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ABSTRACT

OSU-6, an MCM-41 type hexagonal mesoporous silica with strong Bronsted acid properties, has been used to promote the high-yield conversion of carboxylic acids and esters to carboxamides as well as transamidations of primary amides in a one-pot solventless approach. A metal-free heterogeneous catalyst that promotes all of these processes has not been previously reported. OSU-6 enables these transformations to proceed in shorter times and at lower temperatures for a broad range of substrates. An added benefit is that the catalyst can be recycled and reused multiple times without significant loss of activity.

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1. Introduction

Carboxamides are important functional motifs in both natural and unnatural products.¹ Due to their high polarity, stability, H-bond donating and accepting capability, and conformational diversity,^{1a, 2} these groups are prevalent in many bioactive molecules.³ In chemical structures, amide linkages serve as important scaffolds for pharmaceuticals, agrochemicals, polymers, and materials.^{1b, 3b, 4} A recent report estimated that more than 25% of known drugs contain amide functional groups.⁵ Hence, improved methods for the synthesis of carboxamides involving a straightforward catalytic approach are in high demand.

Traditional methods for amide synthesis involve acylation of an amine by an acid chloride or anhydride, or a dehydrative coupling between an amine and a carboxylic acid.⁶ These procedures are often limited by harsh reagents, high temperatures, isolation problems or the generation of stoichiometric quantities of waste. Recently, organic chemists have shown a great deal of interest in catalyst-promoted syntheses of amides from acids and esters. For example, acids have been converted to amides with metal-based catalysts $ZrCl_4$ and Cp_2ZrCl_2 ,⁷ as well as non-metals $B(OH)_3$ ⁸ and related boron derivatives,⁹ silica,¹⁰ alumina,¹¹ and Starbans-400.¹² The ester-to-amide interconversion has been reported using Lewis acids such as InI_3 ¹³ and $Zr(O-t-Bu)_4$.¹⁴ These approaches permit reactions at lower temperatures and give cleaner products, but in most cases their use has been limited to amide formation from only one acyl derivative.

Among the non-metal catalysts for the acid-to-amide conversion, $B(OH)_3$ ⁸ and mesoporous silica SBA-15^{10d} appear to have the most promise. Boric acid is readily available, inexpensive, and promotes the reaction in refluxing toluene. However, reported procedures simply precipitate the amide product from the crude reaction mixture without specifying how residual $B(OH)_3$ is removed from the product. SBA-15 also promotes this process in refluxing toluene. It has acidic properties, a high surface area and good hydrothermal stability,¹⁵ but it has only been reported for this singular process and is not commercially available.

Transamidation is also an attractive route for the synthesis of amides. However, due to the intrinsic stability of the amide C-N bond and the acidic nature of the N-H bond, this is often a difficult process. Transamidations generally require high temperatures (180 °C) and long reaction times, and thus are restricted in their scope. Although various metal-based catalysts, including $AlCl_3$,¹⁶ polymer-bound $HfCl_4$,¹⁷ $Eu(OTf)_3$,¹⁸ $ZrCl_4$,¹⁹ $Sc(OTf)_3$,²⁰ $Ti(NMe_2)_4$,²¹ CeO_2 ,²² Cp_2ZrCl_2 ,²³ $[Mn(Hbpoh)(OAc)(H_2O)]_2 \cdot 6H_2O$,²⁴ $Fe(NO_3)_3 \cdot 9H_2O$ ²⁵ and Rh(II) NHC complexes²⁶ have been reported to promote this transformation, most of these metals require anhydrous and inert atmosphere conditions, long reaction times, or toxic solvents. In recent years, a number of researchers have focused on developing greener methods, that use catalysts such as $NH_2OH \cdot HCl$,²⁷ L-proline,²⁸ $B(OH)_3$,²⁹ chitosan³⁰ and heteroanion-based ionic liquids.³¹ Among the non-metal catalysts for this process, $B(OH)_3$ and chitosan appear to be the most versatile. Although these catalysts give the desired products, both suffer from application to a relatively narrow selection of substrates. Furthermore, chitosan also requires higher reaction temperatures.

From an environmental viewpoint, developing a clean method to promote both the conversion of acids and esters to amides and transamidations of primary amides has been a challenge. Though

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various methods are reported for these reactions, most involve metal-based catalysts that are often hazardous and require remediation prior to disposal. Other potential drawbacks of metal-based catalysts are that they can be deactivated by coordination with heterocyclic substrates³² or contaminate the final products.

Our recent endeavors have demonstrated the potency of OSU-6 as a catalyst for the formation of 3-oxoisindoline-1-carbonitriles and carboxamides³³ as well as 2-alkyl- and 2-aryl- (3-oxoisindolin-1-yl)phosphonates.³⁴ OSU-6 is an MCM-41 type, hexagonal, mesoporous silica developed by Al Othman and Apblett.³⁵ It has acidic properties (due to aging with 2 M HCl during its preparation) and robust characteristics similar to SBA-15 but is more readily available. Based on our earlier work, we envisioned a platform by which various methods for amide formation could be achieved by reaction of acids or esters with amines or by exchanging the amine portion of a primary amide using OSU-6 as a catalyst. To the best of our knowledge, a metal-free heterogeneous catalyst that promotes all three of these transformations has not been previously reported.

2. Results and Discussion

I. Synthesis of amides from acids. Our study first sought to establish the feasibility of this process by reacting benzoic acid (**1a**) with 4-methoxybenzylamine (**2a**) to prepare amide **3aa** in various solvents using 10 wt% (relative to **1a**) of OSU-6. Initially, the reaction was attempted in polar aprotic media such as DMF, DMSO or NMP at 140 °C, but these solvents gave unacceptably low yields (Table 1). We then evaluated non-polar media such as toluene and xylene. In these solvents, the reaction proceeded cleanly within 24 h at 120 °C and 140 °C, respectively. Intrigued by this finding, we increased the catalytic loading from 10 to 15, 20, 30, and 50 wt% in an effort to accelerate the reaction. These experiments revealed that 20 wt% of OSU-6 was optimum, producing high yields of the amide within 8–12 h. To improve sustainability, we eliminated the solvent and evaluated the reaction at 120 °C, 140 °C, and 160 °C. These experiments demonstrated that reactions performed at 120 °C provided cleaner products and higher yields. Under these conditions,

Table 1. Solvent and temperature optimization.

Entry	Solvent	Temp (°C)	Yield (%) ^a
1	DMF	140	25
2	NMP	140	trace
3	DMSO	140	40
4	chlorobenzene	140	18
5	toluene	120 ^b	46
6	xylene ^c	120	68
7	xylene ^c	140	72
8	xylene ^c	160 ^b	84
9	no solvent	120	94
10	no solvent	140	90
11	no solvent	160	88

^a Isolated yields. ^b Reaction was run under N₂ in a screw-top pressure tube. ^c A mixture of *o*, *m*, and *p* isomers was used.

we found that volatile aliphatic and readily carbonated and oxidized benzylic amines gave better results when reacted under N₂ in a screw-top pressure tube.

Once a relatively mild catalytic procedure for the acid-to-amide conversion had been established, we turned our attention towards increasing the substrate scope. To this end, we explored the reaction using benzoic acid (**1a**), 2-chloro-5-bromobenzoic acid (**1b**), 4-

nitrobenzoic acid (**1c**), and nicotinic acid (**1d**) with various amines **2** to form **3aa–3dm**. Our results are summarized in Table 2.

Using the optimized conditions, all of these acids were rapidly converted to amides in excellent isolated yields. Acids **1b** and **1c** had the potential to undergo nucleophilic aromatic substitution, but this was not observed. Furthermore, catalyst deactivation by acid **1d**, expected for metal-based Lewis acids, was not a problem with OSU-6. The reaction was successful for benzylic, aromatic, and aliphatic amines and tolerated a wide range of electronically diverse substituents on the benzylic and aromatic amines, including ethers, halides, trifluoromethyl, and 4-pyridyl. Apart from the high yields achieved, OSU-6 also offered a simple workup and purification procedure involving (1) dilution with ethyl acetate, (2) filtration to remove the catalyst, (3) washing the filtrate with mild acid and base, and (4) concentration. Most solid amides were purified by recrystallization from ethanol, but for analytical samples, chromatographic purification on a short silica gel column eluted with ethyl acetate in hexanes was necessary.

Table 2. Conversion of acids to amides.

ArCO ₂ H + RNH ₂		20 wt% OSU-6 no solvent 120 °C	ArCONHR		
1	2		3		
Ar	R	Pdt	Time (h)	Yield (%) ^a	
1a:	2a: 4-CH ₃ OC ₆ H ₄ CH ₂	3aa	8	88	
C ₆ H ₅	2b: 4-CF ₃ C ₆ H ₄	3ab	12	72	
	2c: 4-pyridyl	3ac	12	88	
	2d: C ₆ H ₅ CH ₂ CH ₂	3ad	8	91	
1b:	2a: 4-CH ₃ OC ₆ H ₄ CH ₂	3ba	8	94	
2-Cl-	2e: C ₆ H ₅ CH ₂	3be	8	92	
5-Br-C ₆ H ₃	2f: CH ₂ =CH-CH ₂	3bf	14	80	
	2g: morpholino ^b	3bg	12	76	
1c:	2f: CH ₂ =CH-CH ₂	3cf	14	82	
4-NO ₂ -	2h: 4-FC ₆ H ₄ CH ₂	3ch	10	78	
C ₆ H ₄	2i: 4-CH ₃ OC ₆ H ₄	3ci	8	92	
	2j: <i>c</i> -C ₆ H ₁₁	3cj	8	86	
1d:	2h: 4-FC ₆ H ₄ CH ₂	3dh	12	86	
3-NC ₅ H ₄	2k: C ₆ H ₅	3dk	15	88	
	2l: 4-CF ₃ OC ₆ H ₄	3dl	18	78	
	2m: (CH ₃) ₂ CHCH ₂	3dm	18	85	

^a Isolated yields. ^b Morpholine was used as the amine.

II. Synthesis of *N*-substituted phthalimides from aromatic *o*-diacids. Following our work with monocarboxylic acids, we turned our attention to the preparation of *N*-substituted phthalimides from aromatic *o*-diacids (**4a–c**). This ring-forming bis-amidation process

required relatively high temperatures but proceeded cleanly for a series of reacting partners with varied electronic properties (Table 3).

