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Organocatalytic Radical Involved Oxidative Cross-Coupling of *N*-Hydroxyphthalimide with Benzylic and Allylic Hydrocarbons

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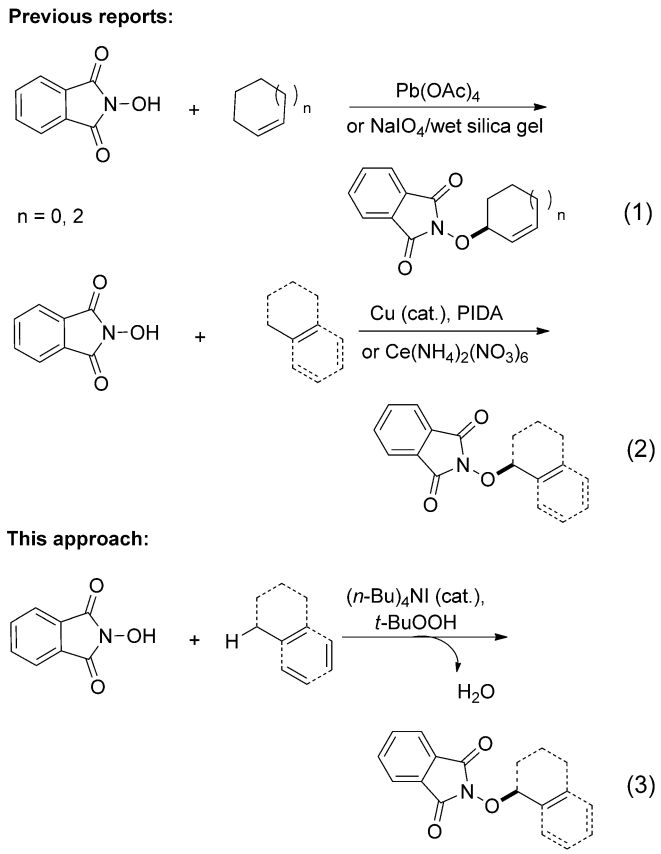
Abstract: The cross-coupling reaction between *N*-hydroxyphthalimide and various benzylic and allylic hydrocarbons was realized through an organocatalytic radical-mediated process involving C(sp^3)–O bond formation using *tert*-butyl hydroperoxide (*t*-BuOOH) as an oxidant and tetra-*n*-butylammonium iodide [(*n*-Bu)$_4$NI] as a catalyst, during which the phthalimide *N*-oxyl (PINO) radical and benzylic and allylic radicals were generated *in situ* and underwent the selective radical/radical cross-coupling reaction. This novel method provides a convenient metal-free approach to the synthesis of *O*-alkylated hydroxy imides under mild reaction conditions.

Keywords: C–H functionalization; hydrocarbons; metal-free conditions; oxidative cross-coupling; radicals

In modern organic synthesis, intensive studies have been focusing on identifying novel direct C–H bond functionalization since this avoidss prefunctionalization of substrates therefore improves atom economy and energy efficiency.[1] Among the various C–H bond functionalization reactions, selective radical involved coupling reactions have been widely utilized owing to their high efficiency in forming new chemical bonds.[2] However, the existing reports on such cross-coupling reactions often require the participation of transition metals as catalysts or oxidants serving to stabilize the transient radical intermediates generated during the reaction process.[3] Radical cross-coupling reactions without the involvement of transition metals have been rarely reported.[4] In this regard, development of novel radical cross-coupling reactions under metal-free conditions should therefore be highly desirable.[5]

Research in the past decades has revealed a highly reactive, oxidative intermediate, namely, the phthalimide *N*-oxyl radical (PINO), in many *N*-hydroxyphthalimide (NHPI)-catalyzed organic reactions.[6] PINO has also been used as a coupling partner with hydrocarbons to form various *O*-alkylated hydroxy imides,[7] some of which are useful building blocks in organic synthesis.[8] The first coupling reaction between PINO and an allylic radical was realized by using $Pb(OAc)_4$, a heavy metal oxidant back in 1964.[7a] However, the yield as well as the selectivity of the reaction were poor. After that, sodium periodate in wet silica gel was reported to promote the generation of the PINO radical from NHPI which showed its efficiency in the coupling reactions with cyclohexene and cyclooctene[7c] [Scheme 1, Eq. (1)]. In 2008, a copper-catalyzed direct C–O bond formation between NHPI and some simple hydrocarbons was developed with PIDA being used as the oxidant for the generation of the PINO radical *in situ* from NHPI.[7d] Besides, cerium(IV) ammonium nitrate (CAN) was also reported to be used as an oxidant in the cross-coupling reaction of NHPI with benzylic compounds [Scheme 1, Eq. (2)].[7e]

