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Amide Synthesis through the In Situ Generation of Chloro- and Imido-Phosphonium Salts

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ABSTRACT: We describe a methodology for the amidation of carboxylic acids by generating phosphonium salts in situ from *N*-chlorophthalimide and triphenylphosphine. Aliphatic, benzylic, and aromatic carboxylic acids can be transformed into their amide counter parts using primary and secondary amines. This functional group interconversion is achieved at room temperature in good to excellent yields. Mechanistic work shows the in situ formation of chloro- and imido-phosphonium salts that react as activating agents for carboxylic acids and generate an acyloxy-phosphonium species.

INTRODUCTION

Amides are important functional groups in organic chemistry due to their relevance in biological processes (proteins, peptides) and their presence in a diverse set of bioactive compounds.[1] The bioactivity and applications of such compounds are broad and range from pharmaceuticals[2] and pesticides[3] to polymers and adhesives.[4] Additionally, according to a recent analysis of the literature,[5] amide bond syntheses are the most frequently cited synthetic methodologies in medicinal chemistry. The most common approach to access amides involves the activation of carboxylic acids through the use of coupling reagents.[6] The native chemical ligation has also been employed successfully for larger polypeptides and protein syntheses.[7] Such state-of-the-art methodologies gained significant traction in the peptide field in parallel with the development of solid-phase synthesis.[8] Recently, catalytic methods for activating carboxylic acids have also been developed using boronic acid catalysts.[9]

Yet, it is often the case that simple amides resist formation, which has led to the development of ever more complex and toxic coupling reagents and methods.[10] Both carbodiimide[11] and phosphonium salt reagents[12] are among the most commonly used coupling agents due to their high reactivity and ability to minimize epimerization (Figure 1A,B). Unfortunately, carbodiimide reagents have to be handled with caution since they can cause severe allergic skin reactions and decompose with atmospheric moisture.[6] Similarly, phosphonium salt reagents are highly moisture sensitive, and they produce supra-stoichiometric amounts of carcinogenic hexamethylphosphoramide (HMPA).[12a,b] Some also contain high-energy benzotriazole moieties,[12c,d] which represent an explosion hazard[13a] (Figure 1A,B) and, in some cases, lead to an unwanted nucleophilic competitor.[13b]

In our recent work, we observed that *N*-chloroimides could be activated to perform radical reactions using lithium *tert*-butoxide.[14] Presumably, *N*-chloroimides can react with strong
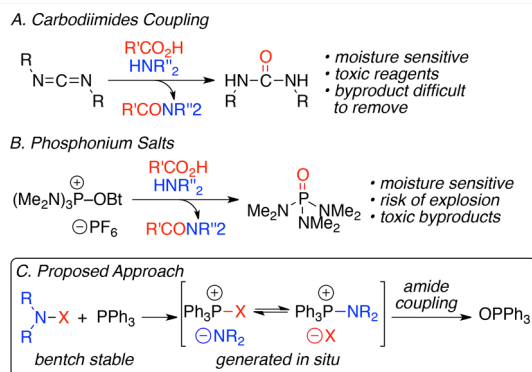

Figure 1. Selected examples of coupling technologies.

nucleophiles via halogen bonding interactions[15] and generate reactive species with new or unexplored reactivity. We recognized the possibility of generating phosphonium salts from bench-stable reagents to produce coupling agents in situ (Figure 1C), therefore minimizing current drawbacks such as reagent stability.

In the past decade, various reports have been published generating phosphonium salts in situ from activated halogen sources.[16] Indeed, the use of I_2,[16a]d 2,4,4,6-tetrabromo-2,5-cyclohexadienone,[16b] and 2,4,6-trichloro-1,3,5-triazine[16c] in the presence of PPh_3 has been used as means to perform amide bond couplings. Similar strategies using *N*-halogenated reagents have been developed.[17] For instance, in spite of its

high cost, *N*-chlorobenzotriazole has been used to generate phosphonium salts in situ.[17a] The use of *N*-haloimides has been explored as a more cost-effective alternative by Prakash et al.[17b] and Tang et al.[17c] using *N*-bromosuccinimide (NBS) and selectfluor to generate acyl fluorides. While the use of *N*-chlorosuccinimide (NCS) has been reported to generate amides from carboxylic acids,[17d] this method requires multiple steps, cooling, and premixing to avoid rapid decompositions for the active species. Additionally, none of these reports[16,17] provided a detailed characterization of the reactive phosphonium species to support a detailed mechanism.

The methodology we have developed generates amides through the simple mixture of *N*-chlorophthalimide in the presence of PPh₃ and the desired carboxylic acid and amine reagents to couple. Our ^{31}P NMR experiments show that mixing *N*-chloroimides in the presence of PPh₃ generates two phosphonium salts (chloro- and imido-phosphonium species) that efficiently activate carboxylic acids toward amide bond formation (Figure 1C). Our work is the first to observe and characterize this imido-phosphonium intermediate using ^{31}P NMR and high-resolution mass-spectrometry (HR-MS). This observation provides more detailed insights into the mechanism and can help design better methodologies involving in situ formation of phosphonium salts.

■ RESULTS AND DISCUSSION

We began our investigation using benzoic acid (**1a**) as our carboxylic acid substrate and both benzylamine (**2a**) and benzylmethylamine (**2b**) as I° and II° amine substrates. Optimal reaction conditions (Table 1, entry 1) were obtained using 1.5 equiv of PPh₃ and *N*-chlorophthalimide (NCPhth) at room temperature for 12 h. Primary amine **2a** consistently afforded the corresponding amide in better yield than secondary amine **2b**. Presumably, the increase in steric hindrance is responsible for the reduced yield. The use of other commercially available *N*-haloimides such as NCS, NBS,

and *N*-iodosuccinimide (NIS) also generated the desired products but in lower yields (Table 1, entries 2−4). Importantly, control experiments in the absence of phosphine or *N*-haloimide reagents did not provide the desired amides in significant yields (entries 5 and 6). Screening of other phosphines as suitable activators of *N*-chlorophthalimide (Table 1, entries 7−9) gave mixed results, while tricyclohexylphosphine (PCy₃, entry 7) did afford product **3aa** in good yields (85%), the formation of product **3ab** seems to be lackluster (43%). Similarly, tributylphosphine (P(*n*-Bu)₃) and tri(*o*-tolyl) phosphine (P(*o*-tol)₃) proceeded through the reaction but with lower yields (entries 8 and 9). The increase in the Tolman angle[18] from PPh₃ (145°), PCy₃ (179°), and P(*o*-tol)₃ (194°) may be preventing the efficient nucleophilic attack of the *N*-chlorophthalimide. Finally, the reaction also proceeds efficiently in a variety of anhydrous polar aprotic solvents such as dichloromethane, ethyl acetate, and acetonitrile for the formation of product **3aa** (entries 10−12). Product **3ab** is also formed under those conditions but anhydrous acetonitrile provides the best yields at 72% (entry 12).