The diacids examined included phthalic acid (**4a**), 4-hydroxyphthalic acid (**4b**), and 2,3-pyridinedicarboxylic acid (**4c**) to prepare **5ae-5co**. In these cyclizations, unsubstituted **4a**, as well as electron-rich **4b** and electron-poor **4c**, gave isolated yields of the corresponding phthalimides ranging from 78-91%. As in the monoacid-to-amide transformation, benzylic and aliphatic amines gave superior results when performed under N₂ without solvent in a screw-top pressure tube. Electron-donating and withdrawing substituents on the benzylamines had no negative impact on the reaction outcome. For aromatic amines, only aniline and derivatives bearing resonance electron-donating groups (4-OMe, 4-F³⁶) afforded clean cyclization products. Arylamines substituted by resonance electron-withdrawing groups (e.g. 4-NO₂) gave complex mixtures of unreacted and partially reacted materials. Since the nitro group can deactivate reactants through resonance, this outcome was not unexpected.

Table 3. Conversion of aromatic *o*-diacids to *N*-substituted phthalimides.

X Y	R	Pdt	Time (h)	Yield (%) ^a
4a: X = CH, Y = H	2e: C ₆ H ₅ CH ₂	5ae	18	84
X = CH	2h: 4-FC ₆ H ₄ CH ₂	5ah	18	78
Y = H	2n: 3-CH ₃ OC ₆ H ₄	5an	18	86
(4a)	2o: <i>n</i> -C ₆ H ₁₃	5ao	24	90
4b: X = CH, Y = 4-OH	2e: C ₆ H ₅ CH ₂	5be	16	88
X = CH	2h: 4-FC ₆ H ₄ CH ₂	5bh	18	84
Y = 4-OH	2p: 4-CF ₃ C ₆ H ₄ CH ₂	5bp	26	78
4c: X = CH, Y = 4-OH	2a: 4-FC ₆ H ₄ CH ₂	5ca	18	85
X = N	2d: C ₆ H ₅ CH ₂ CH ₂	5cd	18	89
Y = H	2e: C ₆ H ₅ CH ₂	5ce	18	91
	2h: 4-FC ₆ H ₄ CH ₂	5ch	24	87
	2o: <i>n</i> -C ₆ H ₁₃	5co	14	91

^a Isolated yields.

III. Synthesis of amides from esters. Esters were also examined as substrates for amide synthesis and were found to proceed smoothly at lower temperatures. Thus, benzoate esters **6a-d** were heated with a selection of benzylic, aliphatic, and aromatic amines **2** at 100 °C to give the corresponding amides **3ae-3dw** within 24 h. Ethyl and methyl esters proved equally successful in the reaction (Table 4).

Table 4. Conversion of esters to amides.

Ar	R	Pdt	Time (h)	Yield (%) ^a
6a:	2e: C ₆ H ₅ CH ₂	3ae	6	91
C ₆ H ₅	2h: 4-FC ₆ H ₄ CH ₂	3ah	18	76
	2q: 5,6,7,8-tetrahydronaphth-2-yl	3aq	10	94
6b:	2n: 3-CH ₃ OC ₆ H ₄	3bn	10	87
2-Cl-	2r: 4-ClC ₆ H ₄ CH ₂	3br	12	88
5-Br-C ₆ H ₃	2s: 4-CH ₃ C ₆ H ₄	3bs	12	91
	2t: HOCH ₂ CH ₂	3bt	16	80
6c:	2o: <i>n</i> -C ₆ H ₁₃	3co	14	86
4-NO ₂ -C ₆ H ₄	2u: 4-CH ₃ C ₆ H ₄ CH ₂	3cu	6	95
	2v: 4-ClC ₆ H ₄	3cv	12	89
6d:	2b: 4-CF ₃ C ₆ H ₄ CH ₂	3db	20	72
3-NC ₅ H ₄	2e: C ₆ H ₅ CH ₂	3de	12	87
	2s: 4-CH ₃ C ₆ H ₄	3ds	14	90
	2v: 4-ClC ₆ H ₄	3dv	16	85
	2w: <i>c</i> -C ₃ H ₅	3dw	28	74

^a Isolated yields.

IV. Transamidation of amides. Based on our success in converting acids and esters to amides under neat conditions with OSU-6, we investigated the application of this catalyst for transamidation reactions. From the literature, it was known that amide exchange promoted by metal-based Lewis acids generally proceeded at 80-100 °C,^{16-17, 20-21, 23, 25} while non-metal based catalysts required 100-150 °C²⁷⁻³⁰ or microwave heating.³¹

In order to assess the potential of OSU-6 for this process, a mixture of benzamide (**8a**) and allylamine (**2f**) was heated with 20 wt% of catalyst without solvent under N₂ at 130 °C in a pressure tube and monitored periodically by TLC. After 30 h, the reaction to form **3af** was complete. The same method was extended to four other amines with **8a** as well as additional amines with 2-chloro-5-bromobenzamide (**8b**) and nicotinamide (**8d**) to prepare **3af-3dy**. Again, compound **8b** was chosen as a substrate to observe whether nucleophilic aromatic substitution of the chlorine by the amine would compete with the desired reaction. Interestingly, this process was not observed, presumably because electron donation from the amide nitrogen to the carbonyl reduced the electron-withdrawing effect of this group on the ring. It was further observed that electron deficient **8d** demanded a higher temperature (145 °C) for efficient conversion. Each amide substrate underwent the desired exchange to give high isolated yields (Table 5).

Table 5. Transamidation of aromatic amides.

ArCONH ₂ + RNH ₂		20 wt% OSU-6 no solvent 130-145 °C		ArCONHR	
8	2			3	
Ar	R	Pdt	Time (h)	Yield (%) ^a	
8a: C ₆ H ₅	2f: CH ₂ =CH-CH ₂	3af	30	83	
	2h: 4-FC ₆ H ₄ CH ₂	3ah	18	90	
	2n: 3-CH ₃ OC ₆ H ₄	3an	18	92	
	2o: <i>n</i> -C ₆ H ₁₃	3ao	24	88	
	2u: 4-CH ₃ C ₆ H ₄ CH ₂	3au	18	94	
8b: 2-Cl-5-Br-C ₆ H ₃	2r: 4-ClC ₆ H ₄ CH ₂	3br	20	92	
	2s: 4-CH ₃ C ₆ H ₄	3bs	24	93	
	2x: 4-FC ₆ H ₄	3bx	24	76	
	2y: piperidin-1-yl ^b	3by	28	82	
	2z: CH ₃ CH ₂	3bz	40	82	
8d: 3-NC ₅ H ₄	2f: CH ₂ =CH-CH ₂	3df	30	86	
	2i: 4-CH ₃ OC ₆ H ₄	3di	28	87	
	2o: <i>n</i> -C ₆ H ₁₃	3do	24	89	
	2p: 4-CF ₃ C ₆ H ₄	3dp	36	70	
	2u: 4-CH ₃ C ₆ H ₄ CH ₂	3du	24	89	
	2x: 4-FC ₆ H ₄	3dx	30	78	
	2y: piperidin-1-yl ^b	3dy	30	76	

^a Isolated yields. ^b Piperidine was used as the amine.

V. Transamidation of phthalimides. To extend our transamidation study, we attempted the amide exchange using phthalimide (**4a**) and 4-hydroxyphthalimide (**4b**) to generate *N*-substituted phthalimides **5aa-5br** (Table 6). In this variant of the reaction, we examined phthalimide **4b** to study the effect of an acidic, electron-donating group on this process. A second substituted derivative, 4-nitrophthalimide (**4c**), was also attempted, but the reaction failed to proceed to completion and several side reactions were noted. Thus, **4a** and **4b** were reacted with benzylic and aromatic amines, bearing both electron-donating and withdrawing substituents, as well as with aliphatic amines. The transamidation of both phthalimides, without solvent, under N₂ in a pressure tube, gave products in excellent isolated yields. Due to the fact that many of these reactions involved two solids, this process required relatively high temperatures (150 °C) for 18-36 h for complete conversion (see discussion below). The poor solubility of these substrates precluded the use of solvent as a means to lower the reaction temperatures for these transformations.

Table 6. Transamidation of phthalimides.

Y		20 wt% OSU-6 no solvent 150 °C		Y	
4a-b	2			5a-b	
Y	R	Pdt	Time (h)	Yield (%) ^a	
4a: H	2a: 4-CH ₃ OC ₆ H ₄ CH ₂	5aa	24	85	
	2d: C ₆ H ₅ CH ₂ CH ₂	5ad	18	91	
	2j: <i>c</i> -C ₆ H ₁₁	5aj	30	86	
	2n: 3-CH ₃ OC ₆ H ₄	5an	24	82	
	2p: 4-CF ₃ C ₆ H ₄ CH ₂	5ap	36	71	
4b: 4-OH	2r: 4-ClC ₆ H ₄ CH ₂	5ar	24	81	
	2x: 4-FC ₆ H ₄	5ax	24	85	
	2j: <i>c</i> -C ₆ H ₁₁	5bj	28	83	
	2r: 4-ClC ₆ H ₄ CH ₂	5br	24	79	

^a Isolated yields.

VI. Transamidations using hydrazine, acetamide and formamide: (a) **Hydrazine.** The transamidation process was extended to include the reaction of benzamide (**8a**) with hydrazine (**9**) to form benzhydrazides **10a-d** (Table 7). Treatment **8a** with 1.1 equivalents of **9** under the standard conditions at 130 °C gave the expected products after 20-24 h. As in previous reactions, electron-donating and withdrawing aromatic substituents did not affect the conversion and isolated yields of 78-87% were realized.

Table 7. Conversion of benzamides to benzhydrazides.

ArCONH ₂ + NH ₂ NH ₂		20 wt% OSU-6 no solvent 130 °C		ArCONHNH ₂	
8	9			10	
Ar	Pdt	Time (h)	Yield (%) ^a		
8a: C ₆ H ₅	10a	24	84		
8d: 4-ClC ₆ H ₄	10b	24	78		
8e: 4-CH ₃ OC ₆ H ₄	10c	20	87		
8f: 4-CH ₃ C ₆ H ₄	10d	24	87		

^a Isolated yields.

(b) **Acetamide.** We also studied the conversion of a series of amines **2** with acetamide (**11**) to *N*-alkyl- and *N*-arylacetamides **12a-e**. Again, benzylic and aliphatic amines underwent efficient product formation at lower temperatures (120 °C) compared with arylamines (140 °C) (Table 8). As a result of the lower temperature conditions, benzylic and aliphatic amines generally afforded cleaner products and higher yields than the arylamines. For example, transamidation of **11** with benzylamine (**2e**) at 120 °C for 24 h gave **12a** in 84% yield after recrystallization, while 3-nitroaniline (**2aa**) required heating at 140 °C for 40 h and chromatographic purification to provide **12e** in 62% yield.

