



Scheme 2. Kinetic Studies and Control Experiments (For standard conditions, see Table **1**, entry 13).

Next, a competition experiment was performed with benzonitrile using a mixture of CH_3OH and CD_3OD (1:1 ratio) which predominantly yielded N-methylbenzamide compare to its D-labelled analogue (Scheme **2D**). In this reaction four different products were generated by the insertion of the two different imines to the corresponding Co-H and Co-D species.[23] For this cascade transformation, kinetic isotope effect (KIE) study using CH_3OH and CD_3OD disclosed $K_{C\text{-}H}/K_{C\text{-}D} = 3.85$. This result suggested that the activation of C-H bond was a kinetically important step during this process (Scheme **2D**).

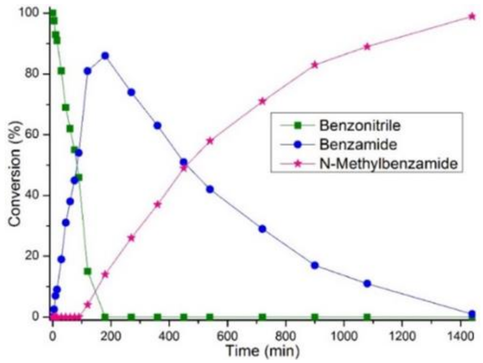


Figure 1. Time course of the reaction during the formation of N-methylated amide from nitrile.

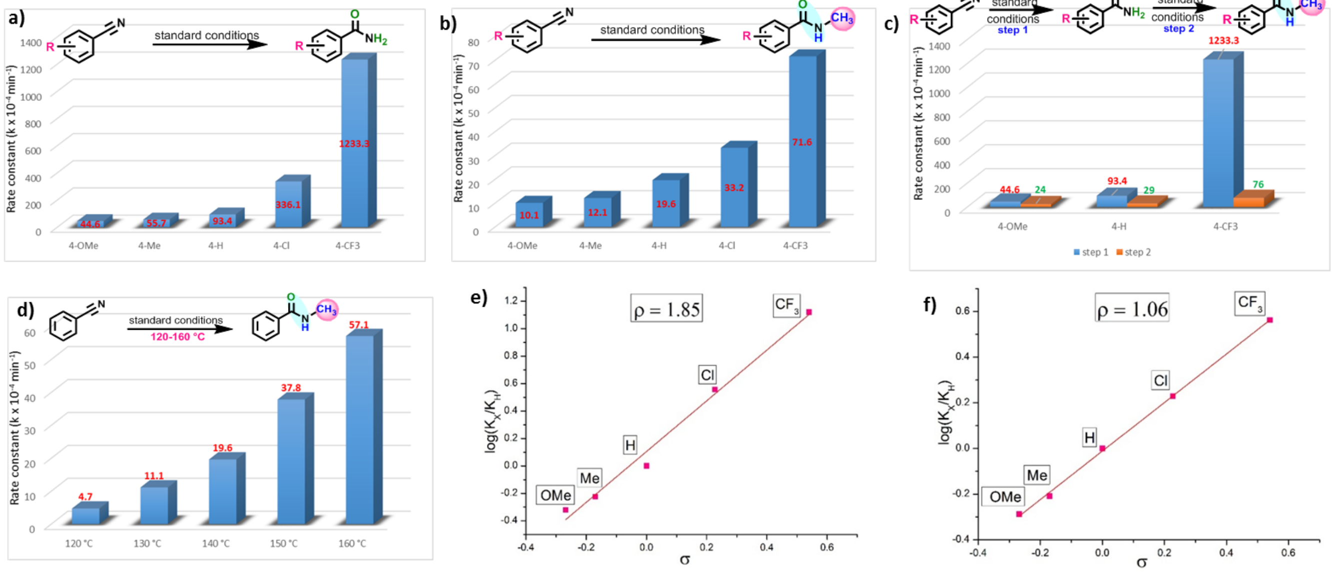


Figure 2. a-d) Dependence of rate constant on the substitution and temperature; **e**) Hammett study for the nitrile hydration; **f**) Hammett study for the N-methylated amide formation from nitrile (For standard conditions, see Table **1**, entry 13).

In this tandem transformation, kinetic studies showed the first order dependency on the nitrile concentration in the reaction rate (see SI, Pages S12-S14). From the time course of the reaction it was observed that the nitrile hydration was much faster compared to the N-methylation of amide. Almost quantitative conversion of benzonitrile to benzamide was achieved within 3 hours, and no N-methylbenzamide was detected after 90 minutes (Figure **1**).

