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Metal-Free Cross-Dehydrogenative C-O Coupling of Carbonyl Compounds with N-Hydroxyimides: Unexpected Selective Behavior of Highly Reactive Free Radicals at an Elevated Temperature

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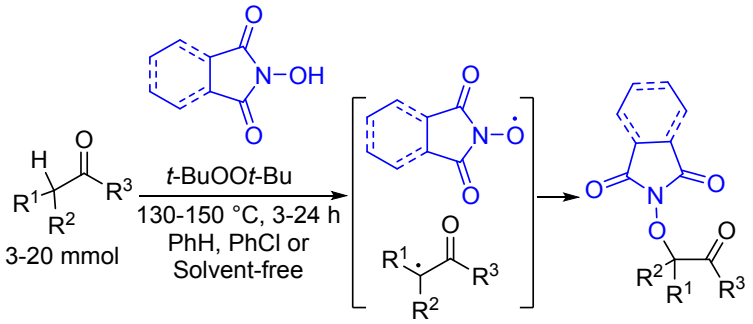
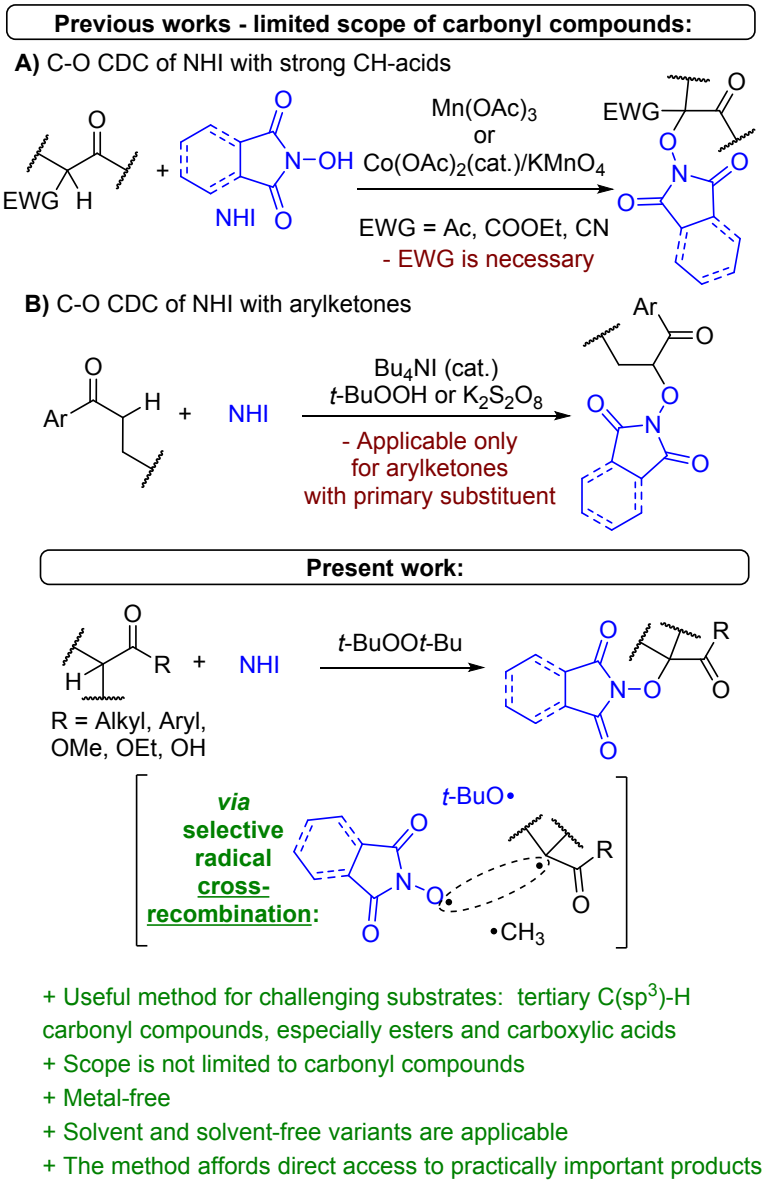


Abstract: Cross-dehydrogenative C-O coupling of *N*-hydroxyimides with ketones, esters, and carboxylic acids was achieved employing the di-*tert*-butyl peroxide as a source of free radicals and a dehydrogenating agent. The proposed method is experimentally simple and demonstrates the outstanding efficiency for the challenging CH-substrates, such as unactivated esters and carboxylic acids. It was shown that *N*-hydroxyphthalimide drastically affects the oxidative properties of *t*-BuOO*t*-Bu by intercepting the *t*-BuO• radicals with the formation of phthalimide-*N*-oxyl radicals - species responsible for both hydrogen atom abstraction from the CH-reagent and the selective formation of the C-O coupling product by selective radical cross-recombination. The practical applicability of the developed method was exemplified by the single-stage synthesis of commercial reagent (known as Baran aminating reagent precursor) from isobutyric acid and *N*-hydroxysuccinimide, whereas in the standard synthetic approach 4 stages are necessary.

Introduction

Cross-dehydrogenative coupling (CDC) is a promising approach in modern organic synthesis targeted towards the construction of complicated molecules from the widely available and simple building blocks in atom-[1] and step-economical[1,2] fashion employing hydrogen atoms as leaving groups.[3-11] Between C-C CDC, C-Heteroatom CDC and Heteroatom-Heteroatom CDC, C-O cross-dehydrogenative coupling is one of the most challenging due to a large number of possible side oxidative processes, such as fragmentation, hydroxylation, and deeper oxidation.[11]

One of the key problems in the development of the CDC methodology is the inertness of C-H bonds. The free-radical chemistry demonstrates high potential in the CDC methodology, especially for the substrates in which a sterically hindered C(sp^3)-H bond has to be involved in a coupling. Such substrates are unfavorable for the most of non-radical CH-activation methods[12] but can undergo the C-H bond cleavage *via* H-atom abstraction by reactive free radicals. Imide-*N*-oxyl radicals proved to be useful H-atom abstracting agents due to the high activity, mild conditions of generation and slow self-decay[13-16] compared to other O-centered radicals. Thus, precursors of such radicals, *N*-hydroxyimides (NHI), were successfully used as OH-reagents in cross-dehydrogenative C-O coupling with substrates containing benzyl,[17-24] allyl,[17,22] aldehyde,[25-34] ether[35,36] moieties and even with cycloalkanes[35,36]. Nevertheless, the imide-*N*-oxyl radical based approach found scant application in the oxidative C-O coupling employing the non-aldehyde carbonyl compounds, presumably due to the inertness of C-H bonds in α-position to the carbonyl group. The scope of such reactions was limited to the highly CH-acidic β-dicarbonyl compounds (Scheme 1, A)[37] and the aryl alkyl ketones having a primary alkyl substituent (Scheme 1, B)[23,38,39].



Scheme 1. Cross-dehydrogenative C-O coupling of *N*-hydroxyimides with different types of substrates.

Carbonyl compounds without other activating groups, especially carboxylic acids and esters are extremely challenging CH-substrates for the CDC. In the present work, a new metal-free method for the C-O CDC of unactivated ketones, esters and carboxylic acids with *N*-hydroxyimides was proposed (Scheme 1, present work). This method is based on widely available organic peroxides as dehydrogenative reagents and opens direct access to compounds, the preparation of which was laborious and time-consuming.

The C-O CDC of CH-reagents with *N*-hydroxyimides leads to O-substituted *N*-hydroxyimides, which are widely used as precursors of O-substituted hydroxylamines[40], alcohols[24] and as substrates for the generation of O-centered radicals and remote CH-

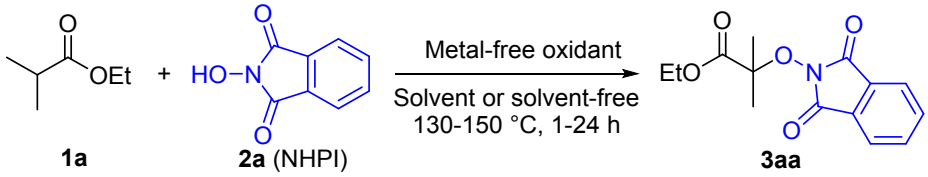
functionalization[41,42]. In particular, α-oxyimido esters and carboxylic acids are used in the synthesis of antimicrobial compounds,[43-47] aminooxypeptides,[48-51] anti-inflammatory agents,[52] free-radical traps,[53] and are known as plant growth-regulators,[54] anticonvulsant compounds,[55] etc. α-(Succinimidooxy)isobutyric acid is the commercially available precursor of Baran aminating reagent.[56]

Results and discussion

The present work was aimed at the development of the metal-free method for the cross-dehydrogenative C-O coupling of *N*-hydroxyimides with inert CH-reagents, such as esters, carboxylic acids, and ketones, for which the use of previously described techniques was ineffective. The idea underlying the present work was to generate imide-*N*-oxyl radicals for the CDC with inert substrates at high temperature, which is necessary for the H-atom abstraction from the inert C-H bond. Thus, organic peroxides that generate free radicals at elevated temperatures were chosen as oxidants.

At the first step, reaction conditions were optimized employing ethyl isobutyrate **1a** and *N*-hydroxyphthalimide (NHPI) **2a** as the model coupling partners (Table 1). The nature of the metal-free oxidant ($PhI(OAc)_2$ or peroxides), the molar ratio of the reagents, the time (1-24 h) and the reaction temperature (130-150 °C) were varied. Reactions were carried out solvent-free or in a solvent (MeCN, PhCN, $MeNO_2$, AcOH, *t*-BuOH, $C_2H_4Cl_2$, PhH, PhCl).