Table 8. Transamidation of acetamides.
$$\text{CH}_3\text{CONH}_2 + \text{RNH}_2 \xrightarrow[\text{no solvent, 120-140 } ^\circ\text{C}]{20 \text{ wt\% OSU-6}} \text{CH}_3\text{CONHR}$$

11	2		12
R	Pdt	Time (h)	Yield (%) ^a
2e: C ₆ H ₅ CH ₂	12a	24	84
2j: <i>c</i> -C ₆ H ₁₁	12b	24	80
2k: C ₆ H ₅	12c	30	77
2o: <i>n</i> -C ₆ H ₁₃	12d	30	84
2aa: 3-NO ₂ C ₆ H ₄	12e	40	62

^a Isolated yields.

(c) **Formamide.** Finally, the amine portion of formamide (**13**) was exchanged with a minimal set of benzylamine derivatives to give *N*-benzylformamides **14a-c** (Table 9). Using the standard protocol at 120 °C, the reaction was complete within 24 h and furnished isolated yields exceeding 80%.

Table 9. Transamidation of formamides.
$$\text{HCONH}_2 + \text{RNH}_2 \xrightarrow[\text{no solvent, 120 } ^\circ\text{C}]{20 \text{ wt\% OSU-6}} \text{HCONHR}$$

13	2		14
R	Pdt	Time (h)	Yield (%) ^a
2e: C ₆ H ₅ CH ₂	14a	24	82
2h: 4-FC ₆ H ₄ CH ₂	14b	24	83
2r: 4-ClC ₆ H ₄ CH ₂	14c	24	81

^a Isolated yields.

Time and temperature requirements for the amidations correlated well with the ease of bringing reactants into a homogeneous state. Liquids, such as esters and low molecular weight amides which solvated their reacting partners, formed products at relatively low temperatures (100-120 °C) and the reactions were complete in a shorter time. Solid reactants, on the other hand, such as acids, diacids, benzamides and phthalimides required heating at ≥130 °C for extended periods. Without solvent, it was necessary for a solid substrate to dissolve in (or melt with) its co-reactant. For amidations involving two solids, the compounds had to melt together before the reaction initiated. Since mixing two solids depressed their melting points, all reactions proceeded at ≤150 °C. The boiling points of the amine substrates were also important in planning these conversions. Low boiling and sensitive amines reacted optimally under N₂ in a pressure tube. Due to evaporative loss, volatile amines also required a slightly greater excess (1.10 equivalents vs 1.05 equivalents) to assure high yields of amides.

From an environmental perspective, recyclability of the catalyst was critical. To evaluate this possibility, the following sequence was repeated five times. Benzamide (**8a**) and 4-methoxybenzylamine (**2a**) were converted to **3aa** in a pressure tube at 120 °C for a period of 12 h and the catalyst was recovered by dissolving the product in ethyl acetate and filtering. The catalyst was then washed alternately with ethanol and water (3 times), dried under high vacuum at 80 °C for 2 h, and reused. The catalyst did not show a significant loss of activity through four cycles, and only a slight decrease in yield was noted in the fifth cycle (Figure 1). In no case did the catalyst require treatment with acid to restore activity.

Figure 1. Recyclability of the catalyst.

A possible mechanism for the transamidation conversion is shown in Figure 2. Throughout this process, OSU-6 serves as a Bronsted acid. Initial protonation of the amide carbonyl of **8** would result in the H-bonded structure **19**. Addition of the amine to the activated carbonyl would then give the H-bonded tetrahedral intermediate **20**. Finally, proton exchange to give **21** and loss of ammonia as ammonium ion (**22**) from the original amide would yield the transamidation product **9**. Although the reaction consumes one equivalent of protons from OSU-6, regeneration and reuse of this catalyst does not require treatment with acid in the first five cycles. Thus, there appears to be a significant number of available protons in the catalyst. In the absence of catalyst, the reaction of **8a** and **2a** at 170 °C for 48 h proceeded to give only 20% of **3aa**, indicating that high temperatures and extended reaction times alone were insufficient to assure complete amide exchange. A similar mechanism can be envisioned for the conversion of acids and esters to amides.

Figure 2. Proposed mechanism for the transamidation.

3. Conclusions

We have developed an efficient strategy for the synthesis of amides by reaction of acyl compounds with amines using OSU-6 as a common catalyst. The method has wide application, including conversion of acids and esters to amides as well as transamidations of primary amides. It also offers several advantages, including (1) high yields, (2) lower temperatures, (3) minimal formation of by-products, and (4) catalyst recyclability. A broad scope of amine substrates is reported, including benzylic, aromatic and aliphatic amines. Aromatic precursors, substituted by electron-donating and withdrawing groups, as well as pyridine derivatives are well tolerated in the reaction. Only nitro substitution elicits capricious behavior, and this likely derives from its resonance electron-withdrawing effect and leaving group ability in nucleophilic aromatic substitutions. The reactivity is related to the ease of bringing the reactants into intimate contact. Liquid reactants, which solvate the reaction mixture, proceed faster and at lower temperatures than poorly soluble solids, which must melt together. Control experiments are reported that confirm the need for catalyst in the reaction, and a mechanism is proposed to account for the formation of the products.

4. Experimental Section

4.1 General experimental details

The OSU-6 catalyst can be purchased from XploSafe LLC (website: www.xplosafe.com) as Product No 9001. All reactions were run under N₂. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521). Column chromatography, when necessary, was performed using silica gel (Davisil[®] grade 62, 60-200 mesh) mixed with UV-active phosphor (Sorbent Technologies, No. UV-05); band elution was monitored using a hand held UV lamp. The saturated NaCl, saturated NH₄Cl, 5% NaHCO₃ and 1 M HCl used in work-up procedures were aqueous solutions. Melting points were uncorrected. FT-IR spectra were run as CH₂Cl₂ solutions between NaCl disks. ¹H- and ¹³C-NMR spectra were measured in CDCl₃ or DMSO-*d*₆ with (CH₃)₄Si as the internal standard. High-resolution mass spectra (HRMS) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer.

4.2. Conversion of acids to amides

A stirred mixture of acid **1** (1.00 mmol), amine **2** (1.05 mmol) and OSU-6 (20 wt% relative to **1**) in a screw-top pressure tube (Chemglass No CG-1880-01) was placed in a pre-heated oil bath at 120 °C for the specified time (Table 2). *Note:* Volatile amines were used in slightly larger excess (1.10 mmol). The crude reaction mixture was dissolved with EtOAc (25 mL) and filtered. The organic layer was washed with 1 M HCl (25 mL), 5% NaHCO₃ (50 mL) and saturated NaCl (50 mL), and then dried (MgSO₄), filtered, and concentrated under vacuum to afford the product. For the nicotinamide derivatives **3dlk-3dm**, the organic layer was washed with saturated NH₄Cl (50 mL) rather than 1 M HCl. In all cases, the products were solids and were purified by recrystallization from EtOH to afford the isolated yields shown in Table 2. To obtain analytical samples, the crude products were purified on 15 cm × 2.5 cm silica gel columns eluted with 40-60% EtOAc in hexanes.

4.2.1. N-(4-Methoxybenzyl)benzamide (3aa): Isolated as an off-white solid, mp 94-95 °C; IR: 3334, 2837, 1636 cm⁻¹; ¹H NMR (CDCl₃): δ 7.77 (d, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.65 (br s, 1H), 4.53 (d, *J* = 5.5 Hz, 2H), 3.77 (s, 3H); ¹³C NMR (CDCl₃): δ 167.4, 159.0, 134.5, 131.5, 130.4, 129.3, 128.5, 127.0, 114.1, 55.3, 43.6. HRMS [ESI] calcd for C₁₅H₁₆NO₂ [M + H]⁺: 242.1181, found: 242.1188.

4.2.2. N-(4-(Trifluoromethyl)phenyl)benzamide (3ab): Isolated as an off-white solid, mp 205-206 °C; IR: 3325, 1650 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.5 (s, 1H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (DMSO-*d*₆): δ 165.2, 143.4, 137.9, 134.2, 131.2, 127.9, 127.2, 121.1, 120.9, 119.7 (q, *J* = 256.5 Hz). HRMS [ESI] calcd for C₁₄H₁₁F₃NO [M + H]⁺: 266.0793, found: 266.0810.

4.2.3. N-(Pyridin-4-yl)benzamide (3ac): Isolated as a white solid, mp 117-119 °C; IR: 3278, 1637 cm⁻¹; ¹H NMR (CDCl₃): δ 8.95 (br s, 1H), 8.68 (d, *J* = 1.9 Hz, 1H), 8.27 (m, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 8.1, 5.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 166.7, 145.2, 141.7, 135.2, 134.2, 132.2, 128.7, 128.0, 127.3, 123.8. HRMS [ESI] calcd for C₁₂H₁₁N₂O [M + H]⁺: 199.0871, found: 199.0878.

4.2.4. N-Phenethylbenzamide (3ad): Isolated as an off-white solid, mp 131-133 °C (lit³¹ mp 133-136 °C); IR: 3341, 1639 cm⁻¹; ¹H NMR (CDCl₃): δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (overlapping d and t, *J* = 7.4 Hz, 3H), 6.28 (br s, 1H), 3.70 (q, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 7.0 Hz, 2H); ¹³C NMR (CDCl₃): δ 167.5, 138.9, 134.7, 131.4, 128.8, 128.7, 128.6, 126.8, 126.6, 41.2, 35.7. HRMS [ESI] calcd for C₁₅H₁₆NO [M + H]⁺: 226.1232, found: 226.1242.

4.2.5. 5-Bromo-2-chloro-N-(4-methoxybenzyl)benzamide (3ba): Isolated as an off-white solid, mp 183-185 °C; IR: 3182, 2838, 1635 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.38 (br s, 1H), 7.45 (d, *J* = 2.0 Hz,

1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 2H), 3.75 (s, 3H); ¹³C NMR (DMSO-*d*₆): δ 168.2, 159.7, 144.6, 131.8, 131.6, 131.0, 130.8, 129.2, 127.2, 119.7, 114.3, 55.6, 42.2. HRMS [ESI] calcd for C₁₅H₁₄BrClNO₂ [M + H]⁺: 353.9896, found: 353.9899.