With the established optimal conditions in hand, we proceeded to first examine the scope of amine substrates **2** compatible with our reaction conditions. Gratifyingly, the protocol was efficient for the amidation of a diverse set of I° and II° amines (Figure 2). Our protocol was effective for a

Table 1. Reaction Optimization[a]

entry	PR₃	XNR₂	solvent	yield[b] (**3aa/3ab**)
1	PPh₃	NCPhth	toluene	94% (83%)[c] / 63%
2	PPh₃	NCS	toluene	74% / 26%
3	PPh₃	NBS	toluene	66% / 54%
4	PPh₃	NIS	toluene	59% / 59%
5		NCPhth	toluene	6% / 0%
6	PPh₃		toluene	2% / 2%
7	PCy₃	NCPhth	toluene	85% / 43%
8	P(*n*-Bu)₃	NCPhth	toluene	57% / 42%
9	P(*o*-tol)₃	NCPhth	toluene	34% / 27%
10	PPh₃	NCPhth	CH₂Cl₂	91% / 60%
11	PPh₃	NCPhth	EtOAc	81% / 59%
12	PPh₃	NCPhth	CH₃CN	90% / 72% (65%)[c]

[a]All reactions were performed using 1 mL of anhydrous, solvent, 0.164 mmol (1 equiv) of benzoic acid, 0.246 mmol (1.5 equiv) of *N*-haloimide and phosphine reagents, and 0.492 mmol (3 equiv) of amine substituent. The reactions were performed at room temperature (24 °C) with constant stirring for 12 h. [b]NMR yield obtained using dibromomethane as the internal standard. [c]Isolated yield.
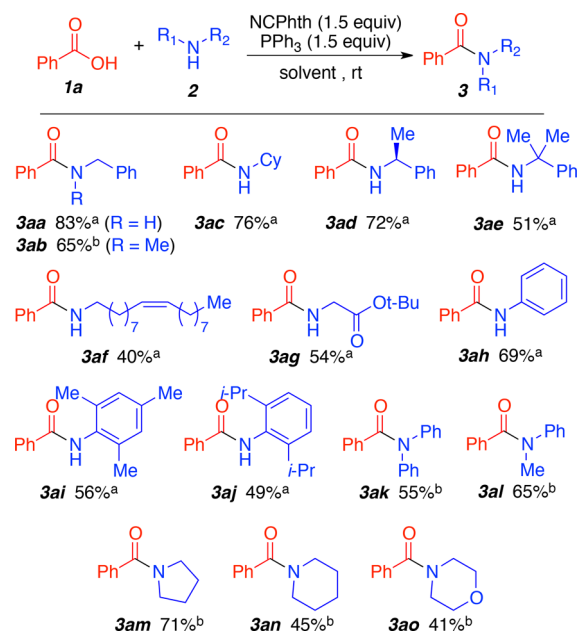

Figure 2. Reaction scope for amines. All reactions were performed in 3 mL of solvent, **1a** (0.82 mmol) **2** (2.4 mmol), NCPhth (1.2 mmol), and PPh₃ (1.2 mmol) (unless otherwise specified (see Experimental Section). [a]Reactions performed using toluene as the solvent. [b]Reactions performed using acetonitrile as the solvent. Yields reported are isolated yields.

variety of aliphatic amines (**3aa**−**3af**) with yields ranging from moderate to excellent. However, the increase of steric hindrance in the α-position of I° alkyl amines has a deleterious effect on yield. Indeed, coupling products **3ad** through **3ae** were obtained in lower yields as more substituents were added in the α-position. The alkene functionality in oleylamine is tolerated (product **3af**), but isolation of the corresponding

amide was challenging using column chromatography. Bulky esters that do not readily transamidate are also tolerated and provided product **3ag** in 54% yield (Figure 2). Interestingly, both I° and II° aniline derivatives also afforded the corresponding amides (**3ah−3aj**) in moderate to good isolated yields. While aniline reacted in 69% yield, increasing sterics around the nitrogen led to erosion in yield with **3ai** and **3aj** providing the amides in 56 and 49% yields, respectively. Yet, our protocol seems more efficient at coupling sterically bulky aniline derivatives compared to analogous protocols.[16,17a]

Additionally, this methodology possesses a wider scope with respect to secondary amine substrates than similar procedures.[16] Reactions using diphenylamine and *N*-methylaniline worked in moderate yields at 55 and 65%, respectively. Cyclic II° amines also amidated in moderate to good yields with pyrrolidine affording product **3am** in 71% yield, piperidine affording product **3an** in 45% yield, and morphiline generating product **3ao** in 41% yield (Figure 2).

Next, we examined the compatibility of our optimal reaction conditions with different carboxylic acids (**1b−1k**) and using benzyl amine **2a** and benzylmethylamine **2b** as the amine substrates. As shown in Figure 3, the method enabled the
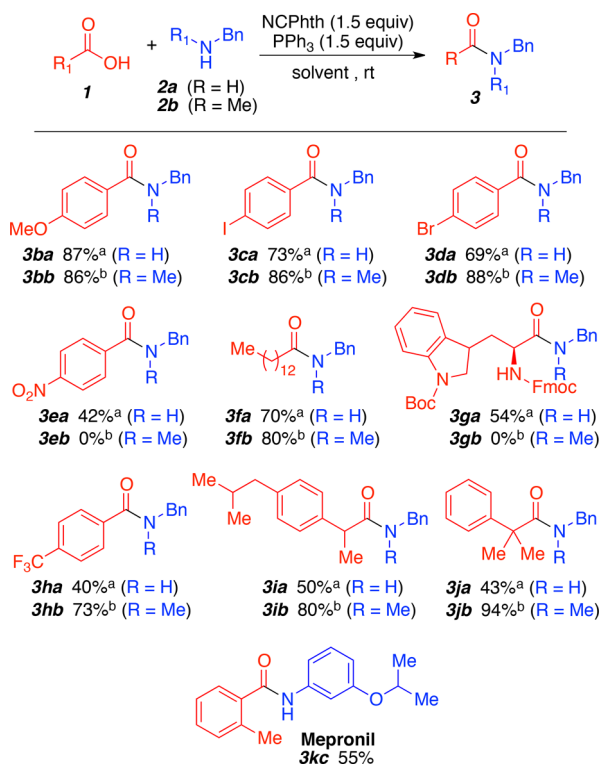

Figure 3. Scope of carboxylic acid substrates. All reactions were performed in 3 mL of solvent, **1** (100 mg), **2a** (3 equiv), **2b** (3 equiv), NCphth (1.5 equiv), PPh₃ (1.5 equiv). *a*Reactions performed using toluene as the solvent. *b*Reactions performed using acetonitrile as the solvent. Yields reported are isolated yields.

amidation of electron rich (**3ba/b** (87%/86%)) and electron poor (**3ea** 42% and **3 ha/b** (40%/73%)) aryl carboxylic acids in good to excellent yields. However, reactivity varied significantly among substrates, and secondary amines seem to sometimes fail to perform the transformation (**3eb**). Aryl halides provided the desired products in good to excellent yields for both I° and II° amines (**3da, 3db**). Alkyl carboxylic acids were also well tolerated and afforded products in

moderate to excellent yields (**3fa/b**, **3ia/b**, and **3ja/b**). Protected tryptophan amino acid was also converted into the corresponding amide in moderate yields when coupling with primary amines (**3ga** 54% yield) but failed to provide the desired product with secondary amines (**3gb**) most likely due to amine-induced Fmoc deprotection. Finally, our method enabled the synthesis of antifungal agrochemical Mepronil **3lc** from the *ortho*-substituted carboxylic acid in 55% yield in milder conditions than current approaches.[16d,20]

Another possible transformation we envisioned with our methodology was the direct formation of acyl phthalimides from carboxylic acids in the cases where amine coupling partners are not added to the reaction mixture (Figure 4). Acyl
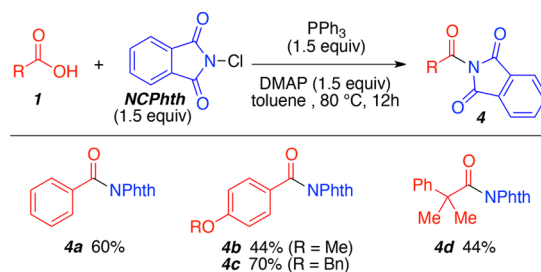

Figure 4. Synthesized acyl phthalimides. All reactions were run in 3 mL of solvent, carboxylic acid (100 mg), NCPhth (1.5 equiv), PPh₃ (1.5 equiv), and DMAP (1.5 equiv).

phthalimides are important precursors for the formation of the biologically active *N*-,*O*-acetal motifs found in several natural products.[19] Acyl phthalimides also hold merit as potential anxiolytic, antibacterial, and antifungal compounds.[20] Synthetic applications have also been explored using acyl imides as efficient acylating and coupling agents in metal-catalyzed reactions.[21] Lastly, acyl imides have been used as trans-amidation agents in metal-free methodologies.[22]

After a brief optimization, we found that mixing *N*-chlorophthalimide and PPh₃ in the presence of carboxylic acids and 4-dimethylaminopyridine (DMAP) at 80 °C in toluene afforded the best yields. The use of heat is required here to promote the nucleophilic attack of the phthalimide unto the activated carboxylic acid. The use of a non-nucleophilic base was also required to ensure deprotonation of the phthalimide.