However, in most of these existing radical involved cross-coupling approaches, the use of metallic oxidants was inevitable. Concerning the environmental problems and health issues associated with heavy metal residues,[9] the search of an environmentally friendly oxidative system to realize such cross-coupling reactions *via* direct oxidation of alkyl C–H bonds is still in demand. In 2015, Li and co-workers developed a PIDA-mediated oxidative cross-coupling reaction between NHPI and benzylic C–H bonds, in which the C(sp^3)–H oxidation was activated by a polyfluorophenylamide group.[10] Herein, we describe an (*n*-Bu)$_4$NI/*t*-BuOOH-mediated,[11] highly selective organocatalytic oxidative cross-coupling *via* the PINO radical, generated *in situ* from NHPI under mild reac-



Scheme 1. Different approaches for the cross-coupling reactions of NHPI with hydrocarbons *via* the PINO radical.

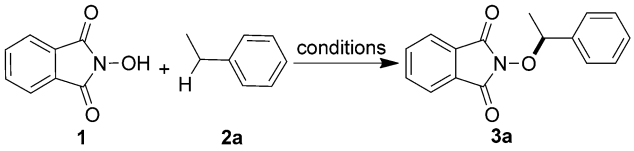
tion conditions, and a benzylic or allylic carbon radical, oxidized from benzylic or allylic hydrocarbon, in forming an *O*-alkylated hydroxy imide as the cross-coupling product [Scheme 1, Eq. (3)].

Recently, we reported an organocatalytic amination reaction of alkyl ethers *via* the $(n\text{-Bu})_4$NI/*t*-BuOOH-mediated radical involved oxidative cross-coupling.[12] Based on this new finding, we took on the study of applying this strategy to see if it could facilitate the selective radical involved cross-coupling reaction between *N*-hydroxyphthalimide and hydrocarbons.

The study started out with ethylbenzene being chosen as the alkyl substrate to react with NHPI. The initial trial produced the desired cross-coupling product **3a** in 30% yield (Table 1, entry 1). Screening for the optimal reaction conditions involved tests of other catalysts, solvents, and fine-tuning the amount of the oxidant. These results showed that other catalysts such as NaI, KI gave poorer yields (Table 1, entries 2 and 3), solvent MeCN was far better than any of the other four solvents, and gave the highest yield of the desired product **3a** of 91% (Table 1, entries 1, 4–7), and larger amounts of $(n\text{-Bu})_4$NI (up to 20 mol%) virtually had no influence on the yield (Table 1, entry 8).

Additional control experiments indicated that both $(n\text{-Bu})_4$NI and *t*-BuOOH played an indispensible role

Table 1. Optimization of the reaction conditions.[a]



