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Nickel Catalyzed Phosphine Free Direct N-alkylation of Amides with Alcohols

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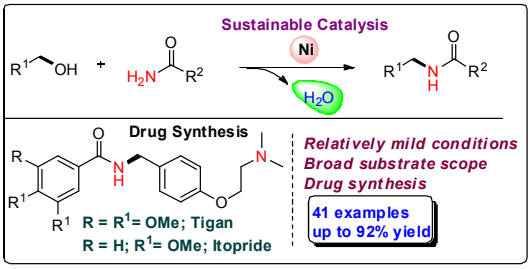
*Supporting Information

ABSTRACT:



Herein, we developed an operational simple, practical and selective Ni-catalyzed synthesis of secondary amides. Application of renewable alcohols, earth-abundant and non-precious nickel catalyst facilitates the transformations, releasing water as by product. The catalytic system is tolerant to variety of functional groups including nitrile, allylic ether and alkene and could be extended to the synthesis of bis-amide, antiemetic drug Tigan and dopamine D2 receptor antagonist Itopride. Preliminary mechanistic studies, revealed the participation of benzylic C-H bond in the rate-determining step.

Transition metal-catalyzed efficient and selective synthesis of amide C-N bond represents a key challenge and most commonly used in chemical transformations in the synthesis of pharmaceuticals, peptides, and in natural products (Figure 1).[1] In this direction, sustainable and atom-economic technology for amide synthesis, which minimize the waste generation is recognized by the ACS Pharmaceutical Roundtable as one of the important area where significant method development is most desirable.[2]

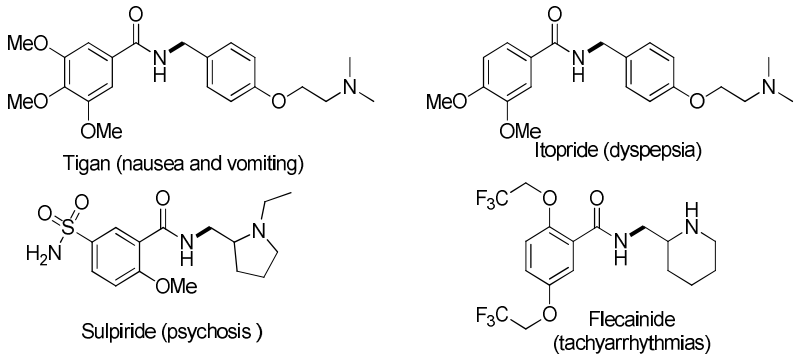
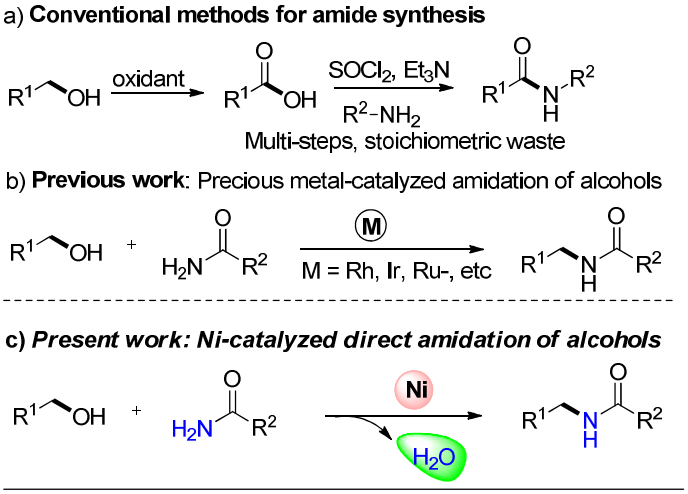


Figure 1: Selected examples of important pharmaceuticals with amide functionalities

Traditionally, laboratory scale synthesis of amides rely on the condensation of carboxylic acids or their derivatives (such as, acid chlorides, anhydrides and esters) with amines.[3] In addition, aryl and alkenyl halides were also employed for N-alkylation of amide.[4] Unfortunately, in spite of broader applications, these methodologies inevitably generates stoichiometric equivalent of waste and involves multi-step synthesis (Scheme 1a).[5]

Notably, the direct application of an alcohol would represent a promising alternative to the above processes.[5d] Alcohols are highly abundant renewable feedstocks, low cost, non-toxic and easy to handle. However, strong binding and poor leaving ability of hydroxyl group makes it inferior substrate class for such transformations and required harsh reaction conditions. Nevertheless, in terms of sustainability, metal catalyzed borrowing hydrogen or hydrogen auto-transfer (BH/HA) approach renders an elegant technology for formal C-N bond forming reactions.[6] This catalytic method involves a tandem dehydrogenation of alcohol to an electrophilic aldehyde followed by condensation with an amide. Advantageously, the newly formed C=N bond get hydrogenated by metal-hydride to the N-alkylated amide and water is formed as sole byproduct. Over the past decades, BH/HA strategy for N-alkylation of amines using alcohols has been well documented (Scheme 1b).[6]

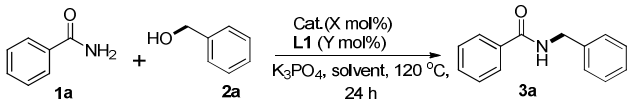
On the other hand, N-alkylation of primary amides are quite limited, because of poor nucleophilicity compare to amines and often required higher catalyst loadings or higher reaction temperature. In this direction, notable breakthrough by the group of Watanabe,[7a] and Jenner,[7b] for N-alkylation of amide with alcohols using Ru-catalyst at 180^{o} C-210^{o} C is worth mentioning. Later, precious metal-catalysts, such as, Ir-[7], Ru-[8a] and Au/Pd,[9b] in combination with expensive phosphine or highly reactive N-heterocyclic carbene ligands for amidation of alcohols were developed.



Scheme 1: Approaches for synthesis of amides: (a) Conventional methods for amide synthesis; (b) Precious metal-catalyzed *N*-alkylation of amides with alcohols; (c) Nickel-catalyzed amidation of alcohols.

