Regioselective α-Amination of Ethers Using Stable *N*-Chloroimides and Lithium *tert*-butoxide

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Supporting Information Placeholder

ABSTRACT: Herein we describe a metal-free regioselective α-amination of ethers mediated by *N*-chloroimides in ethereal solvents in the presence of lithium *tert*-butoxide. This reactivity of *N*-chloroimides leads to the synthesis of hemiaminal ethers in good to excellent yields at room temperature. This C–H functionalization is achieved without the use of light, heat source, or external radical initiators. Initial mechanistic work indicates that the reaction proceeds through a radical pathway.

The hemiaminal ether moiety[1] is embedded within numerous natural products[2] and pharmaceutical agents (Figure 1).[3] The bioactivity of such compounds is wide and ranges from anticancer (tegafur) to anti-HIV (zalcitabine and didanosine) activity, and some also exhibits lyase and hepatitis C inhibition. Traditional approaches to generating hemiaminal ethers proceed *via* metal-catalyzed hydroamination of enol ethers[4] or through the substitution of a leaving group in the α-position of an ether substrate.[5] These methods possess limitations as enol ethers are acid-sensitive functional groups and α-halogenated ethers are inherently unstable.

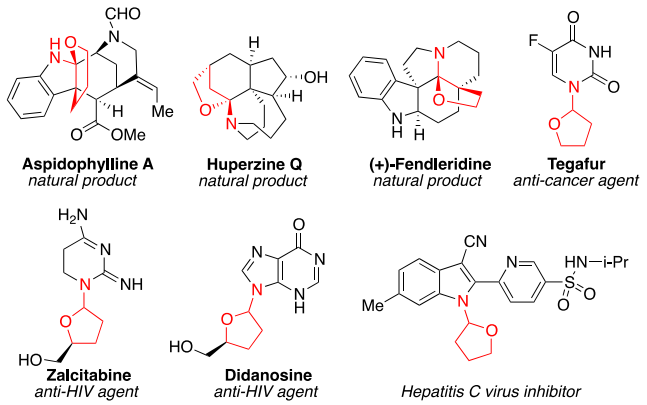

Figure 1. Selected examples of natural products and bioactive agents containing hemiaminal ether skeletons.

More recently, direct C(sp^3)–H amination of ethers has represented a more efficient approach that enables late-stage functionalization of complex molecules.[6, 7] Methods that access α-aminated ethers through such C(sp^3)–H activation processes can be divided into three main categories that depend on the nature of the aminating agent employed: i) transition-metal catalyzed nitrene insertion[8] ii) metal-free organonitrenoid insertion[9] and iii) radical-based[10] or metal-catalyzed[11] cross-coupling reaction of NH-amines (Figure 2).

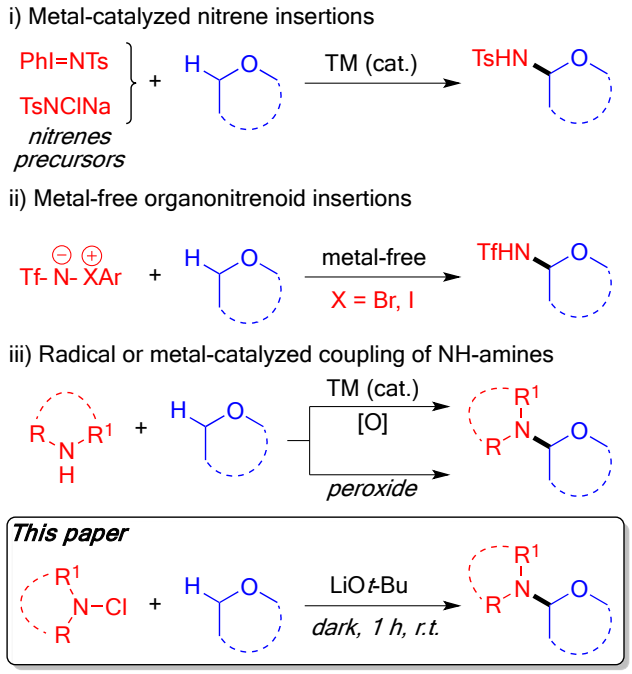

Figure 2. Different methods to generate hemiaminal ethers.

Despite the advances made towards the regioselective α-amination of C(sp^3)–H bonds utilizing the methods mentioned above, there still remains the challenge of developing more environmentally friendly and atom-economical reactions that do not require the use of strong oxidants or external radical initiators. Herein, we describe a novel metal-free, regioselective α-amination

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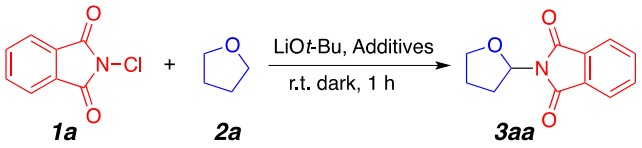
of cyclic and acyclic ethers using stable *N*-chloroimides as the aminating agent. Our method generates the desired products in good yields at room temperature without the need for transition metal catalysts, external radical initiators, heat, or light. We found that stable *N*-chloroimides can selectively aminate in the presence of lithium *tert*-butoxide at room temperature (Figure 2).