Compared to the conventional nitrile hydration, relatively less amount of water (10 equiv.) was used in this process. Thus, to understand this transformation more clearly, rate constants for the nitrile hydration and N-methylation reactions using different nitriles were measured (Figure **2**). The rate constants for the nitrile hydration were higher than the N-methylation process, and for the nitrile bearing strong electron withdrawing substituent (*p*-CF_3), the rate constant was significantly larger.

In this direct conversion of nitrile to N-methylated amide, electronic effect was observed in nitrile hydration and N-methylation steps (Figure **2a-c**). Therefore, Hammett study was carried out using various substituted benzonitriles. In this study, a good linear relationship was observed when relative rates with these substituted benzonitriles [$\log(k_X/k_H)$] were plotted against the substituent constant (σ). In the Hammett plot, positive ρ values of +1.85 and +1.06 were observed for the nitrile hydration and direct conversion of nitrile to N-methylated amide, respectively (Figure **2e** and **2f**). Importantly, the electronic effect was more prominent in the nitrile hydration step than the methylation process. In addition, a very good linearity was observed in the plot of log (k_X/k_H) vs σ- (Figure S10). This result suggested that the electron withdrawing group should facilitate the reaction and it was consistent with the reactivity of the nitrile substrates reported in the Table **2**.

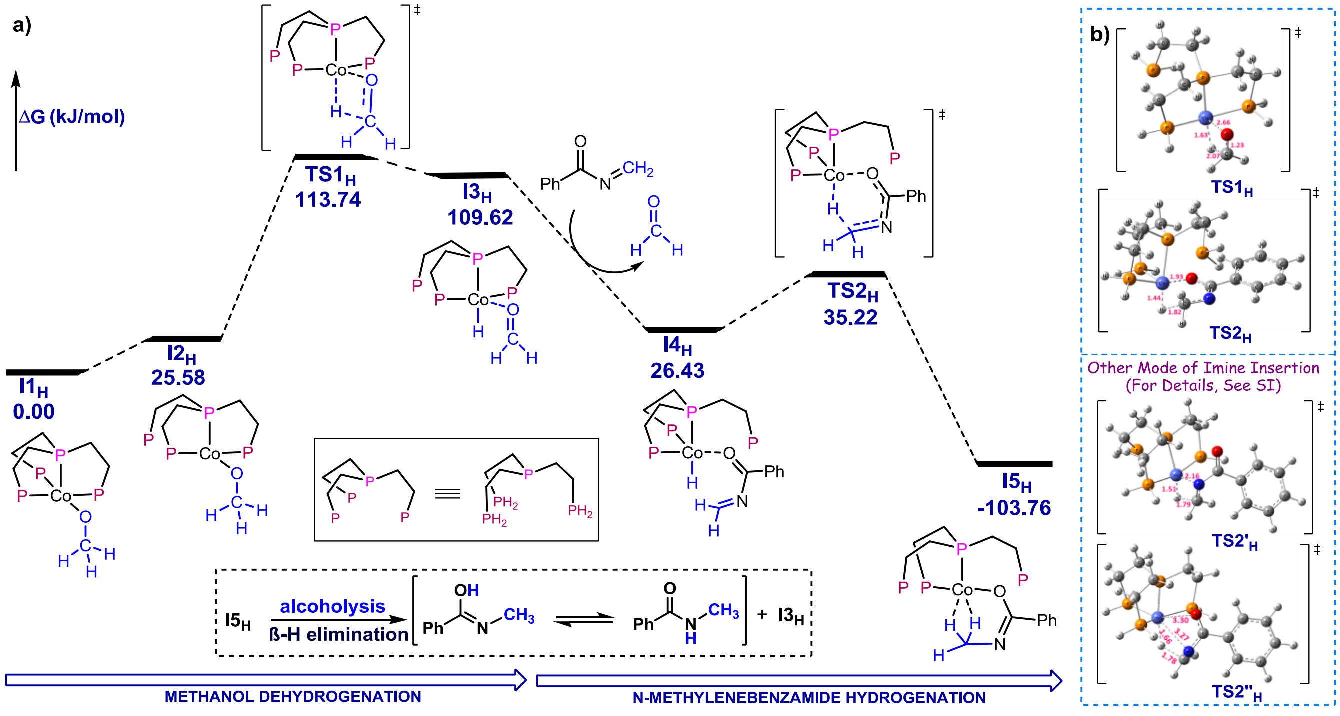


Figure 3. a) Computed pathway for the N-methylation process; and **b**) ball and stick model of the transition states (bond length in Å).