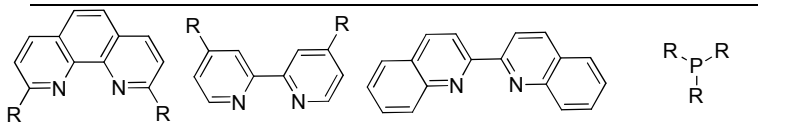
To explore the scope of earth-abundant base-metal-catalysts, we became interested in the nickel-catalyzed amidation of alcohols with primary amide. High natural abundance and inexpensive nature associated with nickel would serve an attractive sustainable alternative to palladium-catalysts.[10] To the best of our knowledge, till date no nickel catalyzed general methodology for amidation of primary alcohols is known.[11,12] Herein, for the first time we developed an inexpensive nickel catalyst system in combination with nitrogen ligands that enables selective mono-alkylation of a variety of amides with primary alcohols (Scheme 1c).[13] Notably, optimized protocol could be applied in the presence of nitrile, allylic and alkene moieties as reducible functional groups. The key features of the methodology provide a general synthesis of bis-amide, and drug molecules Tigan and Itopride.

Table 1: Optimization for standard conditions[a]



1a + 2a → 3a

Entry	Catalyst	Ligand	Solvent	**3a**(%)[b,c]
1	$NiCl_2$	L1	Toluene	15
2	$NiBr_2$	L1	Toluene	75
3	$Ni(acac)_2$	L1	Toluene	60
4	$NiCl_2$.dme	L1	Toluene	58
5	$Ni(cod)_2$	L1	Toluene	7
6	$NiBr_2$	L2	Toluene	1
7	$NiBr_2$	L3	Toluene	7
8	$NiBr_2$	L4	Toluene	12
9	$NiBr_2$	L5	Toluene	0
10	$NiBr_2$	L6	Toluene	45
11	$NiBr_2$	L7	Toluene	65
12	$NiBr_2$	L1	Xylene	22
13	$NiBr_2$	L1	Dioxane	30
14	$NiBr_2$	L1	DMA	0
15	$NiBr_2$	L1	DMF	0
16[c]	$NiBr_2$	L1	Toluene	98(83)
17[c,d]	$NiBr_2$	L1	Toluene	70
18[c,e]	$NiBr_2$	L1	Toluene	45
19[c,f]	-	L1	Toluene	0
20[c,g]	$NiBr_2$	-	Toluene	20
21[c,h]	$NiBr_2$	L1	Toluene	0



R = H; L1, 98% **R = Me; L2, 1%** | **R = H; L3, 7%** **R = Me; L4, 12%** | **L5, 0%** | **R = Ph; L6, 45%** **R = Cy; L7, 65%**

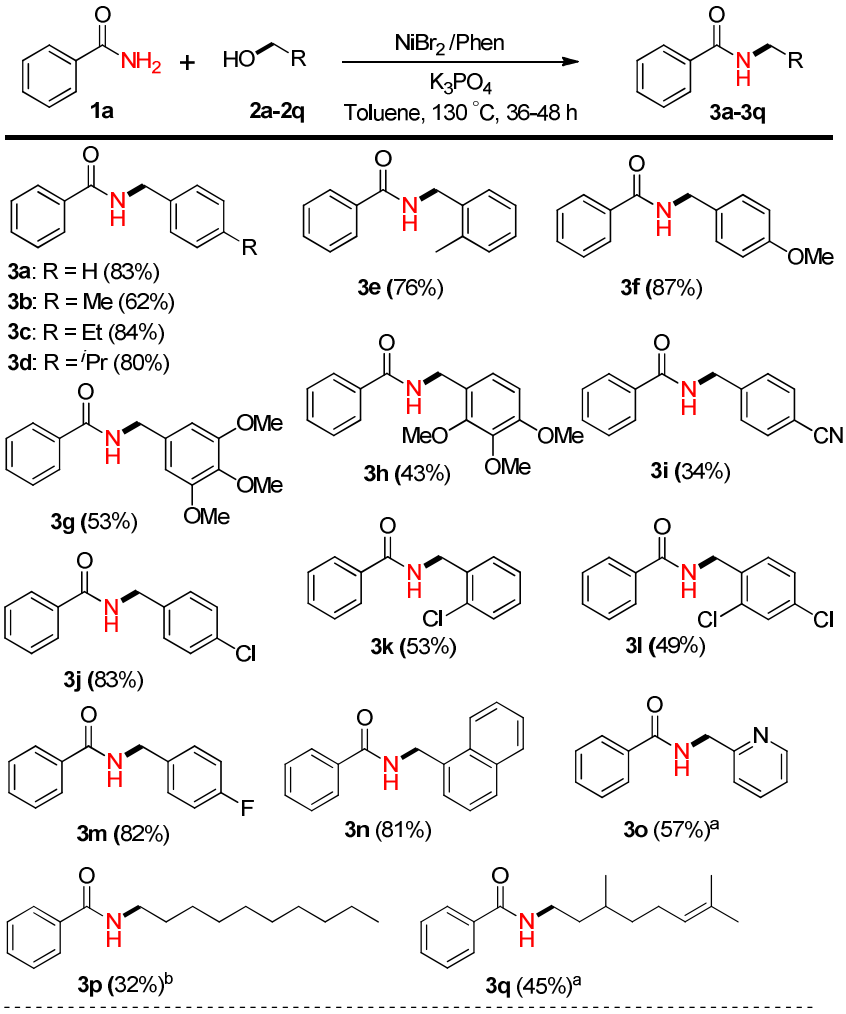
[a] Unless specified, the reaction was carried out with **1a** (0.25 mmol), **2a** (1.0 mmol), Ni-cat. (10 mol %), ligand (20 mol %), K_3PO_4 (0.5 mmol), solvent (2.0 mL), Schenk tube under nitrogen

atmosphere, 120 ºC in oil bath, 24 h. [b]Conversion was determined by GC-MS or ^{1}H-NMR yield using diphenylmethane as an internal standard (isolated yield in parenthesis, average yield of two runs). [c]Reaction was performed at 130 ºC. [d]5 mol % $NiBr_2$ and 10 mol % **L1** was used. [e]2.5 mol % $NiBr_2$ and 5 mol % **L1** was used. [f]No catalyst was used. [g]No ligand was used. [h]No K_3PO_4 was used.