Figure 4 shows the scope of carboxylic acids that were used to acylate phthalimide. Overall, our conditions were found to generate the desired products albeit in moderate yields. Electron-neutral and electron-rich carboxylic acids (**4a−4c**) reacted to afford the acyl phthalimide adducts in 60, 44, and 70% yield, respectively. It should be noted that this method did not work with a substrate bearing an electron-withdrawing group. Aliphatic carboxylic acids were also transformed in moderate yields (**4d**).

To gain insights into the mechanism of the amidation reaction, we carried out a series of ³¹P NMR experiments with the hope of identifying and characterizing the reactive intermediates in this methodology. To our surprise, ³¹P NMR experiments showed that *N*-chlorophthalimide and triphenylphosphine react together to form two phosphonium salt species: (i) a chloro-phosphonium salt at 64 ppm and (ii) an imido-phosphonium salt at 32 ppm (Figure 5). Triphenylphosphine oxide and unreacted Ph₃P were also present.
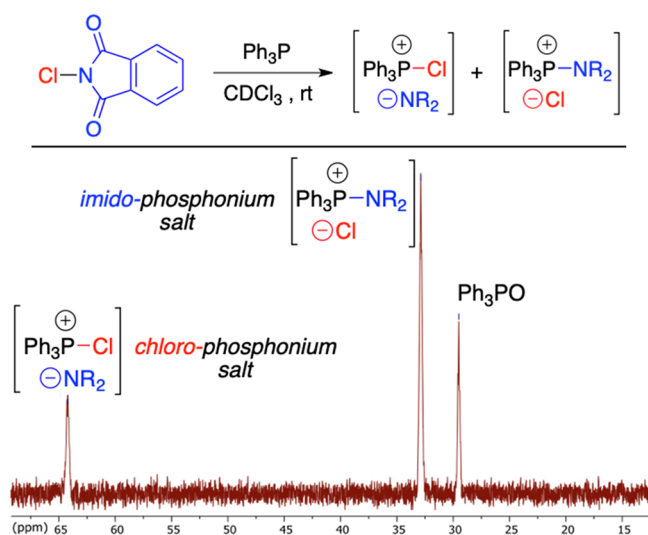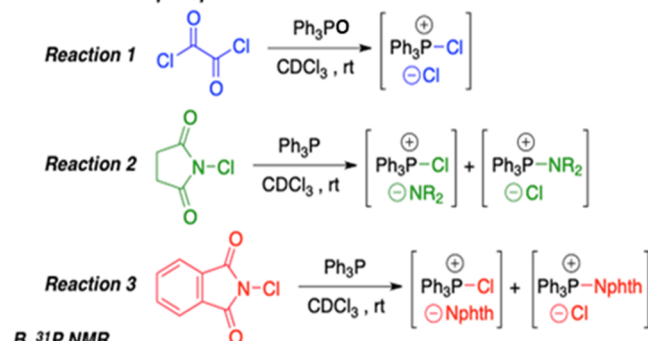
Figure 5. In situ generated phosphonium salts observed via ^{31}P NMR. Reaction mixture consisted of triphenylphosphine (0.08 mmol, 1 equiv) and NCPhth (0.08 mmol, 1 equiv) dissolved in CDCl$_3$.

We confirmed the identity of the chloro-phosphonium salt at 64 ppm through its synthesis using oxalyl chloride[23] and comparing it with different *N*-chlorimides (Figure 6). These experiments further emphasized our hypothesis that the peak
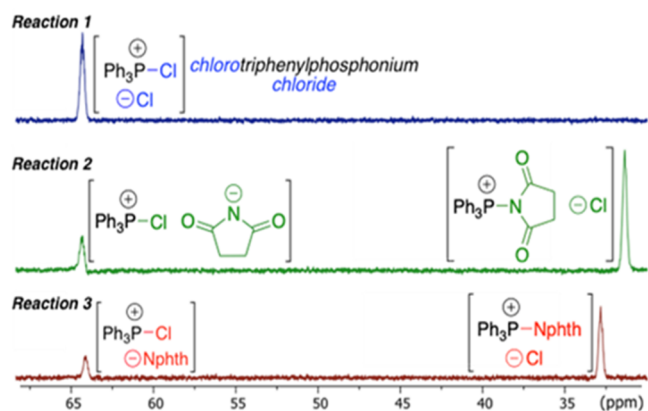

Figure 6. In situ generated phosphonium salts observed via ^{31}P NMR. Reaction 1 mixture consisted of triphenylphosphine oxide (Ph$_3$PO) (0.07 mmol, 1 equiv) and oxalyl chloride (COCl)$_2$ (0.09 mmol, 1.3 equiv). Reaction 2 mixture consisted of triphenylphosphine (0.08 mmol, 1 equiv) and *N*-chlorosuccinimide (0.08 mmol, 1 equiv). Reaction 3 consisted of triphenylphosphine (PPh$_3$) (0.08 mmol, 1 equiv) and NCPhth (0.08 mmol, 1 equiv). All reaction mixtures were dissolved in CDCl$_3$.

at 32 ppm corresponds to the imido-phosphonium salt. We confirmed this observation using high-resolution mass spectrometry (HR-MS). To the best of our knowledge, these imido-phosphonium salts had not been characterized before.

Following the identification and characterization of the phosphonium salts generated in situ, we attempted to observe other intermediates formed throughout the reaction. To do so, we added sodium benzoate to the previous NCPhth/PPh$_3$ mixture, and we observed a new peak at 23 ppm by ^{31}P NMR (Figure 7). We identified this new signal as being the (acyloxy)-phosphonium salt species for which a HR-MS was also obtained (see the Supporting Information).
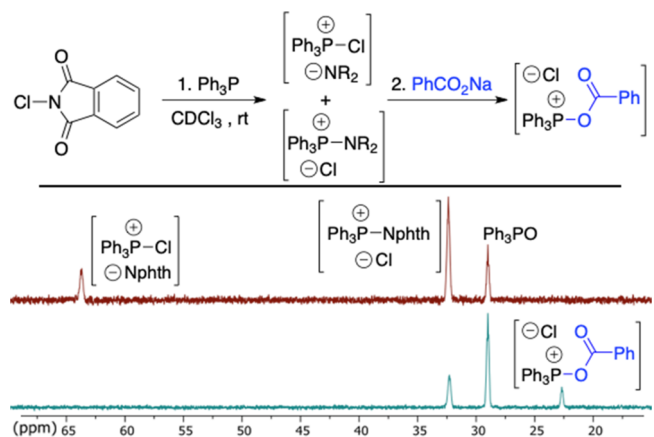

Figure 7. ^{31}P NMR (acyloxy)-phosphonium intermediate detection. Reaction mixture consisted of PPh$_3$ (1 equiv), NCPhth (1 equiv), and PhCOONa (0.5 equiv), all solids dissolved in CDCl$_3$.