Table 1. Reaction optimization and influence of base on reaction outcome.



1a ***2a*** ***3aa***

Entry	Base	Temperature	Additives	Yield[a]
1	LiO*t*-Bu	26 °C (r.t.)	-	80%[b] (86%)
2	NaO*t*-Bu	r.t.	-	44%
3	KO*t*-Bu	r.t.	-	20%
4	none	r.t.	-	0%
5	LiO*t*-Bu	40 °C	-	76%
6	Cs_2CO_3	r.t.	-	15%
7	K_2CO_3	r.t.	-	0%
8	$LiOH.H_2O$	r.t.	-	19%
9	LiOAc	r.t.	-	0%
10	LiOMe	r.t.	-	41%
11	Et_3N	r.t.	-	19%
12	Pyridine	r.t.	-	0%
13[c]	LiO*t*-Bu	r.t.	air	22%
14[d]	LiO*t*-Bu	r.t.	light	78%
15[e]	LiO*t*-Bu	r.t.	-	62%
16[f]	LiO*t*-Bu	50 °C	CH_2Cl_2	47%
17[f]	LiO*t*-Bu	50 °C	DCE	72%

All reactions were performed using 1 mL of anhydrous, degassed, non-stabilized THF, 0.14 mmol of *N*-chlorophthalimide and 0.14 mmol of LiO*t*-Bu under argon atmosphere, constant stirring in the dark, and at room temperature, unless stated otherwise. *a*. NMR yield obtained using dibromomethane as internal standard. *b*. Isolated yield. *c*. The reaction was performed in open atmosphere. *d*. The reaction was performed without covering the reactor in aluminium foil to allow ambient light in the reaction flask. *e*. Stabilized reagent-grade THF was used without further purification and without degassing. *f*. The reaction was performed using 1:1 ratio of THF and the additive solvent (total volume 1 mL).

To begin our study, we chose commercially available *N*-chlorophthalimide ***1a*** and tetrahydrofuran (THF) ***2a*** as model substrates. Optimal reaction conditions (Table 1, entry 1) were obtained when using 1 equiv. of LiO*t*-Bu at room temperature in the dark for 1h. The lithium counter ion appears essential for optimal reactivity since the use of sodium or potassium *tert*-butoxide (Table 1, entries 2 and 3) provided the desired product in significantly lower yields. Importantly, a control experiment in the absence of base did not provide the desired product (Table 1, entry 4). Mild heating of the reaction at 40 °C did not have a deleterious effect on product formation (Entry 5). Extensive screening of other inorganic (Table 1, entries 6–10) and organic (Table 1, entries 11 and 12) bases did not provide the desired product in satisfactory useful yields. An important observation from our optimization study was the deleterious effect of oxygen. Lower yields were obtained when the reaction was performed in an open-to-air microwave vial (Table 1, entry 13). Presumably, in the open-to-air reactions, we surmise that atmospheric oxygen is responsible for the quenching of the generated radical species, leading to reduced overall yields. Also, we hypothesize that covering the reaction flask in aluminum foil would prevent light induced decomposition of *N*-chlorophthalimide, but such path seems to be minimal. Indeed, laboratory lighting did not have a considerable effect on product formation (Table 1, entry 14). As such, it was not surprising that the optimal reaction conditions were achieved in the absence of oxygen in an argon atmosphere. The use of reagent grade THF (non-anhydrous and stabilized with 0.025% butylated hydroxytoluene) also afforded the aminated THF product in only 62 % NMR yield (Table 1, entry 15), corroborating further the radical nature of this transformation. Finally, while reactions in neat THF (1 mL) were consistently optimal, the use of a 1:1 (by volume) mixture of dichloroethane (DCE) and THF at 50 °C also gave the desired product in 72 % NMR yield (Table 1, entry 17).

With the established optimal conditions in hand, we proceeded to first examine the scope of ether substrates **2** compatible with our reaction conditions. Gratifyingly, the protocol was efficient for the α-amination of a diverse set of ethers (Scheme 2). Cyclic ethers such as tetrahydrofuran and tetrahydropyran were found to react smoothly to generate the coupling products **3aa** and **3ab** in good isolated yields. Linear ethers were also tolerated and afforded the corresponding products **3ac**, **3ad**, **3ae** and **3af** in moderate to good yields. In a previously published article, diethyl ether **2d** and methyl *tert*-butyl ether **2f** substrates failed to undergo amination due to the poor solubility of the reagents used.[10e] This amination reaction may therefore be complementary to existing amination strategies. Reaction of 2-methyltetrahydrofuran provided an interesting regioselectivity assessment experiment. Interestingly, the aminated product **3ag** was found as a single regioisomer favoring the less sterically hindered C–H bond at the 4 position (**3ag**, Scheme 2) in 72% yield (d.r. = 1:1.5). This result mirrors previous radical amination strategies independently developed by the Hu group[10e]