Table 1. Optimization of oxidant, solvent, and reagent ratio for the cross-dehydrogenative coupling of ethyl isobutyrate **1a** with NHPI **2a**.



Run	Metal-free oxidant	Molar ratio **1a**:**2a**:oxidant	Solvent (mL)	Time, h	**3a** yield, % [a]
1	*t*-BuOO*t*-Bu	10:1:1	neat	3	44 (40)
2	$PhMe_2COOCMe_2Ph$	10:1:1	neat	3	49 (42)
3	BzOO*t*-Bu	10:1:1	neat	3	48
4	$MeEtC(OOt\text{-}Bu)_2$	10:1:0.5	neat	3	38
5	1,1-(OO*t*-Bu)cyclohexane	10:1:0.5	neat	3	20

6	BzOOBz	10:1:1	neat	3	22
7	*t*-BuOOH 70% aq	10:1:1	neat	3	23
8	*t*-BuOOH 5-6M in decane	10:1:1	neat	3	30
9	MCPBA	10:1:1	neat	3	10
10	$PhI(OAc)_2$	10:1:1	neat	3	26
11	*t*-BuOO*t*-Bu	10:1:1	neat	1	17
12	*t*-BuOO*t*-Bu	10:1:1	neat	6	47 (41)
13	*t*-BuOO*t*-Bu	10:1:1.5	neat	3	54
14	*t*-BuOO*t*-Bu	10:1:1.5	neat	6	60
15	*t*-BuOO*t*-Bu	10:1:2	neat	3	64 (61)
16	*t*-BuOO*t*-Bu	10:1:2	neat	6	57
17	*t*-BuOO*t*-Bu	10:1:3	neat	3	61 (55)
18	*t*-BuOO*t*-Bu	5:1:2	neat	3	54 (51)
19	*t*-BuOO*t*-Bu	20:1:2	neat	3	62 (60)
20[b]	*t*-BuOO*t*-Bu	10:1:2	neat	3	64
21[c]	*t*-BuOO*t*-Bu	10:1:2	neat	24	56
22	*t*-BuOO*t*-Bu	5:1:2	MeCN	3	44
23	*t*-BuOO*t*-Bu	5:1:2	PhCN	3	41
24	*t*-BuOO*t*-Bu	5:1:2	$MeNO_2$	3	32
25	*t*-BuOO*t*-Bu	5:1:2	AcOH	3	33
26	*t*-BuOO*t*-Bu	5:1:2	*t*-BuOH	3	45
27	*t*-BuOO*t*-Bu	5:1:2	$C_2H_4Cl_2$	3	50
28	*t*-BuOO*t*-Bu	5:1:2	$C_2H_4Cl_2$	6	54
29	*t*-BuOO*t*-Bu	5:1:2	PhH	3	59 (54)
30	*t*-BuOO*t*-Bu	5:1:2	PhH	6	59
31	*t*-BuOO*t*-Bu	1:1.5:2	PhH	3	45
32	*t*-BuOO*t*-Bu	1:1:2	PhH	3	35
33	*t*-BuOO*t*-Bu	2:1:2	PhH	3	41
34	*t*-BuOO*t*-Bu	3:1:2	PhH	3	48
35	*t*-BuOO*t*-Bu	10:1:2	PhH	3	67 (64)
36	*t*-BuOO*t*-Bu	5:1:1.5	PhH	3	54 (43)
37	*t*-BuOO*t*-Bu	5:1:3	PhH	3	65 (60)

38	*t*-BuOO*t*-Bu	5:1:2	PhH	2	55 (50)
39[c]	*t*-BuOO*t*-Bu	10:1:2	PhH	24	58
40	*t*-BuOO*t*-Bu	5:1:2	PhCl	3	58
41[d]	*t*-BuOO*t*-Bu	5:1:2	PhCl	24	59

General procedure: NHPI (1 mmol), ethyl isobutyrate (1-20 mmol), peroxide (1-3 mmol) and solvent (2 mL, "neat" means no solvent was added) were placed into a hermetic glass tube equipped with a magnetic stirring bar and a screw cap. The mixture was stirred in an oil bath (150 °C) for a given time.

[a] The yields were determined by GC using ethyl benzoate as internal standard. Isolated yields are given in parenthesis.

[b] The reaction mixture was bubbled with argon for 5 min before heating.

[c] The oil bath temperature was set to 130 °C.

[d] The reaction was conducted under reflux conditions at atmospheric pressure in a flask with a reflux condenser, the temperature was limited by PhCl boiling point (131 °C)

In the runs 1-10 the nature of an oxidant was varied. The best results were obtained using di-*tert*-alkyl peroxides (di-*tert*-butyl peroxide and dicumyl peroxide, runs 1-2) and *tert*-butyl peroxybenzoate (run 3), yields of **3aa** 44-49%. It should be noted that previously di-*tert*-butyl peroxide was successfully used in decarbonylative alkylation-aminoxidation of styrene derivatives with aliphatic aldehydes and N-hydroxyphthalimide.[57] Geminal bis-*tert*-butylperoxides (runs 4-5), dibenzoyl peroxide (run 6), and *t*-BuOOH (runs 7-8) afforded the target C-O coupling product **3aa** in 20-38% yield. Using MCPBA[58] (run 9) and $PhI(OAc)_2$[14,17,19] (run 10), known as effective oxidants for the generation of phthalimide-*N*-oxyl radicals from NHPI even at room temperature, gave **3aa** in low yields (10-26%). Thus, it is likely that the gradual generation of phthalimide-*N*-oxyl radicals at high temperature is desirable. Based on runs 1-10, *t*-BuOO*t*-Bu was chosen as the best oxidant for further optimization of reaction conditions despite it was slightly less effective than dicumyl peroxide and *tert*-butyl peroxybenzoate. The reason was the volatility of *t*-BuOO*t*-Bu and its decomposition products, which was convenient for the isolation of the target products of the cross-dehydrogenative coupling.

In the runs 11-12 the reaction time was varied compared to the run 1. The shortening reaction time form 3 h to 1 h (run 11 compared to run 1) resulted in strong decrease of the **3aa** yield (44 to 17%), whereas increase of the reaction time from 3 h to 6 h (run 12 compared to run 1) resulted in insufficient improvement of the **3aa** yield (44 to 47%).

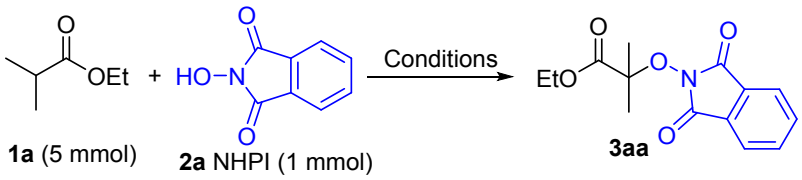
Optimization of reaction conditions was continued with the variation of the molar ratio of reagents, **1a**:**2a** and *t*-BuOO*t*-Bu (runs 13-19). Increase of *t*-BuOO*t*-Bu amount from 1 to 2 mmol (runs 13-16) allowed to reach 64% yield of **3aa** (run 15). Further increase of *t*-BuOO*t*-Bu amount to 3 mmol resulted in slightly lower **3aa** yield 61% (run 17). The optimal amount of ethyl isobutyrate **1a** was about 10 mmol per 1 mmol of NHPI **2a** (run 15). Both increase or decrease of **1a** amount resulted in lower **3aa** yields (runs 18-19, 52-62%).

The bubbling of the reaction mixture with argon before heating (run 20) did not change the **3aa** yield compared the synthesis under air atmosphere (run 15). In the run 21 the temperature of the reaction was decreased from 150 °C to 130 °C compared to run 15. In this case, the longer reaction time was necessary (24 h instead of 3 h) and the lower yield of **3aa** was obtained (56%).

The solvent-free procedure requires a large excess of CH-reagent to play the role of the liquid reaction medium and is not applicable for solid substrates. To make the discovered method of the C-O CDC more general, experiments with the use of solvents were performed (runs 22-41). In runs 22-29 and 40 benzene was identified as the best solvent between the tested group (MeCN, PhCN, $MeNO_2$, AcOH, *t*-BuOH, $C_2H_4Cl_2$, PhH, PhCl), the highest yield was obtained in the runs 28 and 30 (59%). Employing $C_2H_4Cl_2$ (runs 27-28) somewhat lower yield was observed (50-54%). Presumably, the main requirement for the solvent is its inertness with respect to reactive free radicals generated in the reaction mixture. Experiments 40-41 show that chlorobenzene can be used instead of benzene without significant loss in the yield of **3aa**. Importantly, high boiling point of chlorobenzene made it possible to conduct the synthesis at atmospheric pressure with a good yield (59%) although in this case the reaction required 24 hours. (run 41). Chlorobenzene is somewhat less convenient than benzene at evaporation step of the product isolation, but it was used as more safe option for scaling up the synthesis (see below). Analogously to the solvent-free procedure, reagent ratio, reaction time and temperature were optimized for the procedure with benzene as the solvent (runs 30-39). The best yield of **3aa** (67%) was achieved using 10:1:2 ratio of ethyl isobutyrate **1a**, NHPI **2a**, and *t*-BuOO*t*-Bu, reaction temperature 150 °C and reaction time 3 h (run 35).