Upon the formation of the (acyloxy)-phosphonium intermediate, we observed the complete consumption of the chloro-phosphonium salt at 64 ppm, while some imido-phosphonium salts at 32 ppm were still present. This observation highlights the difference in reactivity between these two species. More specifically, this suggests that the chloro-phosphonium species favorably reacts, kinetically, with the carboxylic acid. The imido-phosphonium intermediate may then serve as a precursor to the more reactive chloro-phosphonium species; however, we cannot exclude the possibility that the imido-phosphonium intermediate also reacts with the carboxylic acid at a slower rate.

Another observation worth noting in Figure 6 is the relative ratio of chloro-phosphonium to imido-phosphonium salts across both *N*-haloimides in reactions 2 and 3. When using NCS as the *N*-haloimide source, the ratio of chloro-phosphonium to imido-phosphonium salts is 1:3 (Reaction 2, Figure 6), while it is 1:2 for *N*-chlorophthalimide (Reaction 3, Figure 6). This difference in the formation of both species could be due to the difference in pK_a between succinimide (9.5) and phthalimide (8.3). Given that the chloro-phosphonium intermediate seems to react faster, we believe this could explain some of the different reactivity between our method and previously published ones,[17d] while providing future research on this topic is an avenue for further exploration and optimization.

Based on previous halophosphonium-mediated amidations[16,17] and our experimental observations, we propose that the reaction begins with the in situ generation the chloro- and imido-phosphonium salts, **5** and **6**, respectively (Figure 8).
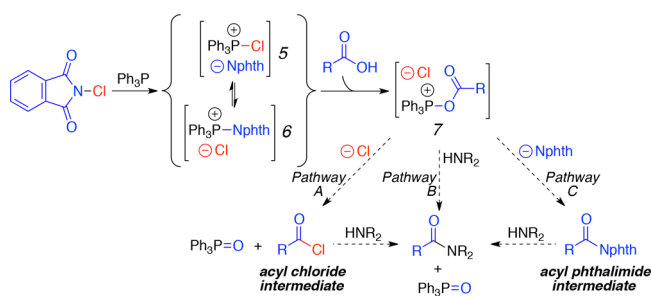
Figure 8. Proposed mechanism with different possible pathways.

These species then react with the carboxylic acids to generate the activated carboxylate **7** in the form of an (acyloxy)-phosphonium salt. From intermediate **7**, three possible pathways (**A**, **B**, and **C**) can lead to the final amide products.

Transformation of (acyloxy)-phosphonium **7** into an acyl chloride via pathway **A** is analogous to previously proposed tranformations that use halophosphonium-mediated amidations.[16a,17b] Similarly, pathway **C** involves the reaction of intermediate **7** with phthalimide to generate acyl phthalimide species, which we have shown can be generated efficiently if the amine coupling partner is replaced by a bulky base (compounds **4a–4d**, Figure 4). Finally, pathway **B** is the direct transformation of the (acyloxy)-phosphonium **7** into the desired amide.

To determine which of these three possible pathways is most likely at play under our reaction conditions, we conducted a ^{31}P NMR study to quantify the rate of decomposition of the (acyloxy)-phosphonium intermediate **7** over time (Figure 9A).
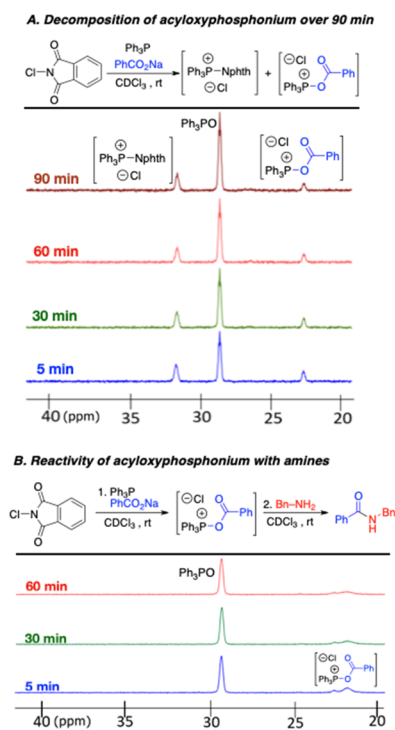

Figure 9. (A) ^{31}P NMR at different time frames of a reaction mixture containing PPh$_3$ (1 equiv), NCPhth (1 equiv), and PhCOONa (0.5 equiv) in CDCl$_3$. (B) ^{31}P NMR at different time frames of a reaction mixture containing PPh$_3$ (1 equiv), NCPhth (1 equiv), benzylamine (1 equiv), and PhCOONa (0.5 equiv), in CDCl$_3$.

We hypothesize that, if pathways **A** and **C** are main contributors for the formation of the final product, then intermediate **7** should decompose relatively quickly into the acyl chloride and the acylphthalimide in a nonreversible reaction that produces triphenylphosphine oxide, even when amine is not present. Indeed, intermediate **7** can react with the chloride or phthalimide anion present in the reaction as counter ions. As shown in Figure 9A, (acyloxy)-phosphonium species **7** does not seem to decompose significantly over the course of 90 min, indicating that pathways **A** and **C** are unlikely to be major contributors under our reaction conditions. On the other hand, as shown in Figure 9B, the addition of benzylamine to the reaction leads to almost the instantaneous consumption of intermediate **7** and the consumption of the imido-phophonium salt **5**.

To further discard pathway **C** that involves the formation of the acyl phthalimides intermediate, which we were able to synthesize in Figure 4, we ran the control reaction presented in Figure 10A. When the acyl phthalimide is reacted with
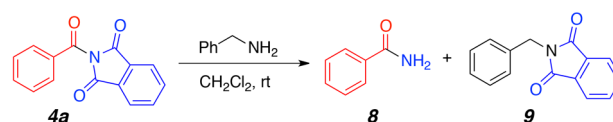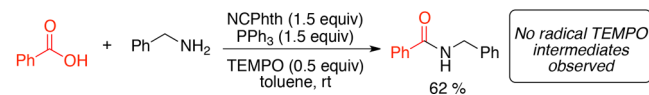

Figure 10. Acyl phthalimide and radical pathway investigations.

benzylamine, it does not produce the corresponding *N*-benzylbenzamide. Instead, it generates the primary benzamide **8** and phthalimide-protected benzylamine **9** via a phthalimide transfer pathway. This observation is also supported by literature precedent showing that when introduced to amine nucleophiles acyl phthalimides cleave to provide the phthalimide-protected amine and primary benzamide derivative.[24] Therefore, this observation further supports that an acyl phthalimide intermediate following pathway **C** is unlikely. Lastly, we conducted a TEMPO radical trapping experiment to discard any possible radical pathways (Figure 10B). Indeed, when TEMPO was added to our reaction mixture, the desired amide product was still generated albeit in slightly eroded yields.

Based on the results above, we propose that the reaction begins with the in-situ generation of the chloro- and imido-phosphonium salts, **5** and **6**, respectively (Figure 11). These
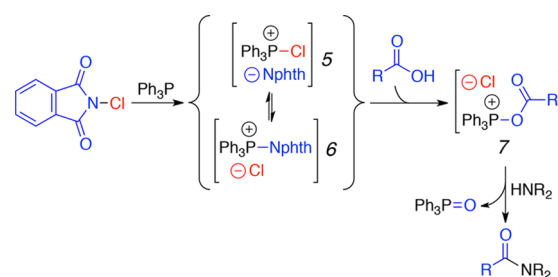

Figure 11. Proposed mechanism and its confirmed intermediates.

species then react with the carboxylic acids to generate the activated carboxylate **7** in the form of an acyloxy-phosphonium salt. Importantly, our NMR experiments indicate that salt **5** is more reactive than **6** in the presence of a carboxylate (Figure 7). Then, the (acyloxy)-phosphonium species **7** undergoes direct amidation generating the desired product and forming triphenylphosphine oxide as a byproduct (Figure 11).