and the Du group.[10g] Other unsymmetrical substrates, such as dimethoxyethane (DME), also provided the expected product **3ae** as single regioisomers in the internal C(sp^3)-H bond. Dioxane and acetals were also tolerated and provided the desired products **3ah** and **3ai** in good yields. These substrates required longer reaction times (4 h instead of 1 h) to achieve a sufficient amount of the desired aminated products. Tetrahydrothiophene **3aj** also reacted under the current reaction conditions, but the transformation only provided the product in moderate yields. An important limitation of the current method remains the poor reactivity of benzyl ethers. As shown in scheme 2, compounds **3ak**, and **3al**, were only provided in trace amount. This, presumably, may be due to decomposition of the reactive intermediates into aldehydes under our reaction conditions.[12]

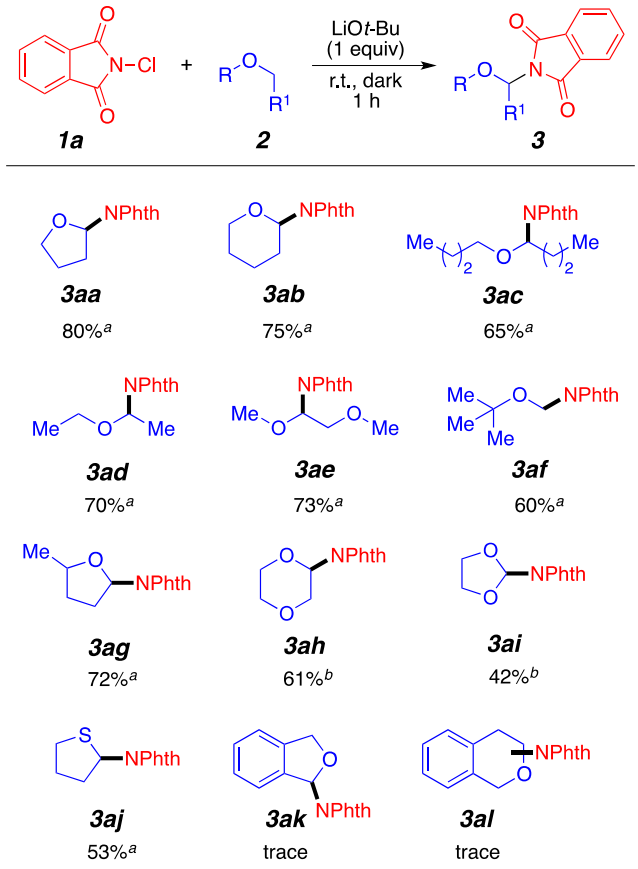


Figure 3. Reaction scope. All reactions were performed under argon atmosphere in 1 mL of solvent, 1a (0.55 mmol) and LiO*t*-Bu (0.55 mmol), unless otherwise specified (see Experimental Section). *a*. Refers to the reaction conditions shown in Table 1, Entry 1 (General Method). *b*. Reaction stirred for 4 h (See Experimental Section). Yields reported are isolated yields.

Next, we examine the compatibility of our optimal reaction conditions with different imide agents (**1b–1h**) using THF ***2a*** as the preferred ether substrate. As shown in Figure 4A, the method enabled the α-amination of THF using some of the tested *N*-chloroimide reagents in moderate yields. *N*-chlorosuccinimide (NCS) provided the desired product **3ba** low yield, however, *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) did not provide the desired product in synthetically useful yields. Presumably, the greater reactivity of NBS and NIS lead to premature decomposition of the reagents. On the other hand, *N*-chloro-3,3-dimethyl-glutarimide (33DMNCG, product **3ca**) provided the desired product in good yield. We surmise that the difference in reactivity between succinimide reagents (NCS, NBS, and NIS) and glutarimide reagents (33DMNCG) arises from the decomposition pathways of these reagents (Figure 4B). Indeed, under radical reaction conditions succinimide-based reagents generally undergoes a radical ring opening after the formation of the *N*-centered radical, while 33DMNCG is a more stable *N*-centered radical and do not decompose *via* ring opening.[13] Unfortunately, the corresponding aminated product for 2-chloro-5-nitroisoindoline-1,3-dione, and 2,4,5,6,7-pentachloroisoindoline-1,3-dione were generated in only trace amounts under our reaction conditions. The lack of product formation with these electron withdrawing *N*-chloroimides was quite surprising to us and we can only surmise at this moment that the *N*-centered radical intermediates of these species were either not generated under our reaction conditions, are not reactive enough to perform a C–H abstraction, or are not stable.