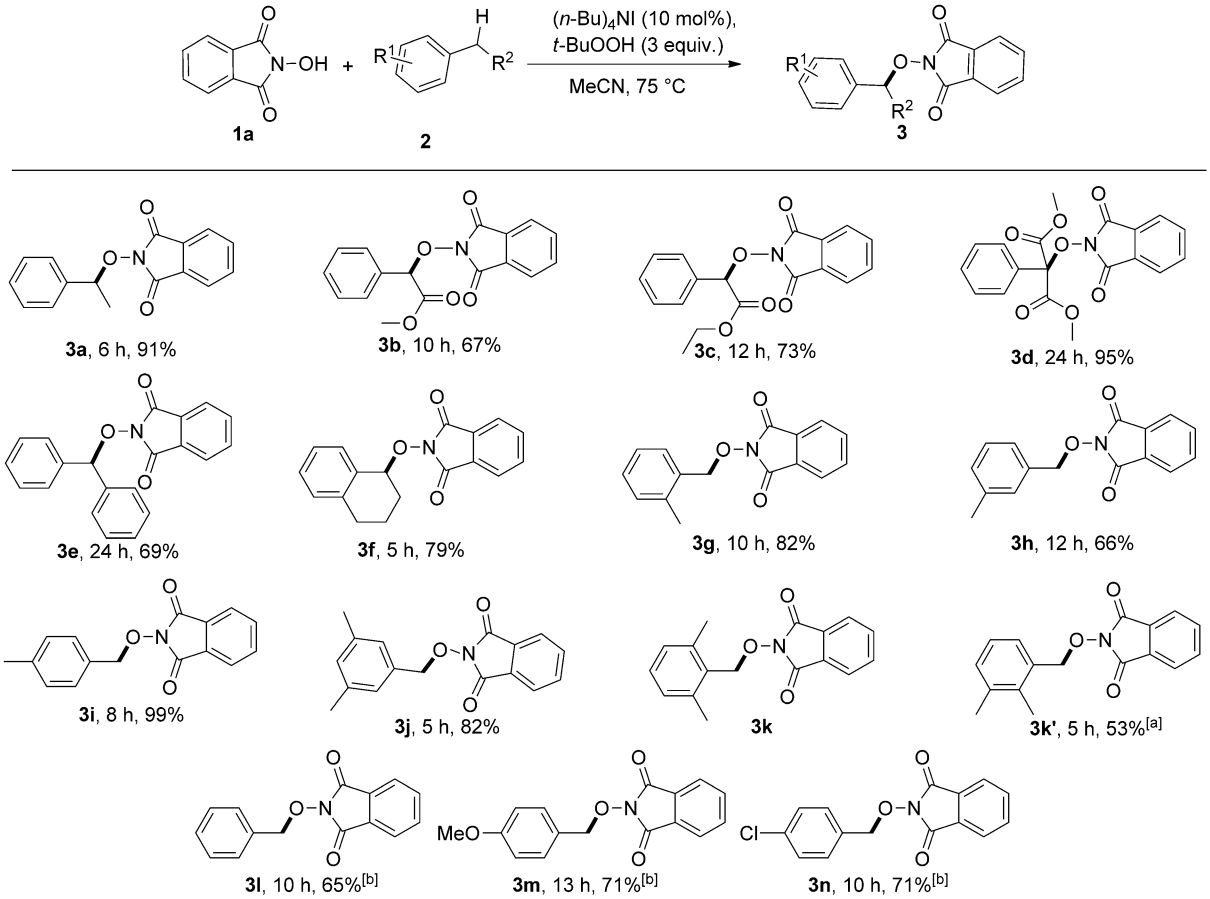
Entry	Oxidant	Catalyst (mol%)	Solvent	Yield[b]
1	*t*-BuOOH[c]	$(n\text{-Bu})_4$NI (10)	EtOAc	30%
2[d]	*t*-BuOOH	KI (10)	EtOAc	15%
3[d]	*t*-BuOOH	NaI (10)	EtOAc	20%
4	*t*-BuOOH	$(n\text{-Bu})_4$NI (10)	DMF	ND
5	*t*-BuOOH	$(n\text{-Bu})_4$NI (10)	DCE	20%
6	*t*-BuOOH	$(n\text{-Bu})_4$NI (10)	PhCl	42%
7	*t*-BuOOH	$(n\text{-Bu})_4$NI (10)	MeCN	91%
8	*t*-BuOOH	$(n\text{-Bu})_4$NI (20)	MeCN	90%
9[d]	none	$(n\text{-Bu})_4$I (10)	MeCN	ND
10[d]	*t*-BuOOH	none	MeCN	20%

[a] *Reaction conditions:* the mixture of **1a** (0.5 mmol), **2a** (2.5 mmol) and the oxidant (1.5 mmol) in solvent (2 mL) was heated at 75 °C for 6 h unless otherwise stated.
[b] All the yields are of isolated products after silica gel chromatography
[c] *t*-BuOOH = *tert*-butyl hydroperoxide, anhydrous unless otherwise stated.
[d] The mixture was heated at 75 °C for 12 h.

in this reaction for forming the desired cross-coupling product **3a** (Table 1, entries 9 and 10).