CONCLUSIONS

In summary, we have developed a mild methodology for the amidation of carboxylic acids with both I° and II° amines. This work uses triphenylphosphine and *N*-chlorophthalimide as bench-stable reagents to generate in situ reactive phosphonium species that efficiently activate carboxylic acids. Our mechanistic work employed ^{31}P NMR and HR-MS techniques to observe and characterize the different intermediates generated throughout the reaction. Our work is the first to characterize imido-phosphonium intermediates and observe its reactivity differences with chloro-phosphonium species. These observations can help the continual improvement of phosphonium-based transformations and characterize the species involved. Future work in our lab aims at employing similar strategies to enable other deoxyamination transformations.

EXPERIMENTAL SECTION

General Considerations. All reagents were purchased and used without further purification unless otherwise noted. All reactions were performed under an inert atmosphere unless otherwise stated. Room temperature refers to 24 °C. Solvents were freshly distilled under anhydrous conditions before use.

Moisture-sensitive reactions were performed using flame-dried glassware under an atmosphere of dry argon (Ar).

Flame-dried equipment was stored in a 130 °C oven before use and either allowed to cool in a cabinet desiccator or assembled hot and allowed to cool under an inert atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via a plastic or glass syringe.

Chromatographic purification of products was accomplished using a flash column chromatography Silicycle Silica flash F60 (particle size: 40−63 μm, 230−400 mesh).

Thin-layer chromatography was performed on EMD Millipore silica gel 60 F$_{254}$ glass-backed plates (layer thickness: 250 μm, particle size: 10−12 μm, impregnated with a fluorescent indicator). Visualization of the developed chromatogram was accomplished by fluorescence quenching under shortwave UV light and/or by staining with phosphomolybdic acid, *p*-anisaldehyde, or KMnO$_4$ stain.

Instrumentation. NMR spectrometry: NMR spectra were obtained on Bruker spectrometers operating at 400 or 500 MHz for ^{1}H NMR and 101 or 126 MHz for ^{13}C{^{1}H} NMR. Chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and the relative integral was made in reference to NMR solvent signals.

Mass spectrometry: gas chromatograph-mass spectrometry were obtained using a Hewlett Packard GC system HP 6890 Series coupled with a HP 5973 mass-selective detector. High-resolution mass spectra were obtained using an Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS with electrospray ionization (ESI).

General Method A: Amide Synthesis. A flame-dried 10 mL microwave vial was charged with *N*-chlorophthalimide (1.5

equiv), triphenylphosphine (1.5 equiv), and the desired carboxylic acid (100 mg, 1 equiv) under an argon atmosphere. A solvent (3 mL of toluene or acetonitrile) was then added, and the resulting solution was stirred for 1 min before adding the desired amine reagent (3 equiv). The resulting mixture was stirred at room temperature for 12 h in an inert atmosphere. The crude reaction was then dissolved in 10 mL of ethyl acetate, and the solution was washed using a saturated solution of sodium bicarbonate (8 mL) and a brine solution (8 mL). The organic layer was dried with sodium sulfate and then concentrated via rotatory evaporation. The corresponding amide was isolated via column chromatography.

General Method B: Acyl Phthalimide Synthesis. A flame-dried 10 mL microwave vial was charged with *N*-chlorophthalimide (1.5 equiv), triphenylphosphine (1.5 equiv), DMAP (1.5 equiv), and the desired carboxylic acid (100 mg, 1 equiv) under an argon atmosphere. Toluene (3 mL) was then added, and the resulting solution was stirred for 12 h at 80 °C in an inert atmosphere. The crude reaction was then dissolved in 10 mL of ethyl acetate, and the solution was washed using a saturated solution of sodium bicarbonate (8 mL) and a brine solution (8 mL). The organic layer was dried with sodium sulfate and then concentrated via rotatory evaporation. The corresponding acyl phthalimide was isolated via column chromatography.

Compounds Synthesis and Characterization. *Preparation of N-Benzylbenzamide (3aa).* Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 263 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.53, DCM/hexane/EtOAc = 5:3:1) and isolated in 83% yield, 140 mg. Spectra data matched reported data.[25] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83−7.60 (m, 2H), 7.44−7.35 (m, 1H), 7.36−7.25 (m, 2H), 7.25 (m, 4H), 6.51 (s, 1H), 4.53 (d, *J* = 5.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 167.4, 138.3, 134.5, 131.5, 128.8, 128.6, 127.9, 127.6, 127, 44.1.

Preparation of N-Benzyl-N-methylbenzamide (3ab). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 199 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.62, DCM/hexane/EtOAc = 5:3:1) and isolated in 65% yield, 120 mg. Spectra data matched reported data.[26] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41−7.08 (m, 10H), 4.49 (d, 2H), 2.79 (d, *J* = 72.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 169, 136.3, 129.6, 128.8, 128.5, 127.6, 127, 126.9, 55.2, 50.9, 37, 33.2.

Preparation of N-Cyclohexylbenzamide (3ac). Using general method A, (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 244 mg of cyclohexylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.59, DCM/hexane/EtOAc = 5:3:1) and isolated in 76% yield, 130 mg. Spectra data matched reported data.[27]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82−7.74 (m, 2H), 7.53−7.45 (m, 1H), 7.44−7.38 (m, 2H), 6.14 (s, 1H), 3.99 (m, 1H), 2.03 (m, 2H), 1.81−1.70 (m, 2H), 1.70−1.61 (m, 1H), 1.48−1.35 (m, 2H), 1.32−1.13 (m, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 166.5, 135.2, 131.2, 128.5, 126.9, 48.7, 33.2, 25.6, 25.

Preparation of (S)-N-(1-Phenylethyl)benzamide (3ad). Using general method A (100 mg of benzoic acid, 322 mg

of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 298 mg of (*S*)-(−)-1-phenylethylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.63, DCM/hexane/EtOAc = 5:3:1) and isolated in 72% yield, 150 mg. Spectra data matched reported data.[28]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71−7.66 (m, 2H), 7.43−7.37 (m, 1H), 7.35−7.25 (m, 6H), 7.21−7.17 (m, 1H), 6.36 (s, 1H), 5.25 (p, *J* = 7.1 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 166.9, 143.2, 134.7, 131.4, 128.8, 128.6, 127.5, 127, 126.3, 49.2, 21.8.

Preparation of N-(2-Phenylpropan-2-yl)benzamide (3ae). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 332 mg of cumylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.67, DCM/hexane/EtOAc = 5:3:1) and isolated in 51% yield, 100 mg. Spectra data matched reported data.[29]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83−7.76 (m, 2H), 7.56−7.46 (m, 3H), 7.50−7.40 (m, 2H), 7.38 (t, *J* = 8.6, 7.6, 7.0 Hz, 2H), 7.30−7.25 (m, 1H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 166, 146.9, 135.5, 131.3, 128.6, 128.5, 126.9, 126.8, 124.8, 56.3, 29.2.

Preparation of (Z)-N-(Octadec-9-en-1-yl)benzamide (3af). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 657 mg of oleylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.76, DCM/hexane/EtOAc = 5:3:1) and isolated in 40% yield, 122 mg. Spectra data matched reported data.[30]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (dd, *J* = 7.0, 1.8 Hz, 2H), 7.51−7.39 (m, 3H), 6.36 (s, 1H), 5.44−5.32 (m, 2H), 3.44 (m, 3H), 2.17−1.90 (m, 4H), 1.62 (p, *J* = 7.1 Hz, 2H), 1.43−1.21 (m, 22H), 0.87 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 167.5, 135, 134.5, 131.2, 130.6, 129.8, 128.9, 128.5, 126.9, 40.1, 31.9, 29.8, 29.7, 29.5, 27.2, 22.7, 14.1.