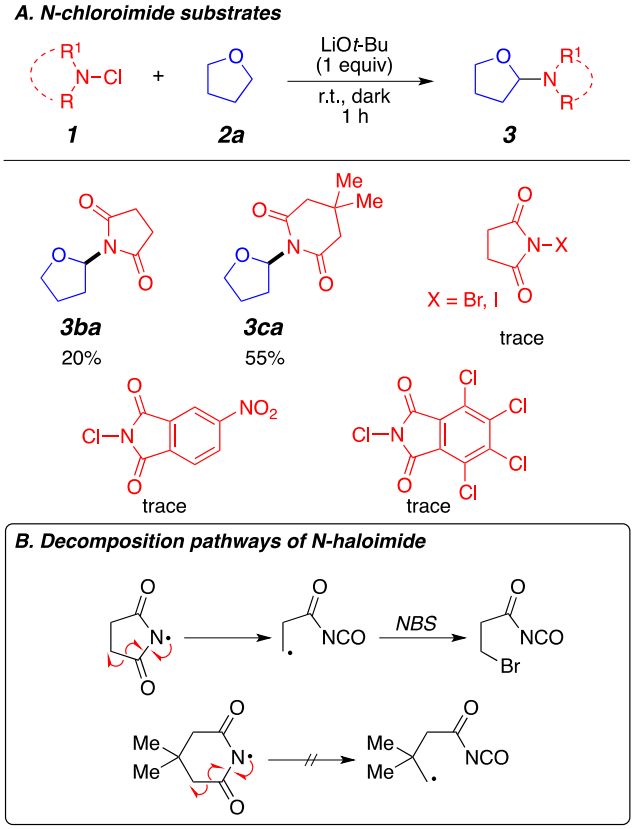


Figure 4. A. Scope of imide reagents. B. Radical decomposition pathways of *N*-halosuccinimide *versus* 3,3-dimethyl-*N*-haloglutarimide.

Of major interest, *N*-chlorosulfonimides also generated the desired product **3da** in good yield (Figure 5). Similarly, 1-chlorobenzotriazole provided a separable mixture of two regioisomeric products **3ea**/**3e'a** in good yield as well. Similar regioisomeric mixtures from reactive benzotriazole reagents have been reported in the literature.[10f] Interestingly, 1-chloroindoline-2,3-dione did not aminate THF under our reaction conditions.

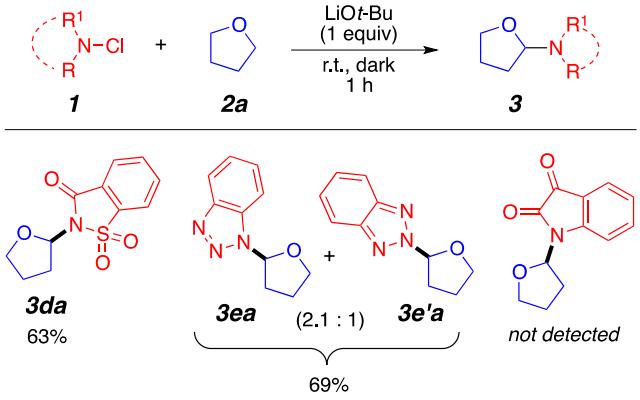
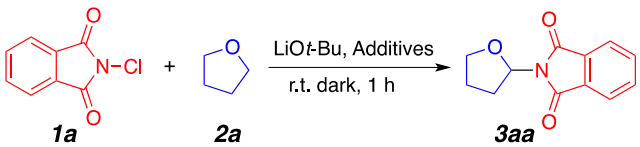


Figure 5. Scope of other aminating agents.

To gain insight into the possible mechanism of this reaction, we carried out a number of experiments, some of which are illustrated in Table 2. An important observation from these experiments was the relationship between the equivalents of base used and the overall yield of the reaction. When sub-stoichiometric amounts of LiO*t*-Bu (e.g., 0.5 equiv) were used the desired product was generated in only 48% yield (Table 2, entry 1). Similarly, super-stoichiometric amounts of base (1.5 equiv) was also detrimental to the reaction forming the desired product in 65% yield (Table 2, entries 2).

Table 2. Mechanistic Studies.

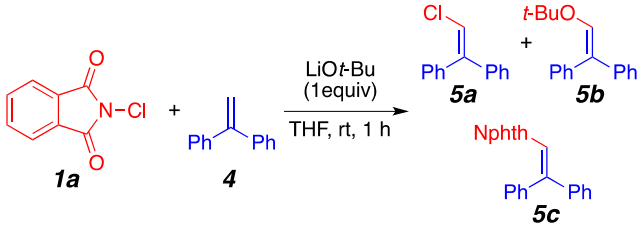
Entry	LiO*t*-Bu	Additives	Yield[a]
1	0.5 equiv.	-	48%
2	1.5 equiv.	-	65%
3	1 equiv.	TEMPO (1 equiv.)	0%
4	1 equiv.	TEMPO (0.5 equiv.)	0%



All reactions were performed using 1 mL of anhydrous, degassed, non-stabilized THF, 0.14 mmol of *N*-chlorophthalimide, and 0.14 mmol of LiO*t*-Bu under Argon atmosphere, constant stirring in the dark, and at room temperature, unless stated otherwise. *a*. NMR yield obtained using dibromomethane as internal standard.