In a recent report, we established an inexpensive Ni-catalyst system for efficient and selective mono-alkylation of anilines with alcohols.[14] Further to explore the direct amidation of alcohols, initially we anticipated two key challenges: (i) the efficiency of the Ni-catalyst to obtain alcohol dehydrogenation and (ii) the ability of the *in situ* formed Ni-hydride species for imide hydrogenation.

To realize this goal, five different nickel complexes having oxidation state of Ni(0) and Ni(II) were assayed for their efficiency to catalyze the model reaction of benzamide **1a** and benzyl alcohol **2a** (Table 1, entries 1-5). Notably, we observed that, a combination of 10 mol% $NiBr_2$, 20 mol% 1,10-phenthroline **L1** and 0.5 mmol of K_3PO_4 at 120 °C in toluene resulted N-alkylated amide **3a** with 75% selectivity in GC-MS analysis of the crude reaction mixture. Further to improve the product yield, a variety of nitrogen ligands **L2-L7** having variable electronic nature were employed and exhibited moderate to poor selectivity of **3a** (Table 1, entries 6-11). The product conversion suppressed significantly, when xylene and 1,4-dioxane were used as solvent instead of toluene (Table 1, entries 12-13). Moreover, the application of polar solvents, such as, N,N-dimethylacetamide (DMA) and N,N-dimethyl-formamide (DMF) did not result any desired product (Table 1, entries 14-15). To our delight, under identical conditions we observed 83% isolated yield of **3a** at 130 °C (Table 1, entries 2 and 16). As expected, lower catalyst loading suppressed the product conversion and no N-alkylated product was observed in absence of catalyst (Table 1, entries 17-19). Control experiments in absence of ligand and base resulted poor or no product conversion (Table 1, entries 20-21 and SI Table S1-S7).

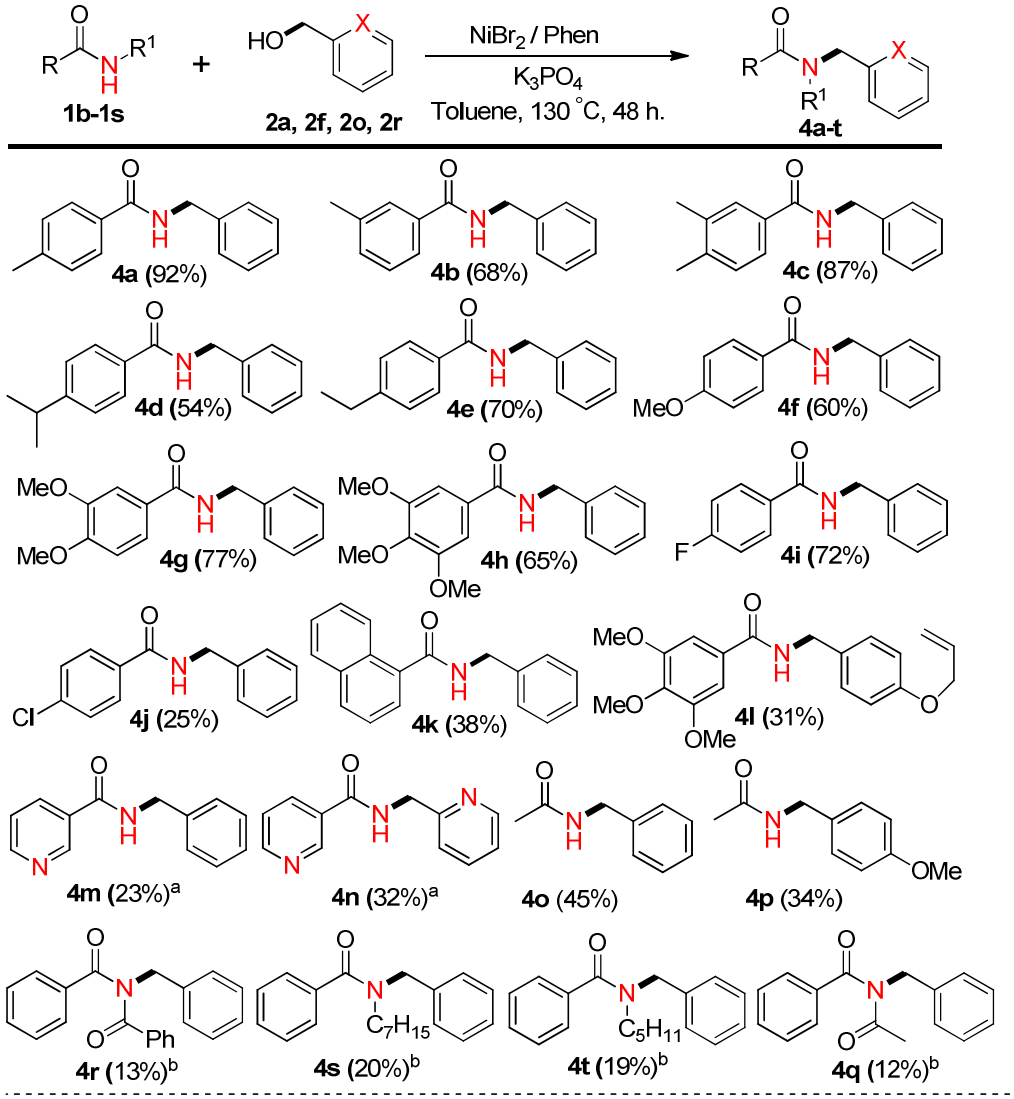
Next, under optimal conditions an *in situ* NMR study was performed using toluene-d_8 at 100 °C and monitor the progress of the reaction. The product formation profile allows the detection of **1a**, benzaldehyde, imide and **3a**, all possible reaction intermediates, which are in strong agreement of the hydrogen borrowing methodology under nickel catalysis (SI, Scheme S1).