The reaction temperature using the mixture of methanol/*m*-xylene solvents under closed condition was difficult to measure accurately, hence we were unable to measure the activation parameters of this transformation. However, considering the oil-bath temperature, rate constants at different temperatures were measured and it was observed that with slight increase in oil-bath temperature, rate constant increased significantly (Figure **2d**).

To realize the probable pathway and the feasibility of this N-methylation process, a detailed DFT calculations considering the singlet state of the active Co(I) species were performed (for details, see SI). In the DFT calculations, for shorter computational time, the phenyl groups in **PP₃** ligand were replaced with H atoms.[24] This process was mainly divided into two parts: a) methanol dehydrogenation and b) hydrogenation of N-methylene benzamide. For the methanol dehydrogenation, initially the intermediate **I1$_H$** underwent ligand dissociation and formed a 16-electron species **I2$_H$** (Figure **3**). Subsequently, Co-H species **I3$_H$** was formed via β-H elimination from **I2$_H$** through the **TS1$_H$** with an overall activation barrier (ΔG‡) of 113.74 kJ/mol. During the hydrogenation of N-methylene benzamide, it can coordinate to the cobalt centre via different pathways. Depending on the coordination mode of the imine, insertion of N-methylene benzamide to the Co-H can proceed via either i) four membered TS or, ii) six-membered TS with strong interaction or, iii) six-membered TS with weak interaction (Figure **3**).

Therefore, the activation energy for these three different pathways were calculated to know the preferential one. The activation barrier through the six-membered transition state with strong interaction TS2$_H$ was 8.79 kJ/mol (Figure **3**). Notably, for the four-membered TS and six-membered TS with weak interaction, the calculated energy barrier (ΔG‡) were 38.80 kJ/mol and 32.87 kJ/mol respectively (see SI, Figure S15). This result advocates that the imine hydrogenation preferentially follows through the six-membered TS with strong interaction.

In the N-methylation of amide step, electronic effect was observed with the functionalized nitriles. However, this electronic effect was not significant as the substituent was far away from the amide bond. Therefore, to understand this effect more clearly, DFT calculations were performed for the insertion of the different *para*- substituted N-methylene amides to the Co-H species (Figure **4**). In this insertion process, six-membered TS having stronger interaction was considered. The calculated activation energy (ΔG‡) for the -CF$_3$, -H and -OMe substituted imines were 0.15, 8.79 and 10.92 kJ/mol respectively. This results stated that the hydrogenation of N-methylene amides having electron withdrawing substituent will be favored, which was consistent with the experimental results (Figure **2c**).