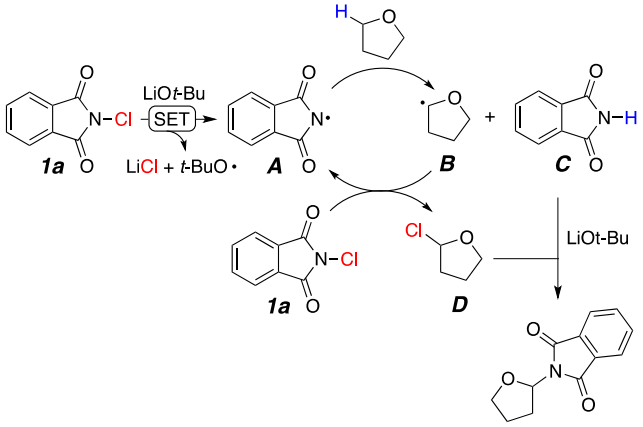
In the absence of a base, no desired product formation was observed *via* NMR analysis, but GC-MS analysis of this crude reaction mixture revealed the formation of a chlorinated THF and phthalimide (See Supporting Information). Similar halogenation of ethers using *N*-halosuccinimide reagents is well documented in the literature.[12] Addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical trapping reagent into the reaction mixture led to complete reaction shutdown (Table 2, entries 3, 4). Importantly, neither desired product nor the chlorinated THF byproducts were observed through GC-MS analysis of these crudes.

In an attempt to trap radical intermediates generated during the reaction, we used 1,1-diphenylethylene (**4**) as a reaction additive (see SI).[14] To our delight, we observed the formation of products **5a**, **5b**, and **5c** by GC-MS (Scheme 1). This result suggests the formation of chlorine, *tert*-butoxy, and phthalimide radicals. Formation of **5a** and **5c** could come from homolytic cleavage of the N–Cl bond[15] of ***1a*** in the ethereal solvent. Such an initiation step is supported by the presence of chlorinated THF in the absence of base.[12] Formation of **5b** and **5c** supports a single electron transfer (SET) step between LiO*t*-Bu and **1a**. Literature precedents for this initiation step are documented.[16]



Scheme 1. Radical trapping experiment.

On the basis of the preliminary mechanistic investigations above and previous literature on functionalization of ethers,[6] we propose a plausible mechanism involving both a radical step and a two-electron substitution (Scheme 2).



Scheme 2. Proposed mechanism.

Single electron transfer (SET) process between LiO*t*-Bu and *N*-chlorophthalimide would generate *tert*-

butoxyl radical and phthalimidyl radical ***A*** (Scheme 2). Literature precedents for this initiation step are documented[16] and in our case supported by the generation of products **5b** and **5c**. Regioselective abstraction of α-hydrogen from THF by radical intermediate ***A*** forms a stable carbon-centered ethereal radical ***B*** and phthalimide ***C***. Stable imidyl radicals have been shown to react as good hydrogen abstractors.[13a] In the propagation step, radical intermediate ***B*** reacts with reagent ***1a*** to form chlorinated THF ***D*** and regenerates the imidyl radical ***A***. Similar radical chlorination mechanisms have been reported with *N*-chlorosulfamate esters.[17] Finally, the base deprotonates phthalimide ***C*** to generate an imide anion that subsequently reacts with ***D*** *via* S_N2 to afford the desired product (Scheme 2).

In summary, we have discovered a mild and metal-free method for the formation of hemiaminal ethers. This new approach enables the regioselective α-amination of various cyclic and acyclic ethers with different *N*-chloroimides such as phthalimides, sulfonimides, and triazoles. Preliminary mechanistic investigations suggest the reaction is initiated *via*, firstly, a radical chlorination of the ether substrate followed by a substitution reaction with the nucleophilic nitrogen source to afford the desired aminated product. This method provides rapid access to many hemiaminal ethers that may serve as useful synthetic or biologically active small molecule intermediates for further functionalization.

EXPERIMENTAL SECTION

General Considerations

All reagents and solvents 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 26 °C.

Moisture-sensitive reactions were performed using flame-dried glassware under an atmosphere of dry argon (Ar). Air- and water-sensitive reactions, were setup in a Vacuum Atmosphere GENESIS glove box held under an atmosphere of argon gas (working pressure 2–6 mbar).

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* plastic or glass syringe.

Chromatographic purification of products was accomplished using 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 $KMnO_4$ stains.

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 $^{13}C\{^1H\}$ NMR. Chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constant, (Hz), relative integral was made in reference to NMR solvent signals.