4.2.6. N-Benzyl-5-bromo-2-chlorobenzamide (3be): Isolated as an off-white solid, mp 108-110 °C; IR: 3205, 1637 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.42 (br s, 1H), 7.51-7.43 (m, 3H), 7.43-7.32 (m, 4H), 7.26 (d, *J* = 8.5 Hz, 1H), 4.02 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.7, 143.8, 134.8, 131.2, 131.1, 130.5, 128.6, 128.4, 128.0, 119.2, 42.1 (1 aromatic C unresolved). HRMS [ESI] calcd for C₁₄H₁₂BrClNO [M + H]⁺: 323.9791, found: 323.9798.

4.2.7. N-Allyl-5-bromo-2-chlorobenzamide (3bf): Isolated as an off-white solid, mp 119-120 °C; IR: 3265, 1645 cm⁻¹; ¹H NMR (CDCl₃): δ 7.80 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.31 (s, 1H), 5.93 (ddt, *J* = 16.8, 10.6, 5.6 Hz, 1H), 5.30 (d, *J* = 17.0 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.09 (t, *J* = 5.8 Hz, 2H); ¹³C NMR (CDCl₃): δ 164.8, 136.5, 134.3, 133.4, 133.0, 131.7, 129.6, 120.9, 117.1, 42.6. HRMS [ESI] calcd for C₁₀H₁₀BrClNO [M + H]⁺: 273.9634, found: 273.9642.

4.2.8. (5-Bromo-2-chlorophenyl)(morpholino)methanone (3bg): Isolated as an off-white solid, mp 165-167 °C; IR: 3396, 1590 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.58 (d, *J* = 2.3 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 3.75 (br t, *J* = 5.3 Hz, 4H), 3.04 (br t, *J* = 5.2 Hz, 4H); ¹³C NMR (DMSO-*d*₆): δ 168.2, 142.8, 131.4, 131.3, 131.2, 128.9, 119.4, 63.7, 42.7; HRMS [ESI] calcd for C₁₁H₁₂BrClNO₂ [M + H]⁺: 303.9740, found: 303.9745.

4.2.9. N-Allyl-4-nitrobenzamide (3cf): Isolated as an off white solid, 113-114 °C; IR: 3318, 1645, 1638, 1545, 1344 cm⁻¹; ¹H NMR (CDCl₃): δ 8.29 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 6.38 (br s, 1H), 5.94 (ddt, *J* = 16.9, 10.6, 5.8 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.12 (t, *J* = 5.8 Hz, 2H); ¹³C NMR (CDCl₃): δ 165.3, 149.6, 140.0, 133.4, 128.2, 123.9, 117.4, 42.8. HRMS [ESI] calcd for C₁₀H₁₁N₂O₃ [M + H]⁺: 207.0770, found: 207.0775.

4.2.10. N-(4-Fluorobenzyl)-4-nitrobenzamide (3ch): Isolated as a white solid, mp 144-145 °C; IR: 3266, 1643, 1548, 1347 cm⁻¹; ¹H NMR (CDCl₃): δ 8.26 (d, *J* = 7.9 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.31 (apparent s, 2H), 7.03 (apparent s, 2H), 6.71 (br s, 1H), 4.61 (s, 2H); ¹³C NMR (CDCl₃): δ 165.4, 162.3 (d, *J* = 247.5 Hz), 149.7, 139.8, 133.3, 129.6 (d, *J* = 8.1 Hz), 128.2, 123.8, 115.7 (d, *J* = 22.2 Hz), 43.7. HRMS [ESI] calcd for C₁₄H₁₂FN₂O₃ [M + H]⁺: 275.0832, found: 275.0837.

4.2.11. N-(4-Methoxyphenyl)-4-nitrobenzamide (3ci): Isolated as a yellow solid, mp 196-197 °C; IR: 3295, 1644, 1533, 1347 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.5 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 3.76 (s, 3H); ¹³C NMR (DMSO-*d*₆): δ 162.7, 155.3, 148.5, 140.1, 131.2, 128.5, 122.9, 121.5, 113.2, 54.6. HRMS [ESI] calcd for C₁₄H₁₃N₂O₄ [M + H]⁺: 273.0875, found: 273.0877.

4.2.12. N-Cyclohexyl-4-nitrobenzamide (3cj): Isolated as a yellow solid, mp 195-196 °C; IR: 3318, 1634, 1544, 1349 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.51 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 8.3 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 2H), 3.79 (m, 1H), 1.85 (m, 2H), 1.76 (m, 2H), 1.63 (d, *J* = 12.7 Hz, 1H), 1.40-1.33 (m, 4H), 1.17 (m, 1H); ¹³C NMR (DMSO-*d*₆): δ 164.1, 149.3, 141.0, 129.2, 123.7, 49.2, 32.7, 25.7, 25.4. HRMS [ESI] calcd for C₁₃H₁₇N₂O₃ [M + H]⁺: 249.1239, found: 249.1234.

4.2.13. N-(4-Fluorobenzyl)nicotinamide (3dh): Isolated as a pale yellow solid, 73-74 °C; IR: 3283, 1645 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 9.26 (br t, *J* = 6.0 Hz, 1H), 9.05 (s, 1H), 8.72 (d, *J* = 4.7 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 4.7 Hz, 1H), 7.38 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 4.49 (d, *J* = 5.9 Hz, 2H); ¹³C NMR (DMSO-*d*₆): δ 165.3, 161.6 (d, *J* = 242.4 Hz), 152.4, 148.9, 135.9 (d, *J* = 3.0 Hz), 135.5, 130.2, 129.8 (d, *J* = 8.1 Hz), 123.9, 115.5 (d, *J* = 21.2

Hz), 42.4. HRMS [ESI] calcd for $C_{13}H_{12}FN_2O$ [M + H]⁺: 231.0934, found: 231.0943.

4.2.14. *N*-Phenylnicotinamide (3dk): Isolated as off-white solid, mp 124-125 °C (lit³⁷ mp 119-120 °C); IR: 3340, 1653 cm⁻¹; ¹H NMR (CDCl₃): δ 9.06 (s, 1H), 8.72 (d, *J* = 4.7 Hz, 1H), 8.41 (br s, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.42-7.31 (m, 3H), 7.17 (t, *J* = 7.5 Hz, 1H); ¹³C NMR (CDCl₃): δ 164.1, 152.4, 147.9, 137.5, 135.4, 130.9, 129.2, 125.1, 123.7, 120.6. HRMS [ESI] calcd for $C_{12}H_{11}N_2O$ [M + H]⁺: 199.0871, found: 199.0876.

4.2.15. *N*-(4-(Trifluoromethoxy)phenyl)nicotinamide (3dl): Isolated as a white solid, mp 136-137 °C; IR: 3336, 1651 cm⁻¹; ¹H NMR (CDCl₃): δ 9.10 (s, 1H), 8.83 (s, 1H), 8.71 (d, *J* = 4.2 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.39 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (CDCl₃): δ 164.2, 152.4, 148.0, 145.8, 136.3, 135.6, 130.5, 123.7, 121.9, 121.8, 120.5 (q, *J* = 258.5 Hz). HRMS [ESI] calcd for $C_{13}H_{10}F_3N_2O_2$ [M + H]⁺: 283.0694, found: 283.0699.

4.2.16. *N*-Isobutylnicotinamide (3dm): Isolated as a brown solid, mp 50-51 °C (lit³⁸ mp 49-52 °C); IR: 3299, 1644 cm⁻¹; ¹H NMR (CDCl₃): δ 8.98 (s, 1H), 8.69 (d, *J* = 5.0 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.81 (br s, 1H), 3.29 (t, *J* = 6.5 Hz, 2H), 1.93 (nonet, *J* = 6.8 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (CDCl₃): δ 165.8, 152.0, 147.8, 135.1, 130.6, 123.5, 47.5, 28.6, 20.2. HRMS [ESI] calcd for $C_{10}H_{15}N_2O$ [M + H]⁺: 179.1184, found: 179.1186.

4.3. Conversion of *o*-diacids to *N*-substituted phthalimides

These compounds were prepared using the same procedure as reported above, but at 150 °C for 18-26 h. Following workup, the crude products were purified on 15 cm × 2.5 cm silica gel columns eluted with 60-80% EtOAc in hexanes. The isolated yields are given in Table 3. *Note:* Saturated NH₄Cl was used for washing the pyridine derivatives instead of 1 M HCl.

4.3.1. 2-Benzylisoindoline-1,3-dione (5ae): Isolated as an off-white solid, mp 111-113 °C (lit³⁹ mp 114-116 °C); IR: 1765, 1710 cm⁻¹; ¹H NMR (CDCl₃): δ 7.85 (m, 2H), 7.71 (m, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 4.85 (s, 2H); ¹³C NMR (CDCl₃): δ 168.0, 136.4, 134.0, 132.1, 128.7, 128.6, 127.8, 123.3, 41.6. HRMS [ESI] calcd for $C_{15}H_{12}NO_2$ [M + H]⁺: 238.0868, found: 238.0877.

4.3.2. 2-(4-Fluorobenzyl)isoindoline-1,3-dione (5ah): Isolated as an off-white solid, mp 120-121 °C; IR: 1766, 1710 cm⁻¹; ¹H NMR (CDCl₃): δ 7.84 (m, 2H), 7.72 (m, 2H), 7.42 (dd, *J* = 8.3, 5.4 Hz, 2H), 6.99 (t, *J* = 8.5 Hz, 2H), 4.81 (s, 2H); ¹³C NMR (CDCl₃): δ 168.0, 162.4 (d, *J* = 247.5 Hz), 134.1, 132.2 (d, *J* = 3.0 Hz), 132.1, 130.6 (d, *J* = 9.1 Hz), 123.4, 115.6, 115.3 (d, *J* = 22.2 Hz), 40.9. HRMS [ESI] calcd for $C_{15}H_{11}FNO_2$ [M + H]⁺: 256.0774, found: 256.0782.

4.3.3. 2-(3-Methoxyphenyl)isoindoline-1,3-dione (5an): Isolated as a gray solid, mp 108-110 °C; IR: 2836, 1772, 1721 cm⁻¹; ¹H NMR (CDCl₃): δ 7.96 (m, 2H), 7.80 (m, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.99 (br s, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H); ¹³C NMR (CDCl₃): δ 167.2, 160.0, 134.4, 132.7, 131.8, 129.8, 123.8, 118.9, 114.1, 112.4, 55.4. HRMS [ESI] calcd for $C_{15}H_{12}NO_3$ [M + H]⁺: 254.0817, found: 254.0822.