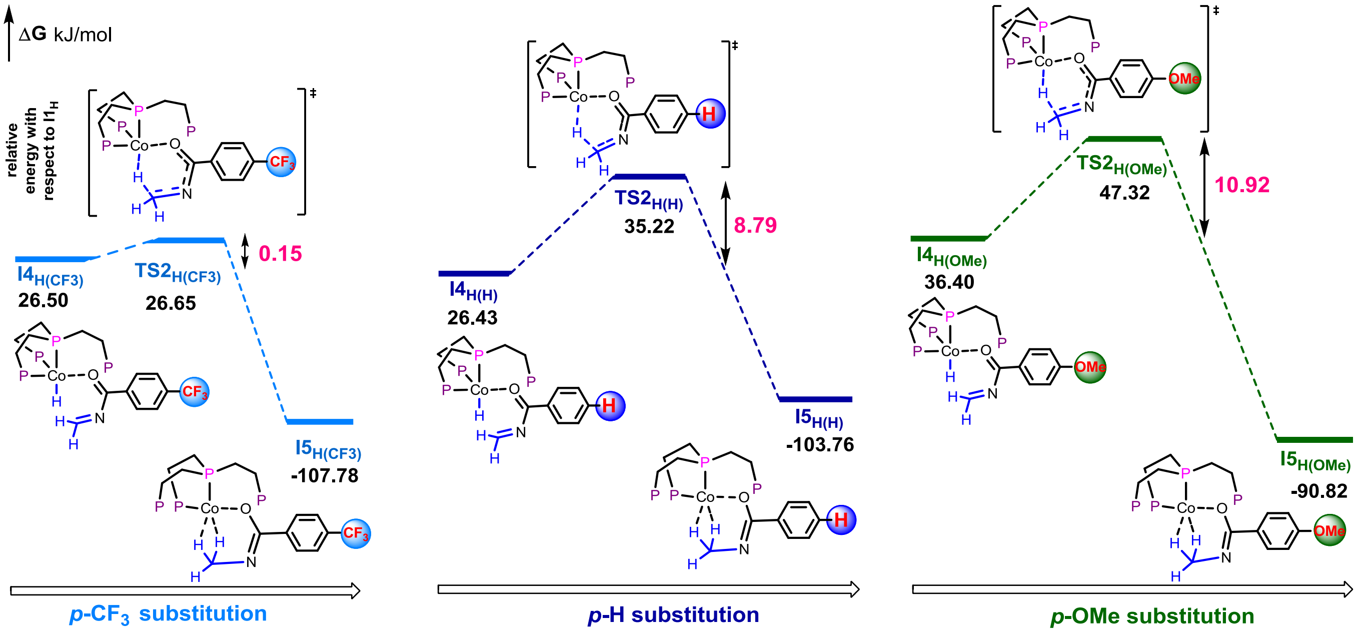
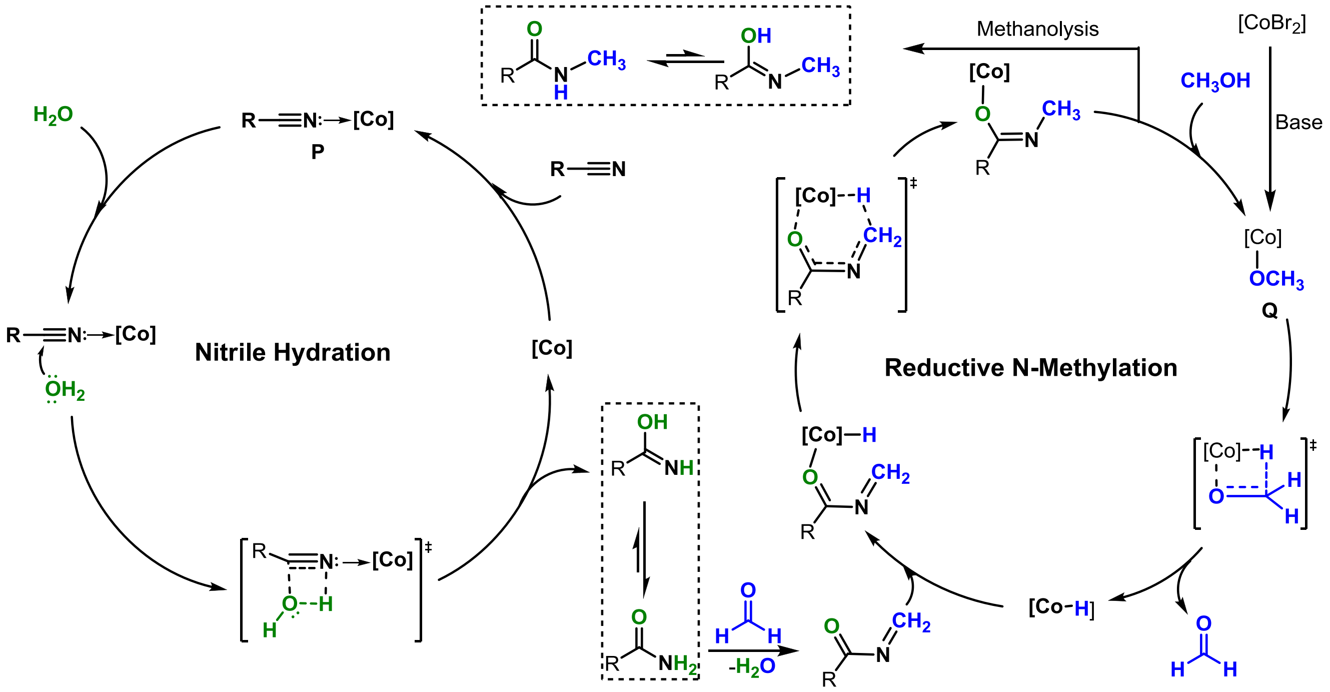


Figure 4. DFT Study for the electronic effect during the imine hydrogenation.



Scheme 3. Plausible Catalytic Cycle.