Mass Spectrometry: Gas chromatograph-mass spectrometry were obtained using Hewlett Packard GC System HP 6890 Series coupled with a HP 5973 Mass Selective Detector. High-resolution mass spectra were obtained using Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS with electrospray ionization (ESI).

Optimization Method

General Method: On a bench top, a 10 mL microwave vial was charged with the appropriate *N*-chloroimide (0.55 mmol), covered with a Kim wipe and tighten with a rubber band. The vial was then brought into an argon filled glovebox before adding base (0.55 mmol) and capped with a 20 mm microwave crimp caps with septa in the glovebox. The vial was removed from the glovebox, covered completely with aluminum foil and 2 mL of the corresponding ether solvent was added. The reaction was then stirred at room temperature for 1 hour unless otherwise stated. After completion, the reaction mixture was prepared directly for chromatography without workup.

Compounds Synthesis and Characterization

1-chloro-4,4-dimethylpiperidine-2,6-dione, 1c. A 25 mL round bottom flask was flame dried and allowed to cool to room temperature. The flask was then cooled to 0 °C and charged with 3,3,-dimethylglutarimide (240 mg, 1.70 mmol, 1 equiv.). 10 mL anhydrous DCM was subsequently added to dissolve the 3,3,-dimethylglutarimide. Isocyanuric chloride (500 mg, 2.15 mmol, 1.30 equiv.) was added in one portion and the resulting solution stirred at 0 °C for 4 h. After this time, the reaction mixture was prepared for flash chromatography (solid deposition) without any workup. The desired product was isolated as a white solid in 92 % yield. Spectra data matched reported data.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6 H), 2.73 (s, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 27.4, 29.5, 47.4, 167.4.

2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione, 3aa. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrofuran), product 3aa is isolated in 80% yield (96 mg) after column chromatography (R_f = 0.39, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 – 2.07 (m, 1 H), 2.24 – 2.33 (m, 1 H), 2.35 – 2.44 (m, 1 H), 2.51 – 2.59 (m, 1 H), 3.92 – 3.97 (m, 1 H), 4.17 – 4.23 (m, 1 H), 6.04 (dd, J = 4.84, 4.96 Hz, 1 H), 7.71 – 7.73 (m, 1 H), 7.82 – 7.85 (m, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 26.0, 29.1, 69.8, 80.9, 123.3, 132.0, 134.1. 167.8.

2-(tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione, 3ab. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL tetrahydropyran),

product 3ab is isolated in 75% yield (96 mg) after column chromatography (R_f = 0.41, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 – 1.80 (m, 4 H), 2.04 – 2.08 (m, 1 H), 2.74 – 2.80 (m, 1 H), 3.65 – 3.71 (m, 1 H), 4.11 – 4.15 (m, 1 H), 5.35 (dd, J = 11.4, 2.2 Hz, 1 H), 7.34 – 7.56 (m, 2 H), 7.87 – 7.90 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.6, 24.9, 27.9, 68.9, 79.4, 123.5, 131.8, 134.2, 167.4.

2-(1-butoxybutyl)isoindoline-1,3-dione, 3ac. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL dibutyl ether), product 3ac is isolated in 65% yield (99 mg) after column chromatography (R_f = 0.28, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.36 Hz, 3 H), 0.96 (t, J = 7.40 Hz, 3 H),1.21 – 1.59 (m, 3 H), 1.41 – 1.50 (m, 1 H), 1.51 – 1.59 (m, 1 H), 2.10 – 2.15 (m, 1 H), 2.22 – 2.31 (m, 1 H), 3.41 – 3.51 (m, 2 H), 5.38 (t, J = 7.04 Hz, 1 H), 7.74 – 7.78 (m, 2 H), 7.86 – 7.89 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.6, 13.7, 18.8, 19.2, 31.4, 34.6, 68.8, 82.0, 123.5, 131.7, 134.2, 168.1.

2-(1-ethoxyethyl)isoindoline-1,3-dione, 3ad. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL diethyl ether), product 3ad is isolated in 70% yield (85 mg) after column chromatography (R_f = 0.50, hexane: ethyl acetate, 3:1) and. Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.04 Hz, 3 H), 1.76 (d, J = 6.32 Hz, 3 H), 3.46 – 3.52 (m, 2 H), 5.56 (q, J = 6.32 Hz, 1 H), 7.71 – 7.74 (m, 2 H), 7.83 – 7.85 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.9, 19.3, 64.2, 78.0, 123.4, 131.7, 134.2, 168.9.

2-(1,2-dimethoxyethyl)isoindoline-1,3-dione, 3ae. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg. lithium *tert*-butoxide and 2 mL 1,2-dimethoxyethane), product 3ae is isolated in 73% yield (95 mg) after column chromatography (R_f = 0.35, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 3 H), 3.33 (s, 3 H), 3.88 – 3.98 (m, 2 H), 5.39 (t, J = 6.52 Hz, 1 H), 7.67 – 7.69 (m, 2 H), 7.78 – 7.81 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 56.9, 59.2, 70.9, 81.4, 123.6, 131.7, 134.3, 168.0.