The efficiency of the developed method was compared with that of the previously documented procedures for the C-O CDC involving NHPI and other types of CH-reagents (Table 2). The cross-dehydrogenative coupling between ethyl isobutyrate **1a** and NHPI **2a** was conducted in accordance with the published procedures, which had been developed for other types of CH-reagents (Table 2, runs 3-8), the obtained yields of **3aa** were compared to those achieved in the present work (Table 2, runs 1-2).

Table 2. Efficiency of the previously documented procedures and the developed *t*-BuOO*t*-Bu-based method in the synthesis of **3aa** from ethyl isobutyrate **1a** and NHPI **2a**



Run	Conditions	**3aa** yield, %[a]	The procedure adapted from:
1	*t*-BuOO*t*-Bu (2 mmol), 150 °C, 3 h	51	Table 1, run 18
2	*t*-BuOO*t*-Bu (2 mmol), PhH (2 mL) 150 °C, 3 h	54	Table 1, run 29
3	CuCl (0.1 mmol), $PhI(OAc)_2$ (1 mmol), MeCN (2 mL), Ar atm, 70 °C, 6 h	24	See ref. 17
4	$(NH_4)_2Ce(NO_3)_6$ (2 mmol), Acetone (5 mL) - H_2O (3 mL) 20-25 °C, 30 min	10	See ref. 18
5[b]	TBAI (0.1 mmol), *t*-BuOOH in decane 5.5 M (1 mmol), DMA, 100 °C, 2 h	0	See ref. 38
6	TBAI (0.2 mmol), *t*-BuOOH in decane 5.5 M (3 mmol), MeCN (4 mL) 75 °C, 6 h	0	See ref. 21
7	$Co(OAc)_2•4H_2O$ (0.05 mmol), $KMnO_4$ (0.4 mmol), AcOH (5 mL), 80 °C, 20 min	21	See ref. 37
8	$Mn(OAc)_3•2H_2O$ (2 mmol), AcOH (5 mL), 80 °C, 20 min	15	See ref. 37

[a] Isolated yields are given.

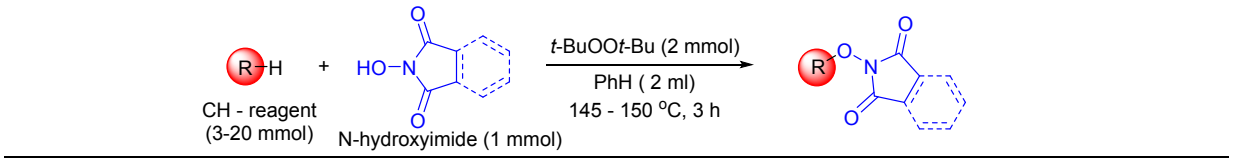
[b] The quantities of reagents were changed according to the procedure described in Ref. 38: **1a** (1 mmol), NHPI (3 mmol).

As can be seen, the literature procedures for the C-O CDC involving NHPI (runs 3-8, yield 0-24%) were sufficiently less effective in the synthesis of **3aa** compared to the developed method (runs 1-2, yield 51-54%). TBAI/*t*-BuOOH combination, that was developed for the C-O CDC of *N*-hydroxyimides with arylalkylketones[21,38] gave no **3aa** at all. This fact indicates that the

TBAI/*t*-BuOOH system is very sensitive to the nature of carbonyl compound employed as the CH-reagent.

To test the scope of the proposed method, a number of products of the C-O CDC of *N*-hydroxyimides (NHPI, *N*-hydroxysuccinimide, tetrachloro-*N*-hydroxyphthalimide, and 4,5-dichloro-N-hydroxyphthalimide) with various CH-reagents (esters, ketones, β-dicarbonyl compounds, nitriles, alkylarenes, and ethers) was synthesized (Table 3).

Table 3. Cross-dehydrogenative C-O coupling of various CH-reagents (esters, ketones, β-dicarbonyl compounds, nitriles, alkylarenes, and ethers) with *N*-hydroxyimides (*N*-hydroxyphthalimide, *N*-hydroxysuccinimide, tetrachloro-*N*-hydroxyphthalimide, and 4,5-dichloro-N-hydroxyphthalimide).



3aa
64% (10, PhH)
61% (10, neat)
60% (20, neat)

3ac
30% (10, PhH)

3ad
29% (10, PhH)

3ba
43% (10, PhH)
47% (20, neat)

3ca
65% (10, PhH)
74% (20, neat)

3da
45% (10, PhH)
42% (10, neat)

3ea
83% (5, PhH)

3fa
51% (10, PhH)
30% (10, neat)

3fb
51% (10, PhH)
27% (10, neat)

3ga
45% (10, PhH)
68% (20, neat)

3ha
32%(10, PhH)
40% (10, neat)

3ia
58% (10, PhH)
56% (10, neat)

3ja
65%(10, PhH)
61% (10, neat)

3jb
56% (5, PhH)

3ka
57% (10, PhH)
52% (10, neat)

3la
65%(10, PhH)
57%(10, neat)

3ma
26% (10, PhH)

3na
25%(5, PhH)
55%(10, PhH)

3oa
17% (5, PhH)

3pa
47% (5, PhH)

3qa
45% (3, PhH)

3ra
64% (3, PhH)

3sa
75% (3, PhH)

3ta
47% (20, neat)
41% (10, neat)

3ua
19% (5, PhH)
16% (10, neat)

3va
54% (5, PhH)

3wa
44% (5, PhH)

3xa
20% (20, neat)

3ya
34% (5, PhH)

4
0% (10, PhH)

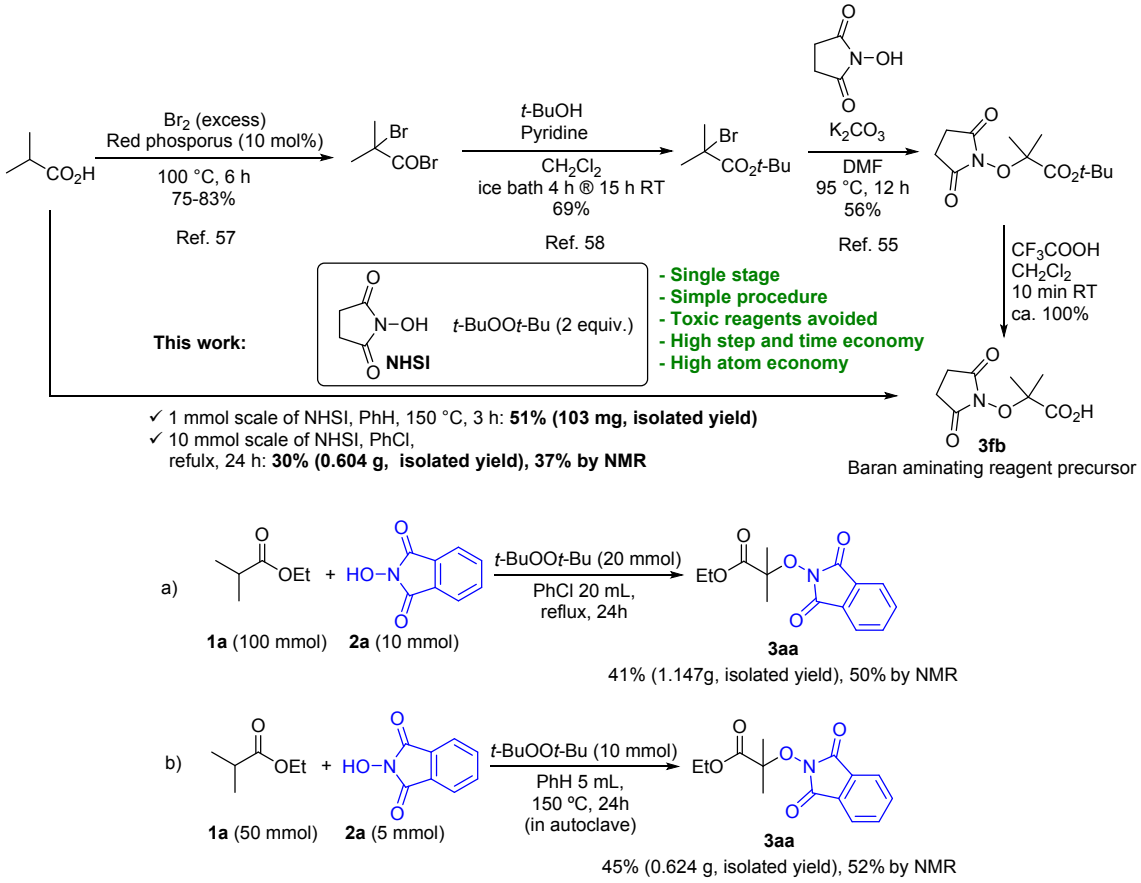
5
0% (20, neat)
0% (10, PhH)

General reaction conditions: NHPI (1 mmol), CH-reagent (3 – 20 mmol, values are given in brackets for each product), *t*-BuOO*t*-Bu (2 mmol) and PhH (2 mL, "neat" means no solvent was added) were placed into a hermetic glass tube equipped with a magnetic stirring bar and a screw cap. The mixture was stirred in an oil bath at 150 °C for 3 h. Isolated yields are given.