Based on these mechanistic studies, we proposed the pathway for the formation of N-methylated amides from nitriles using methanol and water (Scheme **3**). In this process, mainly two catalytic cycle were involved, namely nitrile hydration and reductive N-methylation. Experimentally, we observed that nitrile hydration was much faster in presence of cobalt catalyst (Figure **1** and Table **1**, entry 21). Based on this, we hypothesized that, in the nitrile hydration process, initially it would coordinate to the cobalt center to form the species **P**. After that, nucleophilic addition of H_2O to the nitrile followed by tautomerization would generate the amide. Additionally, in the methylation process, the methoxy species **Q** would from by treating $CoBr_2/PP_3$ with methanol in presence of Cs_2CO_3. Subsequently, via β-H elimination, this intermediate would transformed to the Co-H species and formaldehyde. Then, the condensation between the amide and formaldehyde would afford the N-methylene amides. Finally, preferential hydrogenation of this imine through six-membered TS followed by methanolysis would provide the desired N-methylated amide and would regenerate the methoxy species (**Q**).

In summary, a cobalt catalyzed tandem conversion of several nitriles to the corresponding N-methylated amides using MeOH and water is reported. Notably, labelling study using H_2O^{18} and CD_3OD confirmed the source of the oxygen atom and the methyl group in the final product. Involvement of active Co(I)-H species and importance of the C-H bond activation of methanol was supported by several kinetic experiments. In addition, Hammett study disclosed that the overall process was favored with the electron deficient nitriles and the electronic effect in the nitrile hydration step was significantly higher than the N-methylation process. The mechanistic investigation was further supported by detailed DFT calculations.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

General procedure for the N-methylation experiments, green chemistry metrics, optimization details, CIF data, computational studies, characterization data and NMR spectra of the products are available. This material is available free of charge via the Internet at http://www.acs.org.

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REFERENCES

1. (a) Larcok, R. C., Comprehensive Organic Transformations: A Guide to Functional Group Preparations. *2nd ed; John Wiley & Sons, Inc.: New York* **1999**; (b) Ping, Y.; Ding, Q.; Peng, Y., Advances in C–CN Bond Formation via C–H Bond Activation. *ACS Catal.* **2016**, *6*, 5989-6005; (c) Kim, J.; Kim, H. J.; Chang, S., Synthesis of Aromatic Nitriles Using Nonmetallic Cyano-Group Sources. *Angew. Chem. Int. Ed.* **2012,** *51*, 11948-11959.

2. Rappoport, Z., Chemistry of the Cyano Group. *Wiley, London* **1970**

3. (a) Legras, J. L.; Chuzel, G.; Arnaud, A.; Gazly, P. Natural nitriles and their metabolism, *World J. Microbiol. Biotechnol.* **1990,** *6*, 83–108; (b) Piotrowski, M., Primary or secondary? Versatile nitrilases in plant metabolism, *Phytochemistry* **2008,** *69*, 2655–2667; (c) Werkmeister, S.;

Bornschein, C.; Junge, K.; Beller, M., Ruthenium-Catalyzed Transfer Hydrogenation of Nitriles: Reduction and Subsequent N-Monoalkylation to Secondary Amines. *Eur. J. Org. Chem.* **2013,** *2013,* 3671-3674.

4. (a) F. Fleming, F., Nitrile-containing natural products. *Nat. Prod. Rep.* **1999,** *16,* 597-606; (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C., Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010,** *53,* 7902-7917.

5. (a) Rosenmund, K. W., Struck, E. , The ring carbon-bonded halogen and its replacement by other substituents. I. Communication: Replacement of the halogen by the carboxyl group, *Ber. Dtsch. Chem. Ges. B* **1919,** *52,* 1749–1756; (b) Sandmeyer, T., On the replacement of the amide group by chlorine in the aromatic substances, *Ber. Dtsch. Chem. Ges. B* **1884,** *17,* 1633–1635; (c) Mowry, D. T., The Preparation of Nitriles. *Chem. Rev.* **1948,** *42,* 189-283; (d) Yang, L.; Liu, Y.-T.; Park, Y.; Park, S.-W.; Chang, S., Ni-Mediated Generation of "CN" Unit from Formamide and Its Catalysis in the Cyanation Reactions. *ACS Catal.* **2019,** *9,* 3360-3365.

6. (a) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K., Conversion of amides to esters by the nickel-catalysed activation of amide C–N bonds. *Nature* **2015,** *524,* 79; (b) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M., The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011,** *111,* 5215-5246.