2-(tert-butoxymethyl)isoindoline-1,3-dione, 3af. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL methyl tert-butyl ether), product 3af is isolated in 60% yield (77 mg) after column chromatography (R_f = 0.43, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 5.04 (s, 2 H), 7.65 – 772 (m, 2 H), 7.80 – 7.84 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 27.8, 61.3, 123.9, 134.2, 134.7, 167.6.

2-(5-methyltetrahydrofuran-2-yl)isoindoline-1,3-dione, 3ag. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL 2-methyltetrahydrofuran), product 3ag is isolated in 72% yield (92 mg) as a mixture of diastereoisomers after column chromatography (R_f = 0.52, hexane: ethyl acetate, 3:1, d.r. = 1:1.5). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.08 Hz, 1.9 H), 1.29 (d, J = 6.0 Hz, 1.2 Hz), 1.50 – 1.58 (m, 0.8 H), 1.94 – 2.02 (m, 0.4 H), 2.05 – 2.15 (m, 0.4 H), 2.20 – 2.28 (m, 1 H), 2.30 – 2.37 (m, 0.8 H), 2.43 – 2.50 (m, 0.4 H), 2.54 – 2.63 (m, 0.7 H), 4.01 – 4.07 (m, 0.3 H), 4.46 – 4.51 (m, 0.6 H), 5.90 (dd, J = 3.76, 3.68 Hz, 0.3 H), 6.03 (dd, J = 5.80, 3.64 Hz, 0.6 H), 7.63 – 7065 (m, 2 H), 7.76 – 7.78 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.3, 20.8, 29.6, 29.8, 32.5, 33.9, 80.3, 80.7, 123.3, 132.0, 134.1, 168.0.

2-(1,4-dioxan-2-yl)isoindoline-1,3-dione, 3ah. Using the General Method and stirring for 4 h, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL 1,4-dioxane), product 3ah is isolated in 61% yield (78 mg) after column chromatography (R_f = 0.26, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 – 3.82 (m, 3 H), 3.97 – 4.00 (m, 2 H), 4.62 (dd, J = 10.2, 10.2 Hz, 1 H), 5.57 (dd, J = 2.84, 2.84 Hz, 1 H), 7.77 – 7.80 (m, 2 H), 7.89 – 7.92 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 65.8, 66.4, 67.5, 76.2, 123.7, 131.6, 134.5, 167.1.

2-(1,3-dioxolan-2-yl)isoindoline-1,3-dione, 3ai. Using the General Method and stirring for 4 h, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL 1,3-dioxolane), product 3ai is isolated in 42% yield (51 mg) after column chromatography (R_f = 0.40, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 – 4.13 (m, 2 H), 4.46 – 4.49 (m, 2 H), 6.80 (s, 1 H), 7.75 – 7.77 (m, 2 H), 7.87 – 7.89 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 66.6, 100.7, 123.6, 131.9, 134.4, 166.8.

2-(tetrahydrothiophen-2-yl)isoindoline-1,3-dione, 3aj. Using the General Method, (100 mg *N*-chlorophthalimide, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrothiophene), product 3aj is isolated in 53% yield (68 mg) after column chromatography (R_f = 0.57 , hexane: ethyl acetate, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 – 2.02 (m, 1 H), 2.22 – 2.29 (m, 1 H), 2.39 – 2.53 (m, 2 H), 2.86 – 2.91 (m, 1 H), 3.29 – 3.35 (m, 1 H), 5.99 (dd, J = 5.52, 5.68 Hz, 1 H), 7.63 – 7.65 (m, 2 H), 7.45 – 7.77 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.9, 34.36, 34.47, 57.5, 123.8, 132.0, 134.1, 167.4. Low resolution MS (EI): 233 (M+), 200, 186, 174, 158, 149, 130, 117, 104, 86, 76, 59, 50. HRMS (ESI) for $C_{12}H_{12}NNaO_2S$ [M+Na]+: calcd 256.0403, found 256.0414.

1-(tetrahydrofuran-2-yl)pyrrolidine-2,5-dione, 3ba. Using the General Method, (73.6 mg *N*-chlorosuccinimide, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrofuran), product 3ba is isolated in 20% yield (19 mg) after column chromatography (R_f = 0.41, hexane: ethyl acetate, 1:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 – 1.97 (m, 1 H), 2.06 – 2.15 (m, 1 H), 2.20 – 2.27 (m, 1 H), 2.31 – 2.38 (m, 1 H), 2.60 (s, 4 H), 3.81 – 3.87 (m, 1 H), 4.08 (q, J = 6.80 Hz, 1 H), 5.80 (dd, J = 5.0, 5.0 Hz, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 26.1, 28.2, 28.5, 70.2, 81.6, 176.7.