Both solvent (PhH) and solvent-free procedures were tested and showed similar results. The excess of CH-reagent depended on the convenience of its separation from the target product. It was minimized in case of the substrates with high boiling points and R_f values close to those of the C-O coupling products. *N*-Hydroxysuccinimide, tetrachloro-*N*-hydroxyphthalimide and 4,5-dichloro-N-hydroxyphthalimide gave somewhat lower yields of the C-O coupling products in comparison with NHPI (products **3aa** and **3ac-3ad**, **3fa** and **3fb**, **3ja** and **3jb**). The developed method was successfully applied to the C-O CDC of *N*-hydroxyimides with esters (products **3aa**, **3ac**, **3ad**, **3ba**, **3ca**, **3da**, **3ea**), carboxylic acids (products **3fa**, **3fb**), ketones (products **3ga**, **3ha**, **3ia**, **3ja**, **3jb**, **3ka**, **3la**, **3ma**, **3na**), β-dicarbonyl compounds (products **3oa**, **3pa**, **3qa**) and benzylmalononitrile (product **3ra**), compounds containing benzyl fragment (products **3ea**, **3na**, **3qa**, **3sa**, **3ta**, **3ua**, **3va**, **3wa**), THF (product **3xa**), and 1,1,2,2-tetrachloroethane (product **3ya**). In case of non-symmetric dialkyl ketones more substituted side was functionalizaed selectively (products **3ga**, **3ha**, **3ia**) In contrast to propiophenone (product **3la**, yield 57-65%), acetophenone gave no target coupling product with NHPI (structure 4), presumably due to higher C-H bond-dissociation energy. Similarly, the target product was not obtained from the reaction of NHPI with cyclohexane. Thus, the general method was developed for functionalization of diverse classes of CH-reagents and its scope is not limited to carbonyl compounds. The most important result was the successful C-O CDC of *N*-hydroxyimides with not activated esters, carboxylic acids and ketones (products **3aa**, **3ac**, **3ad**, **3ba**, **3ca**, **3da**, **3fa**, **3fb**, **3ga**, **3ha**, **3ia**, **3ja**, **3jb**, **3ka**, **3la,** and **3ma**) with functionalization of a secondary or tertiary C(sp^3) atom. Despite the yields are moderate (26-65%), such compounds are hardly achievable by other CDC methods and traditional synthetic approaches.

Scheme 2 demonstrates the practical applicability of the developed method for the synthesis on 10 mmol scale. Compound **3fb** is known as a commercial product - the precursor of Baran aminating reagent.[56] It was previously synthesized in 2 stages starting from *tert*-butyl 2-bromo-2-methylpropionate,[56] that can be prepared from isobutyric acid in another 2 stages[59,60]. The synthetic sequence starting from isobutyric acid consists of 4 stages, the overall yield can be estimated as 29-32%. Using the newly developed method, compound **3fb** can be obtained from isobutyric acid in a single stage in a superior yield of 51% (Scheme 2). This synthesis was scaled

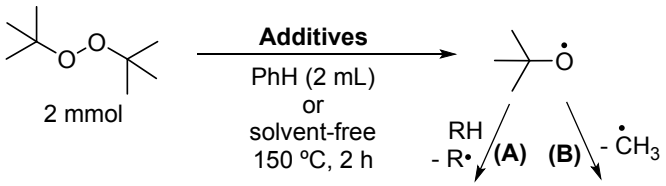
up to 10 mmol of N-hydroxysuccinimide employing the PhCl-based atmospheric pressure procedure for safety reasons. Although lower isolated yield 30% was obtained in this case, the scaled up procedure is still less time consuming and more atom-economical compared to the four-step synthetic sequence.



Scheme 2. Practical applicability of the developed method: the synthesis of the Baran aminating reagent precursor and scale up experiments.

The synthesis of model product **3aa** was also scaled up using two procedures: PhCl-based atmospheric pressure procedure (Scheme 2, a) and standard PhH-based procedure (Scheme 2, b). For procedure b a 25 mL stainless-steel autoclave with PTFE liner and pressure gauge was used as reaction vessel. Similar yields were observed for both procedures (41% for procedure a and 45% for procedure b).

To study the role of *t*-BuOO*t*-Bu in the discovered reaction, the ratio of products of its thermal decay depending on the composition of the reaction mixture was studied by gas chromatography (Scheme 3).



Run	Additives			Unreacted *t*-BuOO*t*-Bu
	Experiments in PhH (2 mL)			
1	-	6%	21%	67%
2	*i*-PrCOOEt (2 mmol)	12%	36%	49%
3	NHPI (1 mmol)	37%	4%	51%
4	NHPI (1 mmol), *i*-PrCOOEt (2 mmol)	47%	6%	42%
	Solvent-free experiments			
5	*i*-PrCOOEt (10 mmol)	34%	30%	34%
6	NHPI (1 mmol), *i*-PrCOOEt (10 mmol)	49%	12%	35%

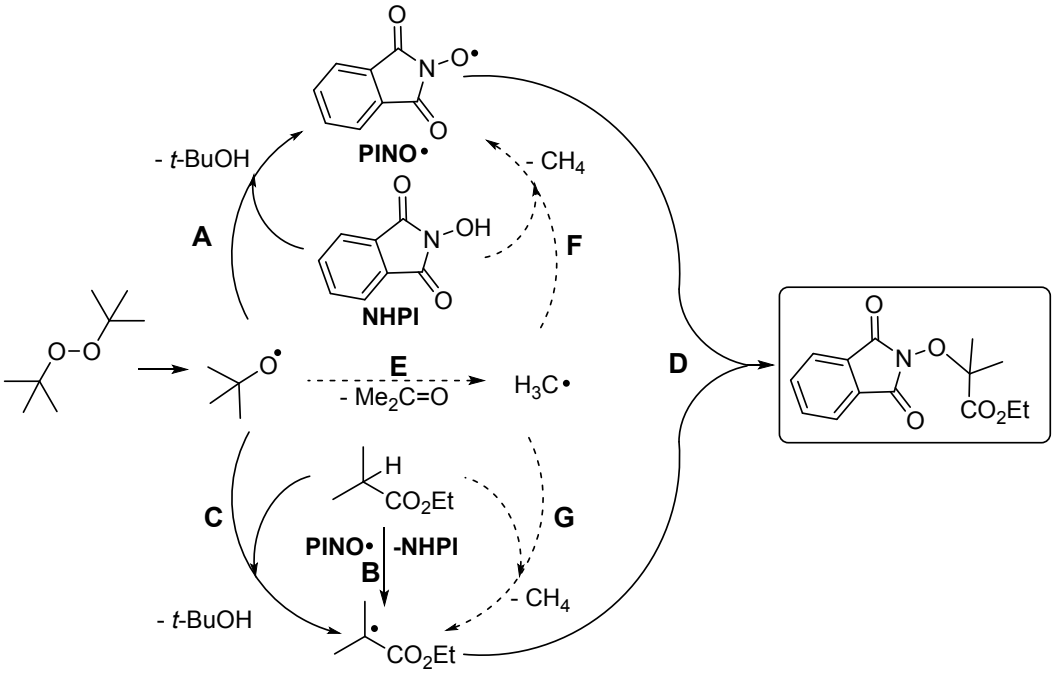
Scheme 3. Influence of NHPI and *i*-PrCOOEt on the ratio of the thermal decomposition products of *t*-BuOO*t*-Bu

It is known that *t*-BuOO*t*-Bu thermally decomposes to *tert*-butoxyl radicals, which can abstract hydrogen from the medium to give *t*-BuOH (Scheme 3, pathway **A**) or undergo β-scission to give methyl radical and acetone (Scheme 3, pathway B). The ratio between pathways **A** and **B** was studied by monitoring the yields of *t*-BuOH and acetone by GC. The runs 1-4 were performed in benzene to model the solvent-based general procedure, and runs 5-6 were performed in *i*-PrCOOEt to model the solvent-free general procedure. The conversion of *t*-BuOO*t*-Bu was not dramatically influenced by the composition of reaction mixture but was higher in *i*-PrCOOEt (35-39% of unreacted *t*-BuOO*t*-Bu was observed) then in PhH (42-67% of unreacted *t*-BuOO*t*-Bu was observed). In pure PhH (run 1) *t*-BuOO*t*-Bu was decomposed mainly by pathway **B**: acetone yield (21%) was more than 3 times higher than the yield of *t*-BuOH (6%). Addition of *i*-PrCOOEt (run 2) did not change **A** / **B** ratio significantly, indicating the low ability of *i*-PrCOOEt to intercept *tert*-butoxyl radicals by playing the role of a H-atom donor. A strikingly different result was observed when NHPI was added to the reaction mixture (run 3). In this case, pathway **A** became major (**A** / **B** ratio = *t*-BuOH / acetone ratio = 37 / 4), indicating that NHPI effectively intercepts *tert*-butoxyl radicals. The addition of *i*-PrCOOEt (run 4) had a negligible effect on **A** / **B** ratio.

In the case of the *t*-BuOO*t*-Bu decomposition in pure *i*-PrCOOEt **A** / **B** ratio was close to 1:1 (Scheme 3, run 5). The addition of NHPI made pathway **A** major (run 6, **A** / **B** ratio = *t*-BuOH / acetone ratio = 54 / 13) analogously to the previously discussed case of the reaction in benzene (runs 1-4). To sum up, NHPI acts as an effective scavenger of *tert*-butoxyl radicals preventing

their fragmentation to acetone and methyl radicals. This reactive radical scavenging ability of NHPI may be responsible for the good selectivity of the discovered process. It is known that thermolysis of di-*tert*-butylperoxide in *i*-PrCOOMe (analog of *i*-PrCOOEt) leads to its C-C dehydrogenative dimerization[61-63] and telomerization[63] of *i*-PrCOOMe.