Scheme 2: Scope of primary alcohols. Reaction conditions: Unless specified, the reaction was carried out with **1a** (0.25 mmol), **2** (1.0 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), K_3PO_4 (0.5 mmol), 130 °C in toluene (2.0 mL). [a] *t*-BuONa was used. [b] GC-MS yield.

After having identified the optimized conditions, the scope and efficiency of the nickel-catalyzed amidation of alcohols were studied (Scheme 2). Electron donating substituents on benzyl alcohols are well tolerated and furnished 62-84% yield of N-alkylated amides (Scheme 2, **3b-3e**). Benzyl alcohols having multiple electron donating substituent furnished lower product yields (Scheme 2, **3f-3h** and **3j-3l**). Further, naphthalene methanol and *p*-fluoro-benzyl alcohol gave the desired product with excellent isolated yield, 81-82% respectively (Scheme 2, **3m** and **3n**). Gratifyingly, 2-pyridenemethanol, decanol and renewable terpenoid intermediate citronellol were also used for N-alkylation under optimized reaction conditions (Scheme 2, **3o-3q**). Notably, chemo-selective transformation of unsaturated alcohol citronellol and nitrile substituted benzyl

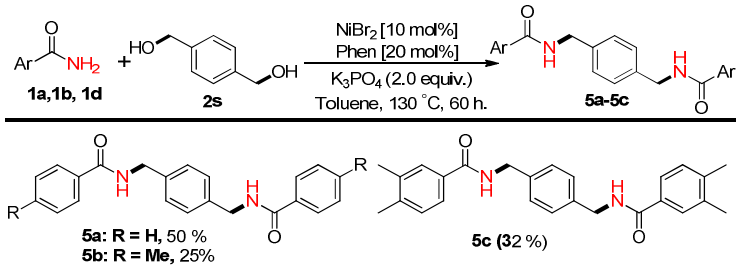
alcohol represents a rare instance, otherwise difficult using precious-metal catalysts (Scheme 2, **3i** and **3q**).[6a-c]



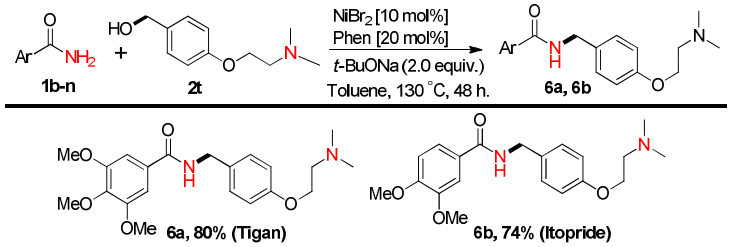
Scheme 3: Scope of amides. Reaction conditions: Unless specified, the reaction was carried out with **1a** (0.25 mmol), **2** (1.0 mmol), $NiBr_2$. (10 mol %), Phen (20 mol %), K_3PO_4 (0.5 mmol), 130 °C in toluene (2.0 mL). [a] *t*-BuONa was used. [b] ^{1}H-NMR yield using diphenylmethane as an internal standard.

Next, selective mono-alkylation of various benzamides were demonstrated using optimum catalytic conditions (Scheme 3). Benzamides bearing electron rich functionalities, such as, methyl, ethyl, isopropyl and methoxy groups are well tolerated and furnished the desired

products in moderate to excellent isolated yield (Scheme 3, **4a-4h** and **4j**). It is to be noted that, electron poor *p*-fluorobenzamide resulted 72% yield of the N-alkylated amide (Scheme 3, **4i**). Importantly, the application of nicotinamide was studied with benzyl alcohol as well as with 2-pyridenemethanol and furnished the corresponding pharmaceutically active nicotinamide derivatives **4m-4n** (Scheme 3). Gratifyingly, more challenging, acetamide yielded the desired products in 34-45% respectively (Scheme 3, **4o-4p**). The catalytic protocol is highly selective for primary amides and the application of secondary amide derivatives under the optimized conditions resulted poor product conversions (Scheme 3, **4q-4t**).



Scheme 4. Amidation with 1,4-phenylenedimethanol



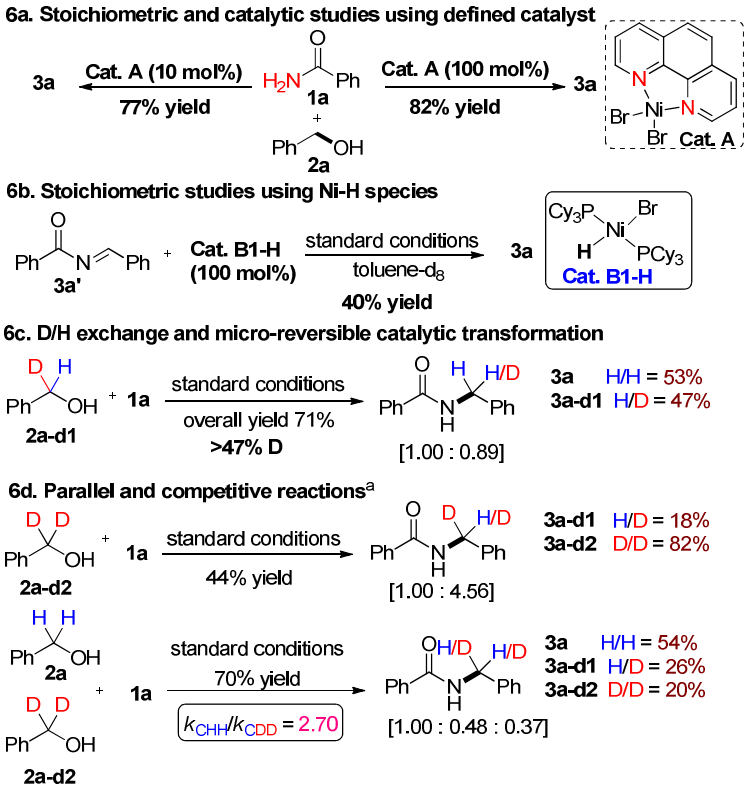
Scheme 5. Synthetic application. *t*-BuONa (0.5 mmol) was used.