7. (a) Chatterjee, J.; Gilon, C.; Hoffman, A.; Kessler, H., N-Methylation of Peptides: A New Perspective in Medicinal Chemistry. *Acc. Chem. Res.* **2008,** *41,* 1331-1342; (b) Chatterjee, J.; Mierke, D.; Kessler, H., N-Methylated Cyclic Pentaalanine Peptides as Template Structures. *J. Am. Chem. Soc.* **2006,** *128,* 15164-15172; (c) Kouzarides, T., Chromatin Modifications and Their Function. *Cell* **2007,** *128,* 693-705; (d) Chatterjee, J.; Rechenmacher, F.; Kessler, H., N-Methylation of Peptides and Proteins: An Important Element for Modulating Biological Functions. *Angew. Chem. Int. Ed.* **2013,** *52,* 254-269.

8. (a) Bernardi, L.; de Castiglione, R.; Scarponi, U., Simple methylation of amides. *J. Chem. Soc., Chem. Commun.* **1975,** 320-321; (b) Bassindale, A. R.; Parker, D. J.; Patel, P.; Taylor, P. G., Chemoselective methylation of amides and heterocycles using chloromethyldimethylsilyl chloride. *Tetrahedron Lett.* **2000,** *41,* 4933-4936.

9. Lohr, T. L.; Marks, T. J., Orthogonal tandem catalysis. *Nat. Chem.* **2015,** *7,* 477.

10. (a) Tietze, L. F., Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996,** *96,* 115-136; (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., Concurrent Tandem Catalysis. *Chem. Rev.* **2005,** *105,* 1001-1020; (c) Gunanathan, C.; Ben-David, Y.; Milstein, D., Direct Synthesis of Amides from Alcohols and Amines with Liberation of H_2. *Science* **2007,** *317,* 790-792; (d) Balaraman, E.; Khaskin, E.; Leitus, G.; Milstein, D., Catalytic transformation of alcohols to carboxylic acid salts and H2 using water as the oxygen atom source. *Nat. Chem.* **2013,** *5,* 122; (e) Kang, B.; Fu, Z.; Hong, S. H., Ruthenium-Catalyzed Redox-Neutral and Single-Step Amide Synthesis from Alcohol and Nitrile with Complete Atom Economy. *J. Am. Chem. Soc.* **2013,** *135,* 11704-11707.

11. (a) Grondal, C.; Jeanty, M.; Enders, D., Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* **2010,** *2,* 167; (b) Dydio, P.; Ploeger, M.; Reek, J. N. H., Selective Isomerization–Hydroformylation Sequence: A Strategy to Valuable α-Methyl-Branched Aldehydes from Terminal Olefins. *ACS Catal.* **2013,** *3,* 2939-2942.

12. (a) Haibach, M. C.; Kundu, S.; Brookhart, M.; Goldman, A. S., Alkane Metathesis by Tandem Alkane-Dehydrogenation–Olefin-Metathesis Catalysis and Related Chemistry. *Acc. Chem. Res.* **2012,** *45,* 947-958; (b) Leitch, D. C.; Lam, Y. C.; Labinger, J. A.; Bercaw, J. E., Upgrading Light Hydrocarbons via Tandem Catalysis: A Dual Homogeneous Ta/Ir System for Alkane/Alkene Coupling. *J. Am. Chem. Soc.* **2013,** *135,* 10302-10305; (c) Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K., Tandem Isomerization/Hydroformylation/Hydrogenation of Internal Alkenes to n-Alcohols Using Rh/Ru Dual- or Ternary-Catalyst Systems. *J. Am. Chem. Soc.* **2013,** *135,* 17393-17400; (d) Huff, C. A.; Sanford, M. S., Cascade Catalysis for the Homogeneous Hydrogenation of CO_2 to Methanol. *J. Am. Chem. Soc.* **2011,** *133,* 18122-18125; (e) Chakraborty, S.; Piszel, P. E.; Hayes, C. E.; Baker, R. T.; Jones, W. D., Highly Selective Formation of n-Butanol from Ethanol through the Guerbet Process: A Tandem Catalytic Approach. *J. Am. Chem. Soc.* **2015,** *137,* 14264-14267.