Preparation of tert-Butyl Benzoylglycinate (3ag). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 323 mg of *tert*-butyl, 2-aminoacetate, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.49, DCM/hexane/EtOAc = 5:3:1) and isolated in 54% yield, 100 mg. Spectra data matched reported data.[31]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87−7.79 (m, 2H), 7.56−7.48 (m, 1H), 7.48−7.40 (m, 2H), 6.71 (s, 1H), 4.15 (d, *J* = 4.9 Hz, 2H), 1.52 (s, 9H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 169.4, 167.2, 134, 131.7, 128.6, 127, 82.5, 42.5, 28.1.

Preparation of N-Phenylbenzamide (3ah). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 229 mg of aniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.84, DCM/hexane/EtOAc = 5:3:1) and isolated in 69% yield, 111 mg. Spectra data matched reported data.[32]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92−7.83 (m, 3H), 7.70−7.61 (m, 2H), 7.59−7.51 (m, 1H), 7.51−7.43 (m, 2H), 7.41−7.32 (m, 2H), 7.20−7.11 (m, 1H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 165.8, 138, 135.1, 131.9, 129.1, 128.8, 127, 124.6, 120.3.

Preparation of N-Mesitylbenzamide (3ai). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 332 mg

of 2,4,6-trimethylaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.28, 100% DCM) and isolated in 56% yield, 110 mg. Spectra data matched reported data.[33]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92−7.76 (m, 2H), 7.55−7.45 (m, 1H), 7.40 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.33 (d, 1H), 6.84 (s, 2H), 2.22 (s, 3H), 2.15 (s, 6H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 166.3, 137.1, 135.3, 134.7, 131.7, 131.3, 129, 128.7, 127.2, 21, 18.4.

Preparation of N-(2,6-Diisopropylphenyl)benzamide (3aj). Using general method A (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 435 mg of 2,6-diisopropylaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.39, 100% DCM) and isolated in 49% yield, 113 mg. Spectra data matched reported data.[34]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87−7.79 (m, 2H), 7.52−7.46 (m, 1H), 7.44−7.38 (m, 2H), 7.33−7.24 (m, 2H), 7.16 (t, *J* = 8.3 Hz, 2H), 3.07 (hept, *J* = 6.8 Hz, 2H), 1.14 (d, *J* = 6.9 Hz, 12H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 166.9, 146.5, 134.7, 131.8, 131.2, 128.9, 128.5, 127.2, 28.9, 23.7.

Preparation of N,N-Diphenylbenzamide (3ak). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 277 mg of diphenylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.55, hexane/EtOAc = 2:1) and isolated in 55% yield, 123 mg. Spectra data matched reported data.[35]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41−7.36 (m, 2H), 7.24−7.17 (m, 5H), 7.15−7.04 (m, 8H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.2, 144, 136.2, 130.2, 129.2, 129.1, 127.9, 127.5, 126.4.

Preparation of N-Methyl-N-phenylbenzamide (3al). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 176 mg of *N*-methylaniline, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.47, DCM/hexane/EtOAc = 5:3:1) and isolated in 65% yield, 112 mg. Spectra data matched reported data.[36]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35−7.27 (m, 2H), 7.26−7.18 (m, 3H), 7.14 (m, 3H), 7.09−6.97 (m, 2H), 3.54−3.47 (m, 3H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.2, 144.9, 136, 129.6, 129.2, 128.7, 127.3, 126.9, 126.5, 38.4.

Preparation of Phenyl(pyrrolidin-1-yl)methanone (3am). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 117 mg of pyrrolidine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.29, DCM/hexane/EtOAc = 5:2:3) and isolated in 71% yield, 102 mg. Spectra data matched reported data.[37]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (m, 2H), 7.30 (m, 3H), 3.62−3.20 (m, 3H), 1.94−1.72 (m, 4H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 169.7, 137.3, 133, 129.7, 128.2, 127.1, 49.5, 46.1, 26.4, 24.4.

Preparation of Phenyl(piperidin-1-yl)methanone (3an). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 139 mg of piperidine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.60, 100% EtOAc) and isolated in 45% yield, 70 mg. Spectra data matched reported data.[38]

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^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 (s, 5H), 3.42 (d, J = 148.3 Hz, 4H), 1.79−1.09 (m, 5H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 170, 136.5, 129.2, 128.3, 126.7, 48.7, 43.1, 26.4, 25.7, 24.5.

Preparation of Morpholino(phenyl)methanone (3ao). Using general method B (100 mg of benzoic acid, 322 mg of triphenylphosphine, 223 mg of *N*-chlorophthalimide, 143 mg of morpholine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.33, petroleum ether/EtOAc = 1:1) at 41% yield, 64 mg. Spectra data matched reported data.[39]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (m, 5H), 3.47 (m, 8H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 170.3, 135.3, 132, 131.9, 129.8, 128.5, 128.4, 127.4, 66.7, 48.1, 42.6.

Preparation of N-Benzyl-4-methoxybenzamide (3ba). Using general method A (100 mg of 4-methoxy-benzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 211 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.14, hexane/EtOAc = 3:1) and isolated in 84% yield, 166 mg. Spectra data matched reported data.[41]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 7.29−7.11 (m, 4H), 6.82 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.40 (s, 1H), 3.75 (s, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 166.8, 162.3, 138.6, 128.8, 128.7, 127.9, 127.5, 126.7, 113.8, 55.4, 44.1.

Preparation of N-Benzyl-4-methoxy-N-methylbenzamide (3bb). Using general method A, (100 mg of 4-methoxy-benzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 160 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.40, hexane/EtOAc = 1:1) and isolated in 87% yield, 182 mg. Spectra data matched reported data.[40]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47−7.39 (m, 2H), 7.39−7.33 (m, 2H), 7.32−7.23 (m, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.65 (s, 2H), 3.81 (s, 3H), 2.95 (s, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 160.8, 137.1, 129, 128, 127, 113.7, 55.3.

Preparation of N-Benzyl-4-iodobenzamide (3ca). Using general method A (100 mg of 4-iodo-benzoic acid, 159 mg of triphenylphosphine, 110 mg of *N*-chlorophthalimide, 121 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.52, EtOAc/hexane/DCM = 1:2.5:1) and isolated in 73% yield, 100 mg. Spectra data matched reported data.[9a]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83−7.76 (m, 2H), 7.56−7.50 (m, 2H), 7.41−7.33 (m, 5H), 6.40 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 166.5, 138, 137.9, 137.8, 133.8, 128.9, 128.6, 128, 127.8, 98.5, 44.3.

Preparation of N-Benzyl-4-iodo-N-methylbenzamide (3cb). Using general method A (100 mg of 4-iodo-benzoic acid, 159 mg of triphenylphosphine, 110 mg of *N*-chlorophthalimide, 98 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.48, DCM/hexane/EtOAc = 1:2.5:1) and isolated in 87% yield, 123 mg. Spectra data matched reported data.[41]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 2H), 7.45−7.07 (m, 7H), 4.61 (d, J = 96.0 Hz, 2H), 2.93 (d, J = 67.1 Hz, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 137.6, 128.8, 127.7, 95.8, 55.2, 51, 37, 33.4.