After having demonstrated the scope of the amidation protocol, we were interested to explore the application of 1,4-phenylenedimethanol with benzamides. Notably, the resulted multi-functional amides **5a-5c** were obtained in 25-50% yield (Scheme 4).[1-2] Further, to explore the synthetic potential of the catalytic protocol, an attempt were established in one step synthesis of antiemetic drug Tigan,[15a] as well as dopamine D2 receptor antagonist, Itopride (Scheme 5).[15b] To our delight, the resulted drugs were obtained in good isolated yields. It is noteworthy to mention that, the catalytic protocol is tolerant to nitrogen heterocycles, allylic ethers, nitrile and alkene, including chloride and alkoxy moieties. Unfortunately, under identical conditions, reducible functional moieties, such as, nitro, carboxylic acids, esters and alkynes were not successful.

However, bromo and iodo substituted benzamides resulted only poor product conversions (SI, Table S8).

This results encouraged us to gain more insight about the preliminary mechanistic investigation of the process. To understand the bifunctional nature of the nickel catalyst, an *in situ* NMR-study was performed and revealed that, proposed amidation of alcohols composed of a multi-step BH/HA technique (SI Scheme S1). Nevertheless, to confirm the participation of the putative Ni-intermediate species, the **Cat.A** was prepared,[16a] and used in catalytic as well as in stoichiometric equiv. in the model reaction. The desired product **3a** was obtained in good isolated yields (Scheme 6a). Nevertheless, the application of defined complex, $Ni(phen)_2Br_2$ diminished the catalytic activity. Therefore, under standard condition addition of any extra ligand **L1** to the defined complex **Cat.A**, resulted only poor product conversion (SI Scheme S7).

In addition, an attempt was made to prepare and detect the Ni-H species of **Cat.A** in combination with **2a.** The *in situ* NMR studies at -75 °C was not successful and we observed benzaldehyde formation (SI Scheme S5).



Scheme 6. Mechanic investigation: [a]*t*-BuONa was used.

The experimental results evident that, the Ni-H species of **Cat.A** is highly unstable to identify even at low temperature (SI, Scheme S8). Gratifyingly, we choose electron rich tri-cyclohexyl phosphine **L7** as ligand (Table 1), the defined complex $NiBr_2(PCy_3)_2$ and the Ni-hydride species $(PCy_3)_2NiBrH$, **Cat.B1-H** were readily prepared.[16b,c] Next, the **Cat.B1-H** was employed in stoichiometric equiv. with imide **3a'** under optimized conditions. To our delight, **3a** was obtained in 40% yield (Scheme 6b). This experimental findings are in agreement for the participation of Ni-H species. In addition, a competition experiment between benzyl alcohol **2a** and 4-methoxy benzyl alcohol **2f** were performed and revealed that, for electron rich substituent amidation occurred at higher rates (SI, Scheme S6).

Further, amidation reaction of **1a** with **2a-d1** was studied and the product distribution analysis using ^{1}H-NMR indicated the formation of **3a-d1** and **3a** along with 47% deuterium incorporation at the benzylic position of **3a-d1** (Scheme 6c and SI Scheme S2). Notably, to gain more insight about the kinetic isotope effect (KIE), an intermolecular competition reaction of **2a** and **2a-d2** with **1a** were studied under the standard catalytic conditions and the observed product ratio on the basis of ^{1}H-NMR as well as HRMS analysis witnessed $k_{CHH}/k_{CDD} = 2.70$. These deuterated experimental evidences are in strong agreement with the literature observation of D/H exchange and the micro-reversible transformation of BH/HA process (Scheme 6d and SI Schemes S2 – S4).[17a] These experimental findings evident the involvement of the benzylic C-H bond cleavage in the rate determining step (Scheme 6d).[17b]

In conclusion, we developed an efficient and selective direct amidation of primary alcohols using earth-abundant and non-precious Ni-catalyst. The transformation could efficiently be performed in the presence of reducible functional moieties, such as, nitrile, allylic ether and alkenes. As a special highlights, we have demonstrated the synthesis of bis-amides, antiemetic drug Tigan **6a**, and dopamine D2 receptor antagonist, Itopride **6b**. Preliminary mechanistic investigation evident the participation of Ni-H species. The kinetic isotope effect (KIE) studies revealed the involvement of the benzylic C-H bond in the rate- determining step.

■ EXPERIMENTAL SECTION

General Experimental Details: All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, F_{254} plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. ^{1}H NMR spectral data were collected at, 400 MHz(JEOL), and ^{13}C NMR were recorded at 100 MHz. ^{1}H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiples), number of protons and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. High-resolution mass spectra (HRMS) were obtained on a Brüker micro TOF-Q II mass spectrometer (ESI-MS). GC-MS were recorded using Perkin-Elmer Mass Spectrometer. Melting points were recorded using Opti-Melt MPA100.

General Procedure for nickel-catalyzed amidation of alcohols: In a 20 mL oven dried Schlenk tube amide (0.25 mmol), base (0.5 mmol), ligand (20 mol %), $NiBr_2$ (10 mol %) and alcohols (1.0 mmol) were added followed by toluene 2 mL under an atmosphere of N_2 and heated at 130 $^\circ$C for 24-48 h. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure products.