13. (a) Tietze, L. F. B., G.; Gericke, K. M. , Domino Reactions in Organic Synthesis. *Wiley-VCH: Weinheim, Germany* **2006**; (b) Young, I. S.; Baran, P. S., Protecting-group-free synthesis as an opportunity for invention. *Nat. Chem.* **2009,** *1,* 193; (c) Midya, S. P.; Sahoo, M. K.; Landge, V. G.; Rajamohanan, P. R.; Balaraman, E., Reversed reactivity of anilines with alkynes in the rhodium-catalysed C–H activation/carbonylation tandem. *Nat. Commun.* **2015,** *6,* 8591; (d) Bhadra, M.; Sasmal, H. S.; Basu, A.; Midya, S. P.; Kandambeth, S.; Pachfule, P.; Balaraman, E.; Banerjee, R., Predesigned Metal-Anchored Building Block for In Situ Generation of Pd Nanoparticles in Porous Covalent Organic Framework: Application in Heterogeneous Tandem Catalysis. *ACS Appl. Mater. Interfaces* **2017,** *9,* 13785-13792.

14. (a) Kukushkin, V. Y.; Pombeiro, A. J. L., Additions to Metal-Activated Organonitriles. *Chem. Rev.* **2002,** *102,* 1771-1802; (b) Lee, W.-C.; Frost, B. J., Aqueous and biphasic nitrile hydration catalyzed by a recyclable Ru(ii) complex under atmospheric conditions. *Green Chem.* **2012,** *14,* 62-66; (c) Zhang, S.; Xu, H.; Lou, C.; Senan, A. M.; Chen, Z.; Yin, G., Efficient Bimetallic Catalysis of Nitrile Hydration to Amides with a Simple $Pd(OAc)_2$/Lewis Acid Catalyst at Ambient Temperature. *Eur. J. Org. Chem.* **2017,** *2017,* 1870-1875.

15. (a) Paul, B.; Chakrabarti, K.; Kundu, S., Optimum bifunctionality in a 2-(2-pyridyl-2-ol)-1,10-phenanthroline based ruthenium complex for transfer hydrogenation of ketones and nitriles: impact of the number of 2-hydroxypyridine fragments. *Dalton Trans.* **2016,** *45,* 11162-11171; (b) Mai, V. H.; Nikonov, G. I., Transfer Hydrogenation of Nitriles, Olefins, and N-Heterocycles Catalyzed by an N-Heterocyclic Carbene-Supported Half-Sandwich Complex of Ruthenium. *Organometallics* **2016,** *35,* 943-949; (c) Garduño, J. A.; García, J. J., Nickel-Catalyzed Transfer Hydrogenation of Benzonitriles with 2-Propanol and 1,4-Butanediol as the Hydrogen Source. *ACS Omega* **2017,** *2,* 2337-2343; (d) Lee, S.-H.; Nikonov, G. I., Inside Back Cover: Transfer Hydrogenation of Ketones, Nitriles, and Esters Catalyzed by a Half-Sandwich Complex of Ruthenium. *ChemCatChem* **2015,** *7,* 169-169; (e) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y., Ruthenium-Catalyzed Nitro and Nitrile Compounds Coupling with Alcohols: Alternative Route for N-Substituted Amine Synthesis. *Chem. Eur. J.* **2011,** *17,* 2587-2591; (f) Liu, S.; Chen, R.; Deng, G. J., Ruthenium-catalyzed formation of tertiary amines from nitriles and alcohols. *Chem. Lett.* **2011,** *40,* 489-491.

16. Kang, B.; Hong, S. H., Hydrogen Acceptor- and Base-Free N-Formylation of Nitriles and Amines using Methanol as C1 Source. *Adv. Synth. Catal.* **2015,** *357,* 834-840.

17. Paul, B.; Shee, S.; Panja, D.; Chakrabarti, K.; Kundu, S., Direct Synthesis of N,N-Dimethylated and β-Methyl N,N-Dimethylated Amines from Nitriles Using Methanol: Experimental and Computational Studies. *ACS Catal.* **2018,** *8,* 2890-2896.

18. (a) Irrgang, T.; Kempe, R., 3d-Metal Catalyzed N- and C-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2018,** *119,* 2524-2549; (b) Deibl, N.; Kempe, R., General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols. *J. Am. Chem. Soc.* **2016,** *138,* 10786-10789.