Preparation of N-Benzyl-4-bromobenzamide (3da). Using general method A (100 mg of 4-bromo-benzoic acid, 196 mg of triphenylphosphine, 135 mg of *N*-chlorophthalimide, 160 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.60, DCM/hexane/EtOAc = 1:2.5:1) and isolated in 69% yield, 100 mg. Spectra data matched reported data.[42]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71−7.60 (m, 2H), 7.61−7.53 (m, 2H), 7.41−7.30 (m, 5H), 4.64 (d, J = 5.6 Hz, 2H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 166.3, 137.9, 133.3, 131.9, 128.9, 128.6, 128, 127.8, 126.3, 44.3.

Preparation of N-Benzyl-4-bromo-N-methylbenzamide (3db). Using general method A (100 mg of 4-bromo-benzoic acid, 196 mg of triphenylphosphine, 135 mg of *N*-chlorophthalimide, 120 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.48, DCM/hexane/EtOAc = 1:2.5:1) and isolated in 88% yield, 133 mg. Spectra data matched reported data.[43]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (m,2H), 7.39−7.22 (m, 6H), 7.22−7.04 (m, 1H), 4.61 (d, J = 97.5 Hz, 2H), 2.94 (d, J = 68.3 Hz, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 206.6, 135.1, 131.7, 128.9, 128.2, 127.7, 126.6, 124, 55.2, 51, 30.9.

Preparation of N-Benzyl-4-nitrobenzamide (3ea). Using general method A (100 mg of 4-nitro-benzoic acid, 236 mg of triphenylphosphine, 163 mg of *N*-chlorophthalimide, 192 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.57, DCM/hexane/EtOAc = 5:3:1) and isolated in 42% yield, 66 mg. Spectra data matched reported data.[44]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.30−8.16 (m, 2H), 8.00−7.89 (m, 2H), 7.40−7.29 (m, 5H), 6.60 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 165.3, 149.7, 140, 137.5, 129, 128.2, 128, 127.9, 123.8, 44.5.

Preparation of N-Benzyltetradecanamide (3fa). Using general method A (100 mg of myristic acid, 173 mg of triphenylphosphine, 119 mg of *N*-chlorophthalimide, 141 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.57, DCM/hexane/EtOAc = 5:3:1) and isolated in 70% yield, 97 mg. Spectra data matched reported data.[45]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32−7.11 (m, 5H), 5.75 (s, J = 5.7 Hz, 1H), 4.36 (d, J = 5.7 Hz, 2H), 2.19−1.97 (m, 2H), 1.56 (q, J = 7.2 Hz, 2H), 1.39−0.97 (m, 19H), 0.90−0.55 (m, 3H).

^{13}C{1H}NMR (100 MHz, CDCl$_3$) δ 173.1, 138.5, 128.7, 127.8, 127.5, 123.5, 43.6, 36.8, 31.9, 29.7, 29.6, 29.5, 29.4, 25.8, 23.7, 14.1.

Preparation of N-Benzyl-N-methyltetradecanamide (3fb). Using general method A (100 mg of myristic acid, 173 mg of triphenylphosphine, 119 mg of *N*-chlorophthalimide, 106 mg of *N*-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.63, DCM/hexane/EtOAc = 5:3:1) and isolated in 80% yield, 116 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39−7.03 (m, 5H), 4.56 (d, J = 24.3 Hz, 2H), 2.92 (d, J = 10.7 Hz, 3H), 2.42−2.27 (m, 2H), 1.67 (m, 2H), 1.41−1.11 (m, 22H), 0.94−0.72 (m, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 173.7, 173.3, 137.7, 128.9, 128.6, 128, 127.6, 127.3, 126.3, 53.4, 50.8, 34.8, 33.9, 33.6, 33.2, 31.9, 29.7, 29.6, 29.5, 29.4, 25.5, 25.2, 22.7, 14.1.

HRMS (ESI): [M + H]⁺ calcd for $C_{22}H_{38}NO^+$, 332.2948 m/z; found, 332.2886 m/z.

IR (cm⁻¹): 2930, 2856, 1653, 1457, 1265, 1094.

Preparation of tert-Butyl 3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino-4-(benzylamino)-4-oxobutyl)-1H-indole-1-carboxylate (3ga). Using general method A (100 mg of Fmoc-Trp(Boc)-OH, 76 mg of triphenylphosphine, 53 mg of N-chlorophthalimide, 61 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.83, DCM/hexane/EtOAc = 2:1:1) and isolated in 54% yield, 63 mg.

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H) 7.6−7.09 (m, 14H), 6.87 (m, 2H), 5.66 (d, J = 146.0 Hz, 2H), 4.51−3.85 (m, 5H), 3.43−2.82 (m, 2H), 1.57 (s, 9H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 170.6, 143.7, 141.3, 137.3, 128.6, 127.8, 127.6, 127.5, 127.1, 125, 124.8, 124.4, 123, 120, 119, 115.4, 83.9, 67.2, 47.1, 43.7, 28.6, 28.2.

HRMS (ESI): [M+ H]⁺ calcd for $C_{38}H_{38}N_3O_5^+$, 616.2806 m/z; found, 616.2550 m/z.

IR (cm⁻¹): 3304, 3064, 1734, 1684, 1649, 1549, 1453, 1374, 1080.

Preparation of N-Benzyl-4-(trifluoromethyl)benzamide (3ha). Using general method A (100 mg of 4-triflourobenzoic acid, 210 mg of triphenylphosphine, 145 mg of N-chlorophthalimide, 170 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.47, DCM/hexane/EtOAc = 7:3:1) and isolated in 40% yield, 59 mg. Spectra data matched reported data.[46]

¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.50−7.16 (m, 5H), 6.55 (s, 1H), 4.67 (d, J = 5.6 Hz, 2H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 166.1, 137.8, 137.7, 128.9, 128, 127.9, 127.5, 125.7, 125.6, 44.3.

Preparation of N-Benzyl-N-methyl-4-(trifluoromethyl)benzamide (3hb). Using general method A (100 mg of 4-triflourobenzoic acid, 210 mg of triphenylphosphine, 145 mg of N-chlorophthalimide, 129 mg of N-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.45, DCM/hexane/EtOAc = 10:3:1) and isolated in 73% yield, 113 mg. Spectra data matched reported data.[26]

¹H NMR (400 MHz, CDCl₃) δ 7.58 (m, 2H), 7.49 (d, m, 2H), 7.26 (m, 4H), 7.07 (m, 1H), 4.54 (d, J = 117.4 Hz, 2H), 2.87 (d, J = 87.4 Hz, 3H),

¹³C{1H} NMR (100 MHz, CDCl₃) δ 170.8, 139.9, 136.7, 136.1, 131.8, 131.4, 129, 128.9, 127.9, 127.7, 55, 50.9, 36.9, 33.3.

Preparation of N-Benzyl-2-(4-isobutylphenyl)propanamide (3ia). Using general method A (100 mg of 2-(4-isobutylphenyl)propanoic acid, 194 mg of triphenylphosphine, 134 mg of N-chlorophthalimide, 157 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.59, DCM/hexane/EtOAc = 7:3:1) and isolated in 50% yield, 71 mg. Spectra data matched reported data.[47]

¹H NMR (400 MHz, CDCl₃) δ 7.20−7.09 (m, 5H), 7.06−6.98 (m, 4H), 5.66 (s, 1H), 4.29 (d, J = 5.8 Hz, 2H), 3.50 (q, J = 7.2 Hz, 1H), 2.37 (d, J = 7.2 Hz, 2H), 1.76 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H), 0.81 (d, J = 6.6 Hz, 6H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 174.4, 140.8, 138.5, 129.7, 128.6, 127.4, 127.3, 46.8, 45, 43.5, 30.2, 22.4, 18.5.