***N*-Benzylbenzamide (3a)**[18a]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.044g, Yield: 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 6.9 Hz, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.32-7.35 (m, 4H), 7.26-7.32 (m, 1H), 6.58 (br s, 1H), 4.63 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.6, 128.9, 128.7, 128.0, 127.7, 127.1, 44.2.

***N*-(4-Methylbenzyl)benzamide (3b)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.035g, Yield: 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 6.7 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 6.34 (br s, 1H), 4.52 (d, J = 5.5

Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 137.5, 135.2, 134.5, 131.6, 129.6, 128.7, 128.1, 127.0, 44.0, 21.2.

***N*-(4-Ethylbenzyl)benzamide (3c)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.050g, Yield: 84%); mp 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.42 (br s, 1H), 4.62 (d, J = 5.6 Hz, 2H), 2.65 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.9, 135.5, 134.5, 131.6, 128.7, 128.4, 128.1, 127.1, 44.0, 28.6, 15.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NONa$ 262.1202; Found 262.1209.

***N*-(4-Isopropylbenzyl)benzamide (3d)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.051g, Yield: 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8.5 Hz, 2H), 7.42 (t, J=7.3Hz, 1H), 7.35 (t, J=7.6Hz, 2H), 7.22 (d, J=7.9 Hz, 2H), 7.15 (d, J=7.9 Hz, 2H), 6.31 (br s, 1H), 4.54 (d, J=5.5Hz, 2H), 2.89-2.78 (m, 1H), 1.17 (d, J=6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 148.5, 135.5, 134.5, 131.6, 128.7, 128.2, 127.0, 126.9, 44.1, 33.9, 24.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NONa$ 276.1359; Found 276.1353.

***N*-(2-Methylbenzyl)benzamide (3e)**[19b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.043g, Yield: 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 2H), 7.41 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 6.7 Hz, 1H), 7.12 (q, J = 6.9 Hz, 3H), 6.22 (br, s, 1H), 4.55 (d, J = 5.5 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 136.7, 135.8, 134.4, 131.6, 130.7, 128.8, 128.7, 128.0, 127.0, 126.4, 42.5, 19.2.

***N*-(4-Methoxybenzyl)benzamide (3f)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:3), (0.053g, Yield: 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 6.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.38 (br s, 1H), 4.57 (d, J = 6.4

Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 159.2, 134.5, 131.6, 130.4, 129.4, 128.6, 127.1, 114.2, 55.4, 43.7.

***N*-(3,4,5-Trimethoxybenzyl)benzamide (3g)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.040g, Yield: 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.3 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 6.68 (br s, 1H), 6.55 (s, 2H), 4.55 (d, J = 6.1 Hz, 2H), 3.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 153.4, 137.3, 134.4, 134.1, 131.7, 128.7, 127.1, 105.0, 60.9, 56.2, 44.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1387; Found 302.1381.

***N*-(2,3,4-Trimethoxybenzyl)benzamide (3h)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.032g, Yield: 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.3 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.05 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.59 (br s, 1H), 4.58 (d, J = 6.1 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 153.7, 152.1, 142.2, 134.7, 131.5, 128.6, 127.0, 124.3, 123.9, 107.3, 61.2, 60.9, 56.1, 39.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1387; Found 302.1383.

***N*-(4-Cyanobenzyl)benzamide (3i)**[19a]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:3), (0.022g, Yield: 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.44-7.47 (m, 4H), 6.60 (br s, 1H), 4.71 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 143.9, 133.9, 132.6, 132.1, 128.8, 128.3, 127.1, 118.8, 111.4, 43.6.

***N*-(4-Chlorobenzyl)benzamide (3j)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.051g, Yield: 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 6.9 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.37-7.41 (m, 4H), 6.50 (br s, 1H), 4.65 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.9, 133.9, 132.6, 132.1, 128.8, 128.3, 127.1, 118.8, 43.6.

***N*-(2-Chlorobenzyl)benzamide (3k)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.033g, Yield: 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 2H), 7.29-7.46 (m, 5H), 7.16-7.19 (m, 2H), 6.57 (br s, 1H), 4.46 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 135.7, 134.3, 133.8, 131.7, 130.6, 129.7, 129.2, 128.7, 127.3, 127.1, 42.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{12}ClNONa$ 268.0500; Found 268.0490.

***N*-(2,4-Dichlorobenzyl)benzamide (3l)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane(1:4), (0.034g, Yield: 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.0 Hz, 1H), 7.36-7.44 (m, 4H), 7.21 (d, J = 8.4 Hz, 1H), 6.72 (br s, 1H), 4.66 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 134.3, 134.0, 133.9, 133.7, 131.9, 131.2, 129.4, 128.7, 127.5, 127.1, 41.6.

***N*-(4-Fluorobenzyl)benzamide (3m)**[18e]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.047g, Yield: 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.21-7.24 (m, 2H), 6.93 (d, J = 8.5, 2H), 6.53 (br s, 1H), 4.51 (d, J = 5.5Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.5, 162.3 (d, $J_{C\text{-}F}$ = 246.4 Hz), 134.3, 134.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 131.7, 129.6, 128.7, 127.1, 115.7 (d, $J_{C\text{-}F}$ = 22.1 Hz), 43.4.

***N*-(Naphthalen-1-ylmethyl)benzamide (3n)**[18b]:The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.053g, Yield: 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J= 9.2 Hz, 1H), 7.77 (d, J = 9.6 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.3 Hz, 2H), 7.35-7.43 (m, 3H), 7.28-7.37 (m, 2H), 7.23 (t, J = 7.6 Hz, 2H), 6.47 (br s, 1H), 4.92 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.4, 134.0, 133.5, 131.6, 128.9, 128.8, 128.6, 127.1, 126.9, 126.8, 126.1, 125.5, 123.6, 42.4.