19. (a) Natte, K.; Neumann, H.; Beller, M.; Jagadeesh, R. V., Transition-Metal-Catalyzed Utilization of Methanol as a C1 Source in Organic Synthesis. *Angew. Chem. Int. Ed.* **2017,** *56,* 6384-6394; (b) Chakrabarti, K.; Mishra, A.; Panja, D.; Paul, B.; Kundu, S., Selective synthesis of mono- and di-methylated amines using methanol and sodium azide as C1 and N1 sources. *Green Chem.* **2018,** *20,* 3339-3345; (c) Choi, G.; Hong, S. H., Selective Monomethylation of Amines with Methanol as the C1 Source. *Angew. Chem. Int. Ed.* **2018,** *57,* 6166-6170; (d) Dang, T. T.; Ramalingam, B.; Seayad, A. M., Efficient Ruthenium-Catalyzed N-Methylation of Amines Using Methanol. *ACS Catal.* **2015,** *5,* 4082-4088; (e) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z., Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol. *Adv. Synth. Catal.* **2017,** *359,* 4278-4283; (f) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z., Methylation of $C(sp^3)$–H/$C(sp^2)$–H Bonds with Methanol Catalyzed by

Cobalt System. *Org. Lett.* **2017,** *19*, 5228-5231; (g) Choi, G.; Hong, S. H., Selective N-Formylation and N-Methylation of Amines Using Methanol as a Sustainable C1 Source. *ACS Sustain. Chem. Eng.* **2019,** *7*, 716-723.

20. (a) Chen, H.; Dai, W.; Chen, Y.; Xu, Q.; Chen, J.; Yu, L.; Zhao, Y.; Ye, M.; Pan, Y., Efficient and selective nitrile hydration reactions in water catalyzed by an unexpected dimethylsulfinyl anion generated in situ from CsOH and DMSO. *Green Chem.* **2014,** *16*, 2136-2141; (b) Midya, G. C.; Kapat, A.; Maiti, S.; Dash, J., Transition-Metal-Free Hydration of Nitriles Using Potassium tert-Butoxide under Anhydrous Conditions. *J. Org. Chem.* **2015,** *80*, 4148-4151; (c) Schmid, T. E.; Gómez-Herrera, A.; Songis, O.; Sneddon, D.; Révolte, A.; Nahra, F.; Cazin, C. S. J., Selective NaOH-catalysed hydration of aromatic nitriles to amides. *Catal. Sci. Technol.* **2015,** *5*, 2865-2868.

21. (a) Turgis, R.; Billault, I.; Acherar, S.; Augé, J.; Scherrmann, M.-C., Total synthesis of high loading capacity PEG-based supports: evaluation and improvement of the process by use of ultrafiltration and PEG as a solvent. *Green Chem.* **2013,** *15*, 1016-1029; (b) Ragupathi, A.; Charpe, V. P.; Sagadevan, A.; Hwang, K. C., Visible Light-Mediated Copper(I)-Catalysed Aerobic Oxidation of Ynamides/Ynamines at Room Temperature: A Sustainable Approach to the Synthesis of α-Ketoimides/α-Ketoamides. *Adv. Synth. Catal.* **2017,** *359*, 1138-1143; (c) Upadhyay, N. S.; Thorat, V. H.; Sato, R.; Annamalai, P.; Chuang, S.-C.; Cheng, C.-H., Synthesis of isoquinolones via Rh-catalyzed C–H activation of substituted benzamides using air as the sole oxidant in water. *Green Chem.* **2017,** *19*, 3219-3224; (d) Sagadevan, A.; Lyu, P.-C.; Hwang, K. C., Visible-light-activated copper(i) catalyzed oxidative Csp–Csp cross-coupling reaction: efficient synthesis of unsymmetrical conjugated diynes without ligands and base. *Green Chem.* **2016,** *18*, 4526-4530.

22. Ghilardi, C. A.; Midollini, S.; Sacconi, L., Reactions of the tripod ligand tris(2-diphenylphosphinoethyl)phosphine with cobalt(II) and nickel(II) salts and sodium borohydride. Structural characterization of a five-coordinate cobalt(I) hydride complex. *Inorg. Chem.* **1975,** *14*, 1790-1795.

23. Wei, D.; Sadek, O.; Dorcet, V.; Roisnel, T.; Darcel, C.; Gras, E.; Clot, E.; Sortais, J.-B., Selective mono N-methylation of anilines with methanol catalyzed by rhenium complexes: An experimental and theoretical study. *J. Catal.* **2018,** *366*, 300-309.

24. Cheng, C.; Kim, B. G.; Guironnet, D.; Brookhart, M.; Guan, C.; Wang, D. Y.; Krogh-Jespersen, K.; Goldman, A. S., Synthesis and Characterization of Carbazolide-Based Iridium PNP Pincer Complexes. Mechanistic and Computational Investigation of Alkene Hydrogenation: Evidence for an Ir(III)/Ir(V)/Ir(III) Catalytic Cycle. *J. Am. Chem. Soc.* **2014,** *136*, 6672-6683.

SYNOPSIS TOC