The plausible reaction pathway is depicted in Scheme 4. Based on the experimental results presented in Scheme 3 and discussed above, the plausible major reaction route is highlighted by plain reaction arrows in Scheme 4. The possible minor routes are represented by dashed reaction arrows.



Scheme 4. Plausible mechanism of the cross-dehydrogenative coupling of NHPI with CH-reagents employing *t*-BuOO*t*-Bu as the dehydrogenation reagent.

First, the thermal decomposition of di-*tert*-butylperoxide produces *tert*-butoxyl radicals (*t*-BuO•). The plausible major reaction route consists of three stages: H-atom abstraction by *t*-BuO• from NHPI to give PINO radical (stage **A**),[64] H-atom abstraction by PINO or t-BuO• from the CH-reagent to give a C-centered radical (stages **B** and **C**, respectively), and coupling of PINO radical with the C-centered radical to form the C-O CDC product (stage **D**). Minor competing routes include β-scission of *t*-BuO• producing methyl radical (stage **E**), H-atom abstraction from NHPI by methyl radical (stage **F**), and H-atom abstraction form CH-reagent by methyl radicals (stage **G**).

Conclusion

Di-*tert*-butyl peroxide mediated metal-free cross-dehydrogenative C-O coupling of *N*-hydroxyimides with various CH-reagents was discovered. The developed procedure is experimentally simple, compatible with solvent-based or solvent-free mode of synthesis, and uses inexpensive di-*tert*-butylperoxide as the dehydrogenation agent. The method is effective for the CH-functionalization of esters, carboxylic acids and ketones that are challenging substrates CH-functionalization and affords 2-5 fold higher yields than previously reported protocols developed for other types of CH-reagents. Based on the control experiments, the plausible major reaction route was proposed. *Tert*-butoxyl radical (*t*-BuO•) abstract hydrogen atom from *N*-hydroxyimide with the formation of imide-*N*-oxyl radical. The hydrogen atom of carbonyl compound is abstracted by imide-*N*-oxyl radical and new C-O bond is formed by recombination of resultant C-centered radical with imide-*N*-oxyl radical. The uncommon feature of the discovered process is the highly selective sequence of hydrogen atom abstraction stages followed by the cross-recombination of free radicals at high temperature. Moreover, generation of imide-*N*-oxyl radicals at lower temperatures by previously known procedures does not allow to reach such efficiency of the C-O coupling.

Experimental

Caution! Experimental procedures involving heating of reaction mixtures in sealed glass tubes impose a potential risk of explosion due to the increased internal pressure. Although no incidents occurred during the course of the present work, the use of protective shields and personal protective equipment is strongly recommended. The given values of the temperatures for carrying out the synthesis (in most cases 150 ° C) relate to the temperature of the oil bath. It must be kept in mind, that the temperature and pressure inside the reaction tube depend on composition of the reaction mixture and heat loss in the upper part of the tube (above the oil level), where the vapor of the boiling mixture is condensed on the inner surface of the walls (photos of the used reaction setup are given in Supporting information). In case of the scaling the synthesis to more than 1 mmol of N-hydroxyimide it is strongly recommended to avoid the use of hermetic reaction vessels made of glass. An autoclave with internal pressure control or an open reaction flask equipped reflux condenser can be used instead (see examples below). In case of usage of peroxides other than di-*tert*-butylperoxide, especially hydroperoxides, quench of peroxide before work up is recommended. The risk of peroxide explosion during or after the concentration of the reaction mixture can be higher in the presence of metal compounds and other initiating impurities.

General

C-O CDC reactions were performed in hermetic borosilicate glass tubes (OD = 18 mm, ID = 15.4 mm, wall thickness = 1.3 mm, height = 18 cm, volume = 30 mL) equipped with screw caps (18 DIN Thread, PTFE coating of the cap seal). The given reaction temperatures (Tables 1,2,3 and Scheme 3) refer to the temperature of an oil bath at which the reaction mixtures were thermostated (±1 °C). See SI for the photos of the reaction heating procedure.

Unless otherwise noted, removal of solvents on rotary evaporator was performed under a vacuum of a water jet pump at 30-50 °C.

GC analysis was performed using a capillary low polarity column (5% Phenyl / 95% Dimethyl Polysiloxane, length 30 m, inner diameter 0.25 mm, film thickness 0.25 μm). The helium flow rate was 3.16 mL/min.

Benzene was distilled over CaH_2. MeCN and PhCN were distilled over P_2O_5. THF was distilled over sodium. *t*-BuOH (99.5%), $MeNO_2$ (99%), glacial acetic acid, $C_2H_4Cl_2$ (99.5%), chlorobenzene (>99%), *N*-Hydroxyphthalimide (98%), *N*-Hydroxysuccinimide (98+%), *t*-BuOO*t*-Bu (99%), dicumyl peroxide ($PhMe_2COOCMe_2Ph$, 99%), *tert*-butyl peroxybenzoate (BzOO*t*-Bu, 98%), 2,2-Di(*tert*-butylperoxy)butane ($MeEtC(OOt\text{-}Bu)_2$, 50% solution in aromatic free mineral spirit), 1,1-Di(*tert*-butylperoxy)cyclohexane (1,1-(OO*t*-Bu)cyclohexane, 50% solution in mineral oil), dibenzoyl peroxide (BzOOBz, 75%, remainder water), *t*-BuOOH (70% solution in water), *t*-BuOOH (5-6M in decane), 3-Chloroperoxybenzoic acid (MCPBA, 70-75%, balance 3-Chlorobenzoic acid and water), (Diacetoxyiodo)benzene ($PhI(OAc)_2$, 98%), ethyl isobutyrate (99%), ethyl propionate (99+%), ethyl benzoate (99+%), methyl isobutyrate (99%), methyl 2-methylbutyrate (98%), methyl phenylacetate (99+%), isobutyric acid (99+%), 3-methyl-2-butanone (98%), 4-Methyl-2-pentanone (99%), 2,4-Dimethyl-3-pentanone (98%), 6-undecanone (97%), propiophenone (99%), 1-phenylbutan-2-one (95%), Ethyl 2-methylacetoacetate (95%), diethyl phenylmalonate (98%), diphenylacetonitrile (99+%), toluene (99.5%), cumene (99%), 4'-Methylacetophenone (95%), ethyl 4-methylbenzoate (99%), 2-hexanone (98%), acetophenone (98%), cyclohexane (>99%), and 1,1,2,2-Tetrachloroethane (98.5%) were used as is.

Tetrachloro-*N*-hydroxyphthalimide,[65] 4,5-dichloro-N-hydroxyphthalimide[14] 2-methyl-1-(pyridin-3-yl)propan-1-one,[66] 3-methyl-2,4-pentanedione,[67] and benzylmalononitrile[68] were prepared as described in the literature.

Experimental details for Table 1

NHPI (163-245 mg, 1-1.5 mmol), ethyl isobutyrate (1-20 mmol, 0.116-2.32 g), peroxide (0.5-3 mmol) and a solvent (2 mL, "neat" means no solvent was added) were placed into a glass tube equipped with a magnetic stirring bar and a hermetic screw cap. The mixture was stirred at 130 or 150 °C for 1-24 h, and then cooled to room temperature. The yields were determined by GC analysis of the reaction mixture using ethyl benzoate as an internal standard. The following GC analysis settings were used: evaporating chamber temperature — 300 °C, column chamber temperature was gradually increased from 70 °C to 300 °C at a rate of 10 °C/min.

To determine the isolated yield of **3aa** (given in parenthesis in Table 1) the reaction mixture was transferred to a round bottom flask using acetone (10 mL), then rotary evaporated under reduced pressure (water jet pump). Product **3aa** was isolated by column chromatography on silica gel using eluent EtOAc/petroleum ether = 2/5.

Experimental details for Table 2

Runs 1-2 are described above in Experimental details for Table 1.

Run 3 (employing CuCl (cat.) / $PhI(OAc)_2$ system) was performed analogously to the procedure described in ref.[17]. N-hydroxyphthalimide (163 mg, 1 mmol), $PhI(OAc)_2$ (322 mg, 1 mmol) and CuCl (9.9 mg, 0.1 mmol) were loaded into a hermetic tube equipped with a magnetic stirring bar and a screw cap, then the tube was flushed with argon. MeCN (2 mL) was added followed by ethyl isobutyrate (581 mg, 5 mmol). The reaction mixture was stirred at 70 °C for 6 h.

The reaction mixture was diluted by CH_2Cl_2 (10 mL) and then by water (30 mL); after shaking the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). All organic extracts were combined, washed with water (2×20 mL), dried over $MgSO_4$ and the solvent was removed using a water-jet vacuum pump. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether = 2/5) to give ethyl 2-(phthalimide-*N*-oxy)-2-methylpropanoate **3aa** (67 mg, 0.241 mmol, 24%).