***N*-(Pyridin-2-ylmethyl)benzamide (3o)**[18c]: The title compound was isolated as a yellow solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (2:3), (0.030g, Yield: 57%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 4.1 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.59-7.63 (m, 2H), 7.35-7.45 (m, 2H), 7.26 (d, J = 7.8 Hz, 1H), 7.13-7.19 (m, 1H), 4.69 (d, J = 5.0 Hz,

2H), 2.29 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.5, 156.3, 149.0, 137.0, 134.4, 131.6, 128.6, 127.2, 122.5, 122.3, 44.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{12}N_2ONa$ 235.0842; Found 235.0833.

***N*-(3,7-dimethyloct-6-en-1-yl)benzamide (3q)**[20e]: The title compound was isolated as a viscous liquid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.029g, Yield: 45%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.3 Hz, 2H), 8.01 (s, 1H), 7.75 (d, J = 1.8 Hz, 2H), 7.60 (q, J = 4.3 Hz, 1H), 5.09 (t, J = 7.0 Hz, 1H), 2.80-2.94 (m, 2H), 1.96-2.02 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.38-1.44 (m, 1H), 1.24-1.29 (m, 4H), 0.99 (d, J = 6.1 Hz, 3H); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{26}NO$ 260.2009; Found 260.2009.

***N*-Benzyl-4-methylbenzamide (4a)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.052g, Yield: 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.26-7.42 (m, 5H), 7.21 (d, J = 7.6 Hz, 2H), 6.39 (s, 1H), 4.63 (d, J = 5.5Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 142.1, 138.4, 131.6, 129.3, 128.9, 128.0, 127.7, 127.0, 44.18, 21.5.

***N*-Benzyl-3-methylbenzamide (4b)**[19d]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.038g, Yield: 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.55-7.57 (m, 1H), 7.28-7.36 (m, 7H), 6.44 (br s, 1H), 4.64 (d, J = 5.2 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 138.6, 138.3, 134.5, 132.4, 128.9, 128.6, 128.0, 127.8, 127.7, 124.0, 44.2, 21.4.

***N*-Benzyl-3,4-dimethylbenzamide (4c)**[19c]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.052g, Yield: 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.50 (d, J = 8 Hz, 1H), 7.26-7.36 (m, 5H), 7.17 (d, J = 8 Hz, 1H), 6.37 (br s, 1H), 4.64 (d, J = 5.2 Hz, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.7, 138.5, 137.1, 131.9, 129.8, 128.9, 128.3, 128.0, 127.7, 124.4, 44.2, 19.9,19.8.

***N*-Benzyl-4-isopropylbenzamide (4d)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.034g, Yield: 54%); mp 117-118°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2H), 7.30-7.35 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 6.41 (br s, 1H), 4.64 (d, J = 6.0 Hz, 2H), 2.91-2.98 (m, 1H), 1.25 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 152.9, 138.4, 132.0, 128.9, 128.0, 127.6, 127.2, 126.8, 44.2, 34.2, 23.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NONa$ 276.1359; Found 276.1356.

***N*-Benzyl-4-ethylbenzamide (4e)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane(1:4), (0.042g, Yield: 70%); mp 112-113°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.29-7.38 (m, 5H), 7.25 (d, J = 8 Hz, 2H), 6.37 (br s, 1H), 4.65 (d, J = 6.0 Hz, 2H), 2.69 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 148.3, 138.4, 131.8, 128.9, 128.2, 128.0, 127.7, 127.1, 44.2, 28.9, 15.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NONa$ 262.1202; Found 262.1223.

***N*-Benzyl-4-methoxybenzamide (4f)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane(1:4), (0.036g, Yield: 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.8 Hz, 2H), 7.27-7.35 (m, 5H), 6.90 (d, J = 8.4 Hz, 2H), 6.46 (br s, 1H), 4.61 (d, J = 5.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.3, 138.5, 128.9, 128.8, 128.0, 127.6, 126.7, 113.8, 55.5, 44.1.

***N*-Benzyl-3,4-dimethoxybenzamide (4g)**[21b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.052g, Yield: 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 1.8 Hz, 1H), 7.25-7.33 (m, 6H), 6.81 (d, J = 8.5 Hz, 1H), 6.67 (br s, 1H), 4.61 (d, J = 5.5 Hz, 2H), 3.88 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.8, 149.0, 138.5, 128.8, 127.9, 127.6, 127.0, 119.6, 110.7, 110.3, 56.1, 44.2.

***N*-Benzyl-3,4,5-trimethoxybenzamide (4h)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (2:3), (0.049g, Yield: 65%); mp 140-141°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.37 (m, 5H), 7.02 (s, 2H), 6.41 (br s, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.88-3.89 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 153.3,

141.1, 138.3, 129.9, 128.9, 128.0, 127.8, 104.5, 61.0, 56.4, 44.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_4Na$ 324.1206; Found 324.1201.

***N*-Benzyl-4-fluorobenzamide (4i)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.041g, Yield: 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.81 (m, 2H), 7.26-7.39 (m, 5H), 7.08 (t, J = 8.7 Hz, 2H), 6.56 (br s, 1H), 4.61 (d, J = 5.5Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.8 (d, $J_{C\text{-}F}$ = 253.0 Hz), 138.2, 130.6, 129.4 (d, $J_{C\text{-}F}$ = 8.6 Hz), 128.9, 128.0, 127.8, 115.7 (d, $J_{C\text{-}F}$ = 22.2 Hz), 44.3.

***N*-Benzyl-4-chlorobenzamide (4j)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.015g, Yield: 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.30-7.37 (m, 5H), 6.36 (br s, 1H), 4.64 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.0,137.9,132.8, 129.0,128.5, 128.1, 127.9, 127.0, 44.4.

***N*-Benzyl-1-naphthamide (4k)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.026g, Yield: 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.5 Hz, 1H), 7.85-7.91 (m, 3H), 7.60-7.62 (m, 1H), 7.52-7.58 (m, 2H), 7.29-7.45 (m, 5H), 6.30 (brs, 1H), 4.73 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.2, 134.4, 133.8, 130.8, 130.3, 128.9, 128.4, 128.0, 127.8, 127.3, 126.5, 125.5, 125.0, 124.8, 44.2.