Preparation of N-Benzyl-2-(4-isobutylphenyl)propanamide (3ib). Using general method A (100 mg of 2-(4-isobutylphenyl)propanoic acid, 194 mg of triphenylphosphine, 134 mg of N-chlorophthalimide, 116 mg of N-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.68, DCM/hexane/EtOAc = 7:3:1) and isolated in 80% yield, 120 mg.

¹H NMR (400 MHz, CDCl₃) δ 7.37−7.16 (m, 6H), 7.12 (m, 2H), 7.05−7.01 (m, 1H), 4.85−4.28 (m, 2H), 3.91 (m, 1H), 2.89 (d, J = 47.2 Hz, 3H), 2.48 (d, J = 7.1 Hz, 2H), 1.88 (m, 1H), 1.50 (m, 3H), 0.93 (dd, J = 6.6, 2.6 Hz, 6H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 174, 140.3, 140, 139.2, 138.9, 137.6, 136.9, 129.6, 129.5, 128.8, 128.5, 127.9, 127.5, 127.2, 127, 126.5, 52.9, 51.2, 45, 43.1, 42.8, 34.8, 34.1, 30.2, 22.4, 21.1, 20.8.

HRMS (ESI): [M+ H]⁺ calcd for $C_{21}H_{28}NO^+$, 310.2165 m/z; found, 310.2115 m/z.

IR (cm⁻¹): 3048, 2948, 2865, 1740, 1648, 1449, 1267, 1059.

Preparation of N-Benzyl-2-methyl-2-phenylpropanamide (3ja). Using general method A (100 mg of 2-phenylisobutyric acid, 241 mg of triphenylphosphine, 167 mg of N-chlorophthalimide, 196 mg of benzylamine, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.49, DCM/hexane/EtOAc = 7:3:1) and isolated in 43% yield, 66 mg. Spectra data matched reported data.[48]

¹H NMR (400 MHz, CDCl₃) δ 7.33−7.23 (m, 4H), 7.22−7.12 (m, 3H), 7.07−7.00 (m, 2H), 5.39 (s, 1H), 4.29 (d, J = 5.8 Hz, 2H), 1.53 (s, 6H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 177.3, 145.1, 138.6, 128.8, 128.6, 127.3, 127.1, 126.5, 47.1, 43.7, 27.1.

Preparation of N-Benzyl-N,2-dimethyl-2-phenylpropanamide (3jb). Using general method A (100 mg of 2-phenylisobutyric acid, 241 mg of triphenylphosphine, 167 mg of N-chlorophthalimide, 148 mg of N-benzylmethylamine, and 3 mL of MeCN), the product was purified by column chromatography (R_f = 0.65, DCM/hexane/EtOAc = 7:3:1) and isolated in 94% yield, 153 mg. Spectra data matched reported data.

¹H NMR (400 MHz, CDCl₃) δ 7.54−6.61 (m, 10H), 5.10−3.69 (m, 2H), 2.82−2.26 (m, 3H), 1.50 (s, 6H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 176.3, 146.4, 128.9, 128.5, 127.2, 126.4, 124.9, 47.2, 28.4.

HRMS (ESI): [M+ H]⁺ calcd for $C_{18}H_{22}NO^+$, 268.1696 m/z; found, 268.1660 m/z.

IR (cm⁻¹): 3100, 2990, 2925, 2249, 1714, 1648, 1400, 1088.

Preparation of N-(3-Isopropoxyphenyl)-2-methylbenzamide (3kc). Using general method A (100 mg of o-toluic acid, 322 mg of triphenylphosphine, 291 mg of N-chlorophthalimide, 335 mg of 3-isopropoxyaniline, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.54, DCM/hexane/EtOAc = 10:3:1) and isolated in 55% yield, 109 mg. Spectra data matched reported data.[17c]

¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.33−7.24 (m, 2H), 7.24−7.16 (m, 1H), 7.14−7.07 (m, 3H), 7.01−6.94 (m, 1H), 6.60 (dd, J = 8.3, 2.4 Hz, 1H), 4.49 (sept, J = 6.2 Hz, 1H), 2.35 (s, 3H), 1.23 (d, J = 6.1 Hz, 6H).

¹³C{1H} NMR (100 MHz, CDCl₃) δ 168.1, 158.6, 139.3, 136.4, 131.2, 130.2, 129.8, 126.7, 125.9, 112.2, 111.9, 107.6, 70, 60.4, 22.1, 19.8, 14.2.

Preparation of 2-Benzoylisoindoline-1,3-dione (4a). Using general method B (100 mg of benzoic acid, 323 mg of triphenylphosphine, 223 mg of N-chlorophthalimide, 150 mg of DMAP, and 3 mL of toluene), the product was purified by

column chromatography (R_f = 0.4, DCM/hexane = 2:1) and isolated in 60% yield, 123 mg. Spectra data matched reported data.[49]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (m, 2H), 7.90−7.82 (m, 4H), 7.72−7.61 (m, 1H), 7.56−7.43 (m, 2H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 167.9165.9, 135.3, 134.5, 131.5, 130.5, 128.7, 124.5.

Preparation of 2-(4-Methoxybenzoyl)isoindoline-1,3-dione (4b). Using general method B (100 mg of 4-methoxybenzoic acid, 259 mg of triphenylphosphine, 179 mg of *N*-chlorophthalimide, 120 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.7, DCM/hexane/EtOAc = 5:3:1) and isolated in 44% yield, 81 mg. Spectra data matched reported data.[50]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.90−7.81 (m, 4H), 6.96 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 166.1, 164.7, 135.1, 133.2, 131.7, 125, 124.4, 114.1, 55.6.

Preparation of 2-(4-(Benzyloxy)benzoyl)isoindoline-1,3-dione (4c). Using general method B 100 mg of 4-(benzyloxy)-benzoic acid, 173 mg of triphenylphosphine, 120 mg of *N*-chlorophthalimide, 80 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.7, DCM/hexane/EtOAc = 5:3:1) and isolated in 70% yield, 110 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.91−7.81 (m, 4H), 7.13−6.97 (m, 2H), 5.15 (s, 2H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 165.6, 163.5, 135.9, 135.1, 133.2, 131.7, 128.8, 128.4, 127.5, 125.2, 124.4, 115, 70.4.

HRMS (ESI): [M+ H]$^+$ calcd for C$_{22}$H$_{16}$NO$_4$$^+$, 358.1074 *m/z*; found, 358.1101 *m/z*.

IR (cm^{-1}): 3078, 3032, 2946, 1784, 1683, 1510, 1105.

Preparation of 2-(2-Methyl-2-phenylpropanoyl)-isoindoline-1,3-dione (4d). Using general method B (100 mg of 2-phenyl isobutyric acid, 240 mg of triphenylphosphine, 166 mg of *N*-chlorophthalimide, 112 mg of DMAP, and 3 mL of toluene), the product was purified by column chromatography (R_f = 0.6, EtOAc/hexane = 3:5) and isolated in 48% yield, 86 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82−7.78 (m, 2H), 7.76−7.71 (m, 2H), 7.40−7.18 (m, 5H), 1.81 (s, 6H).

^{13}C{1H} NMR (100 MHz, CDCl$_3$) δ 178.9, 165.1, 142.5, 134.9, 131.3, 128.3, 127, 126.5, 124.1, 51.5, 26.9.

HRMS (ESI): [M+ H]$^+$ calcd for C$_{18}$H$_{16}$NO$_3$$^+$, 358.1074 *m/z*; found, 358.1101 *m/z*.

IR (cm^{-1}): 3100, 3060, 2960, 2940, 2000, 1790, 1760, 1500, 1060.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c02309.

^{1}H and ^{13}C{1H} NMR spectra for all aminated products (PDF)

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