Run 4 (employing $(NH_4)_2Ce(NO_3)_6$) was performed analogously to the procedure described in ref.[18]. A mixture of *N*-hydroxyphthalimide (163 mg, 1 mmol), ethyl isobutyrate (581 mg, 5 mmol) and acetone (5 mL) was placed in a round-bottomed flask and then flushed with argon. A solution of $(NH_4)_2Ce(NO_3)_6$ (1096 mg, 2 mmol) in water (3 ml) was added dropwise with vigorous stirring under argon for 10 minutes, and the reaction mixture was stirred at RT for 30 min.

Then it was diluted with H_2O (20 mL). The aqueous layer was and extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with a saturated aqueous $NaHCO_3$

solution (15 mL), and H_2O (2×20 mL). The mixture was dried over $MgSO_4$ and the solvent was rotary evaporated. The residue was purified by column chromatography on silica gel (eluent EtOAc /petroleum ether = 2/5) to give ethyl 2-(phthalimide-*N*-oxy)-2-methylpropanoate **3aa** (29 mg, 0.101 mmol, 10%).

Run 5 (employing TBAI/*t*-BuOOH system in DMA) was performed analogously to the procedure described in ref.[38]. *N*-hydroxyphthalimide (489 mg, 3 mmol), ethyl isobutyrate (116 mg, 1 mmol), *t*-BuOOH in decane 5-6 M (1 mmol, 0.182 mL), Bu_4NI (36.9 mg, 0.1 mmol) and dimethylacetamide (DMA, 2 mL) were placed into a round-bottomed flask. The reaction mixture was stirred at 100 °C for 2 h, then cooled to room temperature, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). Combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), H_2O (2×20 ml). The mixture was dried over $MgSO_4$ and the solvent was rotary evaporated. No product **3aa** was obtained by column chromatography separation of the residue (silica gel, eluent EtOAc/petroleum ether = 2/5).

Run 6 (employing TBAI/*t*-BuOOH system in MeCN) was performed analogously to the procedure described in ref.[21]. *N*-hydroxyphthalimide (163 mg, 1 mmol), ethyl isobutyrate (581 mg, 5 mmol), *t*-BuOOH in decane 5.5 M (3 mmol, 0.546 mL), TBAI (36.9 mg, 0.1 mmol) and MeCN (2 mL) were placed in a round-bottomed flask. The reaction mixture was stirred at 75 °C for 6 h, then cooled to room temperature, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). Combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), and H_2O (2×20 mL). The mixture was dried over $MgSO_4$ and the solvent was rotary evaporated. No product **3aa** was obtained by column chromatography separation of the residue (silica gel, eluent EtOAc/petroleum ether = 2/5).

Run 7 (employing $Co(OAc)_2$•$4H_2O$ and $KMnO_4$ in AcOH) was performed analogously to the procedure described in ref.[37]. *N*-hydroxyphthalimide (163 mg, 1 mmol), ethyl isobutyrate (581 mg, 5 mmol), $Co(OAc)_2$•$4H_2O$ (12 mg, 0.05 mmol), $KMnO_4$ (63 mg, 0.4 mmol) and AcOH (5 mL) were placed in a round-bottomed flask. The reaction mixture was stirred at 80 °C for 20 min, then cooled to room temperature. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). Combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), H_2O (2×20 mL). The mixture was dried over $MgSO_4$ and the solvent was rotary evaporated. The residue was purified by column chromatography on silica gel (eluent EtOAc / Petroleum ether = 2/5) to give **3aa** (58 mg, 0.209 mmol, 21%).

Run 8 (employing $Mn(OAc)_3$•$2H_2O$ in AcOH) was performed analogously to the procedure described in ref.[37]. *N*-hydroxyphthalimide (163 mg, 1 mmol), ethyl isobutyrate (581 mg, 5 mmol), $Mn(OAc)_3$•$2H_2O$ (536 mg, 2 mmol) and AcOH (5 mL) were placed in a round-bottomed

flask. The reaction mixture was stirred at 80 °C for 20 min, then cooled to room temperature. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). Combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), H_2O (2×20 mL). The mixture was dried over $MgSO_4$ and the solvent was rotary evaporated. The residue was purified by column chromatography on silica gel (eluent EtOAc / Petroleum ether = 2/5) to give **3aa** (42 mg, 0.151 mmol, 15%).

Experiments for Table 3

General reaction conditions: NHPI (163 mg, 1 mmol), CH-reagent (3-20 mmol), *t*-BuOO*t*-Bu (293 mg, 2 mmol) and PhH as a solvent (2 mL, "neat" means no solvent was added) were placed into a hermetic tube equipped with a magnetic stirring bar and a screw cap. The mixture was stirred in an oil bath (150 °C) for 3 h, then the mixture was cooled to room temperature, transferred to a round-bottomed flask using acetone (10 mL), and rotary evaporated under reduced pressure (water jet pump, 20 mm Hg, 30-50 °C). Additional evaporation step using rotary vane pump (0.5 mm Hg) at 80 °C was made for the isolation of products **3fa, 3fb** derived from isobutyric acid. The residue was purified by column chromatography on silica gel (eluent is given for each product, see below).

Ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropanoate 3aa: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (60-64%, 0.602-0.642 mmol, 167-178 mg); mp = 74-76 °C (lit.[47] mp = 74-77 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.86-7.79 (m, 2H), 7.79-7.70 (m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.63 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 171.0, 164.6, 134.7, 129.2, 123.7, 86.6, 62.1, 23.1, 14.1; FTIR (KBr): ν_{max} = 1796, 1743, 1727, 1469, 1352, 1296, 1186, 1157, 1138, 1111, 970, 878, 706 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.58; H, 5.42; N, 5.04.

Ethyl 2-methyl-2-((4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)oxy)propanoate 3ac: isolated by column chromatography (EtOAc/petroleum ether from 1/5 to 2/5) as a white solid (30%, 0.301 mmol, 125 mg); mp = 157-158 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 4.25 (q, *J* = 7.1 Hz, 2H), 1.62 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 170.5, 160.2, 140.9, 130.2, 124.9, 87.3, 62.2, 23.1, 14.1; FTIR (KBr): ν_{max} = 1794, 1741, 1369, 1338, 1304, 1288, 1178, 1162, 1133, 1037, 734, 702 cm^{-1}. Anal. Calcd for $C_{14}H_{11}Cl_4NO_5$: C, 40.51; H, 2.67; N, 3.37. Found: C, 40.58; H, 2.68; N, 3.35.

Ethyl 2-((5,6-dichloro-1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropanoate 3ad: isolated by column chromatography (EtOAc/petroleum ether 1/8) as a white solid (29%, 0.29 mmol, 100 mg); mp = 39-40 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.91 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H),

1.61 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 170.7, 162.8, 139.8, 128.2, 125.9, 87.1, 62.2, 23.1, 14.1; FTIR (KBr): ν_{max} = 1794, 1735, 1384, 1344, 1297, 1187, 1139, 1110, 1025, 987, 765, 723 cm^{-1}; HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{13}Cl_2NO_5Na$: 368.0063, 370.0034; found: 368.0059, 370.0030.

Ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)propanoate 3ba: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (43-47%, 0.429—0.471 mmol, 113-124 mg); mp = 73-75 °C (lit.[55] mp = 79-80 °C); ^1H NMR (300.13 MHz, $CDCl_3$) δ 7.89-7.79 (m, 2H), 7.79-7.70 (m, 2H), 4.86 (q, J = 6.9 Hz, 1H), 4.33 – 4.13 (m, 2H), 1.64 (d, J = 6.9 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 169.8, 163.4, 134.7, 129.0, 123.8, 81.5, 61.8, 16.5, 14.1.

Methyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropanoate 3ca: isolated by column chromatography (EtOAc/petroleum ether from 2/5 to 1/2) as a white solid (65-74%, 0.650-0.741 mmol, 171-195 mg); mp = 101-102 °C; ^1H NMR (300.13 MHz, $CDCl_3$) δ 7.87-7.79 (m, 2H), 7.79-7.72 (m, 2H), 3.84 (s, 3H), 1.64 (s, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 171.4, 164.6, 134.8, 129.1, 123.8, 86.6, 53.0, 23.1; FTIR (KBr): ν_{max} = 1794, 1742, 1465, 1374, 1354, 1297, 1187, 1170, 1135, 973, 881, 709 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.33; H, 4.94; N, 5.13.

Methyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylbutanoate 3da: isolated by column chromatography (EtOAc/petroleum ether from 1/4 to 1/3) as a white solid (42-45%, 0.418-0.451 mmol, 116-125 mg); mp = 63-65 °C; ^1H NMR (300.13 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.78-7.70 (m, 2H), 3.84 (s, 3H), 2.21-1.88 (m, 2H), 1.54 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 171.1, 164.6, 134.7, 129.1, 123.7, 90.0, 52.9, 29.8, 19.0, 8.6; FTIR (KBr): ν_{max} = 1790, 1740, 1464, 1355, 1186, 1166, 1117, 966, 879, 706 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.58; H, 5.51; N, 5.03.

Methyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-phenylacetate 3ea: isolated by column chromatography (EtOAc/ $CHCl_3$ from 0/1 to 1/4) as a white solid (83%, 0.829 mmol, 258 mg); mp = 129-130 °C (lit.[21] mp = 128-131 °C); ^1H NMR (300.13 MHz, $CDCl_3$) δ 7.82-7.74 (m, 2H), 7.74-7.68 (m, 2H), 7.65-7.56 (m, 2H), 7.44-7.35 (m, 3H), 5.87 (s, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 168.4, 163.2, 134.7, 132.6, 130.2, 128.8, 128.8, 123.7, 85.7, 52.8; FTIR (KBr): ν_{max} = 1793, 1753, 1732, 1225, 1210, 1187, 1036, 701 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.25; H, 3.96; N, 4.49.