***N*-(4-(allyloxy)benzyl)-3,4,5-trimethoxybenzamide (4l)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (2:3), (0.028g, Yield: 31%); mp 142-143°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 7.02 (s, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.48 (br s, 1H), 6.09-5.99 (m, 1H), 5.41 (dd, J = 17.4, 1.4 Hz, 1H), 5.29 (dd, J = 10.5, 1.4 Hz, 1H), 4.56-4.52 (m, 4H), 3.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.2, 153.3, 141.0, 133.2, 130.5, 129.9, 115.3, 114.8, 104.7, 104.2, 68.9, 61.1, 56.4, 43.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_5Na$ 380.1468; Found 380.1462.

***N*-benzylnicotinamide (4m)**[18c]: The title compound was isolated as a colorless liquidusing silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.008g, Yield: 23%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 1.8 Hz, 1H), 8.71 (d, J = 3.1 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.32-7.40 (m, 6H),6.58 (br s, 1H), 4.66 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 152.5, 147.9, 137.8, 135.4, 130.2, 129.0, 128.0, 127.8, 123.6, 44.4.

***N*-(pyridin-2-ylmethyl)nicotinamide (4n)**[18d]: The title compound was isolated as a viscous yellow oil using silica-gel column chromatography eluting with ethyl acetate/ hexane (7:3), (0.011g, Yield: 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 1.8 Hz, 1H), 8.73 (dd, J = 4.8, 1.6 Hz, 1H), 8.56 (d, J = 4.9 Hz, 1H), 8.21 (dt, J = 7.9, 1.8 Hz, 1H), 7.89 (s, 1H), 7.71 (td, J = 7.6, 1.4 Hz, 1H), 7.40 (q, J = 4.3 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.23-7.26 (m, 1H), 4.77 (d, J = 4.9 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 155.7, 152.2, 149.1, 148.3, 137.1, 135.2, 130.1, 123.6, 122.8, 122.3, 44.7.

***N*-Benzylacetamide (4o)**[19e]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.017g, Yield: 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.52 (m, 2H), 7.37-7.34 (m, 3H), 5.88 (br s, 1H), 4.59 (d, J = 5.5 Hz, 2H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.2, 128.9, 127.9, 127.7, 43.9, 29.8.

***N*-(4-methoxybenzyl)acetamide (4p)**[21c]: The title compound was obtained as sticky solid eluting with ethyl acetate/ hexane (3:7), (0.015g, Yield: 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-6.87 (m, 4H), 6.42 (brs, 1H), 4.38 (d, J = 5.60 Hz, 1H), 3.78 (s, 3H), 2.00 (s, 3H).

***N,N'*-(1,4-phenylenebis(methylene))dibenzamide (5a)**[20d]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane(3:7), (0.022g, Yield: 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 4H), 7.51 (t, J = 7.3 Hz, 2H), 7.42 (t, J = 7.3 Hz, 4H), 7.33 (d, J = 1.2 Hz, 4H), 6.29 (br s, 2H), 4.67 (d, J = 4.3 Hz, 4H). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{20}N_2O_2Na$ 367.1417; Found 367.1409.

***N,N′*-(1,4-phenylenebis(methylene))bis(4-methylbenzamide) (5b)**[20c]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.012g, Yield: 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.9 Hz, 4H), 7.33 (d, J = 7.9 Hz, 4H), 7.22 (d, J = 7.9 Hz, 4H), 6.46 (br s, 2H), 4.60 (d, J = 5.5 Hz, 4H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 142.1, 137.8, 133.0, 130.1, 128.4, 127.0, 45.3, 22.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{24}N_2O_2Na$ 395.1730; Found 395.1764.

***N,N′*-(1,4-phenylenebis(methylene))bis(3,4-dimethylbenzamide) (5c)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (3:7), (0.016g, Yield: 32%); mp 202-203°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 2H), 7.51-7.42 (m, 2H), 7.33 (s, 4H), 7.17 (d, J = 7.9 Hz, 2H), 6.41 (br s, 2H), 4.62 (d, J = 5.5 Hz, 4H), 2.29 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 140.8, 137.8, 137.1, 131.9, 129.8, 128.4, 128.4, 124.4, 43.8, 19.9, 19.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{28}N_2O_2Na$ 423.2043; Found 423.2042.

***N*-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide (6a)**[20a]: The title compound was isolated as a pale yellow solid using silica-gel column chromatography eluting with methanol/ethyl acetate (1:9), (0.078g, Yield: 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 7.03 (s, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.55 (br s, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.14 (t, J = 5.6 Hz, 2H), 3.88 (s, 9H), 2.92-2.89 (m, 2H), 2.46 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.1, 158.0, 153.3, 141.0, 130.8, 129.9, 129.5, 114.8, 104.5, 65.2, 61.0, 57.6, 56.4, 45.1, 43.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_5$ 389.2071; Found 389.2075.

***N*-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4-dimethoxybenzamide (6b)**[20b]: The title compound was isolated as a pale yellow solid using silica-gel column chromatography eluting with methanol/ethyl acetate (1:9), (0.066g, Yield: 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 1.8 Hz, 1H), 7.26-7.30 (m, 3H), 6.89 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 6.33 (br s, 1H), 4.57 (d, J = 5.5 Hz, 2H), 4.15 (t, J = 5.5 Hz, 2H), 3.91 (s, 6H), 2.91 (t, J = 4.6 Hz, 2H), 2.46 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.0, 158.1, 151.5, 148.8, 131.0, 129.4, 127.4, 119.3, 114.8, 110.5, 110.1, 65.1, 57.7, 56.1, 45.1, 43.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}N_2O_4$ 359.1965; Found 359.1956.

ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C and HRMS data for selected compounds.

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

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