The optimization of reaction condition was followed by a scope study of the method. These results summarized in Scheme 2 show that a broad range of the substituted benzylic substrates all yielded the desired products in moderate to excellent yields irrespective of whether the benzylic carbon was bonded to highly electron-withdrawing acyl group(s) (**1b–d**), in a sterically disfavored environment (**1e–f**), or bonded to an aromatic ring substituted by mildly electron-donating methyl group(s) (**1g–k**), with a strongly electron-donating methoxy group (**1m**), or with a slightly electron-withdrawing Cl group (**1n**). One compelling advantage of this method is its high regioselectivity – except for **1k** which contains two unequivalent benzylic carbons, only one mono-oxygenated coupling product was formed for all substrates, with the coupling sites being specifically the benzylic carbon and the oxygen atom at NHPI. An inseparable regioisomeric mixture of products **3k** and **3k′** was obtained in a total yield of 53% (the ratio is about 5:1).

Building upon the successful results from the benzylic hydrocarbons, we extended our investigations to the alkene series. The results are listed in Table 2. As predicted, the coupling products were prepared, with the same high regioselectivity between the allylic carbon and the oxygen atom at NHPI, all in satisfactory yields. Substrate **4e**, containing three unequivalent allylic carbons, yielded an inseparable regioiso-



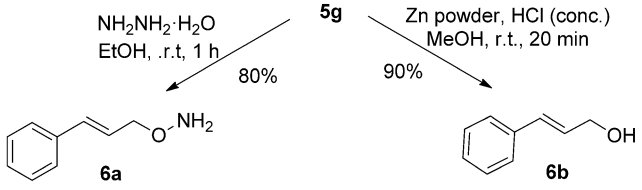
[a] Inseparable isomeric products, **3k**:**3k'** = 5:1.
[b] 20 equiv. of the hydrocarbon were added, the neat mixture was heated at 100 °C.

Scheme 2. Scope of benzylic substrates. *Reaction conditions:* **1a** (0.5 mmol), **2** (2.5 mmol), $(n\text{-Bu})_4\text{NI}$ (10 mol%), anhydrous *t*-BuOOH (1.5 mmol), 75 °C, MeCN (2 mL), sealed tube, unless otherwise stated. All the yields were of isolated products.

meric mixture of compounds **5e** and **5e′** (the ratio is about 3.8:1), with the *Z*-form of **5e′** not being formed. For a linear terminal alkene such as 1-hexene, the reaction provided an isomerized cross-coupling product **5f** as an inseparable *Z*/*E* mixture (the ratio of *E*/*Z* is about 2.2:1).[13] However, the reaction of allylbenzene as well as safrole afforded the isomerized cross-coupling products **5g** and **5h** in only the *E*-configuration. To our delight, safrole was successfully converted to **5h** with the reactive moiety of the methylene ether being well tolerated.[14]

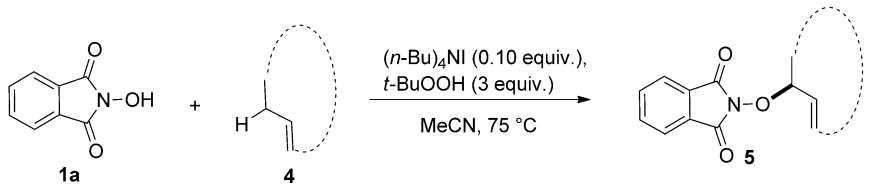
It is worth mentioning that the cross-coupling products could be selectively deprotected to form the corresponding alcohols or the hydroxylamines, both are useful synthetic building blocks in the construction of the heterocyclic compounds or the pharmaceutical intermediates.[15] For example, product **5g** could be readily converted to the allylic hydroxylamine **6a** *via* hydrazolysis or to cinnamic alcohol **6b** through Zn-mediated reduction (Scheme 3).

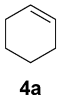
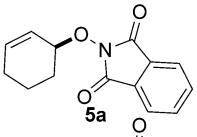
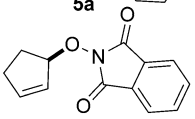
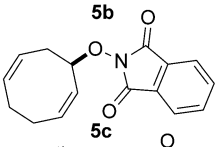
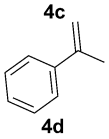
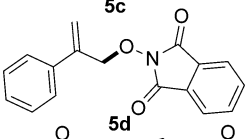
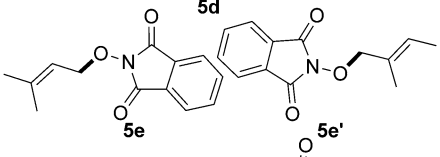
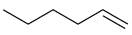
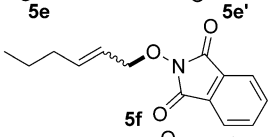
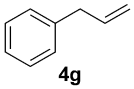
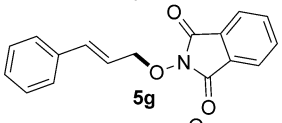
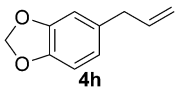
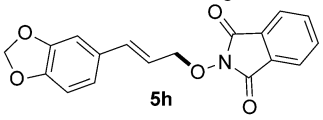
We carried out several control experiments in order to explore the mechanism of this cross-coupling reaction (Scheme 4). One control experiment showed that the desired product **3a** was obtained in lower yields if the catalyst was removed or switched to KI or I_2, suggesting that the iodide anion played an important role in the activation of *t*-BuOOH. However, based on the result of the control experiment of Scheme 4d, we tentatively propose that this process did not involve the generation of the hypervalent iodine species as