4,4-dimethyl-1-(tetrahydrofuran-2-yl)piperidine-2,6-dione, 3ca. Using the General Method, (100 mg 1-chloro-4,4-dimethylpiperidine-2,6-dione, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrofuran), product 3ca is isolated in 55% yield (62 mg) after column chromatography (R_f = 0.29, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[10f] ^{1}H NMR (400 MHz, CDCl3) δ 1.00 (s, 6

H)),1.85-1.90 (m, 1 H), 2.04 – 2.12 (m, 1 H), 2.17 – 2.25 (m, 1 H), 2.42 (s, 4 H), 3.79 (td, *J* = 4.60 Hz, 4.14 Hz, 1 H), 4.14 (q, *J* =7.12 Hz, 1 H), 6.35 (dd, *J* = 4.64, 3.09 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 26.4, 27.6, 28.9, 29.0. 29.6, 47.3, 70.0, 83.0. 172.0

2-(tetrahydrofuran-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide, 3da. Using the General Method, (100 mg *N*-chlorosaccharin, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrofuran), product 3da is isolated in 63% yield (73 mg) after column chromatography (R_f = 0.31, hexane: ethyl acetate, 3:1). Spectra data matched reported data.[6] ^{1}H NMR (400 MHz, CDCl3) δ 2.02 – 2.09 (m, 1 H), 2.30 – 2.43 (m, 1 H), 2.69 – 2.76 (m, 1 H), 3.98 – 4.03 (m ,1 H), 4.25 – 4.31 (m, 1 H), 6.11 (dd, *J* = 3.68, 3.36 Hz, 1 H), 7.81 – 7.90 (m, 3 H), 8.03 (d, *J* = 7.16 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 24.6, 30.3, 70.1, 85.8, 120.7, 125.1, 126.8, 134.2, 135.0, 138.4, 159.2.

1-(tetrahydrofuran-2-yl)-1H-benzo[d][1,2,3]triazole, 3ea *and* ***2-(tetrahydrofuran-2-yl)-2H-benzo[d][1,2,3]triazole, 3e'a***. Using the General Method, (100 mg 1-chlorobenzotriazole, 44 mg lithium *tert*-butoxide and 2 mL tetrahydrofuran), products are isolated in 69% yield (85 mg, combined) after column chromatography. Spectra data matched reported data.[19] **3ea** (47% yield, 58 mg). ^{1}H NMR (400 MHz, CDCl3) δ 2.05 – 2.16 (m, 1 H), 2.26 – 2.38 (m, 1 H), 2.40 – 2.50 (m, 1 H), 3.03 – 3.10 (m, 1 H), 3.94 – 4.05 (m, 2 H), 6.45 (dd, J = 2.61 Hz, 4.81 Hz, 1 H), 7.29 – 7.33 (m, 1 H), 7.40 – 7.44 (m, 1 H), 7.65 (d, *J* = 8.82 Hz, 1 H), 8.00 (d, *J* = 8.82 Hz, 1 H). ^{13}C NMR (100 MHz, CDCl3) δ 24.4, 30.8, 69.2, 87.9, 110.4, 119.7, 124.1, 127.4, 132.8, 146.3. **3e'a** (22% yield, 27 mg). ^{1}H NMR (400 MHz, CDCl3) δ 2.04 – 2.11 (m, 1 H), 2.39 – 2.50 (m, 2 H), 2.64 – 2.72 (m, 1 H), 4.07 (q, *J* = 6.32 Hz, 1 H), 4.24 – 4.30 (m, 1 H), 6.52 (dd, *J* = 2.21, 4.46 Hz, 1 H), 7.29 – 7.33 (m, 2 H), 7.79 – 7.82 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 24.3, 32.3, 70.2, 94.2, 118.5, 126.6, 144.3.

Radical Trapping: Formation of Compounds 5a-c

A microwave vial was charged with 250 mg of *N*-chlorophthalimide. The vial was then brought into a glovebox and 110 mg of lithium *tert*-butoxide was added, capped and removed from the glovebox. The vial was completely covered with an aluminum foil before adding 500 µL of 1,1-diphenylethylene in 500 µL of THF. The resulting solution was stirred at room temperature for 1 h after which the crude mixture was filtered through a short pad of silica gel. GC-MS and NMR analysis of the crude mixture showed the formation of products **5a**, **5b**, and **5c** (See SI for GC-MS spectrum).

ASSOCIATED CONTENT

Supporting Information

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for all aminated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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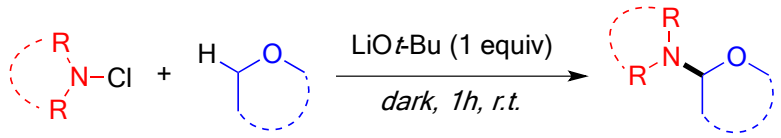

Metal-free, Initiator-free, Oxidant-free
Mild reaction conditions

up to 80% yield