4.3.4. 2-Hexylisoindoline-1,3-dione (5ao): Isolated as an off-white solid, mp 91-94 °C (lit⁴⁰ mp 94-96 °C); IR: 1774, 1716 cm⁻¹; ¹H NMR (CDCl₃): δ 7.84 (m, 2H), 7.71 (m, 2H), 3.68 (t, *J* = 7.3 Hz, 2H), 1.65 (quintet, *J* = 7.2 Hz, 2H), 1.38-1.26 (m, 6H), 0.89 (distorted t, *J* = 6.7 Hz, 3H); ¹³C NMR (CDCl₃): δ 168.4, 133.8, 132.2, 123.1, 38.1, 31.4, 28.6, 26.5, 22.5, 14.0. HRMS [ESI] calcd for $C_{14}H_{18}NO_2$ [M + H]⁺: 232.1338, found: 232.1346.

4.3.5. 2-Benzyl-5-hydroxyisoindoline-1,3-dione (5be): Isolated as an off-white solid, mp 171-173 °C; IR: 3345, 1767, 1695 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 11.0 (br s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.34-7.24 (m,

5H), 7.16 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.72 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.4, 167.4, 163.4, 136.8, 134.2, 128.5, 127.3, 127.2, 125.3, 121.5, 120.3, 109.8, 40.6. HRMS [ESI] calcd for $C_{15}H_{12}NO_3$ [M + H]⁺: 254.0817, found: 254.0828.

4.3.6. 2-(4-Fluorobenzyl)-5-hydroxyisoindoline-1,3-dione (5bh): Isolated as an off-white solid, mp 206-208 °C; IR: 3278, 1763, 1685 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 11.0 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.33 (m, 2H), 7.15 (s, 1H), 7.17-7.12 (m, 3H), 4.70 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.4, 167.3, 163.3, 161.3 (d, *J* = 242.4 Hz), 134.2, 133.0 (d, *J* = 3.0 Hz), 129.5 (d, *J* = 9.1 Hz), 125.3, 121.5, 120.3, 115.2 (d, *J* = 22.2 Hz), 109.8, 39.9. HRMS [ESI] calcd for $C_{15}H_{11}FNO_3$ [M + H]⁺: 272.0723, found: 272.0726.

4.3.7. 5-Hydroxy-2-(4-(trifluoromethyl)benzyl)isoindoline-1,3-dione (5bp): Isolated as an off-white solid, mp 160-162 °C; IR: 3300, 1770, 1698 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 11.0 (br s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 3H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 4.82 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.43, 167.37, 163.4, 141.5, 134.3, 128.0 (q, *J* = 32.2 Hz), 128.0, 125.4 (q, *J* = 4.0 Hz), 124.1 (d, *J* = 272.7 Hz), 121.6, 120.4, 109.9, 40.3 (1 aromatic C unresolved). HRMS [ESI] calcd for $C_{16}H_{11}F_3NO_3$ [M + H]⁺: 322.0691, found: 322.0696.

4.3.8. 6-(4-Methoxybenzyl)-5H-pyrrolo[3,4-*b*]pyridine-5,7(6H)-dione (5ca): Isolated as an off-white solid, mp 142-143 °C; IR: 1729, 1723 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.98 (d, *J* = 5.0 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.79 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 4.73 (s, 2H), 3.72 (s, 3H); ¹³C NMR (CDCl₃): δ 165.98, 165.88, 159.37, 155.18, 151.83, 131.15, 130.35, 128.10, 127.41, 127.30, 114.07, 55.27, 41.32. HRMS [ESI] calcd for $C_{15}H_{13}N_2O_3$ [M + H]⁺: 269.0926, found: 269.0933.

4.3.9. 6-Phenethyl-5H-pyrrolo[3,4-*b*]pyridine-5,7(6H)-dione (5cd): Isolated as an off-white solid, mp 114-116 °C; IR: 1778, 1716 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.96 (d, *J* = 4.9 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.77 (br t, *J* = 6.4 Hz, 1H), 7.29-7.18 (m, 5H), 3.85 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H); ¹³C NMR (CDCl₃): δ 166.1, 165.9, 155.2, 151.7, 137.6, 131.1, 128.8, 128.6, 127.3, 127.3, 126.8, 39.5, 34.5; HRMS [ESI] calcd for $C_{15}H_{13}N_2O_2$ [M + H]⁺: 253.0977, found: 253.0986.

4.3.10. 6-Benzyl-5H-pyrrolo[3,4-*b*]pyridine-5,7(6H)-dione (5ce): Isolated as an off-white solid, mp 141-142 °C; IR: 1774, 1718 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.99 (d, *J* = 4.8 Hz, 1H), 8.33 (d, *J* = 7.5 Hz, 1H), 7.80 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.36-7.26 (m, 5H), 4.81 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 166.0, 165.8, 155.3, 151.8, 135.8, 131.2, 128.81, 128.77, 128.1, 127.4, 127.3, 41.9. HRMS [ESI] calcd for $C_{14}H_{11}N_2O_2$ [M + H]⁺: 239.0821, found: 239.0828.

4.3.11. 6-(4-Fluorobenzyl)-5H-pyrrolo[3,4-*b*]pyridine-5,7(6H)-dione (5ch): Isolated as an off-white solid, mp 141-142 °C; IR: 1775, 1717 cm⁻¹; ¹H NMR (CDCl₃): δ 8.97 (d, *J* = 5.0 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.45 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 4.88 (s, 2H); ¹³C NMR (CDCl₃): δ 165.9, 165.8, 162.5 (d, *J* = 247.5 Hz), 155.3, 151.7, 131.7, 131.7 (d, *J* = 4.0 Hz), 131.3, 130.8 (d, *J* = 8.1 Hz), 127.40, 127.35, 115.7 (d, *J* = 21.2 Hz), 41.1. HRMS [ESI] calcd for $C_{14}H_{10}FN_2O_2$ [M + H]⁺: 257.0726, found: 257.0734.

4.3.12. 6-Hexyl-5H-pyrrolo[3,4-*b*]pyridine-5,7(6H)-dione (5co): Isolated as an off-white solid, mp 120-121 °C; IR: 1778, 1710 cm⁻¹; ¹H NMR (CDCl₃): δ 8.97 (d, *J* = 3.4 Hz, 1H), 8.17 (d, *J* = 7.4 Hz, 1H), 7.62 (br t, *J* = 6.7 Hz, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 1.71 (m, 2H), 1.34 (apparent s, 6H), 0.88 (apparent s, 3H); ¹³C NMR (CDCl₃): δ 166.4, 166.2, 155.1, 151.9, 131.0, 127.3, 127.2, 38.4, 31.3, 28.5, 26.5, 22.5, 14.0. HRMS [ESI] calcd for $C_{13}H_{17}N_2O_2$ [M + H]⁺: 233.1290, found: 233.1297.

4.4. Conversion of esters to amides

These compounds were prepared using the same procedure as reported above, but at 100 °C for 6-28 h. Following workup, the products (all solids) were recrystallized from EtOH to afford the

isolated yields shown in Table 4. For analytical samples, purification was achieved by chromatography on a 15 cm $\times$ 2.5 cm silica gel column eluted with 40-60% EtOAc in hexanes.

4.4.1. *N*-Benzylbenzamide (3ae): Isolated as a white solid, mp 106-108 °C (lit²⁵ mp 108-109 °C); IR: 3327, 1642 cm⁻¹; ¹H NMR (CDCl₃): δ 7.79 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.37-7.27 (complex, 5H), 6.43 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ 167.3, 138.2, 134.4, 131.6, 128.8, 128.6, 127.9, 127.7, 126.9, 44.2. HRMS [ESI] calcd for C₁₄H₁₄NO [M + H]⁺: 212.1075, found: 212.1078.

4.4.2. *N*-(4-Fluorobenzyl)benzamide (3ah): Isolated as a white solid, mp 114-115 °C; IR: 3318, 1638 cm⁻¹; ¹H NMR (CDCl₃): δ 7.78 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.28 (m, 2H), 6.99 (t, J = 8.5 Hz, 2H), 6.73 (br s, 1H), 4.56 (d, J = 5.8 Hz, 2H); ¹³C NMR (CDCl₃): δ 167.4, 162.2 (d, J = 247.5 Hz), 134.2, 134.1 (J = 3.0 Hz), 131.6, 129.5 (J = 8.1 Hz), 128.6, 127.0, 115.5 (J = 22.2 Hz), 43.3. HRMS [ESI] calcd for C₁₄H₁₃FNO [M + H]⁺: 230.0981, found: 230.0979.

4.4.3. *N*-(5,6,7,8-Tetrahydronaphthalen-2-yl)benzamide (3aq): Isolated as an off-white solid, mp 164-165 °C; IR: 3284, 1645 cm⁻¹; ¹H NMR (CDCl₃): δ 7.86 (d, J = 7.5 Hz, 2H), 7.70 (br s, 1H), 7.54 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.40 (s, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 2.83-2.71 (m, 4H), 1.84-1.75 (m, 4H); ¹³C NMR (CDCl₃): δ 165.5, 137.9, 135.2, 135.2, 133.7, 131.7, 129.6, 128.8, 127.0, 120.7, 117.7, 29.6, 28.9, 23.2, 23.1. HRMS [ESI] calcd for C₁₇H₁₈NO [M + H]⁺: 252.1388, found: 252.1398.

4.4.4. 5-Bromo-2-chloro-*N*-(3-methoxyphenyl)benzamide (3bn): Isolated as a gray solid, mp 179-180 °C; IR: 3265, 2834, 1655 cm⁻¹; ¹H NMR (CDCl₃): δ 10.6 (br s, 1H), 7.83 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.40 (s, 1H), 7.26 (d, J = 4.3 Hz, 1H), 6.71 (br s, 1H), 3.75 (s, 3H); ¹³C NMR (CDCl₃): δ 163.2, 159.4, 139.7, 138.5, 133.7, 131.6, 131.3, 129.5, 129.3, 119.9, 111.8, 109.4, 105.5, 54.9. HRMS [ESI] calcd for C₁₄H₁₂BrClNO₂ [M + H]⁺: 339.9740, found: 339.9748.