Scheme 3. Selective deprotection of product **5g**.

Table 2. Scope of allylic compounds.[a]



Entry	Substrate	Product	Time	Yield [%]
1	 4a	 5a	4 h	67
2	 4b	 5b	1.5 h	58
3	 4c	 5c	5 h	67
4	 4d	 5d	1.5 h	50
5	 4e	 5e 5e'	3 h	72[b]
6	 4f	 5f	24 h	50[b]
7	 4g	 5g	1 h	87
8	 4h	 5h	20 h	50

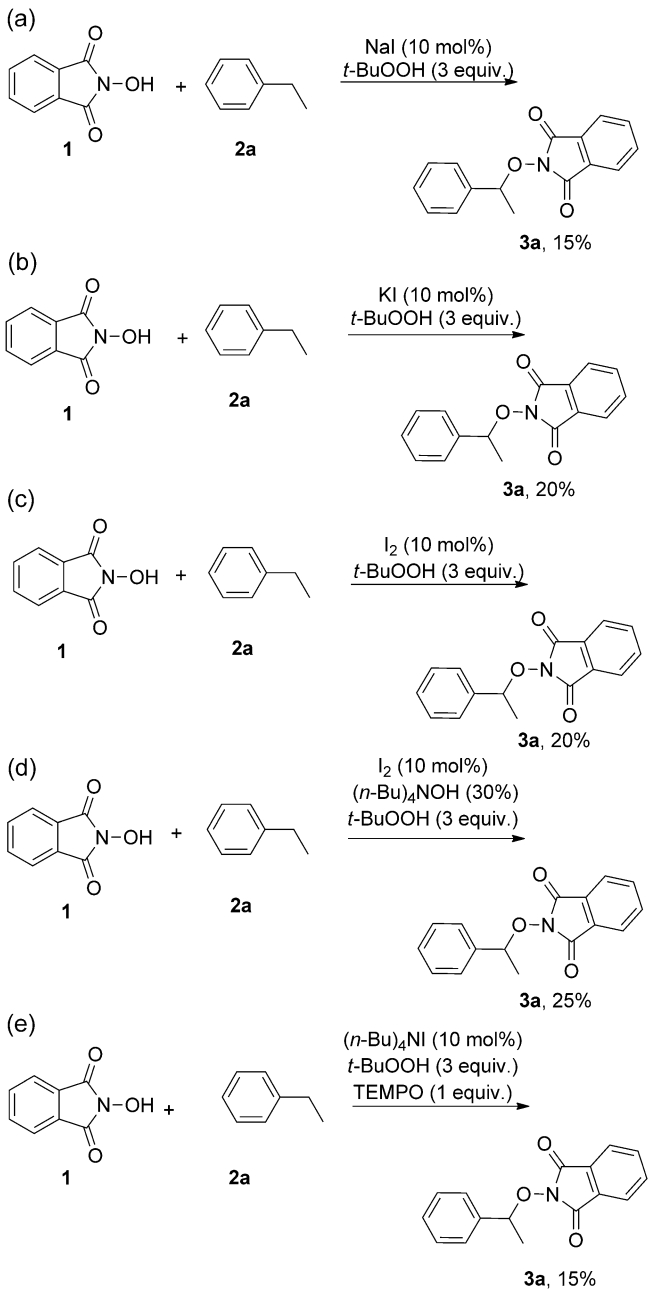
[a] *Reaction conditions:* **1a** (0.5 mmol), **4** (2.5 mmol), $(n\text{-Bu})_4\text{NI}$ (10 mol%), anhydrous *t*-BuOOH (1.5 mmol), 75 °C, MeCN (2 mL), sealed tube, unless otherwise stated. All the yields are of isolated products.