2-((1,3-Dioxoisoindolin-2-yl)oxy)-2-methylpropanoic acid 3fa: isolated by column chromatography (EtOAc/petroleum ether/AcOH = 50/50/1) as a white solid (30-51%, 0.301-

0.510 mmol, 75-127 mg); mp = 127-129 °C (lit.[46] mp = 133-135 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 9.03 (bs, 1H), 8.00-7.67 (m, 4H), 1.68 (s, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 174.2, 165.5, 135.3, 128.8, 124.3, 88.3, 23.7; FTIR (KBr): ν_{max} = 1794, 1752, 1745, 1714, 1468, 1374, 1352, 1311, 1188, 1145, 1114, 1081, 1067, 975, 879, 790, 704, 521 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 58.07; H, 4.65; N, 5.45.

2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-methylpropanoic acid 3fb: isolated by column chromatography (EtOAc/CH_2Cl_2/AcOH = 10/100/1) as a white solid (27-51%, 0.268-0.512 mmol, 54-103 mg); mp = 129-130 °C (Recrystallized from diethyl ether, lit.[56] mp = 130–131 °C); ^{1}H NMR (300.13 MHz, DMSO-d6) δ 2.64 (s, 4H), 1.39 (s, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, DMSO-d6) δ 173.1, 171.9, 85.8, 25.4, 23.0.

2-((2-Methyl-3-oxobutan-2-yl)oxy)isoindoline-1,3-dione 3ga: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (45-68%, 0.449-0.679 mmol, 111-168 mg); mp = 56-58 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.86-7.79 (m, 2H), 7.79-7.73 (m, 2H), 2.50 (s, 3H), 1.48 (s, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 207.9, 164.9, 134.8, 129.1, 123.8, 91.8, 25.2, 22.5; FTIR (film): ν_{max} = 1794, 1738, 1721, 1467, 1357, 1189, 1150, 1130, 1081, 976, 878, 706 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.14; H, 5.38; N 5.40.

2-((2-Methyl-4-oxopentan-3-yl)oxy)isoindoline-1,3-dione 3ha: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (32-40%, 0.321-0.398 mmol, 84-104 mg); mp = 75-78 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.84-7.70 (m, 4H), 4.05 (d, J = 8.1 Hz, 1H), 2.45 (s, 3H), 2.30-2.08 (m, 1H), 1.27 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 207.6, 163.5, 134.8, 128.9, 123.8, 98.3, 30.2, 26.0, 18.9, 18.1; FTIR (KBr): ν_{max} = 1792, 1741, 1715, 1467, 1377, 1352, 1233, 1188, 1124, 1081, 1015, 982, 878, 703, 518 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.31; H, 5.80; N, 5.39.

2-((2-oxohexan-3-yl)oxy)isoindoline-1,3-dione 3ia: isolated by column chromatography (EtOAc/petroleum ether = form 1/10 to 1/4) as a white solid (56-58%, 0.56-0.58 mmol, 146-152 mg); mp = 110-111°C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.78-7.68 (m, 2H), 4.43 (t, J = 6.4 Hz, 1H), 2.45 (s, 3H), 2.04-1.86 (m, 1H), 1.83-1.67 (m, 1H), 1.66-1.49 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 207.3, 163.5, 134.8, 128.9, 123.8, 92.9, 32.9, 25.7, 18.2, 14.0. FTIR (KBr): ν_{max} = 1792, 1732, 1463, 1361, 1187, 1113, 1074, 982, 874, 702, 517 cm^{-1}; HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{15}NO_5$+Na^+: 284.0893; found: 284.0895.

2-((2,4-Dimethyl-3-oxopentan-2-yl)oxy)isoindoline-1,3-dione 3ja: isolated by column chromatography (EtOAc/petroleum ether form 1/2 to 2/3) as a white solid (61-65%, 0.610-0.650 mmol, 168-179 mg); mp = 82-83 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.93-7.82 (m, 2H), 7.82-7.72 (m, 2H), 3.61 (heptet, J = 6.8 Hz, 1H), 1.49 (s, 6H), 1.19 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 214.1, 165.3, 134.8, 129.3, 123.8, 93.2, 35.3, 23.8, 19.3; FTIR (KBr): ν_{max} = 1794, 1737, 1708, 1467, 1380, 1364, 1349, 1190, 1149, 1110, 1042, 974, 877, 712, 699 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.48; H, 6.33; N, 4.83.

1-((2,4-Dimethyl-3-oxopentan-2-yl)oxy)pyrrolidine-2,5-dione 3jb: isolated by column chromatography (EtOAc/petroleum ether from 1/2 to 2/3) as a white solid (56%, 0.559 mmol, 127 mg); mp = 57-59 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 3.65-3.45 (m, 1H), 2.75 (s, 4H), 1.41 (s, 6H), 1.15 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 213.8, 172.5, 93.2, 35.1, 25.6, 23.6, 19.4; FTIR (KBr): ν_{max} = 1784, 1728, 1466, 1378, 1366, 1187, 1154, 1078, 1043, 998, 942, 816, 656 cm^{-1}; HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{17}NO_4Na$ 250.1050; found 250.1053.

2-((6-Oxoundecan-5-yl)oxy)isoindoline-1,3-dione 3ka: isolated by column chromatography (EtOAc/petroleum ether = 1/3) as a viscous gum (52-57%, 0.519-0.570 mmol, 172-189 mg); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.78-7.70 (m, 2H), 4.52-4.43 (m, 1H), 3.05 (dt, J_1 = 18.3, J_2 = 7.4 Hz, 1H), 2.64 (dt, J_1 = 18.3, J_2 = 7.4 Hz, 1H), 2.05-1.87 (m, 1H), 1.86-1.70 (m, 1H), 1.69-1.20 (m, 10H), 0.98-0.81 (m, 6H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 209.1, 163.6, 134.8, 129.0, 123.8, 92.7, 38.0, 31.5, 30.7, 26.9, 22.7, 22.6, 14.1, 13.9; FTIR (film): ν_{max} =2958, 2932, 2872, 1792, 1738, 1467, 1374, 1314, 1292, 1242, 1220, 1189, 1172, 1159, 1125, 1082, 984, 877, 702 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.68; H, 7.62; N, 4.17.

2-((1-Oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione 3la: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (57-65%, 0.569-0.650 mmol, 168-192 mg); mp = 91-92 °C (lit.[23] mp = 87-88 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 8.18-8.12 (m, 2H), 7.85-7.77 (m, 2H), 7.77-7.68 (m, 2H), 7.62-7.54 (m, 1H), 7.52-7.44 (m, 2H), 5.73 (q, J = 6.7 Hz, 1H), 1.67 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 195.4, 163.7, 134.8, 134.7, 133.8, 129.3, 128.9, 128.8, 123.7, 83.7, 16.3.

2-((2-Methyl-1-oxo-1-(pyridin-3-yl)propan-2-yl)oxy)isoindoline-1,3-dione 3ma: isolated by column chromatography (EtOAc/petroleum ether = 1/2) as a slightly yellow solid (26%, 0.264 mmol, 82 mg); mp = 134-136 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.81-8.62 (m, 2H), 7.88 – 7.70 (m, 4H), 7.48-7.37 (m, 1H), 1.71 (s, 6H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 197.6, 164.8, 152.7, 151.4, 138.1, 135.0, 130.9, 129.0, 123.9, 123.2, 92.6, 24.1; FTIR

(KBr): ν_{max} = 1792, 1736, 1690, 1584, 1569, 1469, 1459, 1418, 1388, 1372, 1351, 1320, 1289, 1202, 1189, 1144, 1107, 1078, 970, 921, 877, 741, 705, 652, 519 cm^{-1}; HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_4$: 311.1026; found 311.1017.

2-(2-Oxo-1-phenylbutoxy)isoindoline-1,3-dione 3na: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (25-55%, 0.246-546 mmol, 76-169 mg); mp = 108-110 °C (lit.[18] mp = 113-114 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.81-7.65 (m, 4H), 7.56-7.45 (m, 2H), 7.42-7.32 (m, 3H), 5.79 (s, 1H), 2.94-2.74 (m, 1H), 2.72-2.53 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 205.4, 163.3, 134.7, 133.2, 129.8, 128.93, 128.87, 128.3, 123.7, 92.0, 32.1, 7.4; FTIR (KBr) : ν_{max} = 1792, 1730, 1465, 1457, 1371, 1355, 1187, 1127, 1114, 983, 973, 876, 757, 701 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.58; H, 4.81; N, 4.54.

2-((3-Methyl-2,4-dioxopentan-3-yl)oxy)isoindoline-1,3-dione 3oa: isolated by column chromatography (EtOAc/petroleum ether = 1/3) as a white solid (17%, 0.167 mmol, 46 mg); mp =105-107 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.90 – 7.72 (m, 4H), 2.53 (s, 6H), 1.49 (s, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 203.0, 164.1, 135.1, 128.8, 124.1, 96.8, 26.3, 16.0; FTIR (KBr) : ν_{max} = 1792, 1736, 1713, 1357, 1188, 1117, 978, 878, 710 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.83; H, 4.62; N, 5.05.

Ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methyl-3-oxobutanoate 3pa: isolated by column chromatography (CH_2Cl_2/EtOAc from 0/1 to 1/5) as a white solid (47%, 0.472 mmol, 144 mg); mp = 90-91 °C (lit.[37] mp =90-91 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.94-7.69 (m, 4H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.63 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 202.6, 167.5, 164.0, 135.0, 128.9, 124.0, 92.3, 62.8, 26.1, 17.2, 14.0.

Diethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-phenylmalonate 3qa: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (45%, 0.448 mmol, 178 mg); mp = 87-88 °C (lit.[37] mp = 81.5-83 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.83-7.63 (m, 6H), 7.39-7.27 (m, 3H), 4.49-4.26 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 6H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 165.9, 163.4, 134.6, 132.1, 130.1, 129.5, 128.9, 128.1, 123.7, 90.0, 62.9, 14.0.

2-Benzyl-2-((1,3-dioxoisoindolin-2-yl)oxy)malononitrile 3ra: isolated by column chromatography (EtOAc/petroleum ether from 1/5 to 2/5) as a white solid (64%, 0.643 mmol, 204 mg); mp = 144-145 °C; Lit. mp = 158 – 159 °C [37]; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 8.05-7.74 (m, 4H), 7.58 – 7.34 (m, 5H), 3.72 (s, 2H); ^{13}C{^{1}H}NMR (75.48 MHz, $CDCl_3$) δ 162.9, 135.7, 130.8, 129.5, 129.3, 129.0, 128.8, 124.8, 111.7, 76.5, 43.5.

2-((1,3-Dioxoisoindolin-2-yl)oxy)-2,2-diphenylacetonitrile 3sa: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (75%, 0.748 mmol, 265 mg);

mp = 141-142 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.81-7.67 (m, 8H), 7.48-7.39 (m, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, CDCl3) δ 163.5, 135.6, 134.9, 130.4, 128.9, 128.7, 128.4, 124.0, 117.6, 88.5; FTIR (KBr): ν_{max} = 1798, 1745, 1452, 1349, 1300, 1186, 1073, 977, 950, 874, 773, 765, 755, 712, 696, 521 cm^{-1}. Anal. Calcd for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.59; H, 3.99; N, 7.98.

2-(Benzyloxy)isoindoline-1,3-dione 3ta: isolated by column chromatography (EtOAc/petroleum ether = 2/5 as a white solid (41-47%, 0.407-0.466 mmol, 103-118 mg); mp =142-143 °C (lit.[18] mp = 144-146 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.85-7.75 (m, 2H), 7.75-7.65 (m, 2H), 7.57-7.49 (m, 2H), 7.42-7.31 (m, 3H), 5.21 (s, 2H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 163.6, 134.5, 133.8, 130.0, 129.4, 129.0, 128.6, 123.6, 80.0.

2-((2-Phenylpropan-2-yl)oxy)isoindoline-1,3-dione 3ua: isolated by column chromatography (EtOAc/petroleum ether = 2/5) as a white solid (16-19%, 0.156-0.192 mmol, 44-54 mg); mp = 125-127 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2H), 7.80-7.67 (m, 4H), 7.47 – 7.29 (m, 3H), 1.81 (s, 6H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 165.6, 143.0, 134.5, 129.4, 128.1, 126.3, 123.5, 88.7, 27.2; FTIR (KBr): ν_{max} = 1790, 1733, 1368, 1352, 1190, 1153, 1118, 1107, 1078, 975, 877, 766, 701, 552, 519 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.65; H, 5.31; N, 4.91.

2-((4-Acetylbenzyl)oxy)isoindoline-1,3-dione 3va: isolated by column chromatography (EtOAc/petroleum ether = 2/3) as a white solid (54%, 0.542 mmol, 160 mg); mp = 144 – 145 °C (lit.[18] mp = 148-149 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.85-7.70 (m, 4H), 7.64 (d, *J* = 7.7 Hz), 5.26 (s, 2H), 2.60 (s, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 197.8, 163.5, 138.9, 137.8, 134.7, 129.8, 128.9, 128.7, 123.7, 79.1, 26.8.

Ethyl 4-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)benzoate 3wa: isolated by column chromatography (EtOAc/$CHCl_3$ from 0/1 to 1/4) as a white solid (44%, 0.437 mmol, 142 mg); mp = 153-154 °C (lit.[18] mp = 151-152 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.84-7.76 (m, 2H), 7.76-7.69 (m, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 5.26 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 166.3, 163.5, 138.6, 134.7, 131.4, 129.9, 129.6, 128.9, 123.7, 79.2, 61.2, 14.4.

2-((Tetrahydrofuran-2-yl)oxy)isoindoline-1,3-dione 3xa: isolated by column chromatography (EtOAc/petroleum ether = form 1/5 to 2/5) as a white solid (20%, 0.197 mmol, 46 mg); mp =120-132 °C (lit.[17] mp = 121-123 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.84-7.75 (m, 2H), 7.75 – 7.60 (m, 2H), 5.76 (d, *J* = 4.6 Hz, 1H), 4.39-4.25 (m, 1H), 4.05-3.91 (m, 1H), 2.34-1.83 (m, 4H); $^{13}C\{^1H\}$NMR (75.48 MHz, $CDCl_3$) δ 164.0, 134.4, 129.2, 123.5, 108.9, 69.2, 30.9, 22.6.

2-(1,1,2,2-tetrachloroethoxy)isoindoline-1,3-dione 3ya: isolated by column chromatography (DCM) as a white solid (34%, 0.34 mmol, 112 mg); mp = 146-147 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 8.10-7.84 (m, 4H), 7.48 (s, 1H); ^{13}C{^{1}H}NMR (75.48 MHz, DMSO-d_6) δ 162.6, 135.6, 128.7, 124.0, 117.6, 75.1; FTIR (KBr): ν_{max} = 1802, 1755, 1290, 1091, 994, 776, 709 cm^{-1}; HR-MS (ESI-TOF) m/z: [M + Na]$^{+}$ calcd for $C_{10}H_5Cl_4NO_3Na$: 349.8916, 351.8887, 353.8857; found: 349.8916, 351.8887, 353.8857.

Experimental for Scheme 2

1 mmol scale synthesis of **3fb** was performed as described in experimental for Table 3.

Scaled-up PhCl-based atmospheric pressure procedure for the synthesis of 3fb and 3aa. N-hydroxyimide (1.15-1.63 g, 10 mmol), isobutyric acid or ethyl isobutyrate (8.81-11.6 g, 100 mmol), di-*tert*-butylperoxide (2.92 g, 20 mmol) and solvent PhCl (20 mL) were placed into a round bottomed flask with a magnetic stirring bar. The mixture was stirred for 24 hours under reflux. Then reaction mixture was cooled to the room temperature.

In the case of **3fb** synthesis the mixture was rotary evaporated under reduced pressure (water jet pump). Additional evaporation step using rotary vane pump (0.5 mm Hg) at 80 °C was conducted to get rid of residual isobutyric acid. The product **3fb** was isolated as slightly yellow powder (0.604 g, 30%) by recrystallization from diethyl ether.

In the case of **3aa** synthesis saturated aqueous $NaHCO_3$ solution (25 mL) was added to the reaction mixture. Product **3aa** was extracted by CH_2Cl_2 (3×20 mL), extracts were combined, washed with H_2O (2×20 mL), dried over $MgSO_4$ and rotary evaporated. Column chromatography on silica gel (EtOAc/petroleum ether = 2/5) gave ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropanoate **3aa** as a white solid (41%, 4.14 mmol, 1.147 g).

Scaled-up PhH-based procedure for the synthesis of 3aa. N-hydroxyphthalimide (816 mg, 5 mmol), di-*tert*-butylperoxide (1.46 g, 10 mmol), ethyl isobutyrate (5.81 g, 50 mmol) and benzene (5 mL) were loaded into PTFE liner of a 25 mL stainless-steel autoclave equipped by pressure gauge. The mixture was stirred for 3 h on an oil bath (150 °C). The pressure inside the autoclave gradually raised from 0 to approximately 0.45 MPa during all reaction time. After 3 h, the reaction mixture was cooled to the room temperature. Saturated aqueous $NaHCO_3$ solution (25 mL) was added to the reaction mixture. Product **3aa** was extracted by CH_2Cl_2 (3×20 mL), extracts were combined, washed with H_2O (2×20 mL), dried over $MgSO_4$ and rotary evaporated. Column chromatography on silica gel (EtOAc/petroleum ether = 2/5) gave ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-2-methylpropanoate **3aa** as a white solid (45%, 2.25 mmol, 0.624 g).

Experimental details for Scheme 3.

t-BuOO*t*-Bu (292 mg, 2 mmol), *i*-PrCOOEt (0, 232, or 1162 mg; 0, 2, or 10 mmol, respectively), NHPI (0 or 163 mg, 0 or 1 mmol, respectively) and PhH (2 mL or not added) were placed into a glass tube equipped with a magnetic stirring bar and a hermetic screw cap. The mixture was stirred at 150 °C for 2 h, then cooled to room temperature. The yields of *t*-BuOH, acetone and the quantity of unreacted *t*-BuOO*t*-Bu were determined by GC analysis of the reaction mixture using flame ionization detector and ethyl propionate as an internal standard. Evaporating chamber temperature for GC analysis was 150 °C, column chamber temperature was gradually increased from 40 °C to 300 °C at a rate of 10 °C/min.

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all products, photos of the reaction heating procedure (PDF)

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