4.4.5. 5-Bromo-2-chloro-*N*-(4-chlorobenzyl)benzamide (3br): Isolated as an off-white solid, mp 111-112 °C; IR: 3281, 1651 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 9.18 (br t, J = 6.1 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.71 (s, 1H), 7.67 (dd, J = 8.6, 2.4 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.5 Hz, 1H), 4.53 (d, J = 6.0 Hz, 2H); ¹³C NMR (DMSO-*d*₆): δ 165.0, 143.6, 138.3, 133.5, 131.6, 131.2, 129.2, 127.8, 125.2, 125.1, 125.1, 119.8, 42.1. HRMS [ESI] calcd for C₁₄H₁₁BrCl₂NO [M + H]⁺: 271.1083, found: 271.1087.

4.4.6. 5-Bromo-2-chloro-*N*-(4-methylphenyl)benzamide (3bs): Isolated as a gray solid, mp 140-141 °C; IR: 3160, 1630 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.92 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.5, 2.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 7.9 Hz, 2H), 6.47 (d, J = 7.9 Hz, 2H), 2.12 (s, 3H), NH not observed; ¹³C NMR (DMSO-*d*₆): δ 165.9, 146.2, 135.5, 134.1, 133.5, 133.0, 131.3, 129.7, 124.7, 120.3, 114.7, 20.6. HRMS [ESI] calcd for C₁₄H₁₂BrClNO [M + H]⁺: 325.9791, found: 325.9794.

4.4.7. 5-Bromo-2-chloro-*N*-(2-hydroxyethyl)benzamide (3bt): Isolated as an off-white solid, mp 127-128 °C; IR: 3259, 1656 cm⁻¹; ¹H NMR (CDCl₃): δ 7.81 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.5, 2.4 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 3.85 (q, J = 4.9 Hz, 2H), 3.64 (q, J = 5.3 Hz, 2H), 2.22 (br s, 1H); ¹³C NMR (CDCl₃): δ 165.8, 134.4, 133.0, 131.7, 129.6, 120.9, 61.8, 42.8. HRMS [ESI] calcd for C₉H₁₀BrClNO₂ [M + H]⁺: 277.9583, found: 277.9590.

4.4.8. *N*-Hexyl-4-nitrobenzamide (3co): Isolated as off-white solid, 82-83 °C; IR: 3304, 1638, 1535, 1350 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.78 (br s, 1H), 8.31 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 3.28 (m, 2H), 1.54 (m, 2H), 1.29 (apparent s, 6H), 0.87 (apparent s, 3H); ¹³C NMR (DMSO-*d*₆): δ 164.9, 149.4, 140.8, 129.1, 123.9, 39.8, 31.5, 29.4, 26.6, 22.5, 14.4. HRMS [ESI] calcd for C₁₃H₁₉N₂O₃ [M + H]⁺: 251.1396, found: 251.1402.

4.4.9. *N*-(4-Methylbenzyl)-4-nitrobenzamide (3cu): Isolated as a yellow solid, 154-155 °C; IR: 3309, 1643, 1533, 1324 cm⁻¹; ¹H NMR (CDCl₃): δ 8.22 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 6.77 (s, 1H), 4.58 (d, J = 5.6 Hz, 2H), 2.34 (s, 3H); ¹³C NMR (CDCl₃): δ 165.3, 149.5, 140.0, 137.7, 134.4, 129.6, 128.2, 127.9, 123.8, 44.2, 21.1. HRMS [ESI] calcd for C₁₅H₁₅N₂O₃ [M + H]⁺: 271.1083, found: 271.1087.

4.4.10. *N*-(4-Chlorophenyl)-4-nitrobenzamide (3cv): Isolated as an off-white solid, mp 229-230 °C; IR: 3333, 1657, 1532, 1342 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.7 (s, 1H), 8.38 (d, J = 8.3 Hz, 2H), 8.19 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H); ¹³C NMR (DMSO-*d*₆): δ 164.4, 149.7, 140.8, 138.1, 129.7, 129.1, 128.3, 124.0, 122.5. HRMS [ESI] calcd for C₁₃H₁₀N₂O₃ [M + H]⁺: 277.0380, found: 277.0383.

4.4.11. *N*-(4-(Trifluoromethyl)phenyl)nicotinamide (3db): Isolated as a white solid, 154-155 °C; IR: 3293, 1664 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.8 (s, 1H), 9.13 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.60 (m, 1H); ¹³C NMR (DMSO-*d*₆): δ 164.0, 151.8, 148.2, 141.9, 135.0, 129.6, 125.4 (q, J = 4.0 Hz), 123.7 (q, J = 271.7 Hz), 123.5, 122.8, 119.5. HRMS [ESI] calcd for C₁₃H₁₀F₃N₂O [M + H]⁺: 267.0745, found: 267.0755.

4.4.12. *N*-Benzylnicotinamide (3de): Isolated as a white solid, mp 75-76 °C (lit⁴¹ mp 78-80 °C); IR: 3296, 1645 cm⁻¹; ¹H NMR (CDCl₃): δ 8.93 (s, 1H), 8.66 (br s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.40-7.25 (complex, 6H), 6.91 (br s, 1H), 4.63 (d, J = 5.6 Hz, 2H); ¹³C NMR (CDCl₃): δ 165.5, 152.2, 147.9, 137.8, 135.3, 130.1, 128.8, 128.0, 127.8, 123.5, 44.2. HRMS [ESI] calcd for C₁₃H₁₃N₂O [M + H]⁺: 213.1028, found: 213.1031.

4.4.13. *N*-(4-Methylphenyl)nicotinamide (3ds): Isolated as a white solid, mp 156-157 °C (lit³¹ mp 152-154 °C); IR: 3249, 1665 cm⁻¹; ¹H NMR (CDCl₃): δ 8.05 (s, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.49 (overlapping d and t, J = 8.0 Hz, 3H), 7.40 (t, J = 7.5 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 2.31 (s, 3H); ¹³C NMR (CDCl₃): δ 165.9, 135.5, 135.0, 134.2, 131.7, 129.5, 128.7, 127.1, 120.5, 20.9. HRMS [ESI] calcd for C₁₄H₁₄NO [M + H]⁺: 212.1075, found: 212.1083.

4.4.14. *N*-(4-Chlorophenyl)nicotinamide (3dv): Isolated as off white solid, mp 169-171 °C; IR: 3286, 1657 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.6 (s, 1H), 9.11 (s, 1H), 8.78 (d, J = 4.8, 1H), 8.30 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.58 (m, 1H), 7.44 (d, J = 8.3 Hz, 2H); ¹³C NMR (DMSO-*d*₆): δ 163.6, 151.6, 148.1, 137.2, 134.9, 129.8, 128.0, 127.0, 122.9, 121.3. HRMS calcd for C₁₂H₁₀ClN₂O [M + H]⁺: 233.0482, found: 233.0479.

4.4.15. *N*-Cyclopropylnicotinamide (3dw): Isolated as a white solid, mp 82-84 °C; IR: 3278, 1644 cm⁻¹; ¹H NMR (CDCl₃): δ 8.95 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.36 (m, 1H), 6.85 (br s, 1H), 2.92 (m, 1H), 0.87 (m, 2H), 0.66 (m, 2H); ¹³C NMR (CDCl₃): δ 167.1, 152.1, 147.9, 135.1, 130.1, 123.5, 23.2, 6.7. HRMS [ESI] calcd for C₉H₁₁N₂O [M + H]⁺: 163.0871, found: 163.0880.

4.5. Transamidation of primary arylamides to *N*-substituted arylamides

These compounds were prepared using the standard procedure at 130 °C (benzamides) or 145 °C (nicotinamide) for 18-40 h. For each reaction, the catalyst was removed by filtration, the EtOAc filtrate was concentrated with 1-2 g of silica gel, and the crude product was purified on a 15 cm $\times$ 2.5 cm silica gel column eluted with 40-60% EtOAc in hexanes. The isolated yields are given in Table 5.

4.5.1. *N*-Allylbenzamide (3af): Isolated as a white solid, mp 119-122 °C (lit⁴² mp 120-123 °C); IR: 3322, 1659 cm⁻¹; ¹H NMR (CDCl₃): δ 7.80 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 6.65 (br s, 1H), 5.91 (ddt, J = 17.0, 10.5, 5.7 Hz, 1H), 5.23 (d, J = 17.0 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 4.05 (t, J = 5.9 Hz, 2H); ¹³C NMR (CDCl₃): δ 167.5, 134.5, 134.2, 131.4, 128.5, 127.0, 116.5,

42.4. HRMS [ESI] calcd for $C_8H_{12}N_2O$ $[M + H]^+$: 152.0950, found: 152.0952.

4.5.2. *N*-(4-Fluorobenzyl)benzamide (**3ah**): See 4.4.2 above.

4.5.3. *N*-(3-Methoxyphenyl)benzamide (**3an**): Isolated as a white solid, mp 108–109 °C; IR: 3356, 2836, 1651 cm^{-1} ; 1H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.44 (overlapping d and t, J = 8.0 Hz, 3H), 7.23 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 160.3, 139.3, 135.0, 131.8, 129.7, 128.8, 127.1, 112.4, 110.6, 105.9, 55.3. HRMS [ESI] calcd for $C_{14}H_{14}NO_2$ $[M + H]^+$: 228.1025, found: 226.1030.

4.5.4. *N*-Hexylbenzamide (**3ao**): Isolated as a colorless oil; IR: 3341, 1638 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.77 (d, J = 7.6 Hz, 2H), 7.55–7.35 (m, 3H), 6.45 (br s, 1H), 3.43 (s, 2H), 1.60 (m, 2H), 1.48–1.25 (m, 6H), 0.89 (apparent s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.6, 134.8, 131.2, 128.5, 126.9, 40.2, 31.5, 29.6, 26.7, 22.6, 14.0. HRMS [ESI] calcd for $C_{13}H_{20}NO$ $[M + H]^+$: 206.1545, found: 206.1553.

4.5.5. 5-Bromo-2-chloro-*N*-(4-chlorobenzyl)benzamide (**3br**): See 4.4.5 above.

4.5.6. 5-Bromo-2-chloro-*N*-(4-methylphenyl)benzamide (**3bs**): See 4.4.6 above.

4.5.7. 5-Bromo-2-chloro-*N*-(4-fluorophenyl)benzamide (**3bx**): Isolated as a gray solid, mp 153–155 °C; IR: 3258, 1654 cm^{-1} ; 1H NMR ($DMSO-d_6$): δ 7.88 (br s, 2H), 7.59 (dd, J = 8.9, 4.9 Hz, 2H), 7.53 (dd, J = 8.9, 1.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.08 (t, J = 8.4 Hz, 2H); ^{13}C NMR ($DMSO-d_6$): δ 163.1, 158.3 (d, J = 242.4 Hz), 138.4, 135.0 (d, J = 3.0 Hz), 133.7, 131.6, 131.3, 129.3, 121.3 (d, J = 7.1 Hz), 119.9, 115.3 (d, J = 22.2 Hz); HRMS [ESI] calcd for $C_{13}H_9BrClFNO$ $[M + H]^+$: 327.9540, found: 327.9548.