[b] Inseparable isomeric products, **5e**:**5e′** = 3.8:1.

[b] Inseparable *Z*/*E* isomeric products, *E*:*Z* = 2.2:1.

proposed before.[12] In addition, when TEMPO was added to the reaction mixture, the cross-coupling product **3a** was isolated in the yield ofonly 15%, which supported the radical nature of the reaction process.[16]

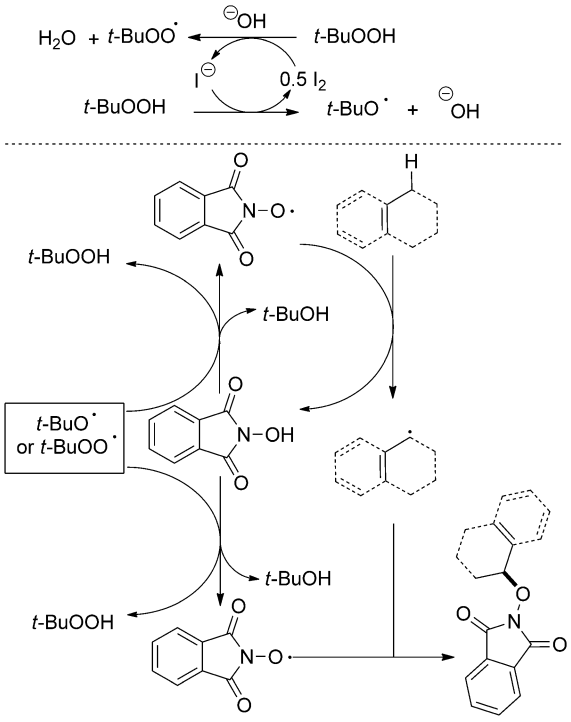
On the basis of all the observations as well as previous literature reports,[17] we propose a plausible mechanistic pathway. As shown in Scheme 5, initially, *t*-BuOOH decomposes to generate the *tert*-butoxyl or *tert*-butylperoxy radical with the assistance of iodide anion. The generated radical subsequently abstracts H from NHPI to afford the PINO radical, which then traps a benzylic or allylic H-atom from the corresponding hydrocarbon to produce the (most stable) carbon radical. The generated NHPI molecules were oxidized again to form the PINO radical for the next cycle of the reaction. Finally, the benzylic/allylic carbon radical and the PINO radical underwent a radi-



Scheme 4. Control experiments to investigate the possible mechanism. *Reaction conditions:* **1** (0.5 mmol), **2a** (2.5 mmol), catalyst and oxidant, MeCN (2 mL), the reaction mixture was heated in a sealed tube at 75 °C for 12 h.

cal combination process and formed the cross-coupling title product of an *O*-alkylated hydroximide.

In summary, we have demonstrated an $(n\text{-Bu})_4$NI/*t*-BuOOH-mediated novel organocatalytic radical involved cross-coupling reaction. In this transformation, the PINO radicals and sp^3 carbon radicals were generated *in situ* and smoothly underwent the cross-coupling reaction, in the absence of any transition metal, providing the corresponding products in moderate to excellent yields. The reaction is highly selective, with



Scheme 5. Proposed possible mechanism.

the coupling sites being the allylic/benzylic C(sp^3) atom and the oxygen atom of NHPI, and the method is applicable to a broad range of substituted hydrocarbons.

Experimental Section

General Procedure for the Organocatalytic Radical Involved Oxidative Cross-Coupling Reaction

To a mixture of hydrocarbon **2** or **4** (2.5 mmol) and $(n\text{-Bu})_4$NI (0.05 mmol, 18.3 mg) in MeCN (2 mL) were added *N*-hydroxyphthalimide **1** (0.5 mmol) and anhydrous *t*-BuOOH (1.5 mmol). The reaction mixture was stirred at 75 °C under an air atmosphere in a sealed tube and the process of the reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with the addition of saturated $Na_2S_2O_8$ (10 mL), and then it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous Na_2SO_4. Then the solvent was removed under vacuum and the residue was purified by silica gel chromatography, using a mixture of PE/EtOAc to afford the desired cross-coupling product **3** or **5**.

Acknowledgements

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