4.5.8. (5-Bromo-2-chlorophenyl)(piperidin-1-yl)methanone (**3by**): Isolated as a off white solid, mp 62–63 °C; IR: 1642 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.42 (overlapping s and d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 3.73 (m, 2H), 3.18 (m, 2H), 1.74–1.55 (m, 5H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 165.1, 138.1, 132.9, 131.1, 130.5, 129.4, 120.8, 47.9, 42.7, 26.3, 25.5, 24.4. HRMS [ESI] calcd for $C_{12}H_{14}BrClNO$ $[M + H]^+$: 301.9847, found: 301.9843.

4.5.9. 5-Bromo-2-chloro-*N*-ethylbenzamide (**3bz**): Isolated as a white solid, mp 123–124 °C; IR: 3275, 1643 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.76 (d, J = 2.4 Hz, 1H), 7.46 (dd, J = 8.6, 2.4 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.22 (br s, 1H), 3.50 (quintet, J = 7.1 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 164.8, 136.8, 134.0, 132.9, 131.6, 129.6, 120.8, 35.2, 14.7. HRMS [ESI] calcd for $C_9H_{10}BrClNO$ $[M + H]^+$: 261.9634, found: 261.9623.

4.5.10. *N*-Allylnicotinamide (**3df**): Isolated as a colorless liquid; IR: 3294, 1645 cm^{-1} ; 1H NMR ($CDCl_3$): δ 9.03 (s, 1H), 8.67 (s, 1H), 8.16 (d, J = 4.7 Hz, 1H), 7.52 (s, 1H), 7.35 (s, 1H), 5.90 (m, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 10.3 Hz, 1H), 4.06 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 165.7, 151.9, 148.2, 135.2, 133.8, 130.3, 123.4, 116.7, 42.5. HRMS [ESI] calcd for $C_9H_{11}N_2O$ $[M + H]^+$: 163.0871, found: 163.0878.

4.5.11. *N*-(4-Methoxyphenyl)nicotinamide (**3di**): Isolated as a off-white solid, mp 143–144 °C; IR: 3325, 2836, 1644 cm^{-1} ; 1H NMR ($CDCl_3$): δ 9.06 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 8.45 (br s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.37 (m, 1H), 6.87 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.9, 156.9, 152.2, 148.0, 135.4, 130.8, 130.6, 123.6, 122.5, 114.2, 55.5. HRMS [ESI] calcd for $C_{13}H_{13}N_2O_2$ $[M + H]^+$: 229.0977, found: 229.0976.

4.5.12. *N*-Hexylnicotinamide (**3do**): Isolated as a white solid, mp 40–41 °C (lit⁴³ mp 43–44 °C); IR: 3285, 1641 cm^{-1} ; 1H NMR ($CDCl_3$): 8.97 (s, 1H), 8.70 (br s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.37 (m, 1H), 6.54 (br s, 1H), 3.46 (q, J = 7.2 Hz, 2H), 1.63 (quintet, J = 7.4 Hz, 2H), 1.39 (m, 2H), 1.38–1.22 (m, 4H), 0.89 (distorted t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.6, 152.0, 147.8, 135.1, 130.6, 123.5,

40.3, 31.5, 29.5, 26.7, 22.5, 14.0. HRMS [ESI] calcd for $C_{12}H_{19}N_2O$ $[M + H]^+$: 207.1497, found: 207.1508.

4.5.13. *N*-(4-(Trifluoromethyl)benzyl)nicotinamide (**3dp**): Isolated as a white solid, mp 125–126 °C; IR: 3294, 1647, 1326 cm^{-1} ; 1H NMR ($CDCl_3$): δ 8.99 (s, 1H), 8.69 (d, J = 4.9 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.44 (d, J = 7.9 Hz, 2H), 7.37 (dd, J = 7.9, 5.0 Hz, 1H), 7.04 (br s, 1H), 4.69 (d, J = 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 165.8, 152.4, 147.9, 141.9, 135.3, 130.0 (q, J = 32.3 Hz), 129.8, 128.0, 125.6 (q, J = 4.0 Hz), 124.0 (q, J = 273.7 Hz), 123.6, 43.6. HRMS [ESI] calcd for $C_{14}H_{12}F_3N_2O$ $[M + H]^+$: 281.0902, found: 281.0897.

4.5.14. *N*-(4-Methylbenzyl)nicotinamide (**3du**): Isolated as brown solid, mp 75–76 °C; IR: 3296, 1644 cm^{-1} ; 1H NMR ($DMSO-d_6$): δ 9.23 (br t, J = 6.0 Hz, 1H), 9.05 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.51 (dd, J = 7.6, 4.8 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 4.45 (d, J = 5.9 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR ($DMSO-d_6$): δ 165.2, 152.3, 148.9, 136.7, 136.3, 135.4, 130.3, 129.3, 127.8, 123.9, 42.8, 21.2. HRMS [ESI] calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$: 227.1184, found: 227.1294.

4.5.15. *N*-(4-Fluorophenyl)nicotinamide (**3dx**): Isolated as a white solid, mp 132–133 °C; IR: 3288, 1651 cm^{-1} ; 1H NMR ($CDCl_3$): δ 9.06 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.35 (br s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.69–7.50 (m, 2H), 7.41 (dd, J = 7.9, 4.8 Hz, 1H), 7.06 (t, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 164.0, 159.8 (d, J = 245.4 Hz), 152.5, 147.8, 135.5, 133.5, 130.6, 123.7, 122.5 (d, J = 8.1 Hz), 115.8 (d, J = 22.1 Hz). HRMS [ESI] calcd for $C_{12}H_{10}FN_2O$ $[M + H]^+$: 217.0777, found: 217.0779.

4.5.16. Piperidin-1-yl(pyridin-3-yl)methanone (**3dy**): Isolated as a colorless oil; IR: 1630 cm^{-1} ; 1H NMR ($CDCl_3$): δ 8.66 (overlapping s and d, J = 4.8 Hz, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.35 (dd, J = 7.7, 4.8 Hz, 1H), 3.73 (apparent s, 2H), 3.36 (apparent s, 2H), 1.70 (apparent s, 4H), 1.55 (apparent s, 2H); ^{13}C NMR ($CDCl_3$): δ 167.6, 150.5, 147.7, 134.7, 132.2, 123.4, 48.8, 43.2, 26.6, 25.5, 24.4. HRMS [ESI] calcd for $C_{11}H_{15}N_2O$ $[M + H]^+$: 191.1184, found: 191.1193.

4.6 Transamidation of phthalimides to *N*-substituted phthalimides

These compounds were prepared using the standard procedure at 150 °C for 18–36 h. For each reaction, the crude product was adsorbed onto silica gel and purified on a 15 cm $\times$ 2.5 cm silica gel column eluted with 60–80% EtOAc in hexanes. The isolated yields are given in Table 6.

4.6.1. 2-(4-Methoxybenzyl)isoindoline-1,3-dione (**5aa**): Isolated as a pale yellow solid, mp 118–120 °C; IR: 2838, 1767, 1714 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.82 (m, 2H), 7.69 (m, 2H), 7.38 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 4.78 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.1, 159.2, 133.9, 132.2, 130.2, 128.7, 123.3, 114.0, 55.3, 41.1. HRMS [ESI] calcd for $C_{16}H_{14}NO_3$ $[M + H]^+$: 268.0974, found: 268.0979.

4.6.2. 2-Phenethylisoindoline-1,3-dione (**5ad**): Isolated as yellow solid, mp 125–127 °C (lit³¹ mp 126–128 °C); IR: 1771, 1699 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.83 (m, 2H), 7.70 (m, 2H), 7.32–7.18 (complex, 5H), 3.93 (t, J = 7.8 Hz, 2H), 2.99 (t, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 168.2, 138.0, 133.9, 132.1, 128.9, 128.6, 126.6, 123.2, 39.3, 34.6. HRMS [ESI] calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$: 252.1025, found: 252.1029.

4.6.3. 2-Cyclohexylisoindoline-1,3-dione (**5aj**): Isolated as an off-white solid, mp 169–172 °C; IR: 1761, 1707 cm^{-1} ; 1H NMR ($CDCl_3$): δ 7.81 (m, 2H), 7.69 (m, 2H), 4.11 (tt, J = 8.5, 3.9 Hz, 1H), 2.21 (qd, J = 12.3, 1.7 Hz, 2H), 1.87 (d, J = 13.1 Hz, 2H), 1.72 (t, J = 13.1 Hz, 3H), 1.45–1.20 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 133.7, 132.1, 123.0, 50.9, 29.9, 26.0, 25.1. HRMS [ESI] calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.0081, found: 230.0086.

4.6.4. 2-(3-Methoxyphenyl)isoindoline-1,3-dione (**5an**): See 4.3.3. above.

4.6.5. 2-[4-(Trifluoromethyl)benzyl]isindoline-1,3-dione (5ap**):** Isolated as an off-white solid, mp 100–102 °C; IR: 1772, 1714, 1325 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.93 (m, 2H), 7.88 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 4.88 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.9, 140.2, 134.2, 132.0, 130.1 (q, *J* = 32.3 Hz), 129.0, 125.7 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 272.7 Hz), 123.5, 41.1. HRMS [ESI] calcd for C₁₆H₁₁F₃NO₂ [M + H]⁺: 306.0742, found: 306.0744.

4.6.6. 2-(4-Chlorobenzyl)isindoline-1,3-dione (5ar**):** Isolated as an off-white solid, mp 116–117 °C; IR: 1767, 1713 cm⁻¹; ¹H NMR (CDCl₃): δ 7.84 (m, 2H), 7.71 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.80 (s, 2H); ¹³C NMR (CDCl₃): δ 167.9, 134.8, 134.1, 133.8, 132.0, 130.1, 128.8, 123.4, 40.9. HRMS [ESI] calcd for C₁₅H₁₁ClNO₂ [M + H]⁺: 272.0478, found: 272.0487.

4.6.7. 2-(4-Fluorophenyl)isindoline-1,3-dione (5ax**):** Isolated as a gray solid, mp 178–180 °C; IR: 1756, 1712 cm⁻¹; ¹H NMR (CDCl₃): δ 8.03–7.89 (m, 2H), 7.80 (quintet, *J* = 4.8 Hz, 2H), 7.49–7.37 (m, 2H), 7.29–7.12 (m, 2H); ¹³C NMR (CDCl₃): δ 167.4, 162.1 (d, *J* = 248.5 Hz), 134.7, 131.8, 128.5 (d, *J* = 9.1 Hz), 127.7 (d, *J* = 3.0 Hz), 124.0, 116.3 (d, *J* = 23.2 Hz). HRMS [ESI] calcd for C₁₄H₉FNO₂ [M + H]⁺: 242.0617, found: 242.0620.

4.6.8. 2-Cyclohexyl-5-hydroxyisindoline-1,3-dione (5bj**):** Isolated as a gray solid, mp 262–264 °C; IR: 3335, 1763, 1680 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.9 (br s, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.10 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 3.91 (tt, *J* = 12.9, 3.9 Hz, 1H), 2.04 (m, 2H), 1.78 (d, *J* = 12.9 Hz, 2H), 1.70–1.59 (m, 3H), 1.31 (m, 2H), 1.18 (m, 1H); ¹³C NMR (DMSO-*d*₆): δ 167.5, 167.5, 163.2, 134.1, 124.9, 121.4, 120.2, 109.4, 49.8, 29.4, 25.4, 24.8. HRMS [ESI] calcd for C₁₄H₁₆NO₃ [M + H]⁺: 246.1130, found: 246.1140.

4.6.9. 2-(4-Chlorobenzyl)-5-hydroxyisindoline-1,3-dione (5br**):** Isolated as an off-white solid, mp 194–196 °C; IR: 3259, 1763, 1685 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 11.0 (br s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 4.71 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 167.4, 167.3, 163.3, 135.8, 134.2, 131.9, 129.2, 128.4, 125.3, 121.5, 120.4, 109.8, 40.0. HRMS [ESI] calcd for C₁₅H₁₁ClNO₃ [M + H]⁺: 288.0427, found: 288.0435.

4.7. Conversion of benzamides to benzhydrazides

These compounds were prepared using the standard procedure at 130 °C for 20–24 h. For each reaction, the crude product was adsorbed onto silica gel and purified on a 15 cm × 2.5 cm silica gel column eluted with 80% EtOAc in hexanes. The isolated yields are given in Table 7.

4.7.1. Benzhydrazide (10a**):** Isolated as a pale yellow solid, mp 111–113 °C (lit³⁹ mp 112–114 °C); IR: 3298, 3194, 1660, 1617 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 9.78 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 4.50 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 166.4, 133.8, 131.5, 128.8, 127.4. HRMS [ESI] calcd for C₇H₉N₂O [M + H]⁺: 137.0715, found: 137.0719.

4.7.2. 4-Chlorobenzhydrazide (10b**):** Isolated as a yellow solid, mp 162–164 °C (lit³⁹ mp 162–165 °C); IR: 3307, 3209, 1660, 1615 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 9.87 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 4.54 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 165.3, 136.3, 132.5, 129.3, 128.9. HRMS [ESI] calcd for C₇H₉N₂O [M + H]⁺: 171.0325, found: 171.0331.

4.7.3. 4-Methoxybenzhydrazide (10c**):** Isolated as a white solid, mp 136–138 °C (lit³⁹ mp 136–140 °C); IR: 3314, 3177, 1622 cm⁻¹; ¹H NMR (CDCl₃): δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.58 (br s, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.07 (br s, 2H), 3.85 (s, 3H); ¹³C NMR (CDCl₃): δ 168.3, 162.5, 128.7, 124.9, 113.9, 55.4. HRMS [ESI] calcd for C₈H₁₁N₂O₂ [M + H]⁺: 167.0821, found: 167.0830.

4.7.4. 4-Methylbenzhydrazide (10d**):** Isolated as a white solid, mp 114–116 °C (lit³⁹ mp 116–118 °C); IR: 3303, 3214, 1660, 1614 cm⁻¹; ¹H NMR (CDCl₃): δ 8.05 (br s, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.21

(d, *J* = 7.9 Hz, 2H), 4.17 (br s, 2H), 2.38 (s, 3H); ¹³C NMR (CDCl₃): δ 168.7, 142.3, 129.8, 129.3, 126.9, 21.5. HRMS [ESI] calcd for C₈H₁₁N₂O [M + H]⁺: 151.0871, found: 151.0874.

4.8. Transamidation of acetamides

These compounds were prepared using the standard procedure at 120 °C (benzylic and aliphatic amines) and 140 °C (aromatic amines) for 24–40 h. For each reaction, the crude product was adsorbed onto silica gel and purified on a 15 cm × 2.5 cm silica gel column eluted with 40–60% EtOAc in hexanes. The isolated yields are given in Table 8.

4.8.1. *N*-Benzylacetamide (12a**):** Isolated as a off-white solid, mp 61–62 °C (lit²⁵ mp 62–64 °C); IR: 3294, 1640 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 8.35 (br s, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (overlapping d and t, *J* = 7.7 Hz, 3H), 4.25 (d, *J* = 5.9 Hz, 2H), 1.87 (s, 3H); ¹³C NMR (DMSO-*d*₆): δ 169.6, 139.7, 128.7, 127.7, 127.2, 42.6, 23.0. HRMS [ESI] calcd for C₉H₁₂NO [M + H]⁺: 150.0919, found: 150.0925.

4.8.2. *N*-Cyclohexylacetamide (12b**):** Isolated as a white solid, mp 102–104 °C (lit⁴⁴ mp 106 °C); IR: 3289, 1642 cm⁻¹; ¹H NMR (CDCl₃): δ 5.51 (br s, 1H), 3.75 (m, 1H), 1.96 (s, 3H), 1.91 (dm, *J* = 12.5 Hz, 2H), 1.71 (dt, *J* = 13.6, 4.0 Hz, 2H), 1.62 (dt, *J* = 12.7, 4.2 Hz, 1H), 1.42–1.29 (m, 2H), 1.21–1.05 (m, 3H); ¹³C NMR (CDCl₃): δ 169.1, 48.2, 33.2, 25.5, 24.9, 23.6. HRMS [ESI] calcd for C₈H₁₆NO [M + H]⁺: 142.1232, found: 142.1240.

4.8.3. *N*-Phenylacetamide (12c**):** Isolated as a white solid, mp 112–114 °C (lit³⁹ mp 113–115 °C); IR: 3293, 3261, 1662 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 9.91 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 2.04 (s, 2H); ¹³C NMR (DMSO-*d*₆): δ 168.7, 139.8, 129.1, 123.4, 119.4, 24.5. HRMS [ESI] calcd for C₈H₁₀NO [M + H]⁺: 136.0762, found: 136.0771.

4.8.4. *N*-Hexylacetamide (12d**):** Isolated as a colorless oil; IR: 3304, 1659 cm⁻¹; ¹H NMR (CDCl₃): δ 6.31 (br s, 1H), 3.22 (q, *J* = 6.8 Hz, 2H), 1.98 (s, 3H), 1.50 (quintet, *J* = 7.3 Hz, 2H), 1.38–1.24 (m, 6H), 0.88 (distorted t, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃): δ 170.2, 39.6, 31.5, 29.5, 26.6, 23.1, 22.5, 13.9. HRMS [ESI] calcd for C₈H₁₈NO [M + H]⁺: 144.1388, found: 144.1392.

4.8.5. *N*-(3-Nitrophenyl)acetamide (12e**):** Isolated as a white solid, mp 155–156 °C (lit³⁹ mp 154–158 °C); IR: 3306, 3260, 1673, 1526, 1351 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 10.4 (s, 1H), 8.63 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 8.1 Hz, 1H), 2.12 (s, 3H); ¹³C NMR (DMSO-*d*₆): δ 168.5, 147.4, 139.9, 129.5, 124.3, 116.9, 112.5, 23.5. HRMS [ESI] calcd for C₈H₉N₂O₃ [M + H]⁺: 181.0613, found: 181.0621.

4.9. Transamidation of formamides

These compounds were prepared using the standard procedure at 120 °C for 24 h. For each reaction, the crude product was adsorbed onto silica gel and purified on a 15 cm × 2.5 cm silica gel column eluted with 40–60% EtOAc in hexanes. The isolated yields are given in Table 9.

4.9.1. *N*-Benzylformamide (14a**):** Isolated as an off-white solid, mp 59–61 °C (lit²⁵ mp 61–63 °C); IR: 3279, 1651, 1646 cm⁻¹; ¹H NMR (CDCl₃): δ 8.26 (s, 1H), 7.40–7.22 (m, 5H), 5.88 (br s, 1H), 4.48 (d, *J* = 5.9 Hz, 2H); ¹³C NMR (CDCl₃): δ 161.1, 137.8, 129.0, 128.0, 127.3, 42.4. HRMS [ESI] calcd for C₈H₁₀NO [M + H]⁺: 136.0762, found: 136.0770.

4.9.2. *N*-(4-Fluorobenzyl)formamide (14b**):** Isolated as an off-white solid, mp 59–60 °C; IR: 3280, 1654 cm⁻¹; ¹H NMR (CDCl₃): δ 8.23 (s, 1H), 7.25 (m, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.13 (br s, 1H), 4.43 (d, *J* = 6.0 Hz, 2H); ¹³C NMR (CDCl₃): δ 162.2 (d, *J* = 246.4 Hz), 161.0, 133.4, 129.5 (d, *J* = 9.1 Hz), 115.6 (d, *J* = 21.1 Hz), 41.4. HRMS [ESI] calcd for C₈H₉FNO [M + H]⁺: 154.0668, found: 154.0673.

4.9.3. *N*-(4-Chlorobenzyl)formamide (**14c**): Isolated as an off-white solid, mp 85-87 °C; IR: 3282, 1649, 1635 cm⁻¹; ¹H NMR (CDCl₃): δ 8.23 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.20 (br s, 1H), 4.42 (d, *J* = 6.1 Hz, 2H); ¹³C NMR (CDCl₃): δ 161.1, 136.2, 129.1, 128.9, 128.3, 41.4. HRMS [ESI] calcd for C₈H₉ClNO [M + H]⁺: 170.0373, found: 170.0377.

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Supplementary data

Copies of ¹H and ¹³C NMR spectra for all amide products can be found in the online version at <http://dx.doi.org/1016/j.tet>.

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